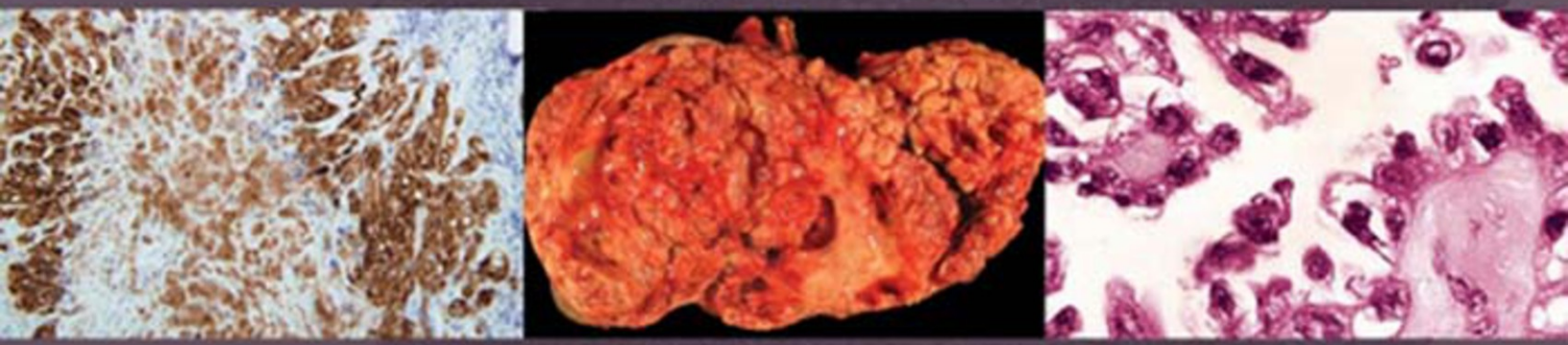
HIGH-YIELD PATHOLOGY

Gynecologic and Obstetric Pathology

Christopher P. Crum Charles M. Quick Anna R. Laury
William A. Peters III Michelle S. Hirsch



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Gynecologic and Obstetric Pathology

HIGH-YIELD PATHOLOGY

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GYNECOLOGIC AND OBSTETRIC PATHOLOGY:
HIGH-YIELD PATHOLOGY

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PREFACE

Navigating the Seven "Cs" of Decision Making in Pathology

Consultations, whether intradepartmental or extradepartmental, are a vital component of patient care and are designed to come as close as possible to the theoretical ideal of an error-free practice. This book is intended to touch on both routine and potentially problematic areas of diagnosis; hence, the "pitfalls" designation for many of the chapters and the appendix, which summarizes many of the problems we have encountered in our experience. No summary can possibly cover all of the potential traps awaiting the practitioner, but the following guidelines (the seven Cs are offered based on our own experience) are intended to reduce errors in interpretation. They are as follows:

1. When examining a case as consultants, are we paying attention to the submitter's *concerns*? This is an aspect that can be quite variable and requires careful review of the submitted records. In particular, the letter from the person requesting the consultation must be read carefully to ascertain not only the history but also the reasons for the consultation request. In many cases the reason for the consultation may not be clearly stated but implied in the preliminary diagnosis. It is imperative that the concerns of the submitter be ascertained.
2. Is the suspected entity *cryptic* as in rare or unusual? In most cases the entity under review or the question being asked is a common one. Is this an endometrial intraepithelial neoplasia/atypical hyperplasia or a benign proliferation? Is it differentiated VIN or lichen simplex chronicus; atypical leiomyoma or STUMP? Such cases *usually* do not have a hidden pitfall. For others, the process or the question is not readily apparent, that is, the features on the slide do not conjure up an instant differential.
3. Are we getting *consultation* from other colleagues or experts, including nongynecologic pathologists? Every pathologist knows that discussion with other pathologists is particularly helpful with unusual, or rarely encountered, problematic lesions. When obtaining consultation, the pathologist must consider three things. First, they obviously must make sure that the pathologists are experienced; second, they must make sure that the pathologists are fully attentive to the case; and third they must make certain that the opinion of their consultant(s) is reasonable. Ultimately, the pathologist seeking consultation must formulate the diagnosis, and this goes for not just the original pathologist but also the "expert" who is being asked to review the case. The value of additional consultation from the literature cannot be overestimated, notwithstanding the limitations in illustration. A "perfect match" between the slide and an image in the literature should be viewed with caution!
4. Are we about to *contradict* the diagnosis of the submitter? Pathologists are by nature independent in their assessments, a natural and necessary aspect of maintaining objectivity. That being said, the submitting pathologist has often gone to considerable effort to understand and describe the difficulties of a particular case. In a nonreferral routine practice, problematic cases are less common and thus receive careful scrutiny. The consultant is well advised to carefully consider the impressions of the submitter and be certain when he or she contradicts their diagnosis. In our experience the submitter is correct in the large proportion of cases.
5. Are we exercising *caution* in our interpretation? One of the biggest threats to a correct diagnosis is overconfidence and a "snap diagnosis" because it short-circuits the slower but more orderly process of weighing the differential diagnoses, obtaining confirmatory opinions, and making the soundest judgment possible.
6. Is a *creative* diagnosis being considered, that is, one that is not in the books? Most of the diagnoses rendered pertain to common questions as discussed earlier. When a consultant encounters something that is particularly unusual, there may be the temptation to apply a diagnosis that is nonstandard. The risk is that the consultant is missing an unusual presentation of something more common. Creative diagnoses should always be made with care, especially if the diagnosis implies a specific line of therapy.
7. Have we reviewed the mundane but critical clerical component? Always verify that the slides sent belong to the patient whom they should represent. Similarly, always make sure that the abnormality belongs to the patient by excluding laboratory contaminants (floaters).

Much of the above information is intuitive to most pathologists, but it is intended to reinforce the great value of taking an organized approach to pathologic diagnosis, whether one is the initial reviewer or consultant. This book will address as many of the potential problems as possible. There will certainly be more, and we welcome input from the readers as we hope to include them in a subsequent edition.

Christopher P. Crum, MD

CONTENTS

B. Endometrial Glandular Neoplasia and Its Mimics

C. Mesenchymal Lesions of the Uterus

SECTION 1

Lower Anogenital Tract

ECZEMATOUS DERMATITIS

Definition—A constellation of inflammatory conditions caused by a reaction to exogenous or endogenous factors. Including, but not limited to, exogenous dermatitis, irritant contact dermatitis, allergic contact dermatitis, atopic dermatitis, and nummular dermatitis.

Clinical Features

Epidemiology

- Seen in all demographic groups.

Presentation

- Clinically, the disorders follow a progression starting with erythema, pruritus, and discomfort, followed by vesicle and bulla formation.
- A superficial yellow crust can form after vesicle rupture.

Prognosis and Treatment

- Prognosis—excellent, responds well to treatment.
- Treatment—avoidance of irritants, hygiene, and steroid ointments.

Pathology

Histology

- Epidermal spongiosis is the defining feature.
- Three phases can be seen histologically: acute, subacute, and chronic.
- In the acute phase a mixed inflammatory infiltrate can be seen in the epidermis and papillary dermis. Spongiosis can progress to vesicle and bulla formation. Necrotic keratinocytes can be seen.
- The subacute phase is marked by acanthosis (frequently psoriasiform) and variable hyperkeratosis and hypergranulosis.
- In the chronic phase the degree of spongiosis decreases; however, the acanthosis, hyperkeratosis, and hypergranulosis become more pronounced.
- Not uncommonly, these lesions can progress to resemble lichen simplex chronicus.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Fungal infection.

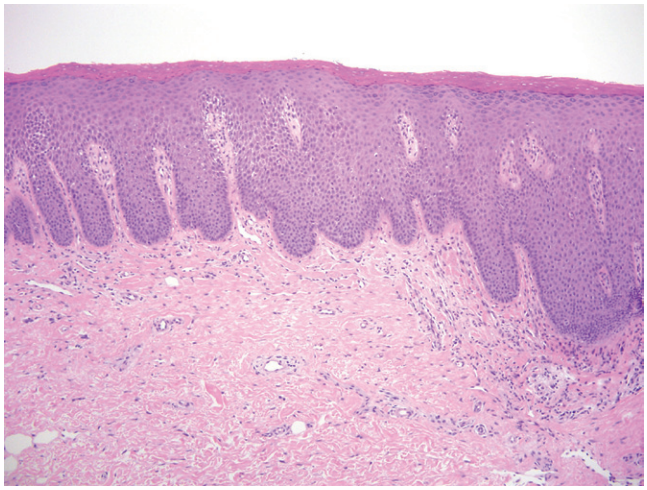

FIGURE 1

Eczematous dermatitis. Acanthosis, hypergranulosis, and hyperkeratosis are present. Note the superficial inflammatory infiltrate in the right aspect of the photo.

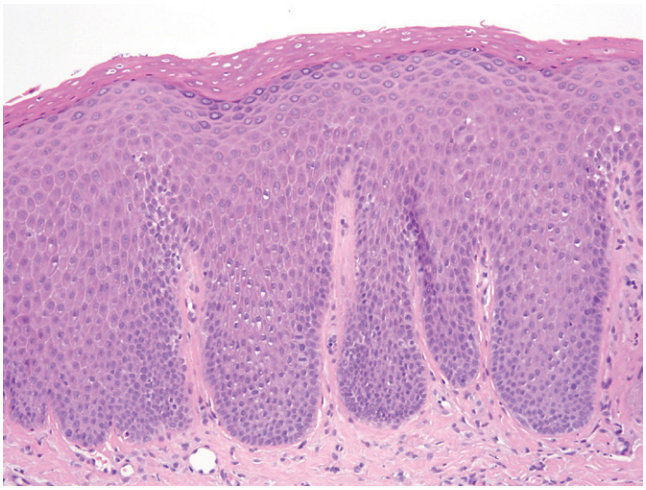

FIGURE 2

Eczematous dermatitis. Acanthosis, hypergranulosis, and spongiosis are present.

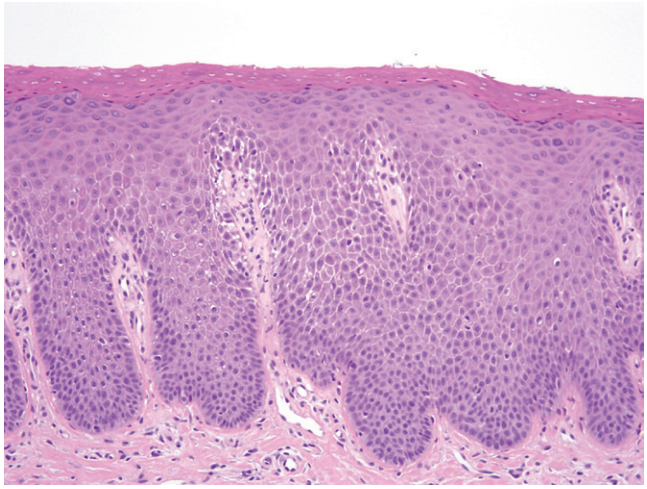

FIGURE 3

Eczematous dermatitis. Marked spongiosis is present in the central aspect, as well as parakeratosis and hyperkeratosis, which are associated with mechanical irritation.

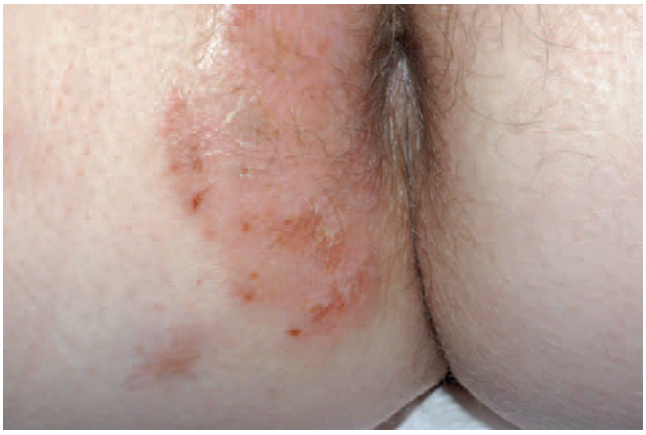

FIGURE 4

Eczematous dermatitis presenting as a pruritic reddened scaly rash in the perianal area. *(Photo courtesy Hope Haefner, MD.)*

LICHEN SIMPLEX CHRONICUS AND PRURIGO NODULARIS

Definition—A cutaneous reaction related to scratching, often superimposed on other dermatoses.

Clinical Features

Epidemiology

- Lichen simplex chronicus (LSC) is not a distinctive disease but a clinical and pathologic response to repeated physical trauma such as rubbing or scratching.
- Often superimposed on eczematous dermatitis.
- Also seen in patients who habitually scratch.
- In the absence of other pathology, it is termed neurodermatitis.
- More commonly seen at perimenopause and postmenopause, but can present at any age.
- Associations have been made with both classic and differentiated vulvar intraepithelial neoplasia (VIN) and certain human leukocyte antigen (HLA) haplotypes.

Presentation

- Chronic pruritus, often accentuated at night.
- LSC presents as thickened skin that has erythema and scaling that is plaquelike, often with overlying excoriation.
- Physiologic skin markings are exaggerated, and visual excoriations are present (Fig. 4). Hyperpigmentation may also be seen.
- Associations have been made with VIN and certain HLA haplotypes.

Prognosis and Treatment

- Prognosis is good with attention to alleviating the symptoms (topical steroids) and interrupting the itch–scratch cycle.
- Recognition and treatment of the underlying cause when present (fungal infection, tinea cruris, chronic eczematous dermatitis, and psoriasis).

Pathology

Histology

- The epidermis shows hyperkeratosis and hypergranulosis.
- Superimposed excoriation and scale crust may be present with vigorous scratching.
- Typically, the rete ridges are elongated.
- Sparse mononuclear infiltrates in the dermis and neutrophils in the epidermis in some cases.

Immunohistochemistry

- Usually noncontributory. In cases with superimposed lichen sclerosus or epithelial atypia, stains for p16ink4 (which will be positive—strong linear staining) and p53 (strong continuous staining of basal cells) may help to rule out a human papillomavirus (HPV)–associated classic VIN or differentiated VIN, respectively.

Main Differential Diagnosis (or Underlying Conditions)

- Eczematous dermatitis—prominent spongiosis will be seen.
- Yeast infections—clusters of neutrophils in the keratin layer, excluded with fungal stains.
- Psoriasis—uniform "test-tube" rete and microabscesses in the apical keratin layer.
- Classic or differentiated VIN—atypia will be present in the basal one-third of the epithelium.

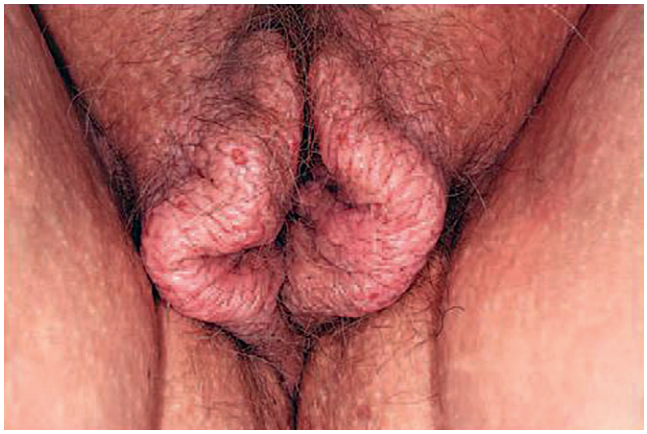

FIGURE 1

LSC. Note the marked symmetrical epithelial thickening due to chronic scratching. *(Photo courtesy Hope Haefner, MD.)*

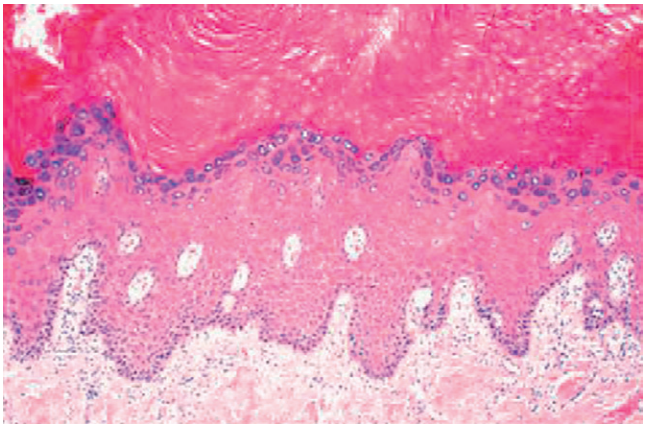

FIGURE 2

LSC. There are prominent acanthosis, hypergranulosis, and hyperkeratosis with a mild dermal mononuclear infiltrate.

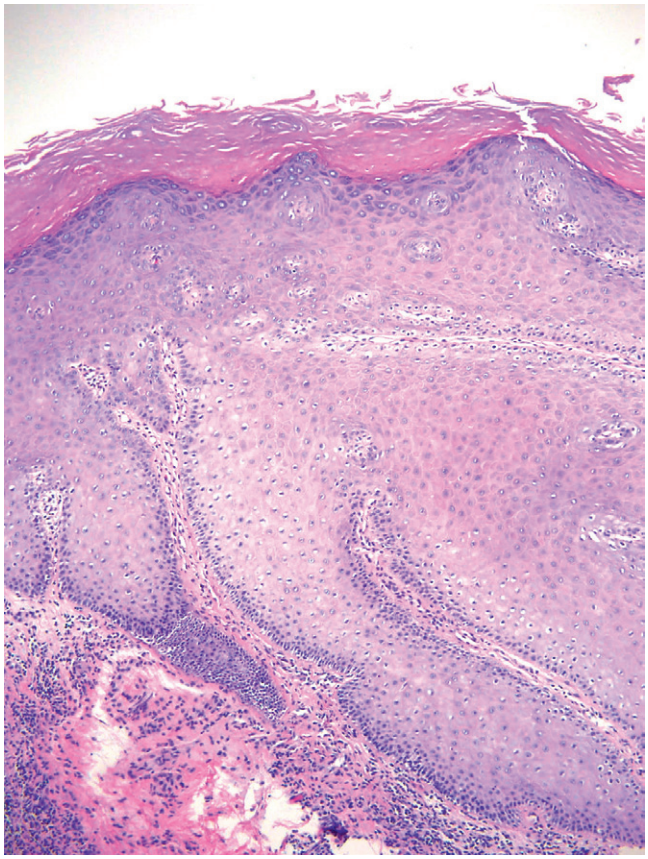

FIGURE 3

LSC. This field shows mild verruciform change.

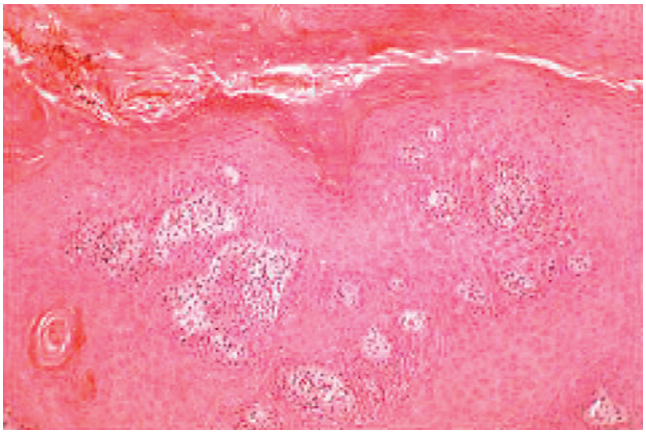

FIGURE 4

Candida infection with superimposed LSC. When suspected, the sections should be evaluated with fungal stains to exclude this treatable cause.

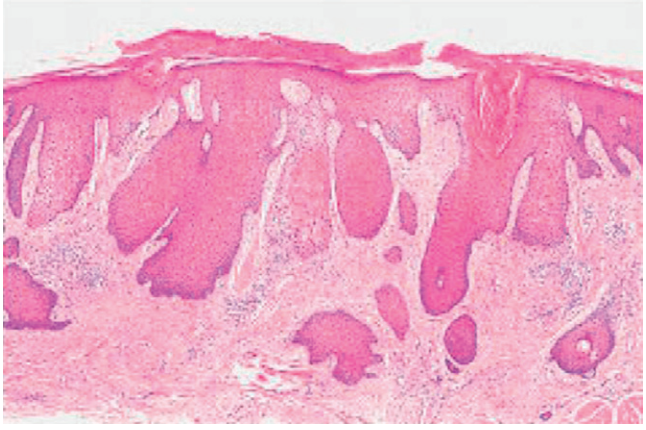

FIGURE 5

LSC. There is prominent epithelial hyperplasia. This pattern overlaps with that of prurigo nodularis, a chronic highly pruritic condition of multiple etiologies characterized by multiple cutaneous nodules and also associated with a severe itch–scratch cycle.

PSORIASIS

Definition—A chronic, hyperproliferative, papulosquamous disorder with a relapsing course.

Clinical Features

Epidemiology

- Affects 1% to 2% of Caucasians.
- Onset is usually in the late 20s.
- A genetic component is likely, as first-degree relatives are also often affected.
- At least one third of the female patients have vulvar involvement, although isolated vulvar involvement is uncommon.

Presentation

- In general, classical (plaque-type) psoriasis is characterized by symmetrically distributed erythematous plaques covered with a silver scale.
- These plaques can be reflected, which results in pinpoint bleeding (Auspitz sign).
- Plaque-type psoriasis is the most common form of psoriasis to affect the vulva, but the lesions are shiny because they lack the silvery scale.
- Guttate psoriasis occurs in young patients, including children, and arises after infection with β-hemolytic streptococcus.
- Guttate psoriasis presents as crops of small subcentimeter erythematous papules without a scale.
- Guttate psoriasis may herald the onset of plaque-type disease.
- Pustular psoriasis displays plaques and superimposed pustules, and is also notable for its prominent systemic symptoms (i.e., fever).
- The development of psoriatic lesions is associated with the Koebner's phenomenon, when the lesions arise at the site of prior trauma.

Prognosis and Treatment

- Prognosis—variable, as this is a chronic disease with a protracted clinical course.
- Debilitating psoriatic arthritis may develop after years of skin disease.
- Treatment—topical or systemic steroids, topical antiproliferative agents, methotrexate, cyclosporine, and other immunomodulatory drugs.

Pathology

Histology

- Epidermal acanthosis with regular elongation and fusion of the rete ridges, also known as psoriasiform hyperplasia, is characteristic.
- Psoriasiform hyperplasia has a "test-tube" appearance due to the regularity of the elongated rete, which can also have rounded club shape.
- Loss of the granular cell layer and confluent parakeratosis, which often contains a neutrophilic infiltrate with intraepidermal pustules, is common.
- Microabscesses or pustules formed in the corneal layer are named Munro's microabscesses.
- When the spinous layer is spongiotic and contains collections of neutrophils, they are termed spongiform pustules of Kogoj.
- The spongiform pustules of Kogoj are more often seen in the pustular variant, as are confluent Munro's microabscesses, which can form macropustules.
- The lesions of guttate psoriasis have more subtle, irregular psoriasiform hyperplasia, and often maintain the granular cell layer.
- The superficial dermal papillae contain ectatic tortuous vessels, and this is often associated with thinning of the overlying epidermis. These areas of the epidermis are very susceptible to trauma and likely account for the Auspitz sign seen clinically.
- The very early changes of psoriasis include superficial vascular plexus dilation accompanied by a mild lymphocytic perivascular and dermal infiltrate.

- Established lesions show marked acanthosis and parakeratosis, with increased epidermal mitotic activity.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Fungal infection.
- Chronic eczematous dermatitis.
- Psoriasiform drug eruption.
- Lichen simplex chronicus.

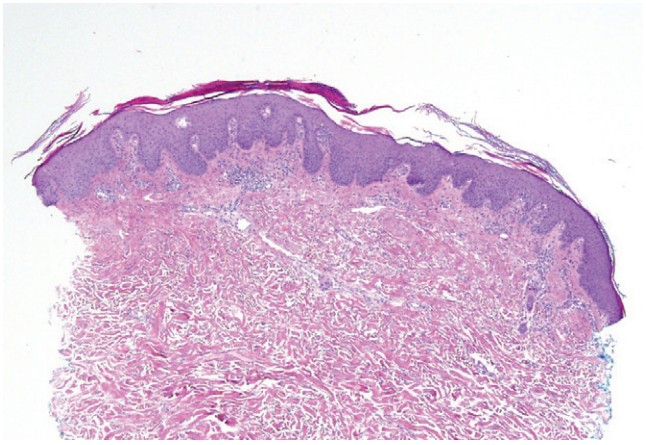

FIGURE 1

Vulvar psoriasis. Acanthosis with regular elongated rete ridges. The rete has round bulbous tips. A mild dermal lymphocytic infiltrate is present.

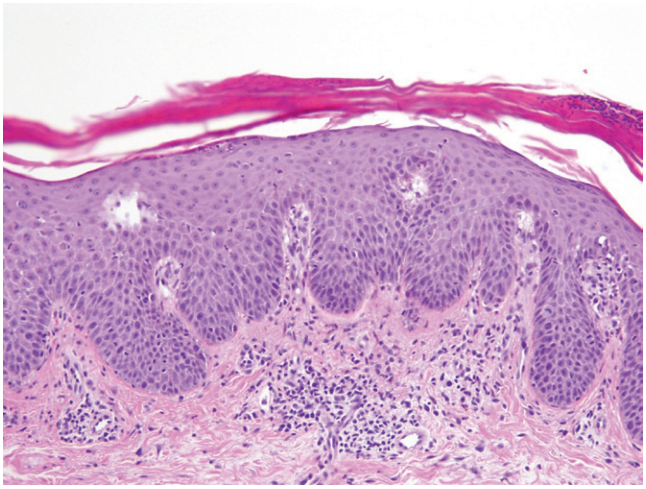

FIGURE 2

Vulvar psoriasis. Confluent parakeratosis with a collection of neutrophils present on the surface. Collections of neutrophils are seen in the superficial epidermis. The bulbous rete is fused.

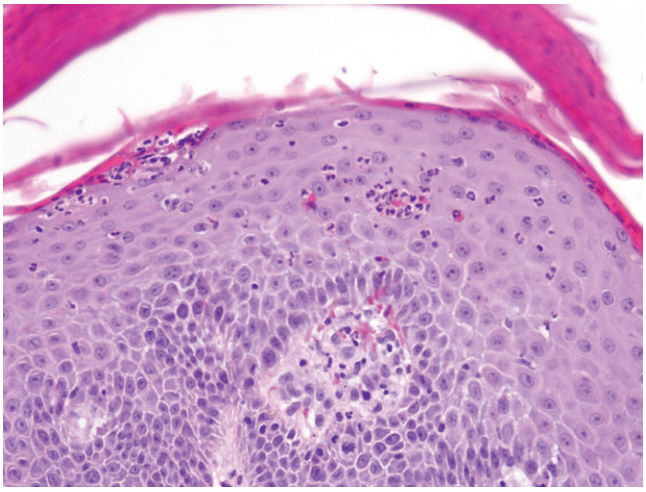

FIGURE 3

Vulvar psoriasis. Munro's microabscesses, which consist of collections of neutrophils within the corneal layer, are present. Spongiosis is prominent.

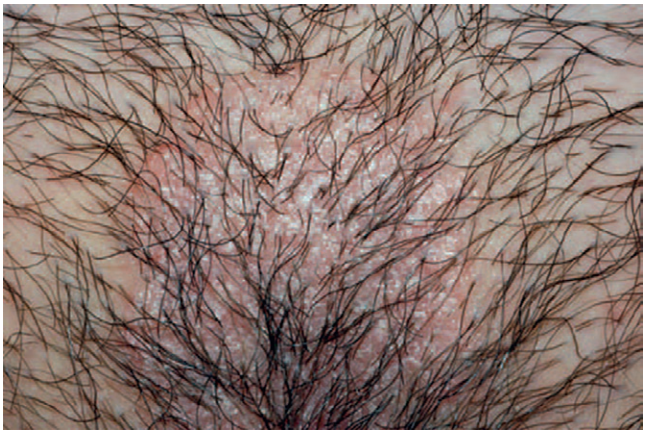

FIGURE 4

Vulvar psoriasis. This close-up view illustrates a typical plaque composed of confluent reddish bumps with a silvery scale. *(Photo courtesy Hope Haefner, MD.)*

SEBORRHEIC DERMATITIS

Definition—A chronic, recurrent dermatitis occurring in areas where sebum is produced marked by red plaques with a yellow scale.

Clinical Features

Epidemiology

- Common.
- Affects all demographic groups.
- Immunosuppressed patients and patients with some chronic conditions (including congestive heart failure and Parkinson's disease) have more severe disease and may develop generalized seborrheic dermatitis.
- The disease characteristically flares in winter and spring, with the resolution of symptoms during the summer months.

Presentation

- A red plaque with a greasy yellow scale is noted on the vulva or perineum of adults.
- The surface is frequently "shiny" in genital lesions.
- Patients may report intermittent burning or itching of the area.

Prognosis and Treatment

- Prognosis—excellent, readily responds to treatment.
- Treatment—medicated shampoo and steroid lotions or creams.

Pathology

Histology

- Variable spongiosis with an underlying dermal lymphocytic infiltrate.
- The epithelium may display psoriasiform acanthosis and parakeratosis.
- Clusters of neutrophils are present, particularly around the follicular ostia.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Fungal infection (candidiasis).
- Eczematous dermatitis.
- Psoriasis.

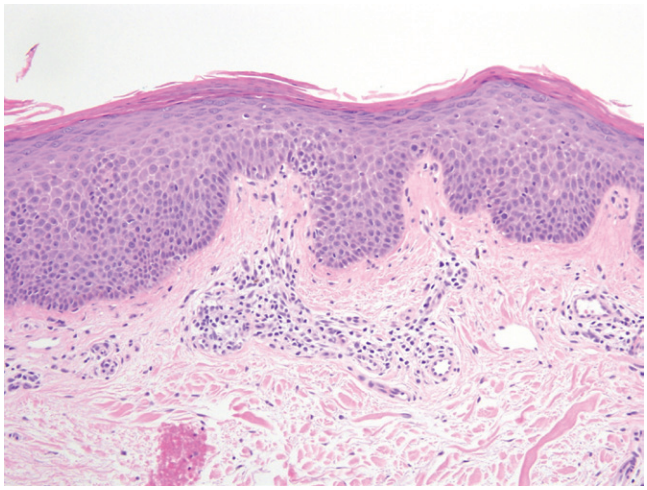

FIGURE 1

Seborrheic dermatitis. Acanthosis with mild hyperparakeratosis and a patchy dermal lymphocytic infiltrate.

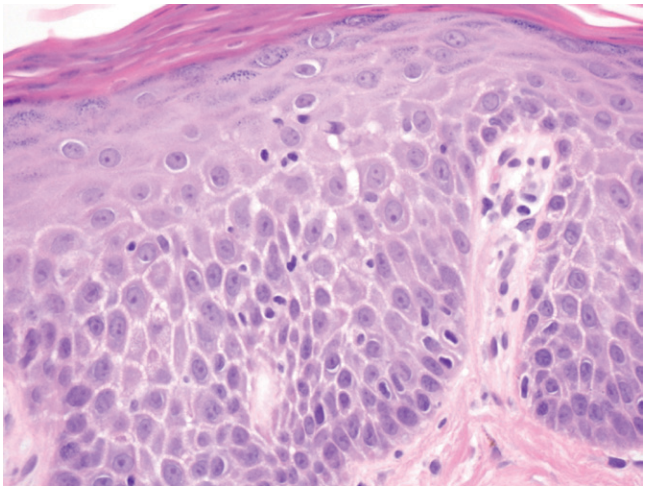

FIGURE 2

Seborrheic dermatitis. Spongiosis and a mild superficial dermal lymphocytic infiltrate.

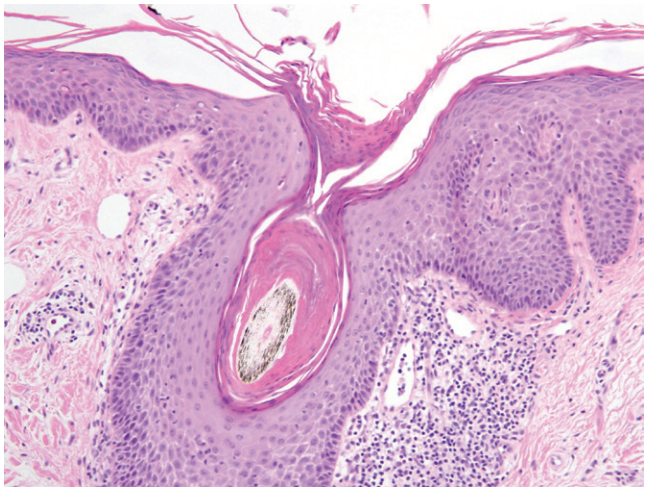

FIGURE 3

Seborrheic dermatitis. Follicular keratosis and perifollicular inflammation, including neutrophils.

LICHEN SCLEROSUS INCLUDING EARLY LICHEN SCLEROSUS

Definition—A chronic inflammatory dermatosis of unknown etiology that commonly affects the vulva.

Clinical Features

Epidemiology

- More commonly seen in perimenopausal and postmenopausal patients; however, can be seen at any age.
- Associations have been made with vulvar intraepithelial neoplasia (VIN) and certain human leukocyte antigen (HLA) haplotypes.

Presentation

- Frequently asymptomatic, but can present with pruritus, burning, and pain.
- Clinically, the lesion appears as a symmetrical white patch that has been compared with parchment or cigarette paper.
- Progressive disease can lead to distortion of the normal architecture with progressive stenosis of the introitus and anus.
- Involvement may be seen in areas of previous trauma (Koebner's phenomenon).

Prognosis and Treatment

- Prognosis—a small, but definite, risk of squamous cell carcinoma (~5%) has been associated with lichen sclerosus (LS).

Pathology

Histology

- Early lesions show vacuolar interface changes with scattered lymphocytes and necrotic keratinocytes.
- The lymphocytic infiltrate may be denser and "band-like" in early lesions.
- Dermal edema or hyalinization involving the superficial reticular dermis or papillary dermis may be present in lesions of any age.
- In well-established lesions, the amount of dermal inflammation can decrease, and there is frequent thinning of the epidermis with loss of rete ridges.
- Changes seen in lichen simplex chronicus (LSC) (hyperkeratosis, hypergranulosis) can be seen in traumatized LS.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Lichen planus (especially early LS lesions).
- Vitiligo (clinically).
- Radiation-related changes.

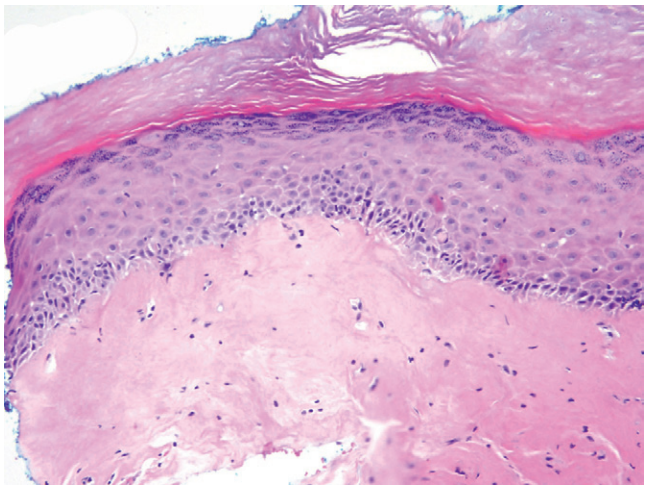

FIGURE 1

LS. Vacuolar changes in the basal layer, as well as loss of the rete ridges and hyalinization of the dermis, are seen.

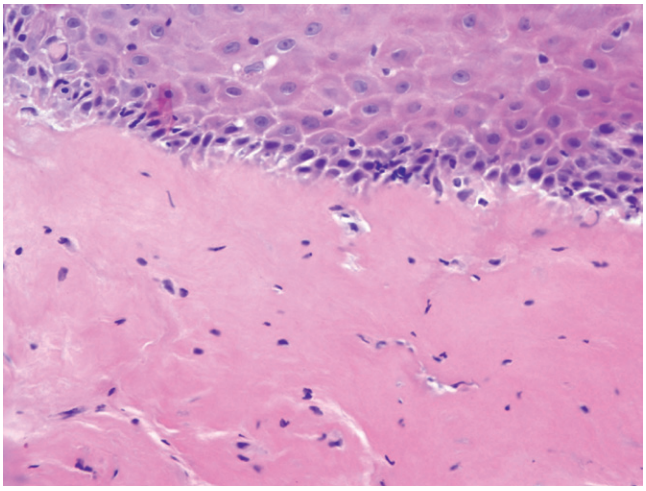

FIGURE 2

LS. High magnification accentuates the vacuolar changes in the basal cells.

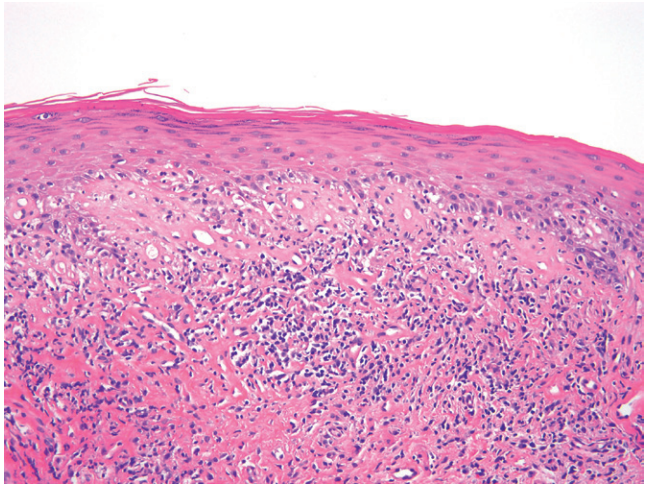

FIGURE 3

Early LS. There is thinning of the epidermis and early basal cell dropout at the interface. The stromal hyalinization change is less conspicuous, and the inflammatory infiltrate is still at the interface.

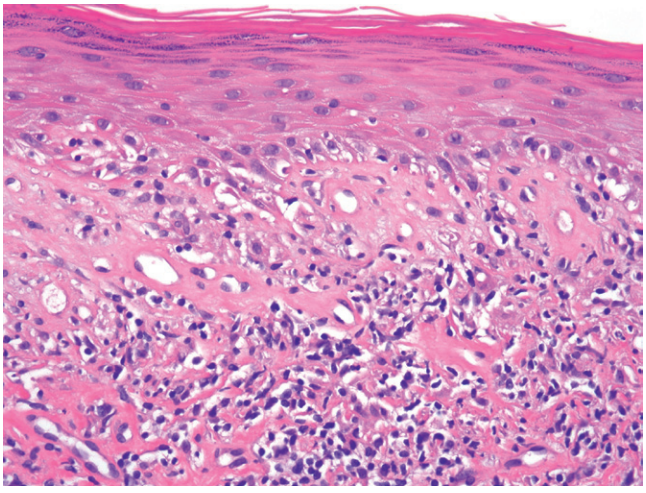

FIGURE 4

Early LS. Higher magnification showing the vacuolar basal cell changes and early subepithelial sclerosis.

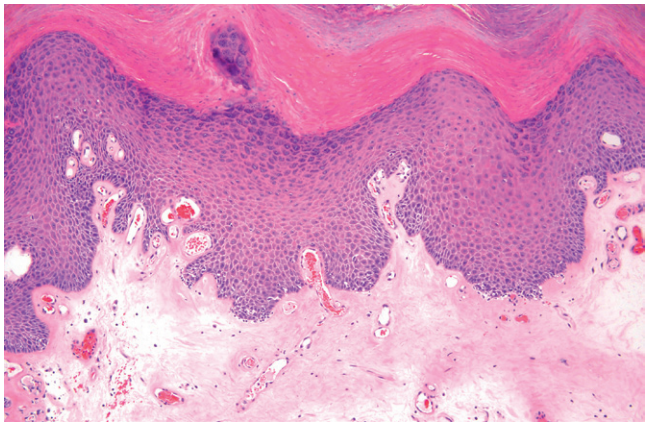

FIGURE 5

LS with superimposed LSC. Note the marked epidermal thickening. This lesion is considered at greater risk for subsequent squamous cell carcinoma.

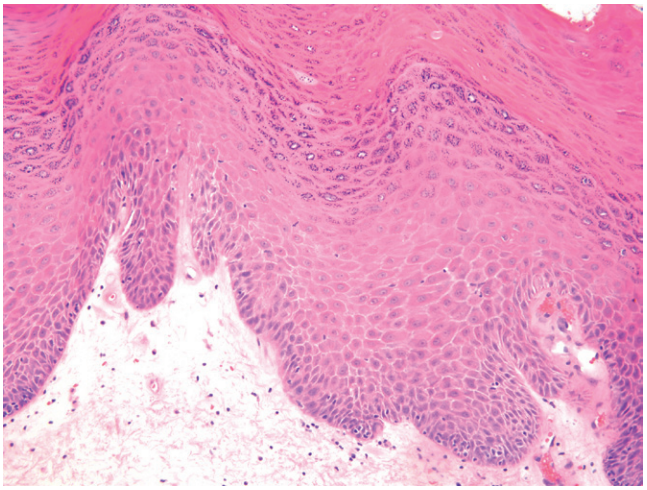

FIGURE 6

LS with superimposed LSC. There is prominent hyperkeratosis and mild spongiosis.

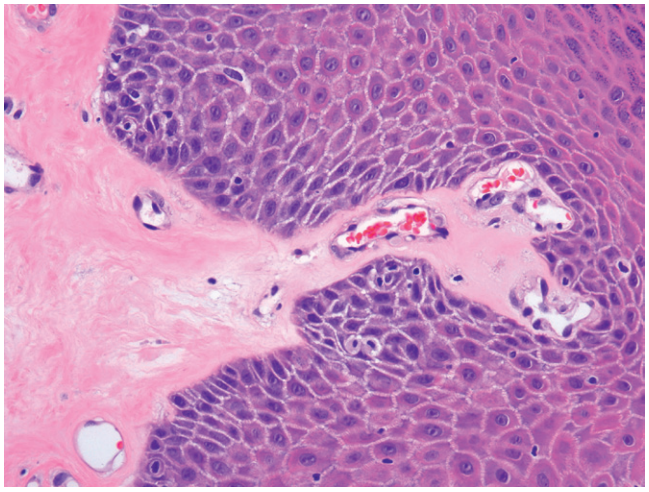

FIGURE 7

LS with superimposed LSC. There is focal basal cell dropout at the interface.

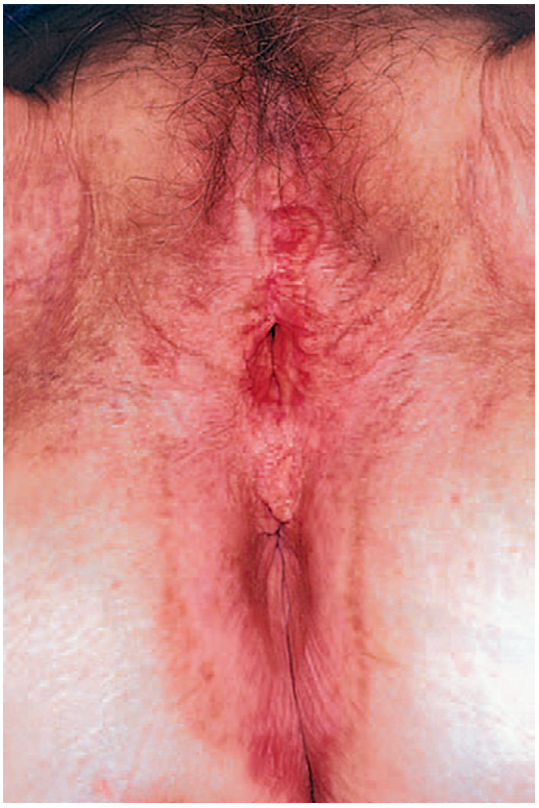

FIGURE 8

LS. Note the atrophy of the labium minus in this clinical picture. *(Photo courtesy Hope Haefner, MD.)*

LICHEN PLANUS

Definition—An uncommon idiopathic mucocutaneous inflammatory dermatosis with a prototypical lichenoid tissue reaction pattern, and a wide range of clinical presentations.

Clinical Features

Epidemiology

- Women at ages of 30 to 60 years.

Presentation

- Papular lichen planus (LP) is characterized by small, intensely pruritic, polygonal violaceous papules.
- Chronic erosive LP (the most common vulvar variant) presents with dyspareunia and clinically appears as a desquamative, ulcerating lesion that can extend into the vagina.
- Vulvar involvement is much less common than cutaneous or oral disease, but a significant number of patients with vulvar disease may also have oral lesions.

Prognosis and Treatment

- Topical steroids and emotional support.
- Papular lesions typically resolve within 2 years, often leaving behind pigmentation.
- Chronic erosive LP is not therapy responsive and may persist for years; it is occasionally associated with squamous cell carcinoma.

Pathology

Histology

- Bandlike lymphocytic infiltrate with interface change (lichenoid reaction pattern), parakeratosis, keratinocyte necrosis in the lower layers of the epidermis, and characteristic loss of the basal layer (squamatization).
- The rete pegs may become pronounced ("saw-tooth" pattern); however, this feature is not always prominent in vulvar lesions; the wedge-shaped hyperkeratosis seen in the cutaneous lesions is not seen in the vulvar lesions.
- The dermal infiltrate is composed predominantly of lymphocytes, with a few macrophages, some of which contain melanin (melanophages).
- Erosive lesions show central ulceration with nonspecific chronic inflammation; the classic features of LP are present at the periphery of the lesion.

Immunopathology (Including Immunohistochemistry)

- Direct immunofluorescence of erosive LP shows only fibrin deposition at the dermal–epidermal junction (no immunoglobulin).

Main Differential Diagnosis

- Early lichen sclerosus (papular LP).
- Bullous disorders (erosive LP).
- Zoon's vulvitis.
- Candida.
- Lichenoid drug eruption.

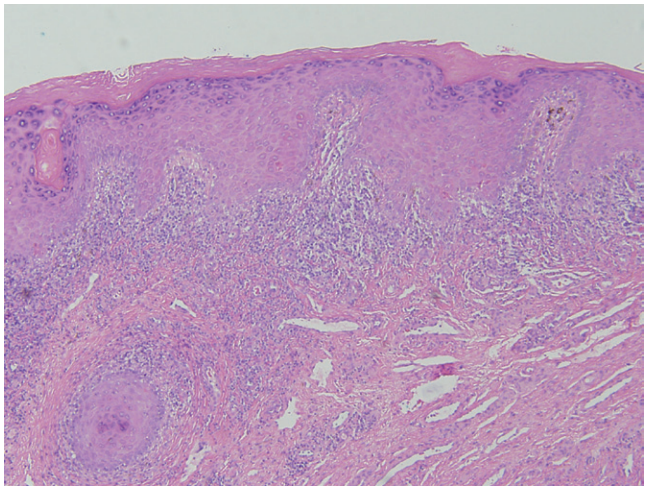

FIGURE 1

LP. A bandlike lymphocyte-predominant lichenoid infiltrate fills the dermis.

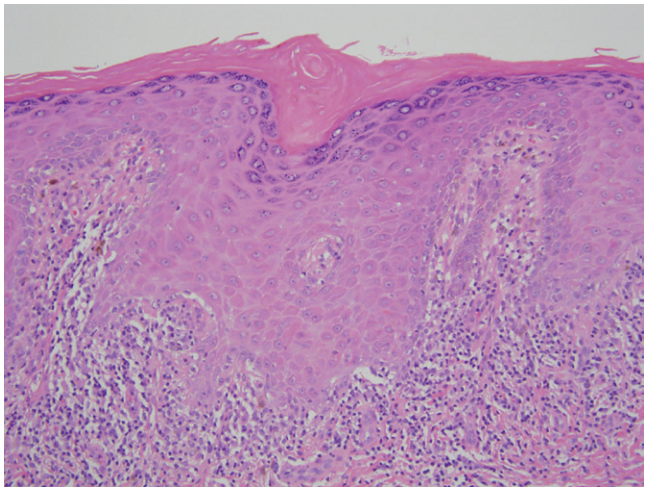

FIGURE 2

LP. The basal layer is not apparent. There is a jagged contour to the epithelial base due to pronounced rete ridges.

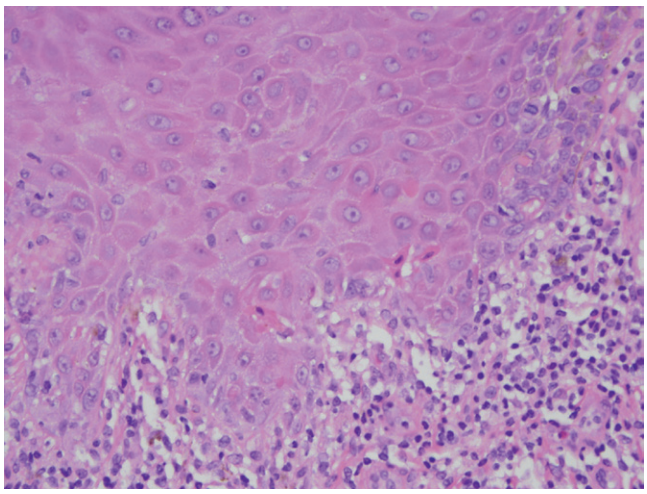

FIGURE 3

LP. Dying keratinocytes (Civatte bodies) can be seen in the bottom layers of the epithelium.

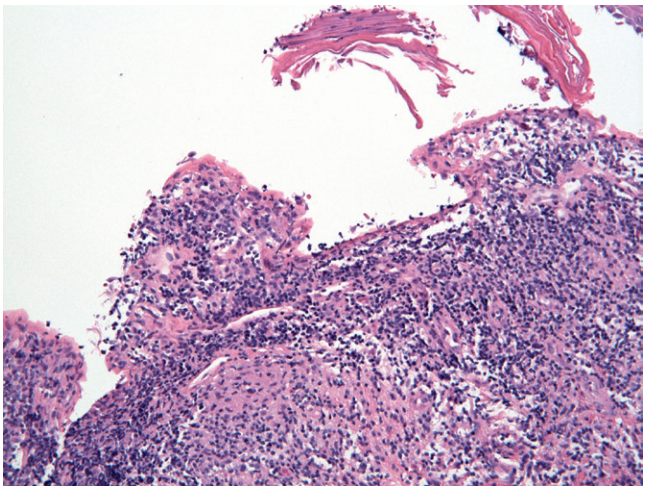

FIGURE 4

LP. Vulvar LP with superficial erosion and a thick, bandlike lymphocytic infiltrate.

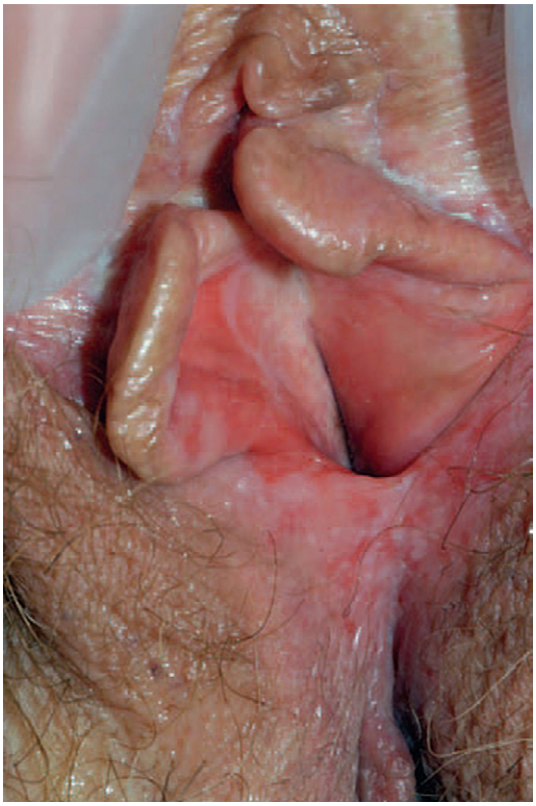

FIGURE 5

LP of the vulva with a white lacelike pattern and erythema. *(Photo courtesy Hope Haefner, MD.)*

ZOON'S VULVITIS

Definition—Plasma cell–mediated vulvitis of unknown etiology.

Clinical Features

Epidemiology

- A rare condition.
- Has also been reported in men, as balanitis chronica circumscripta plasmacellularis.
- Age range is from 25 to 70 years, with middle-aged women most commonly being affected.

Presentation

- A well-defined, shiny red to brown macule.
- Lesions are usually solitary.
- Some cases are asymptomatic; however, itching, burning, and soreness may occur.

Prognosis and Treatment

- Prognosis is favorable.
- Not associated with the development of carcinoma in women, although carcinoma may occur in association with plasma cell balanitis in uncircumscribed male patients.
- The treatment consists of steroids: topical, intravaginal, or intralesional injections.

Pathology

Histology

- A lichenoid infiltrate consisting predominantly of plasma cells within the lamina propria; longstanding lesions have the greatest numbers of plasma cells.
- Lymphocytes, mast cells, and eosinophils are also noted.
- Interface change is absent.
- Spongiosis of the epidermis is frequently present.
- Increased vascularity with extravasation of red blood cells may be present, with or without hemosiderin deposition.
- Epidermal atrophy with loss of the granular cell layer and surface keratin occurs.
- Dermal fibrosis is also seen in the longstanding lesions.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Syphilis.
- Lichen planus.

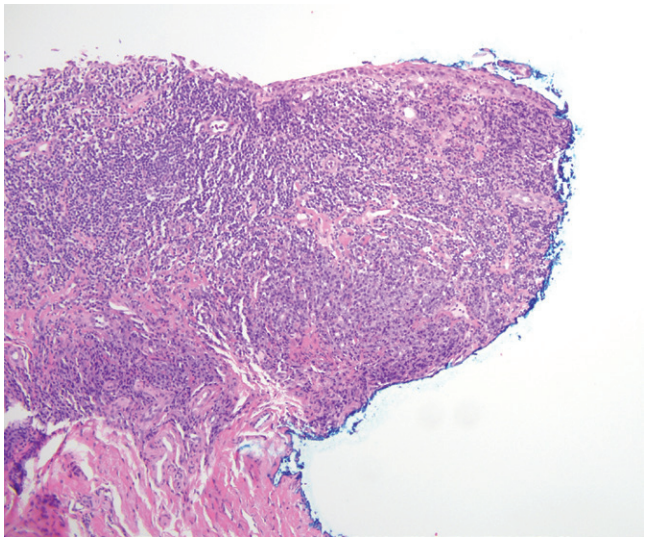

FIGURE 1

Zoon's vulvitis. A dense lichenoid infiltrate is present in the dermis.

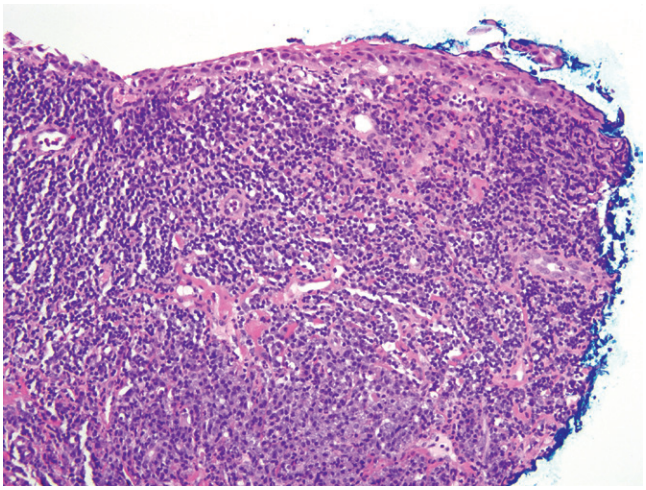

FIGURE 2

Zoon's vulvitis. The overlying epidermis is markedly atrophic. Surface keratinization and the granular cell layer are absent.

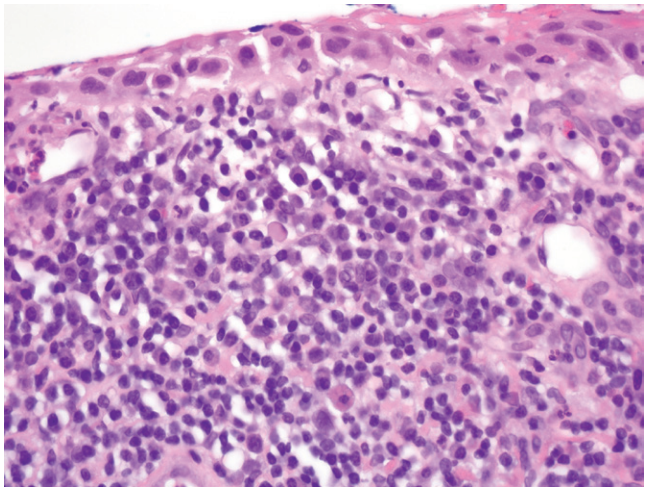

FIGURE 3

Zoon's vulvitis. The infiltrate is composed predominantly of plasma cells. Rare eosinophils are present. Epidermal spongiosis is evident.

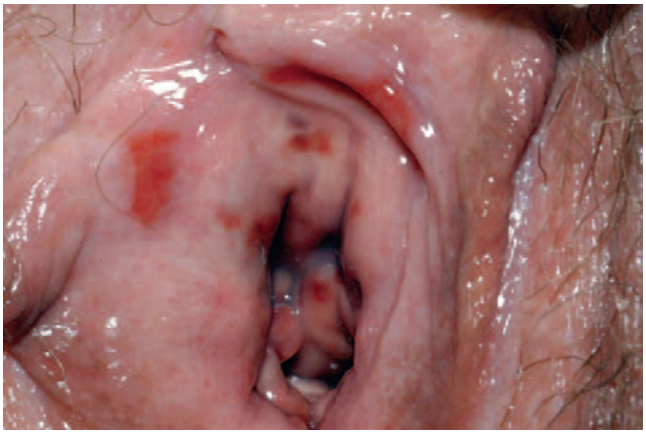

FIGURE 4

Zoon's vulvitis in the introitus. *(Photo courtesy Hope Haefner, MD.)*

BULLOUS PEMPHIGOID

Definition—An autoimmune blistering disorder that is the most common cause of subepidermal blisters. Caused by antibodies to a 230 kD plakin (BPAg1) and a 180 kD glycoprotein (BPAg2).

Clinical Features

Epidemiology

- Primarily seen in older patients and is commonly associated with other autoimmune disorders (lupus, diabetes, primary biliary cirrhosis, ulcerative colitis, and alopecia areata).

Presentation

- Tense vesicles (due to subepidermal nature of the blister) that do not expand with pressure (Nikolsky's sign).
- Vesicles are most frequently seen on the lower abdomen, flexural surfaces of the arms and legs, and the groin.
- The disease can extend to involve mucosal surfaces.
- Onset might be heralded by erythema and urticaria.

Prognosis and Treatment

- Prognosis—chronic disease with periods of remission; however, may become refractory to treatment.
- Steroids are the most common form of first-line treatment.
- Severe cases may require immunomodulatory drugs, plasmapheresis, or intravenous immunoglobulin (IvIg).
- Separation of the labia and vaginal dilation may be used to prevent adhesions.

Pathology

Histology

- Unilocular, subepidermal bullae.
- Numerous eosinophils and neutrophils, admixed with serum and fibrin, are seen within the blister.
- Re-epithelialization may be confused as intraepidermal blister formation.

Immunopathology (Including Immunohistochemistry)

- Immunofluorescence—linear IgG and C3 deposition along the basement membrane.

Main Differential Diagnosis

- Cicatricial pemphigoid.
- Pemphigus vulgaris.
- Lichen planus.

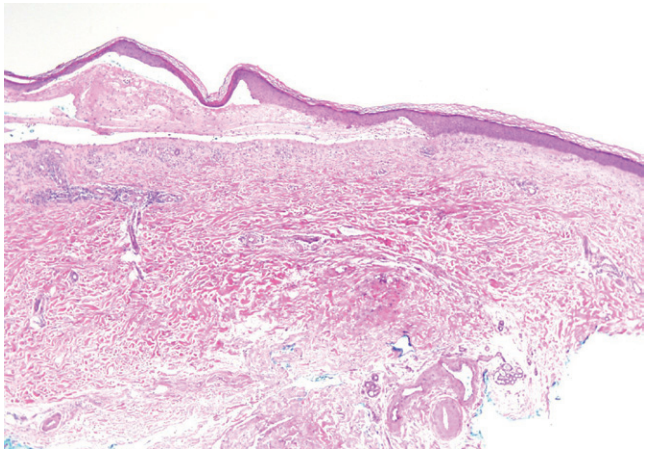

FIGURE 1

Bullous pemphigoid. Low-power view of a single, unilocular vesicle in bullous pemphigoid.

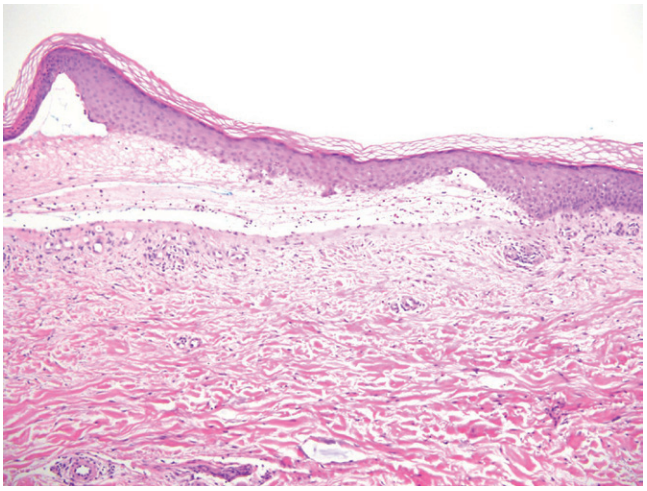

FIGURE 2

Bullous pemphigoid. Note the separation of the epidermis from the underlying dermis (subepithelial split).

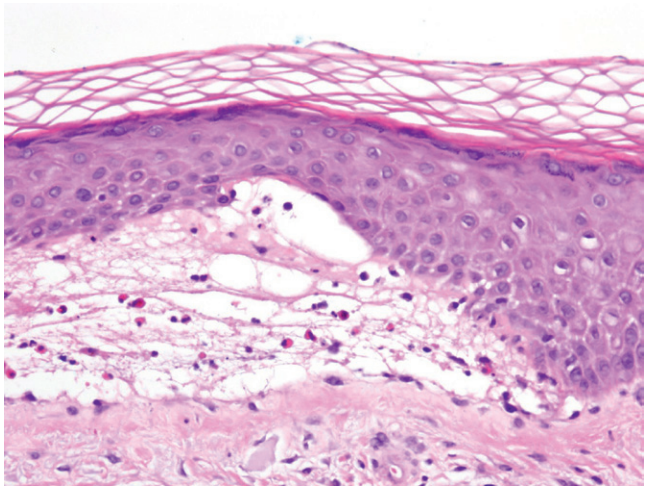

FIGURE 3

Bullous pemphigoid. Eosinophils along with fibrin and rare neutrophils can be seen in the vesicle.

PEMPHIGUS VULGARIS

Definition—An acquired autoimmune (anti–desmoglein 3 antibodies) blistering disorder that is marked by flaccid bullae and mucosal erosions.

Clinical Features

Epidemiology

- Incidence is rare and the disease may affect all age groups.

Presentation

- Mucosal-based erosions, which can be painful, can be seen involving the mucosa of the mouth, nose, and anogenital region.
- Nikolsky's sign, which is extension of the border of the blister with pressure, is commonly present.
- The blisters are fragile and flaccid.
- Vulvar involvement can lead to scarring.

Prognosis and Treatment

- Prognosis—favorable, the disease responds to treatment in most cases.
- Treatment—topical and\or oral steroids. Methotrexate may be used in severe cases.

Pathology

Histology

- Acanthosis with suprabasal blister formation.
- Basal cells may be intact and resemble a "row of tombstones."
- Blister formation overlying vascular papillae may create a "pseudopapillary" pattern.

Immunopathology (Including Immunohistochemistry)

- Immunofluorescence is positive for IgG and C3 in the intercellular regions of the epidermis "fish net pattern."

Main Differential Diagnosis

- Bullous pemphigoid.
- Cicatricial pemphigoid.
- Hailey-Hailey disease.
- Darier's disease.
- Warty dyskeratoma.
- Acantholysis of the vulvocrural area.

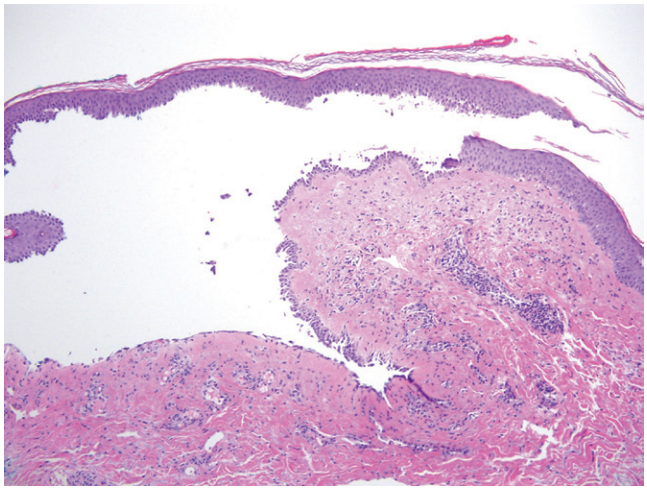

FIGURE 1

Pemphigus vulgaris. Intraepithelial (suprabasal) blister formation.

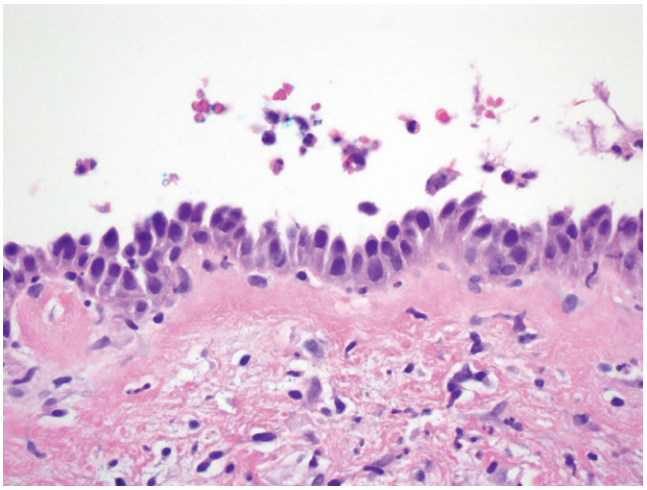

FIGURE 2

Pemphigus vulgaris. Intact basal cells showing a "row of tombstones" formation.

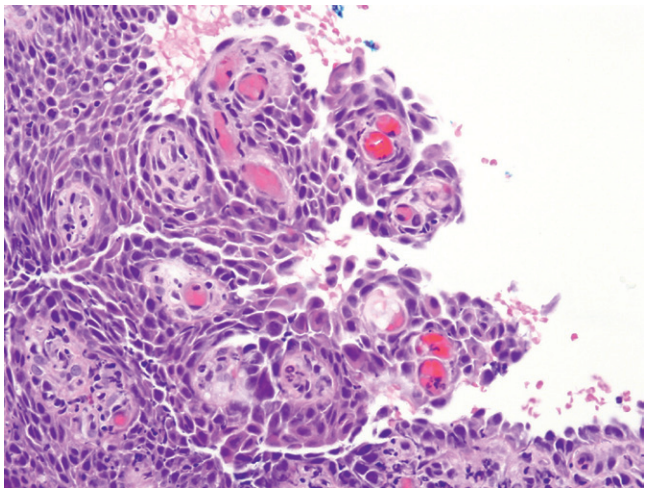

FIGURE 3

Pemphigus vulgaris. Clefting overlying vascular papillae creating a pseudopapillary growth pattern.

HAILEY-HAILEY DISEASE

Definition—An autosomal dominant, acantholytic dermatosis with a predilection for moist body creases.

Clinical Features

Epidemiology

- It is a rare autosomal dominant disease.

Presentation

- Pruritic erosions involving or extending to the vulva that extend centrifugally.
- Over time, a foul-smelling crust can form and depigmentation can occur.
- Scarring is rare.

Prognosis and Treatment

- Currently there is no cure for Hailey-Hailey disease.
- Avoidance of triggers (sunburn, sweat, friction), topical steroid, and antibiotics.
- Topical tacrolimus, systemic steroids, and antibiotics may be used in severe cases.

Pathology

Histology

- Early cases show suprabasal lacunae with evolution into vesicles and bullae that are intraepidermal and have an orderly appearance, referred to as a "brick wall appearance."
- Dyskeratotic cells may be present.
- Variable amounts of acanthosis and hyperkeratosis may be seen.

Immunopathology (Including Immunohistochemistry)

- Immunofluorescence is negative.

Main Differential Diagnosis

- Pemphigus vulgaris.
- Bullous pemphigoid.
- Cicatricial pemphigoid.
- Darier's disease.
- Acantholytic vulvar intraepithelial neoplasia.

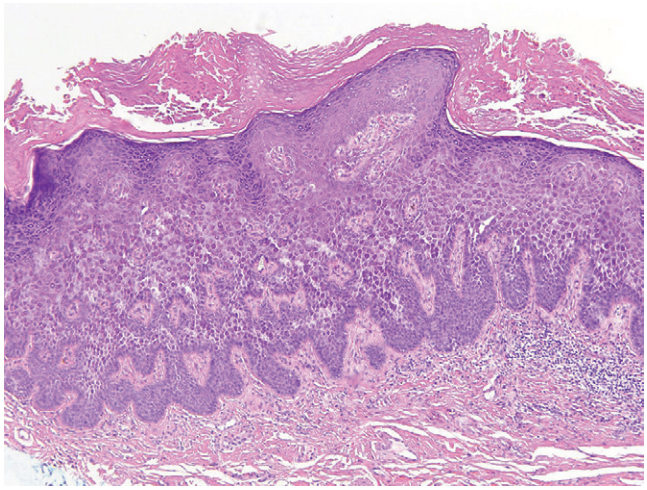

FIGURE 1

Hailey-Hailey disease. Acantholysis of the keratinocytes can be appreciated at low power (brick wall appearance). Several lacunae are present. Note the associated acanthosis, hyperkeratosis, and superficial dermal inflammatory infiltrate.

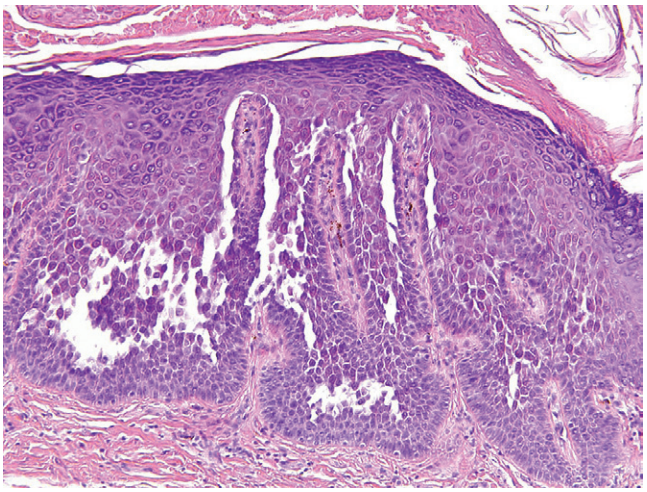

FIGURE 2

Hailey-Hailey disease. Prominent acantholysis forming small clefts.

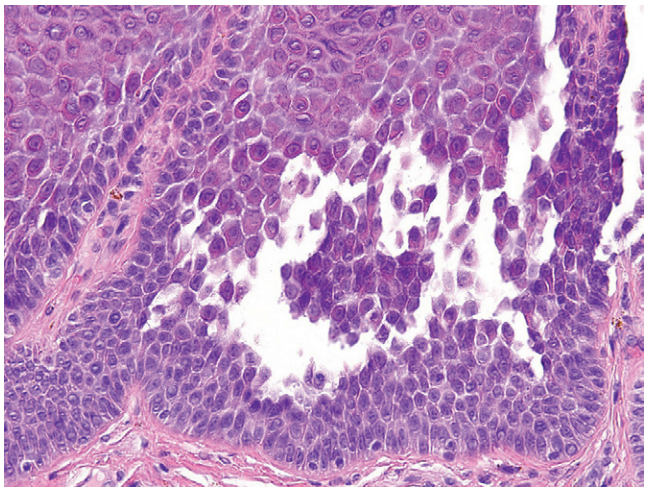

FIGURE 3

Hailey-Hailey disease. Acantholysis with detached cells filling the clefts.

DARIER'S DISEASE

Definition—Autosomal dominant genodermatosis marked by numerous hyperkeratotic papules that usually involve the trunk.

Clinical Features

Epidemiology

- Patients present around puberty; however, they can present later in life.
- Men are more severely affected; however, the incidence is equal in men and women.

Presentation

- Pruritic and warty lesions associated with a foul odor are present.
- Secondary irritation by scratching, as well as superinfection by bacteria or fungi, may occur.
- Patients may suffer from thin, brittle nails.

Prognosis and Treatment

- Currently there is no cure, and long-term remission is rare.
- Avoidance of triggers (sunlight, maceration), sunscreen, and oral retinoids.
- Topical steroids and moisturizers with urea or lactic acid may be used to help with symptoms.

Pathology

Histology

- Acanthosis with parakeratosis (frequently seen in columns) and acantholysis.
- The acantholysis is usually suprabasal and forms small lacunae.
- Overlying epidermis may display hyperkeratosis.
- Dyskeratotic cells (corps ronds and grains of Darier) may be seen in the stratum spinosum and stratum corneum, respectively.

Immunopathology (Including Immunohistochemistry)

- Immunofluorescence is negative.

Main Differential Diagnosis

- Hailey-Hailey disease.
- Warty dyskeratoma.
- Acantholysis of the vulvocrural area.
- Pseudobowenoid papulosis (dyskeratotic cells).

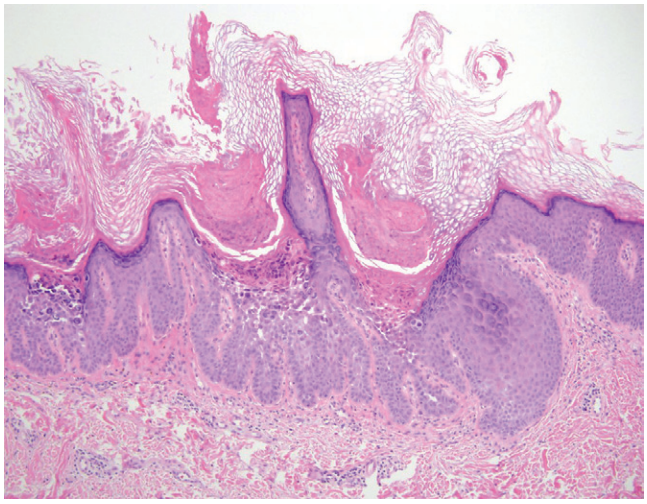

FIGURE 1

Darier's disease. Columnlike acanthosis and parakeratosis. Note the marked hyperkeratosis.

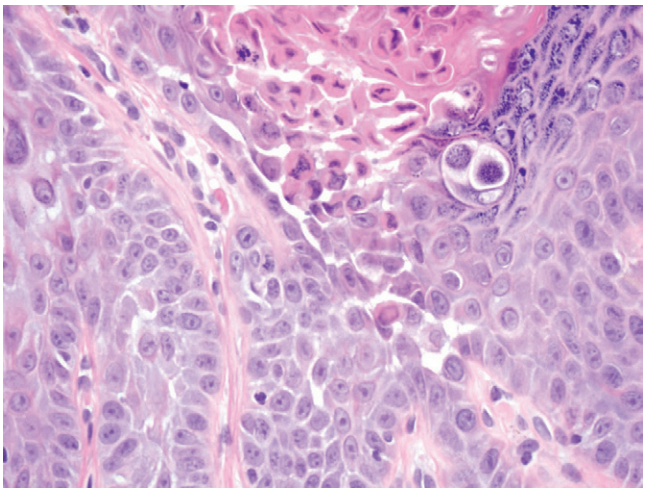

FIGURE 2

Darier's disease. Dyskeratotic cells, identified by their eosinophilic cytoplasm. Suprabasal acantholysis is pronounced.

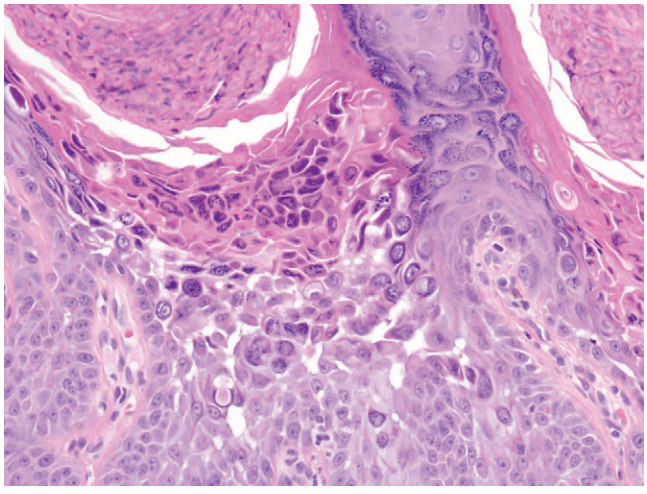

FIGURE 3

Darier's disease. Acantholysis of the superficial keratinocytes.

EPIDERMOLYTIC HYPERKERATOSIS

Definition—Hyperkeratosis marked by discrete, flesh- to white-colored papules to plaques. This entity overlaps with what is called acantholytic dyskeratosis (a term under which other dyskeratoses might fall). In this section we discuss a process that is encountered sporadically.

Clinical Features

Epidemiology

- Epidermolytic hyperkeratosis is an uncommon condition with no demographic predilections.

Presentation

- Single to multiple (can become confluent) flesh- to white-colored papules that may be associated with erythema and pruritus. It can also be encountered as an incidental finding when examining vulvar skin for other disorders.

Prognosis and Treatment

- Prognosis—chronic disease with variable response to treatment. When encountered as an incidental finding, no therapy is required.
- Treatment—topical steroids (rarely effective), electrocautery, and surgical excision, as needed.

Pathology

Histology

- Marked compact hyperkeratosis.
- Acantholysis with separation of intracellular bridges between keratinocytes.
- Scattered dyskeratotic cells may be noted by their brightly eosinophilic cytoplasm (corps ronds and grains of Darier).

Immunopathology (Including Immunohistochemistry)

- Immunofluorescence is negative.

Main Differential Diagnosis

- Darier's disease—a familial disorder, corps ronds usually more conspicuous, and parakeratosis common.
- Hailey-Hailey disease—familial, bullae formation, and disordered keratinocytes forming a "dilapidated brick wall."
- Viral vulvar warts (or VIN1)—prominent keratohyalin granules as seen in acantholytic dyskeratosis would not be expected, and some superficial cell atypia would be more likely.
- Other verruciform acanthoses (e.g., lichen simplex chronicus, verruciform xanthoma) will not demonstrate the prominent combination of acantholysis and keratohyalin granule formation with grains of Darier.

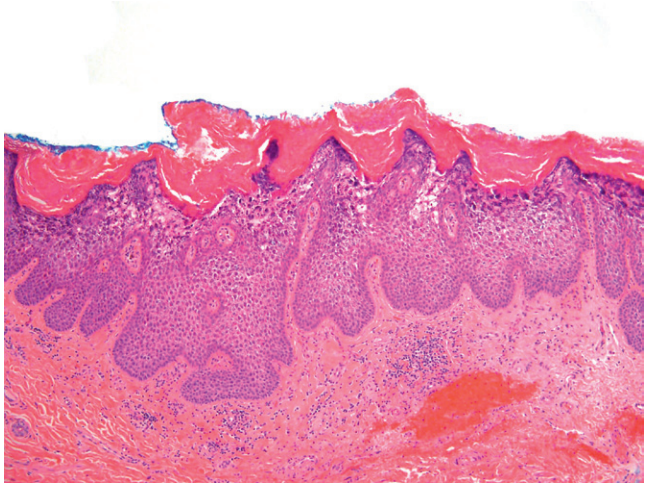

FIGURE 1

Epidermolytic hyperkeratosis. There is thickening of the epidermis (acanthosis) with compact hyperkeratosis and prominent keratohyalin granules.

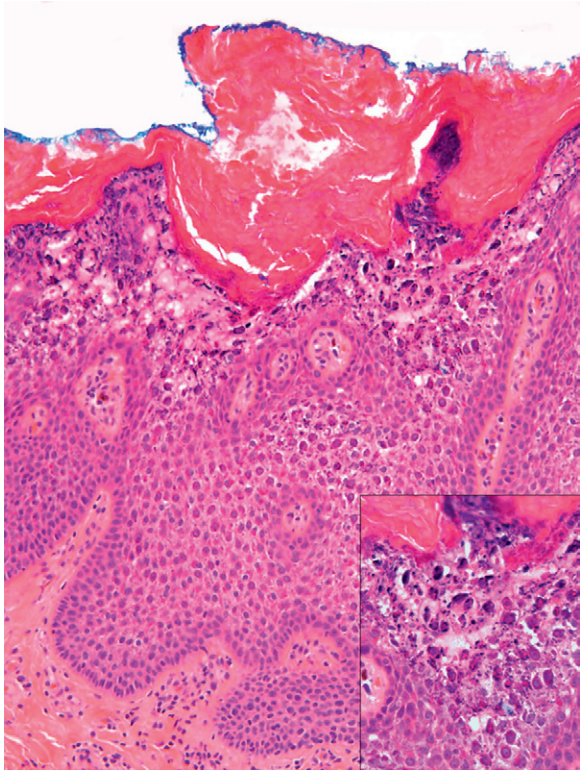

FIGURE 2

Epidermolytic hyperkeratosis. The superficial epidermis shows acantholysis with prominent spaces and vacuoles located between keratinocytes, noted by their intensely eosinophilic cytoplasm (inset).

HIDRADENITIS SUPPURATIVA

Definition—A suppurative inflammatory process that can be associated with fistula tract or abscess formation.

Clinical Features

Epidemiology

- Most commonly seen in young women.
- The most common sites of involvement are the axilla and groin.

Presentation

- Presents with a solitary painful papule.
- Over time, ulceration, abscess, or fistula formation may occur.
- Bacterial superinfection may occur.
- Scarring may occur in severe, chronic cases.

Prognosis and Treatment

- Variable prognosis; severe disease can be chronic and debilitating.
- Antibiotics, topical antiseptics, and compresses are common first-line treatments.
- Severe disease may require systemic corticosteroids and immunomodulatory drugs, in addition to surgery.

Pathology

Histology

- Abscess or sinus tracts with abundant necroinflammatory debris.
- A partial squamous lining may be present.
- Fibrosis and granuloma formation may occur.
- Pseudoepitheliomatous hyperplasia may be present and mistaken for squamous cell carcinoma.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Other causes of abscess formation.
- Vulvar Crohn's disease.
- Fox-Fordyce disease.
- Lymphogranuloma venereum.

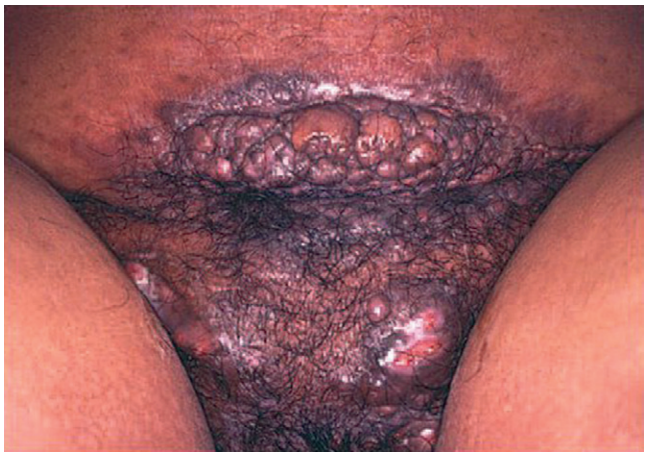

FIGURE 1

Severe case of hidradenitis suppurativa.

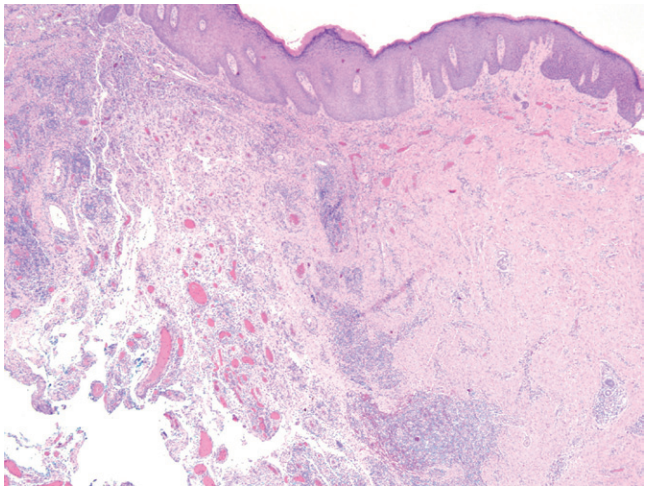

FIGURE 2

Hidradenitis suppurativa. Abscess and granulation tissue formation can be seen on the left side of the photo. Note the presence of acanthosis and hyperkeratosis in the overlying epithelium.

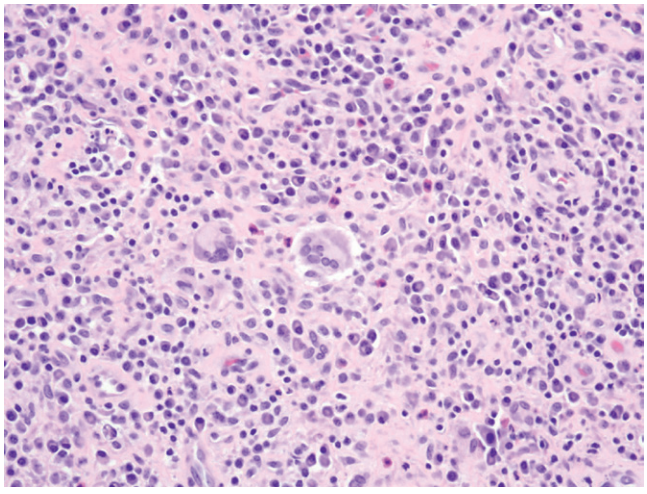

FIGURE 3

Hidradenitis suppurativa. A mixed inflammatory cell infiltrate with occasional foreign body giant cells.

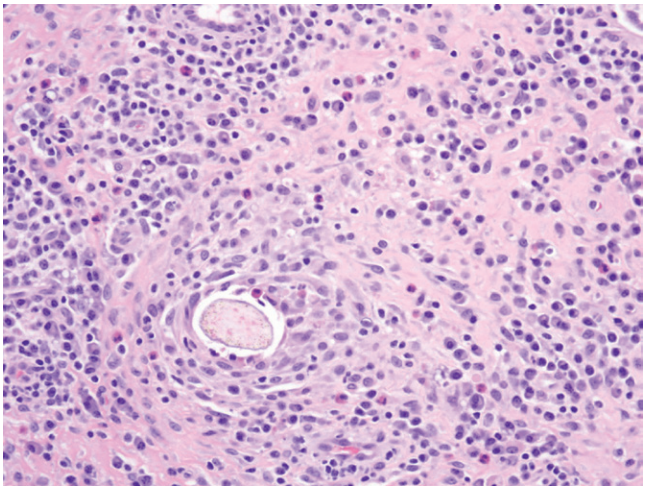

FIGURE 4

Hidradenitis suppurativa. Fragments of foreign material may be present. In this case hair from an adjacent ruptured follicle is seen, surrounded by inflammation.

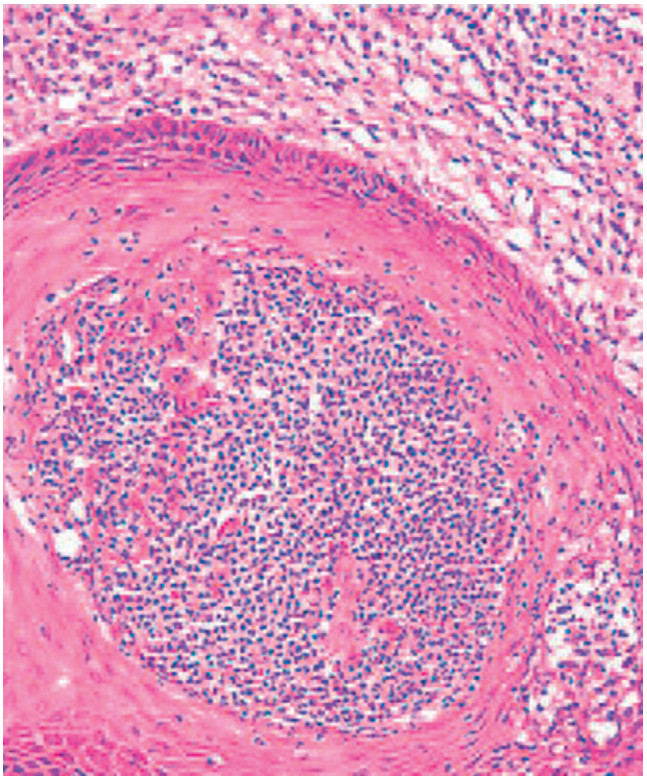

FIGURE 5

High-power view of a sinus with abscess formation.

CROHN'S DISEASE OF THE VULVA

Definition—A granulomatous, inflammatory bowel disease that may spread to involve other sites such as skin and mucosa.

Clinical Features

Epidemiology

- Seen in patients with Crohn's disease.
- Crohn's disease has no gender predilection and usually manifests in the second to third decade of life.
- Vulvar involvement may be contiguous (i.e., fistula formation) or may be isolated (metastatic Crohn's disease) with lower gastrointestinal symptoms.

Presentation

- Edema, drainage, ulceration, and occasionally mass-forming lesions.

Prognosis and Treatment

- Crohn's disease is a progressive disease with tremendous associated morbidity. Immunosuppressants, 5-aminosalicylic acid (5-ASA), and topical steroids are used for treatment.
- Antibiotics may be added for difficult-to-treat cases.
- Surgical excision is an option.

Pathology

Histology

- Nonspecific; consisting of a mixed inflammatory infiltrate composed of histiocytes, giant cells, and plasma cells.
- Superficial ulceration and occasional fistula formation may be present.
- Occasionally, granuloma formation is present.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Herpes virus infection (ulcerative lesions).
- Widespread tuberculosis.
- Inflammation secondary to an irritant (foreign body).

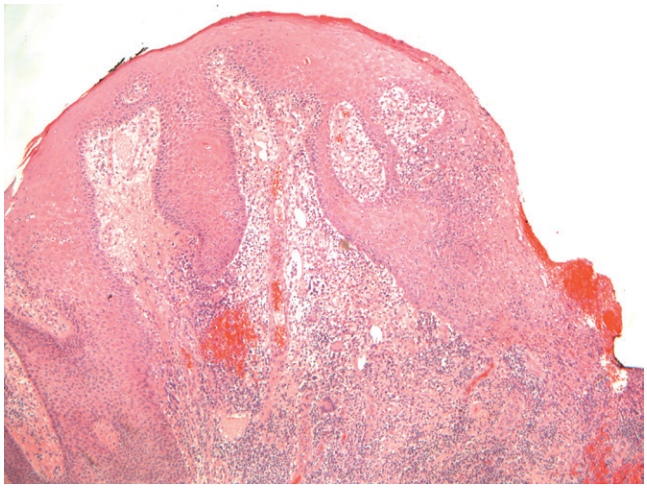

FIGURE 1

Crohn's disease of the vulva. Low-power magnification shows acanthosis and an increased inflammatory infiltrate in the lamina propria. Giant cells can be seen even at scanning magnification.

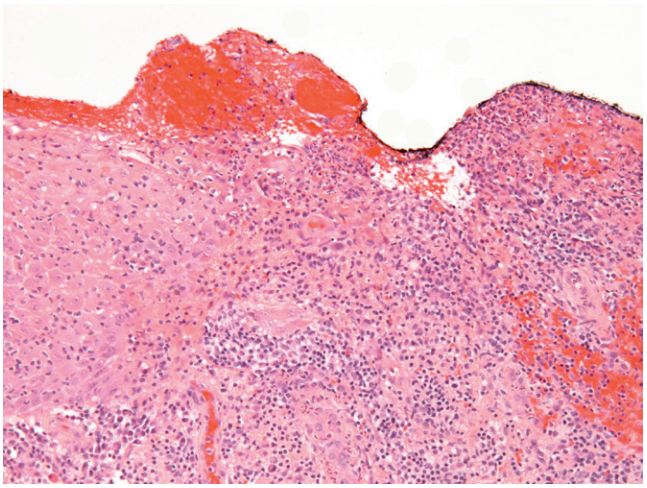

FIGURE 2

Crohn's disease of the vulva. Ulceration or fistula formation may be present.

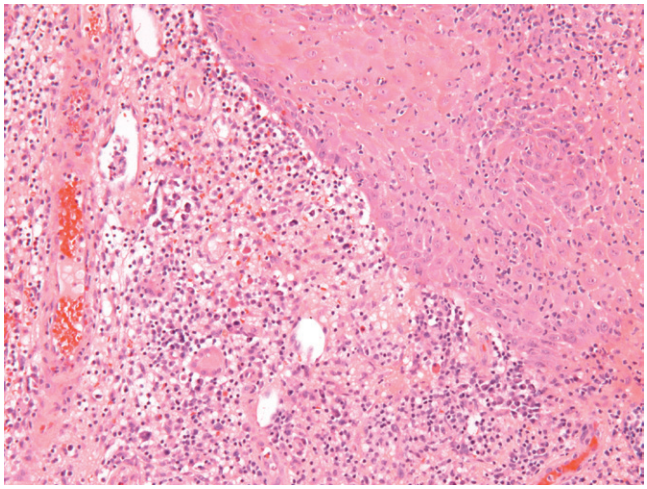

FIGURE 3

Crohn's disease of the vulva. An intense, mixed inflammatory infiltrate is present within the lamina propria. A single giant cell is present.

VULVODYNIA

Definition—The sensation of pain localized to the vulvar vestibule.

Clinical Features

Epidemiology

- Once thought to be a relatively rare condition, it is now known to affect millions of women.

Presentation

- Localized vulvodynia has no clinically identifiable features other than the patient's report of pain.
- Occasional erythema is described; however, the diagnosis of vulvodynia cannot be made in the presence of grossly abnormal vulvar structures.

Prognosis and Treatment

- Due to unknown etiology in the vast majority of cases, prognosis and treatment vary greatly from patient to patient.
- Treatments have ranged from avoidance of irritation, topical treatment, injection of anesthetics, and even surgery.

Pathology

Histology

- The histologic findings are entirely nonspecific.
- If a biopsy of the sample is performed, the results may be normal.
- A mixed inflammatory infiltrate composed of T-lymphocytes, monocytes, and plasma cells has been identified in some resection specimens.
- Occasionally, nonspecific findings such as glandular inflammation, squamous metaplasia, hyperkeratosis, and parakeratosis are identified.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Varies greatly depending on the clinical scenario.

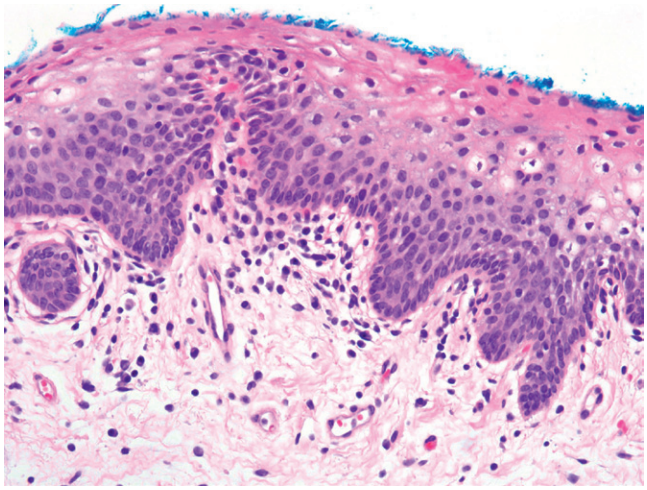

FIGURE 1

Squamous mucosa with mild nonspecific change. There is mild parakeratosis and a mild chronic inflammatory infiltrate in the upper dermis composed of lymphocytes and plasma cells.

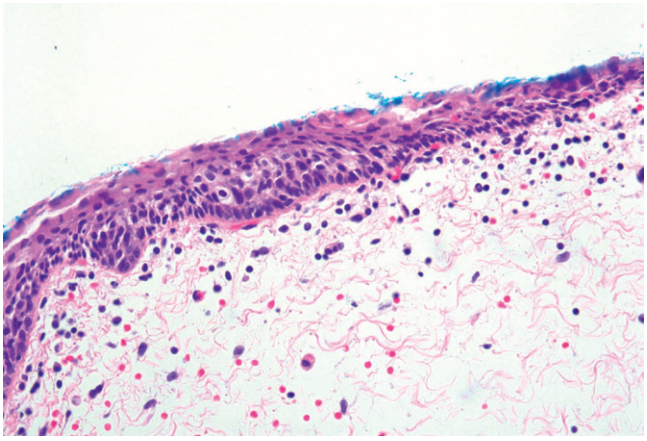

FIGURE 2

Squamous mucosa with mild dermal edema and a mild dermal infiltrate composed of lymphocytes and plasma cells. Mild parakeratosis is also present.

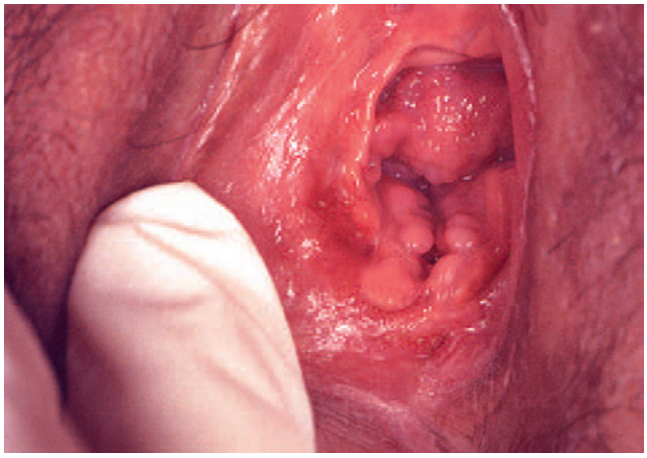

FIGURE 3

Photo of localized vulvodynia showing introital mucosa edema. *(Courtesy Hope Haefner, MD.)*

VULVOVAGINAL CANDIDIASIS

Definition—A fungal infection caused by any member of the Candida species of fungi.

Clinical Features

Epidemiology

- Very common, affecting up to 75% of females starting after menarche and increasing in incidence with peaks in the third or fourth decades.
- Predisposing factors include diabetes; immunocompromised state; and steroid, antibiotic, and oral contraceptive use.

Presentation

- Intense vulvar pruritus, dysuria, edema, erythema, and a white vaginal discharge with a curd-like appearance.

Prognosis and Treatment

- Favorable.
- Treatment with topical (or systemic in severe cases) antifungal medications typically leads to resolution.

Pathology

Histology

- Acanthosis, parakeratosis, psoriasiform epidermal hyperplasia, and neutrophilic infiltration of the epithelium are typically seen.
- Microabscess formation within the epidermis may be noted.
- Variable amounts of spongiosis may be present.

Immunopathology (Including Immunohistochemistry)

- Silver stains or periodic acid–Schiff (PAS) stain (with diastase) may aid in identifying fungal forms.

Main Differential Diagnosis (Fungal Stains Should Be Performed If Clinically Appropriate)

- Eczematous dermatitis
- Lichen simplex chronicus
- Intertrigo
- Psoriasis
- Atypical verruciform acanthosis—fungal infection should always be excluded with any unresolved verruciform acanthosis in which there is a low index of suspicion for malignancy.

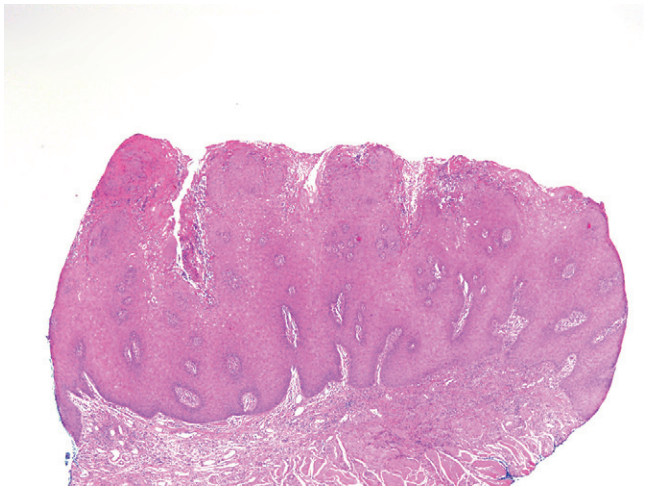

FIGURE 1

Vulvar candidiasis. Marked acanthosis may be seen at low power.

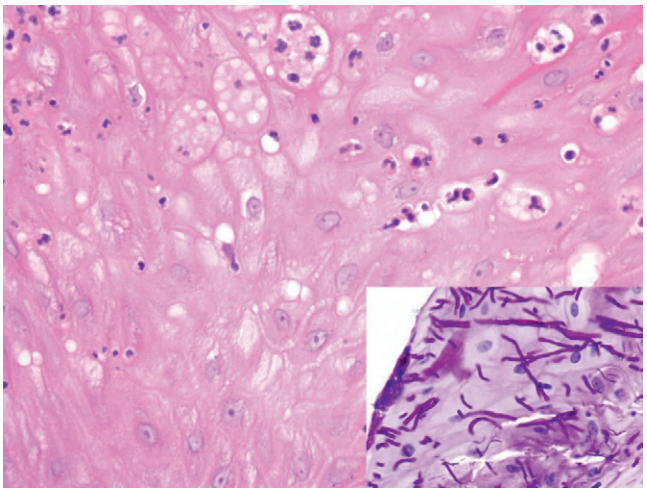

FIGURE 2

Vulvar candidiasis. A neutrophilic infiltrate, with occasional microabscess formation, is typically present. Note the presence of spongiosis in this example. PAS stain highlights organisms *(inset)*.

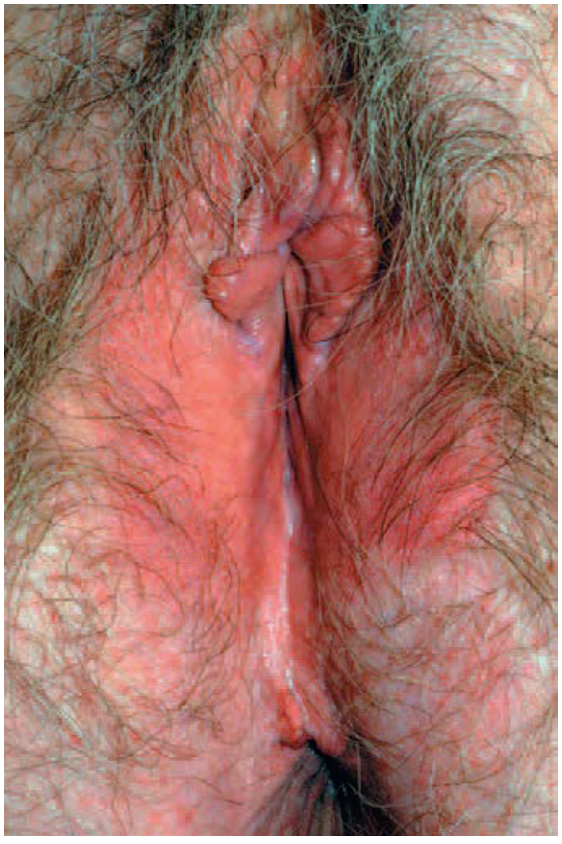

FIGURE 3

Erythema of the labia minora and majora with satellitosis from candidiasis. *(Courtesy Hope Haefner, MD.)*

BACTERIAL VAGINOSIS

Definition—Infection marked by a shift in the vaginal flora. Caused by a decrease in the normal lactobacilli and an increase in numerous other organisms (*Gardnerella vaginalis*, *Mobiluncus*, *Mycoplasma hominis*, *Prevotella*, *Porphyromonas*, *Bacteroides*, and *Peptostreptococcus*).

Clinical Features

Epidemiology

- Most commonly present in young, sexually active women; however, it can be seen across a wide age group.

Presentation

- Patients present with a strong, "fishy" odor and increased vaginal discharge.
- This odor may be worse during menses or after intercourse.
- Itching and irritation may be present.

Prognosis and Treatment

- Treatment with antibiotics (metronidazole and clindamycin) yields excellent results.

Pathology

Histology

- Pap smears show characteristic "clue cells" with decreased to absent numbers of lactobacilli and white blood cells.
- Clue cells are squamous epithelial cells with adherent bacteria that create a "fuzzy" border as opposed to the usually crisp epithelial contour.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Candidiasis (clinical).
- Cervicitis (clinical).
- Chlamydia (clinical).
- Gonorrhea (clinical).
- Herpes (clinical).
- Trichomonas (clinical).
- Desquamative inflammatory vaginitis (clinical).

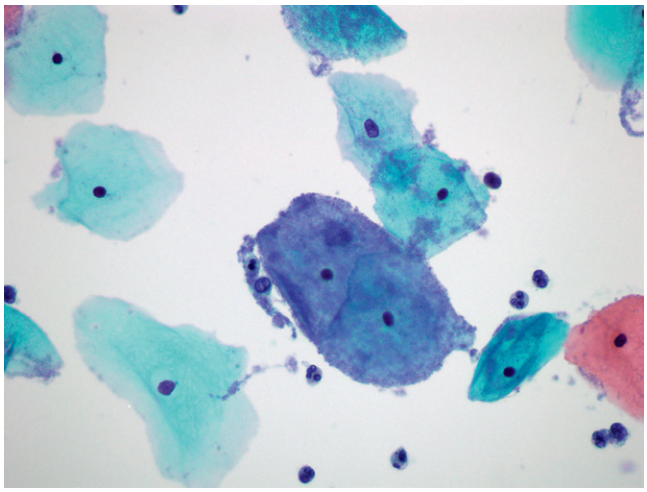

FIGURE 1

Bacterial vaginosis. A clue cell with its characteristic hazy blue color and fuzzy border.

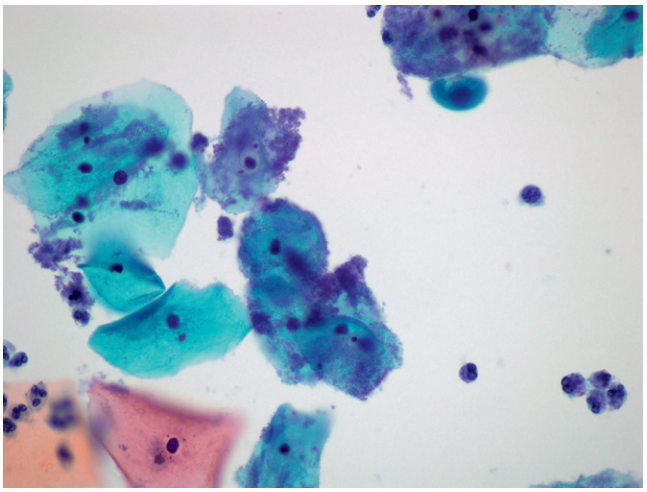

FIGURE 2

Bacterial vaginosis. Multiple clue cells. Note the fragments of bacteria in the left side of the picture as well as the scattered neutrophils.

MOLLUSCUM CONTAGIOSUM

Definition—A viral infection of the skin (often sexually transmitted when involving the genital area) caused by a DNA poxvirus.

Clinical Features

Epidemiology

- Genital infection most commonly occurs in young, sexually active individuals.
- In this population it is commonly transmitted by sexual or fomite contact.
- Cases in children are generally not sexually transmitted.

Presentation

- Dome-shaped, flesh-colored papules typically appear a few weeks after contraction.
- Scattered lesions will have a central umbilication with an underlying material with a cheesy consistency.
- The lesions are not painful.

Prognosis and Treatment

- A self-limited disease that can be treated by curettage, cryotherapy, or topical agents if desired.

Pathology

Histology

- Lesions are typically cup shaped and show epithelial hyperplasia.
- The peripheral basal cells mature toward the center of the lesion and shed keratinous debris into the central cavity.
- Molluscum bodies (diagnostic viral inclusions) are eosinophilic to cyanophilic, and as the cells mature, the inclusion displaces the cytoplasm and marginates the nucleus.

Immunopathology (Including Immunohistochemistry)

- In situ hybridization is available.

Main Differential Diagnosis

- Acrochordon.
- Epidermal inclusion cyst.
- Dermatitis herpetiformis.
- Keratoacanthoma.
- Neurofibroma.
- Condyloma.
- Pyogenic granuloma.
- Herpes infection.
- Basal cell carcinoma.

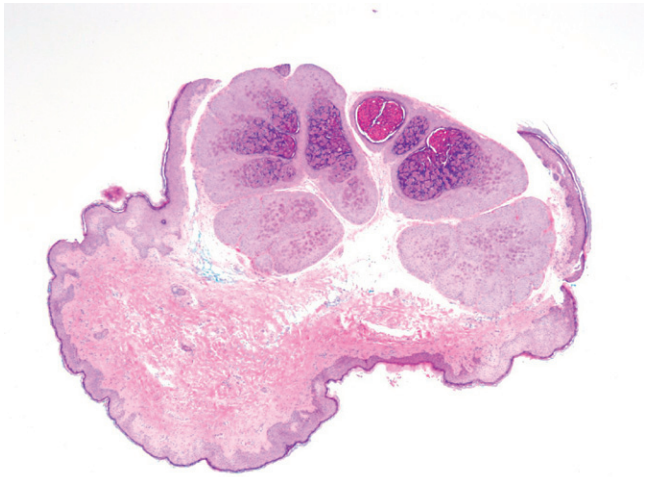

FIGURE 1

Molluscum contagiosum. A cup-shaped lesion with large nests of hyperplastic epithelium.

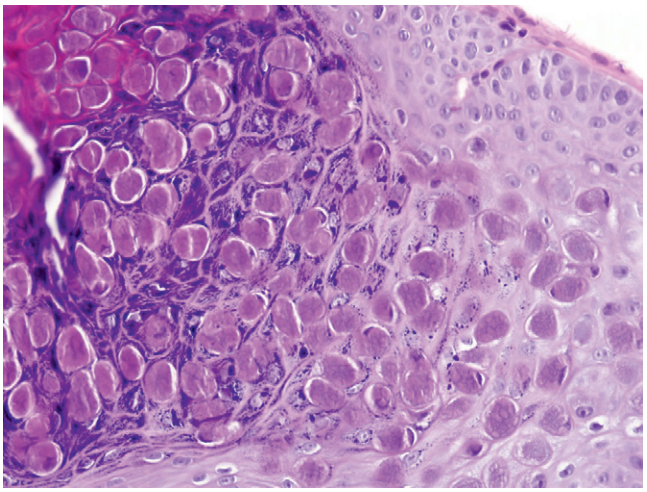

FIGURE 2

Molluscum contagiosum. Orientation of the basal layer of the infected keratinocytes toward the center of the lesion.

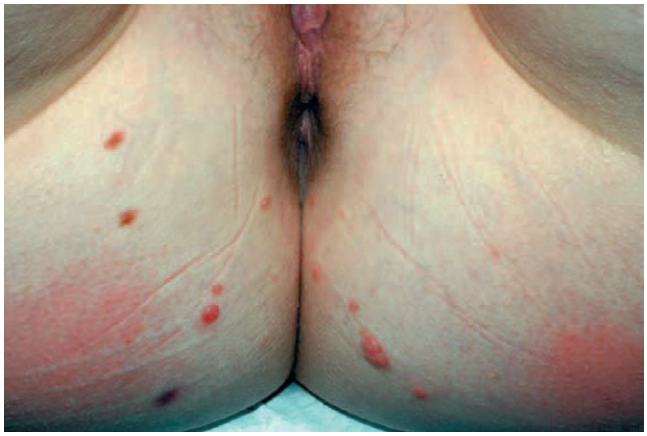

FIGURE 3

Clinical presentation of molluscum, with discrete, dome-shaped, pink-colored papules.

ACUTE HERPES SIMPLEX VIRUS INFECTION

Definition—An ulcerative sexually transmitted disease (STD) caused by the herpes simplex virus (HSV) (double-stranded DNA).

Clinical Features

Epidemiology

- The most common ulcerative disease of the genital tract in developed countries. A prevalence of upward of 20 million cases has been reported in the United States. Chronic erosive HSV infection can be seen in human immunodeficiency virus (HIV)–positive patients and is an AIDS-defining illness if lesions last more than 1 month.

Presentation

- Within 3 to 14 days of exposure the infected area becomes red and swollen with numerous vesicles. These vesicles rupture, and open erosions form, which commonly last for 2 weeks. These outbreaks typically heal without scarring.

Prognosis and Treatment

- HSV infection leads to a chronic course with multiple periods of relapse and remission of clinical disease. Antivirals (acyclovir) are useful in controlling outbreaks; however, there is no cure. HSV infection can cause significant morbidity and mortality in immunocompromised patients and fetuses.

Pathology

Histology

- The biopsy specimen shows epithelial necrosis and an eosinophilic aggregate of affected epithelial cells. The interface of the ulcer and necrotic ulcer bed may display characteristic nuclear inclusions marked by multinucleation with basophilic, "glassy" nuclei. The base of the ulcer may show a dermal inflammatory infiltrate (predominantly neutrophilic).

Immunopathology (Including Immunohistochemistry)

- Immunohistochemical stains for HSV I and II are available and stain infected cells.

Main Differential Diagnosis

- Herpes zoster and cytomegalovirus (CMV) can be excluded by immunohistochemistry.
- Aphthous and other ulcers are excluded by the absence of inclusions or HSV antigens. Epithelial necrosis is particularly characteristic of HSV versus nonviral ulceration.

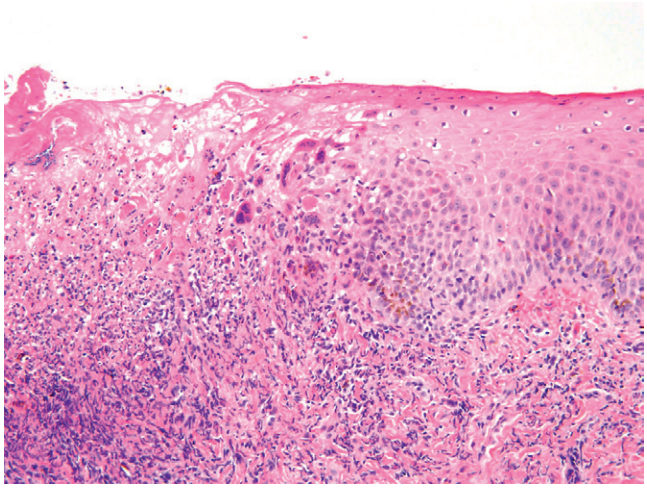

FIGURE 1

Herpes simplex infection of the vulva. Note the frank epithelial necrosis at the left. The herpetic inclusions stand out at the junction of the nonulcerated epithelium and the ulcer.

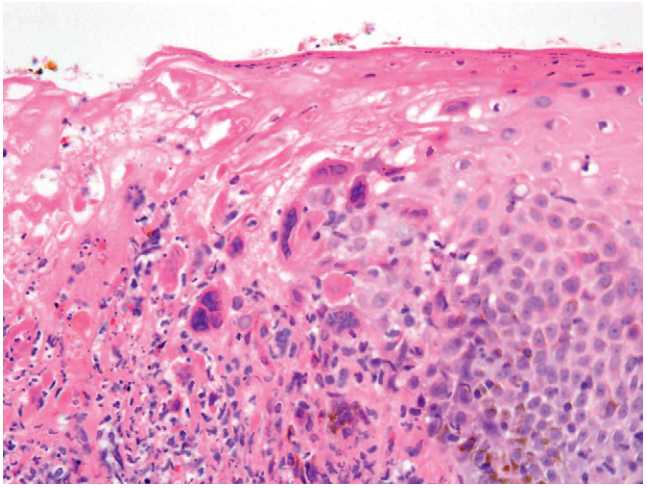

FIGURE 2

Herpes simplex infection. At higher magnification, mononucleated and multinucleated cells contain densely eosinophilic inclusions with opaque chromatin encased in amphophilic cytoplasm.

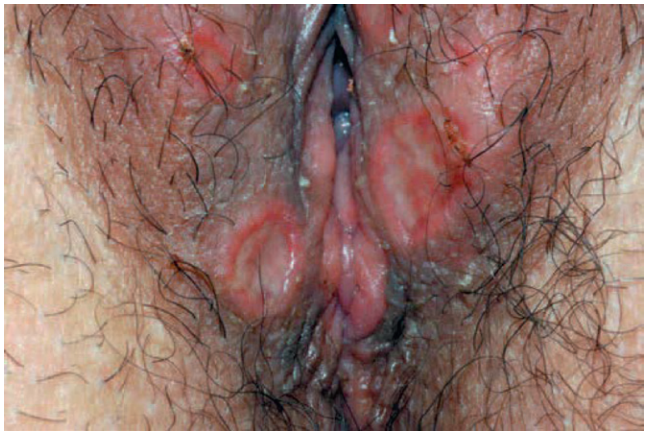

FIGURE 3

Herpetic ulcers with yellow-white bases. *(Photo courtesy Hope Haefner, MD.)*

CHRONIC EROSIVE HERPES SIMPLEX

PITFALL

Definition—A chronic herpes simplex virus (HSV) infection lasting more than 1 month.

Clinical Features

Epidemiology

- This is the most common ulcerative disease of the genital tract in developed countries. A prevalence of upward of 20 million cases has been reported in the United States. Chronic erosive HSV infection can be seen in HIV-positive patients and is an AIDS-defining illness if the lesions last more than 1 month.

Presentation

- The lesions present as both ulcers and hypertrophic proliferations of epithelium.

Prognosis and Treatment

- Because these chronic infections may be resistant to thymidine kinase–dependent antiretroviral drugs, they require additional measures such as drugs targeting viral-dependent DNA polymerases. These drugs (e.g., foscarnet, cidofovir) can generate a dramatic improvement in susceptible infections.
- The risk of disseminated HSV is low with chronic herpes infections, even in immunosuppressed individuals.

Pathology

Histology

- Whereas conventional herpes typically has epithelial necrosis with inclusions at the junction of the epithelium and ulcer, chronic herpes presents with epithelial hyperplasia and a striking subepithelial infiltrate, often over a broad area in the anogenital region.
- Inclusions can often be found at the epithelial–stromal junction.

Immunopathology (Including Immunohistochemistry)

- Immunohistochemical stains for HSV 1 and 2 are available and stain infected cells.

Main Differential Diagnosis

- Syphilis, Behcet's disease, and aphthous ulcers will not contain viral inclusions among other exclusions. Herpes zoster and cytomegalovirus (CMV) can be excluded by immunostains.

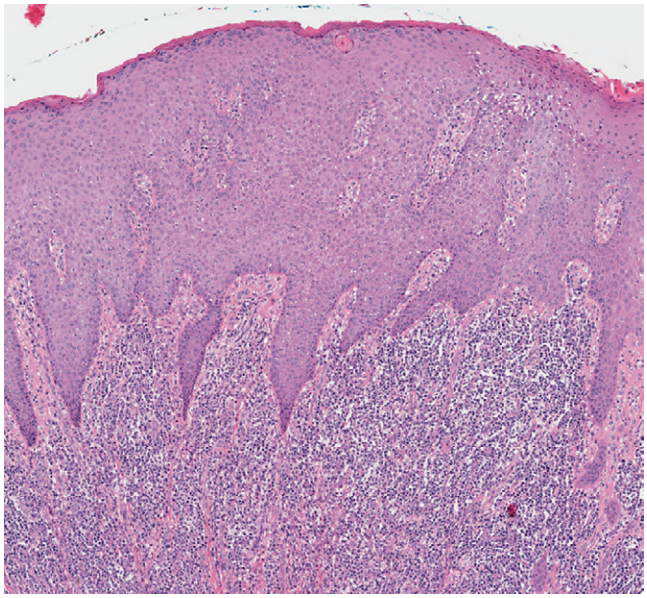

FIGURE 1

Chronic erosive HSV. There is epithelial acanthosis, and an ulcer is not seen in this field. Note the intense inflammatory infiltrate.

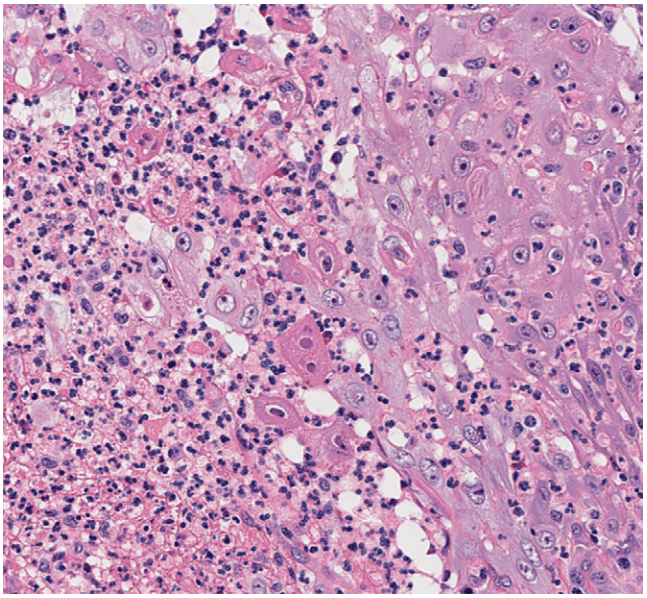

FIGURE 2

Chronic erosive HSV. Numerous inclusions are present at the epithelial–stromal interface.

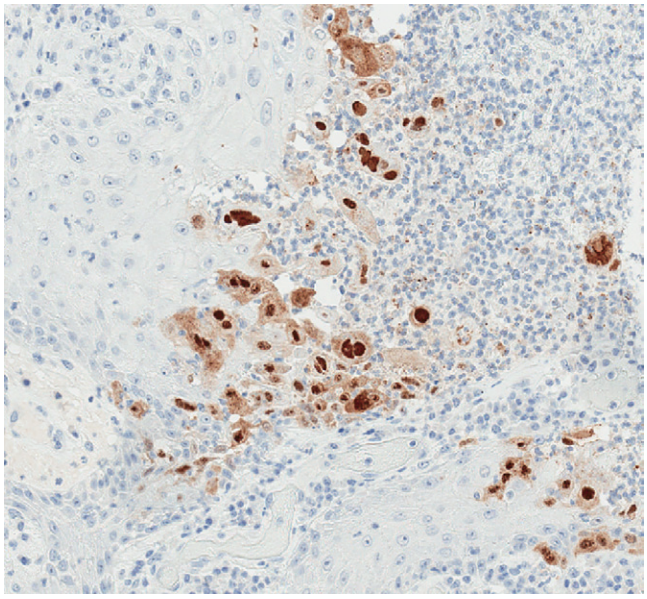

FIGURE 3

Chronic erosive HSV. An immunostain for HSV 1 highlights the inclusions.

SYPHILIS

PITFALL

Definition—A sexually transmitted disease caused by the spirochete *Treponema pallidum*.

Clinical Features

Epidemiology

- Primary syphilis typically occurs in young, sexually active adults.
- Secondary and tertiary disease is much less common due to the effectiveness of antibiotic treatment of the primary infection.
- Secondary syphilis develops in weeks to months in untreated individuals.
- Tertiary syphilis will occur in one third of untreated individuals.

Presentation

- Primary syphilis presents with the characteristic chancre at the exposure site; "kissing" chancres can be seen in the vulva.
- The chancre is a sharply circumscribed macule or papule with central ulceration and is often indurated and edematous.
- Superinfection is common with vulvar lesions.
- Chancres are painless, except when traumatized or superinfected, and usually resolve in 2 weeks or less.
- Adenopathy may or may not be present; vulvar disease may cause unilateral inguinal adenopathy.
- Secondary syphilis evolves in weeks to months, and it may present with systemic symptoms including fever and malaise.
- If secondary maculopapular lesions are present, the distribution is more diffuse and often symmetrical.
- Condyloma lata are the vulvar manifestation of secondary syphilis and can easily be confused with traditional condyloma.

Prognosis and Treatment

- Excellent.
- Primary chancres shed large numbers of organisms, and the disease is highly infectious at this stage.
- *T. pallidum* is highly susceptible to high doses of penicillin.

Pathology

Histology

- Primary syphilis is characterized by a dense dermal infiltrate composed of plasma cells, lymphocytes, histiocytes, and neutrophils.
- Plasma cells may be scarce in early lesions but increase in number as the lesion progresses.
- Plasma cells often congregate around small vessels, causing endothelial swelling and prominence.
- Epidermal hyperplasia is present, and pseudoepitheliomatous hyperplasia may develop, particularly at the edges of lesions.
- The classic lesions of secondary syphilis are also characterized by extensive dermal infiltration by histiocytes and plasma cells, with overlying psoriasiform epidermal hyperplasia (often marked in advanced cases) and a plasmacytic perivascular infiltrate with endothelial swelling and injury.
- The histologic patterns of secondary syphilis are highly variable; neutrophils generally diminish as do the numbers of organisms that can be seen on special stains.
- Late secondary lesions are often granulomatous.
- Condyloma lata are nonulcerated and composed of markedly hypertrophic and hyperkeratotic epidermis.
- Plasma cell "vasculitis" with endothelial injury is often seen with condyloma lata.
- The lesions of tertiary syphilis are granulomatous, with admixed plasma cells.
- The "gumma" of tertiary syphilis is centrally necrotic with a rim of inflammation composed of plasma cells, histiocytes, and lymphocytes.
- Eosinophilic "ghost cells" may be seen in the necroinflammatory debris.

Immunopathology (Including Immunohistochemistry)

- Warthin-Starry and Steiner silver stains may be used to demonstrate organisms.
- Darkfield microscopy of secretions may be helpful in early infections when serologic testing is not particularly sensitive.

Main Differential Diagnosis

- Zoon's vulvitis.
- Chancroid.

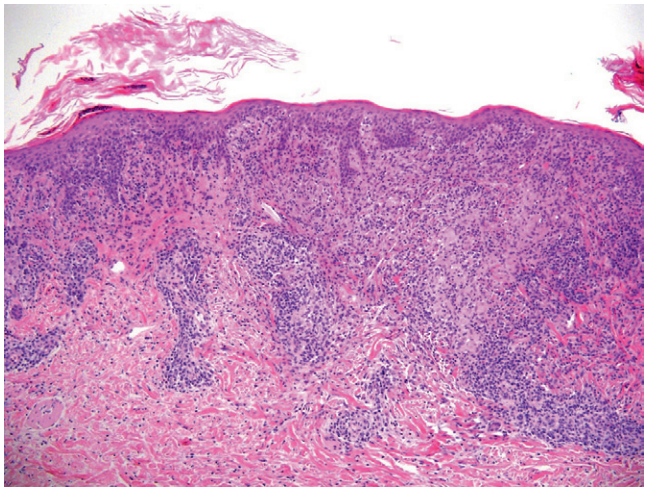

FIGURE 1

Syphilis. Low power of a primary lesion showing a dense superficial and deep lichenoid dermal infiltrate composed of mixed chronic inflammation.

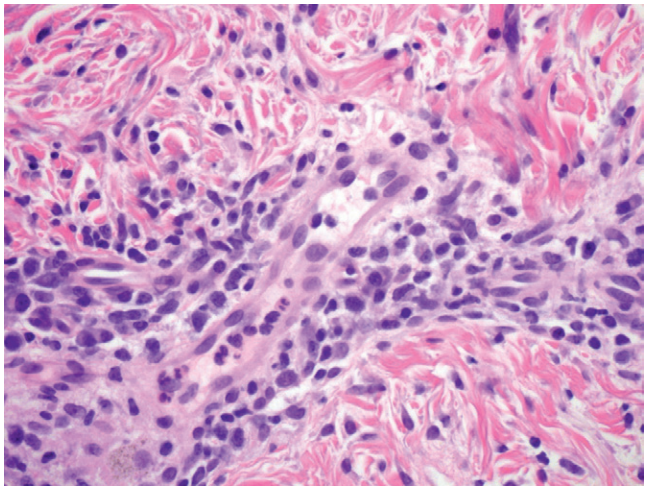

FIGURE 2

Syphilis. Perivascular inflammation composed predominantly of plasma cells. The endothelial cells are plump.

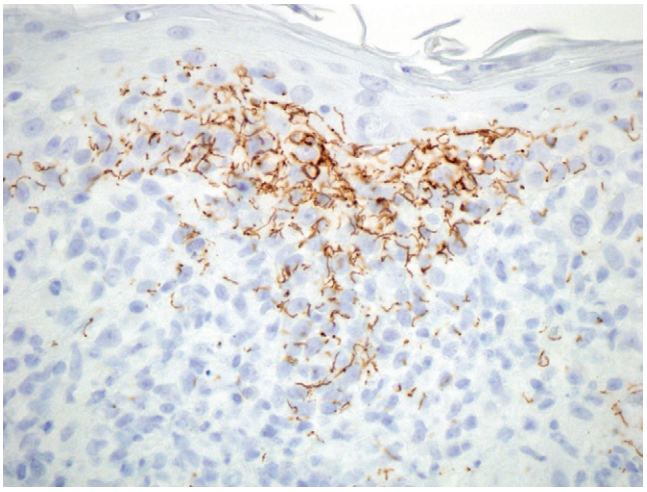

FIGURE 3

Syphilis. Warthin-Starry stain showing spirochetal organisms in the superficial dermis. Organisms can also be identified in the deep dermis (not shown).

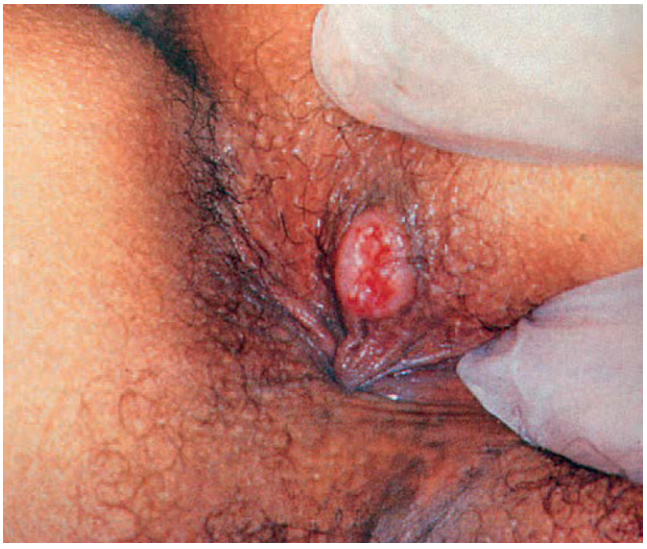

FIGURE 4

Syphilitic chancre in the perianal region. *(From Fiumara NJ: Primary and secondary syphilis. In Rein M, editor: Atlas of Infectious Diseases, Vol. V: Sexually Transmitted Diseases, Philadelphia, 1996, Churchill Livingstone, p 9.7, Fig. 9.19.)*

CHANCROID

Definition—Infection secondary to infection with *Haemophilus ducreyi* marked by painful ulcers and adenopathy.

Clinical Features

Epidemiology

- Most common in tropical and subtropical developing countries.
- It is more common in males than females and is commonly seen in the setting of human immunodeficiency virus (HIV) infection.
- Chancroid is a risk factor for heterosexual transmission of HIV.

Presentation

- Papules and pustules develop 3 to 10 days after infection, which later ulcerate as a result of mechanical irritation.
- The ulcerative lesions are painful, with a ragged border and surrounding erythema.
- Smaller ulcers may coalesce into large lesions.
- Adenopathy develops 1 to 2 weeks after the ulcers appear, and if left untreated, the adenopathy may develop into "buboes" with draining sinus tracts.

Prognosis and Treatment

- Favorable.
- Antibiotic treatment causes rapid resolution of the lesions.

Pathology

Histology

- Lesions display a "zonal" distribution.
- The uppermost portion consists of a neutrophilic infiltrate with admixed blood and fibrin, underneath which lies a layer of granulation tissue.
- The base of the lesion consists of a dense band of plasma cells, lymphocytes, and histiocytes.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Herpes.
- Syphilis.

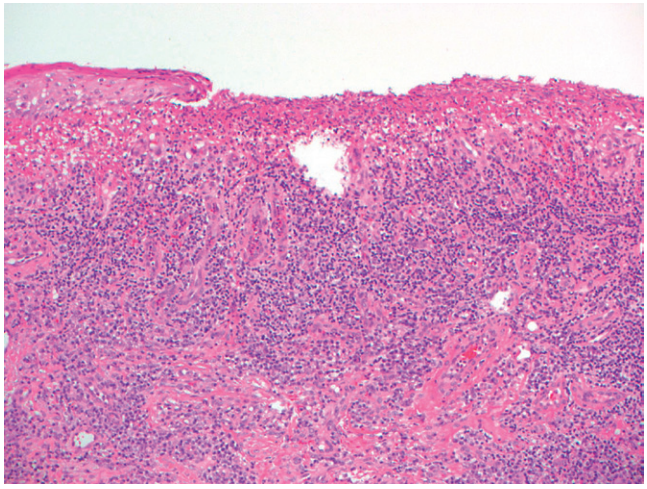

FIGURE 1

Chancroid. The uppermost portion of a chancroid ulcer can be seen here with its accompanying superficial layer of blood and fibrin and underlying granulation tissue.

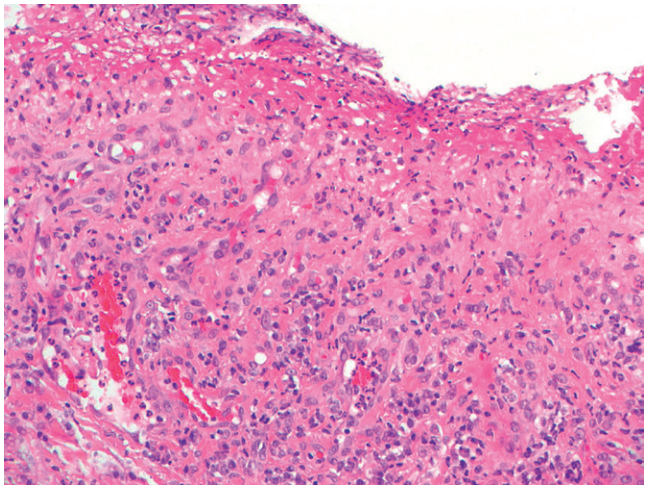

FIGURE 2

Chancroid. Fibrin and granulation tissue in an ulcer bed.

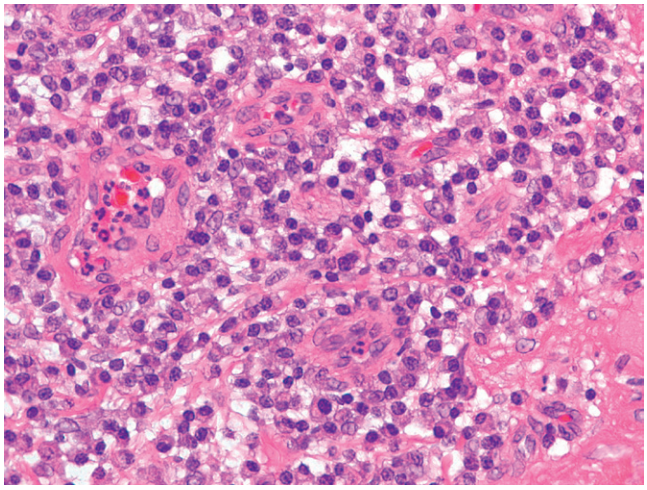

FIGURE 3

Chancroid. Deep to the ulcer a bandlike infiltrate of lymphocytes and plasma cells should be present.

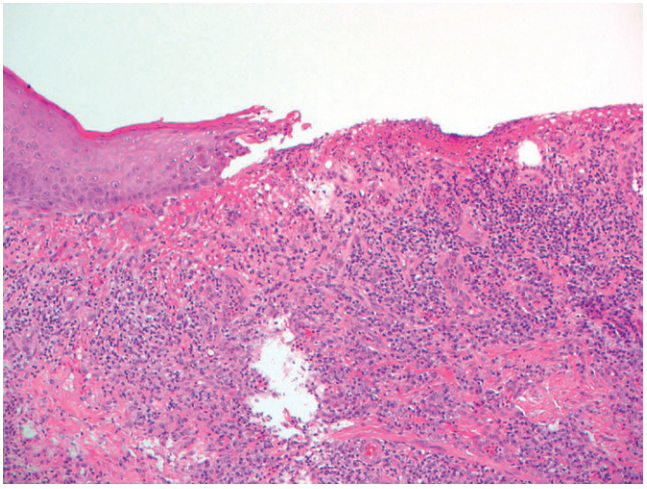

FIGURE 4

Chancroid. In this figure all three layers may be appreciated: the uppermost layer of blood and fibrin, the underlying granulation tissue, and the deep lymphoplasmacytic infiltrate.

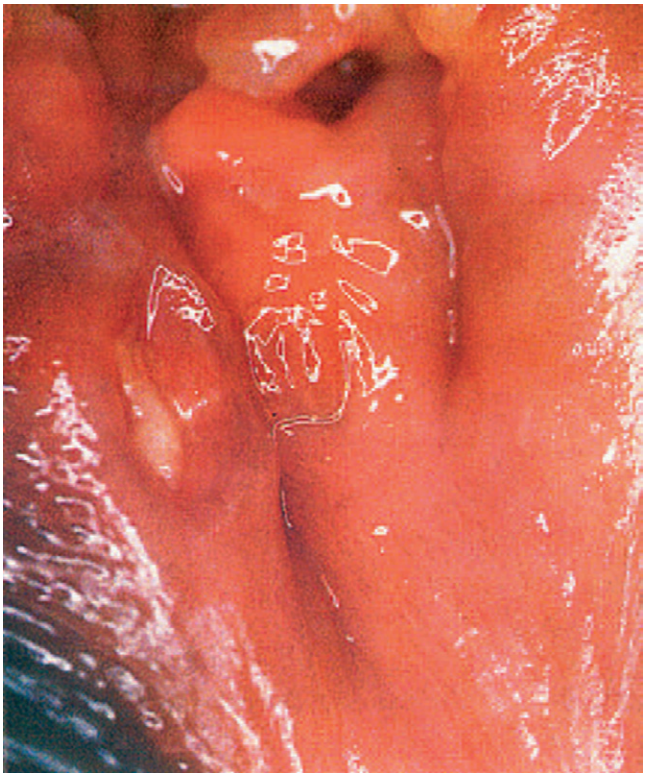

FIGURE 5

Chancroid. Irregular introital mucosa with superficial ulcers. *(From Allen R: Chancroid. In Rein M, editor: Atlas of Infectious Diseases, Vol V: Sexually Transmitted Diseases, Philadelphia, 1996, Churchill Livingstone, p 16.7, Figure 16.18.)*

GRANULOMA INGUINALE

Definition—A sexually transmitted disease, marked by ulceration, caused by the intercellular, gram-negative rod *Klebsiella granulomatis*.

Clinical Features

Epidemiology

- Endemic in tropical and subtropical areas in sexually active adults.
- Sporadic outbreaks do occur in Western countries.

Presentation

- Erythematous papules or small nodular lesions that are painless.
- Lesions expand to form "beefy-red" ulcers that are friable and bleed easily.
- Scarring and hypertrophic forms have been noted.

Prognosis and Treatment

- Excellent; however, long treatment with antibiotics may be required for refractory ulcers.

Pathology

Histology

- Marked, mixed, nonspecific inflammatory infiltrate.
- Donovan bodies (vacuoles in histiocytes containing the organism) may be present.
- Acanthosis, ulceration, and pseudoepitheliomatous hyperplasia of the epidermis may be noted.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Lymphogranuloma venereum.
- Syphilis.
- Chancroid.
- Herpes simplex virus (HSV) infection.
- Candidiasis.
- Amebiasis (genital).

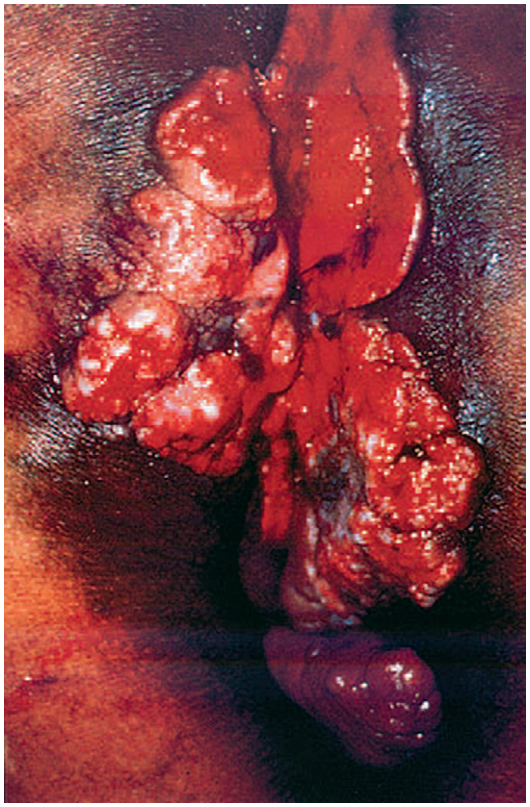

FIGURE 1

Granuloma inguinale, presenting as a combination of hypertrophic mucosa with submucosal edema and focal ulceration. *(From Hart G: Donovanosis: Granuloma inguinale. In Rein M, editor: Atlas of Infectious Diseases, Vol. V: Sexually Transmitted Diseases, Philadelphia, 1996, Churchill Livingstone, p 17.8, Figure 17.21.)*

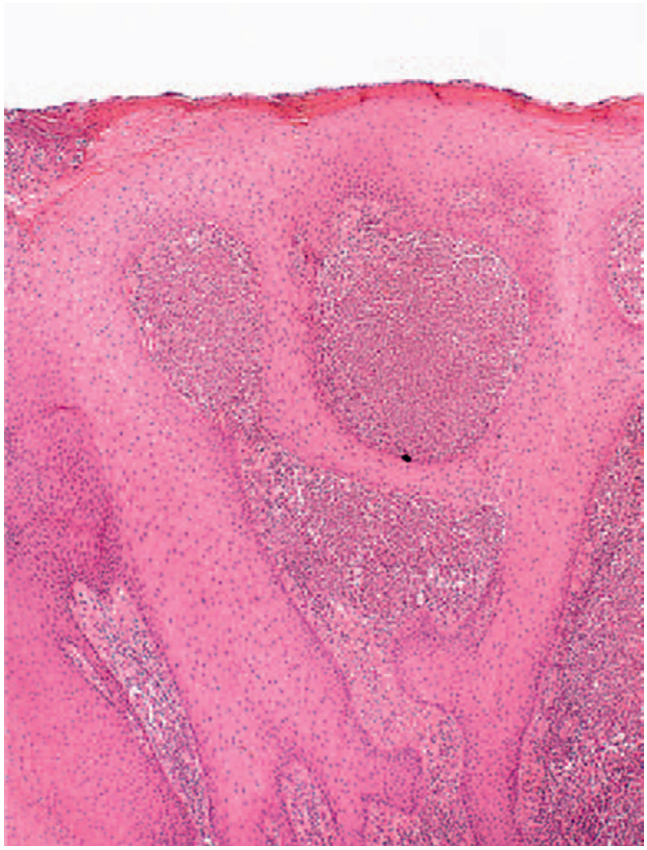

FIGURE 2

Granuloma inguinale. Low-power view of inflammation in granuloma inguinale exhibits both pseudoepitheliomatous hyperplasia and intense submucosal inflammation, corresponding to the clinical presentation (see Figure 1). *(From Crum CP, Nucci MR, Lee KR, editors: Diagnostic Gynecologic and Obstetric Pathology, ed 2, Philadelphia, 2011, Elsevier, Figure 4-20A.)*

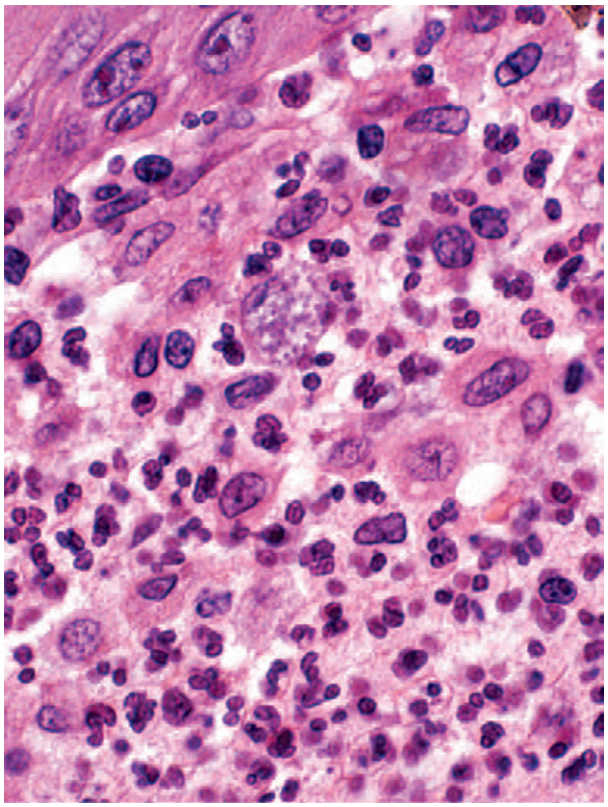

FIGURE 3

Granuloma inguinale. Donovan bodies are discrete cytoplasmic vacuoles containing organisms (center) seen here on hematoxylin and eosin staining. *(From Crum CP, Nucci MR, Lee KR, editors: Diagnostic Gynecologic and Obstetric Pathology, ed 2, Philadelphia, 2011, Elsevier, Figure 4-20B.)*

SCHISTOSOMIASIS

Definition—Infection by trematodes that belong to the superfamily schistosomatidae (*Schistosoma haematobium*, *Schistosoma japonicum*, and *Schistosoma mansoni*).

Clinical Features

Epidemiology

- Endemic in Egypt and the Middle East.
- Genital lesions occur in approximately 5% of patients infected by the trematode.
- Vulvar manifestations are more commonly seen in younger women.
- Infection may be acquired by freshwater swimming in endemic areas.

Presentation

- Swelling and ulceration may or may not be painful, but pruritus is common.
- Skin often has a nodular or eroded surface.
- Clitoromegaly may be seen.
- Papules or warts might be described in patients from nonendemic areas, with patients reporting the presence of an "itchy wart."
- Chronic infection leads to tumorlike masses associated with ulceration and pain.
- Labia majora involvement is most common as the trematodes have easier access to veins in this site.

Prognosis and Treatment

- Favorable.
- Antihelminthic drug treatment cures the infection.
- Skin manifestations resolve a few weeks after initiation of treatment.

Pathology

Histology

- Immature schistosome eggs with intensely basophilic internal structures.
- An intense granulomatous, eosinophilic, and acute inflammatory reaction is usually associated with the eggs.
- Epithelioid histiocytes and noncaseating granulomas may form.

Immunopathology (Including Immunohistochemistry)

- Periodic acid–Schiff (PAS) staining identifies the chitin within the egg structure.

Main Differential Diagnosis

- Nematode infection, including trichuriasis.
- Carcinoma—may be confused clinically.
- Condyloma—may be confused clinically.

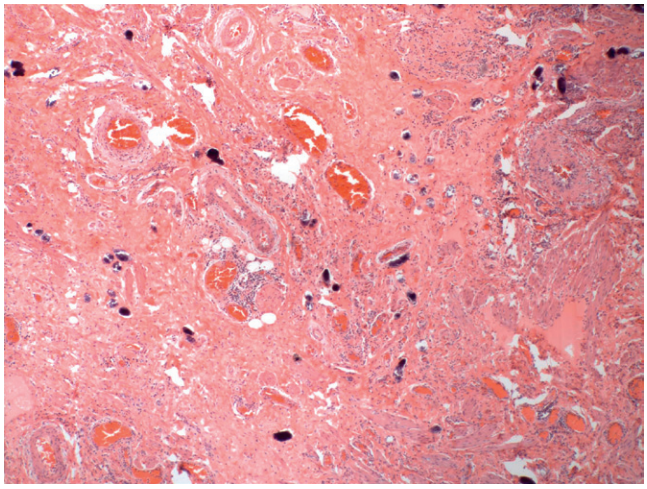

FIGURE 1

Schistosomiasis. At low power a large number of densely basophilic structures can be seen embedded within the vascular soft tissue of the labia majora.

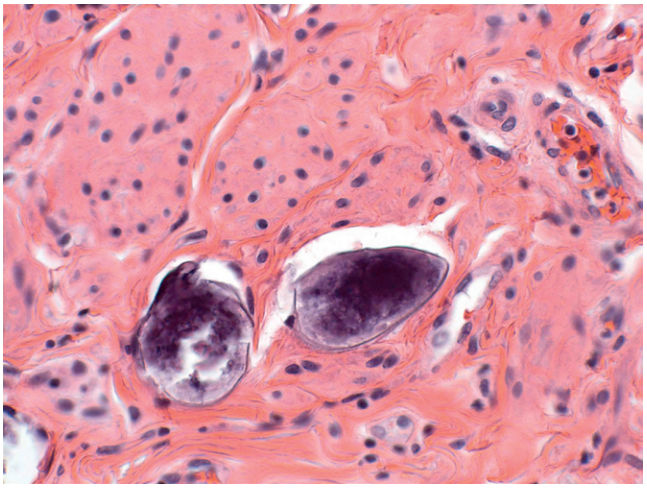

FIGURE 2

Schistosomiasis. Two calcified schistosoma ova.

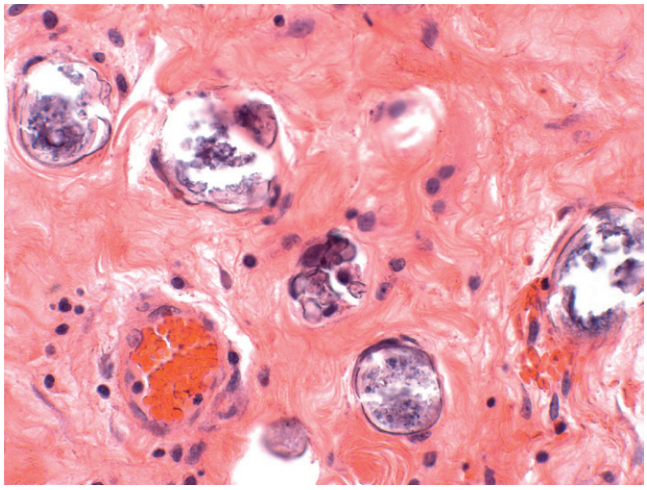

FIGURE 3

Schistosomiasis. Multiple calcified schistosoma ova.

BACILLARY ANGIOMATOSIS

Definition—An opportunistic infection that commonly occurs in the backdrop of human immunodeficiency virus (HIV)/AIDS infection caused by the organisms *Bartonella henselae* or *Bartonella quintana*.

Clinical Features

Epidemiology

- This is a rare, opportunistic disease seen in immunocompromised individuals.

Presentation

- Small red papules that increase in size.
- Larger lesions can ulcerate.
- Deeper, subcutaneous lesions may develop that tend to be lighter (flesh to pink in color).

Prognosis and Treatment

- Favorable; antibiotic therapy (erythromycin) will typically lead to resolution within a week, with longer courses of therapy required for advanced mucosal disease.

Pathology

Histology

- In immunocompetent people a necrotizing granulomatous disease develops within the draining lymph nodes.
- In immunocompromised people a distinct vascular proliferation occurs that is composed of capillaries with "histiocytoid" endothelial cells, which have been noted to protrude into the vessel lumen.
- Scattered endothelial cells, neutrophils, and karyorrhectic debris are noted within edematous stroma.
- Collections of organisms, which may appear as a hazy purple area surrounding vessels, may be seen (best on Warthin-Starry staining).

Immunopathology (Including Immunohistochemistry)

- Silver stains (Warthin-Starry) may help to identify organisms.

Main Differential Diagnosis

- Kaposi's sarcoma.
- Angiosarcoma.
- Ulcerated pyogenic granuloma.

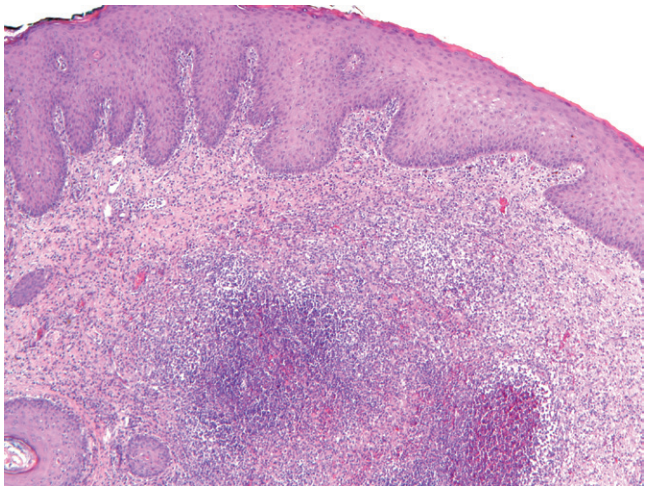

FIGURE 1

Bacillary angiomatosis. At low power a nodular infiltrate of inflammatory cells and vessels is often present.

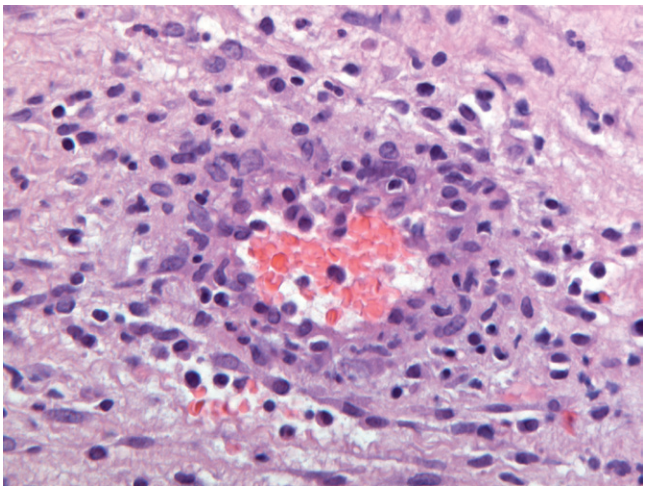

FIGURE 2

Bacillary angiomatosis. Vessels display "histiocytoid" endothelial cells that slough into the lumen. A mixed inflammatory infiltrate is present.

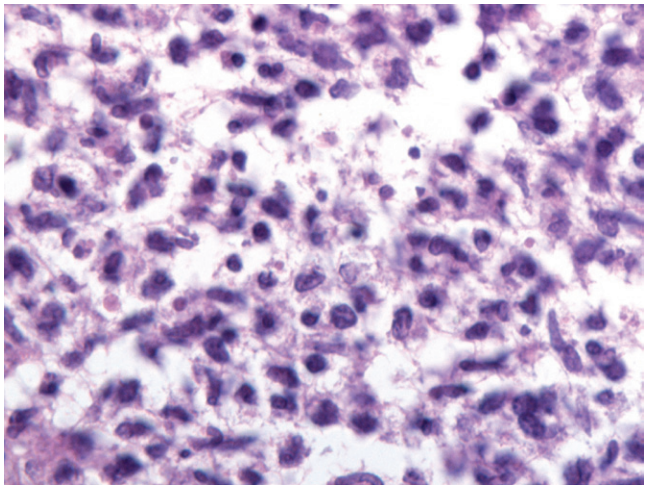

FIGURE 3

Bacillary angiomatosis. An edematous area with a mixed inflammatory infiltrate and a hazy purple background that is composed of clumps and clusters of organisms.

NECROTIZING FASCIITIS

Definition—An aggressive infection of the subcutis and fascia.

Clinical Features

Epidemiology

- Commonly seen in the setting of diabetes.
- Predisposing factors include obesity, hypertension, immune compromise, and history of previous trauma.

Presentation

- Localized erythema and pain that rapidly expands.
- The infected skin will break down and ulcerate and slough.
- Sepsis may occur late in the course of the disease.

Prognosis and Treatment

- Unfavorable; rates of mortality range from 0% to 75% in the literature.
- Aggressive surgical debridement and systemic antibiotics are required.

Pathology

Histology

- Nonspecific; however, the inflammatory exudate may be sparse to abscess forming.
- When present, abscesses are noted along the fascia and dissecting into fat lobules.
- Sheets of bacteria may be noted in the subcutaneous tissue.
- Skeletal muscle necrosis, as well as vessels with fibrin thrombi, may be noted.

Immunopathology (Including Immunohistochemistry)

- Gram stains may be useful in identifying organisms.

Main Differential Diagnosis

- Superficial cellulitis (early).
- Pyoderma gangrenosum.

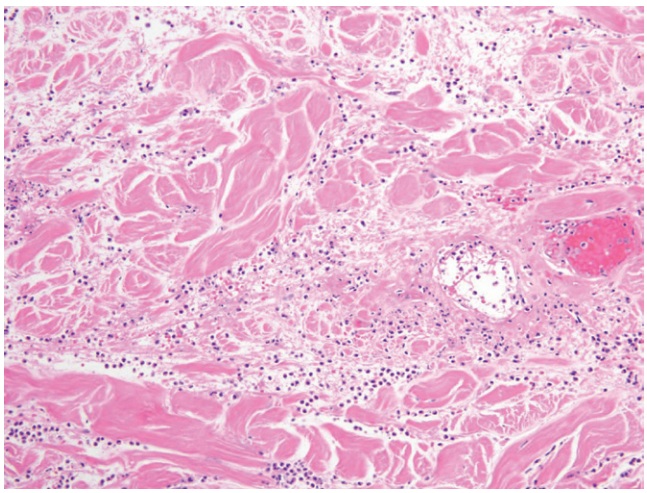

FIGURE 1

Necrotizing fasciitis. Inflammatory cells are present in and around bundles of muscle.

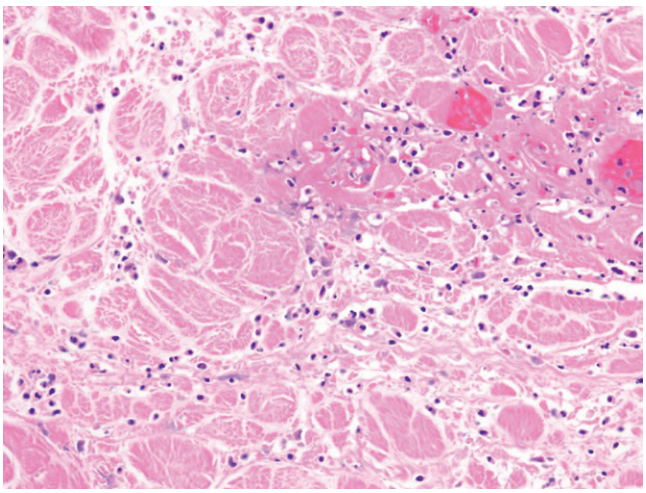

FIGURE 2

Necrotizing fasciitis. A scattered, mixed, inflammatory cell infiltrate with a central area of coagulative necrosis.

VARICELLA ZOSTER

Definition—Infection by the neurotropic varicella-zoster virus (VZV), an alpha-herpesvirus.

Clinical Features

Epidemiology

- Primary VZV infection, commonly known as chickenpox, occurs predominantly in children.
- Recurrences occur later in life.
- Severe, recurrent infections can be seen in the setting of immunodeficiency.
- Herpes zoster (shingles) is the secondary manifestation of VZV infection.

Presentation

- In primary disease a vesiculobullous rash occurs 10 to 21 days after exposure.
- Skin lesions progress from macules to papules and finally to vesicles which rupture, dry, and crust over.
- Lesions are present at a variety of stages in the acutely affected patient.
- Secondary disease is heralded by a prodrome or pain and paresthesias; itching, burning, or tingling, usually in a dermatomal distribution.
- The prodrome is followed by an acute vesiculobullous eruption.
- Fever and headache may or may not be present in secondary reactivation.
- Patients may present with chronic vulvar pain or clitorodynia.

Prognosis and Treatment

- Primary infection is nearly always self-limited in immunocompetent patients.
- Primary infection in immunocompromised patients may be fatal, and high-dose acyclovir is required.
- High-dose acyclovir is also required in any patient with disseminated or visceral zoster, which can (rarely) occur even in immunocompetent patients.
- Secondary VZV reactivation can result in postherpetic neuralgia, and chronic pain may persist for months or years.

Pathology

Histology

- The histologic appearance of VZV is identical to the changes seen in herpes simplex virus (HSV) infection.
- Early lesions are characterized by bullous formation, with acantholysis of keratinocytes.
- Epithelial necrosis with extensive debris in the ulcer bed is seen in later stages.
- Viral inclusion may be seen at the interface of the ulcer and normal epithelium or within the acantholytic cells in bullae.
- The viral inclusions are histologically identical to those seen in HSV infection; they are seen as large glassy pink-red nuclear inclusions.

Immunopathology (Including Immunohistochemistry)

- Immunohistochemistry for VZV is positive.
- Immunohistochemistry for HSV is negative.

Main Differential Diagnosis

- HSV infection—this can be distinguished best by immunohistochemistry.

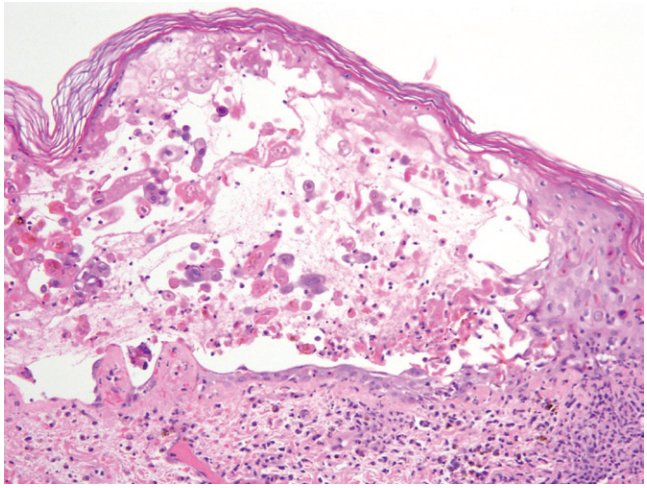

FIGURE 1

Varicella zoster. Bulla formation with epidermal necrosis and necrotic debris.

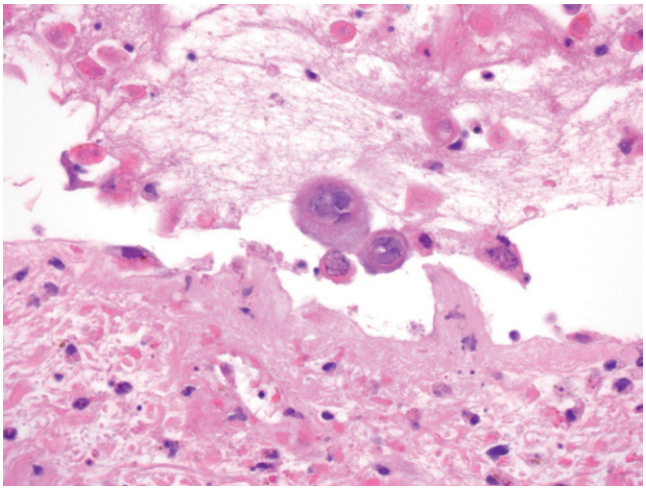

FIGURE 2

Varicella zoster. Glassy nuclear viral inclusions.

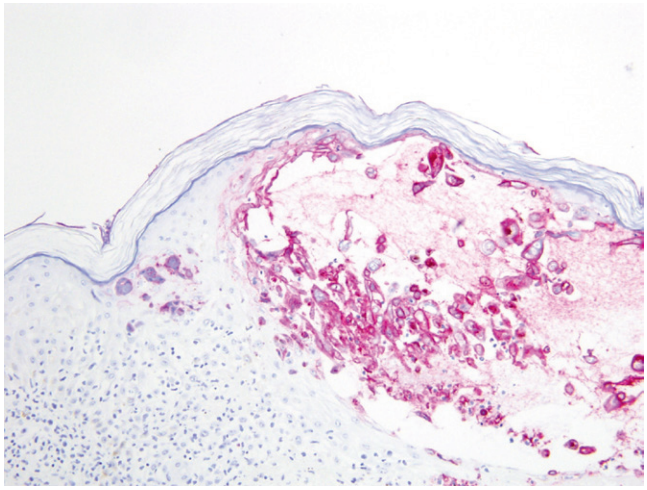

FIGURE 3

Varicella zoster. Immunohistochemical stain for VZV.

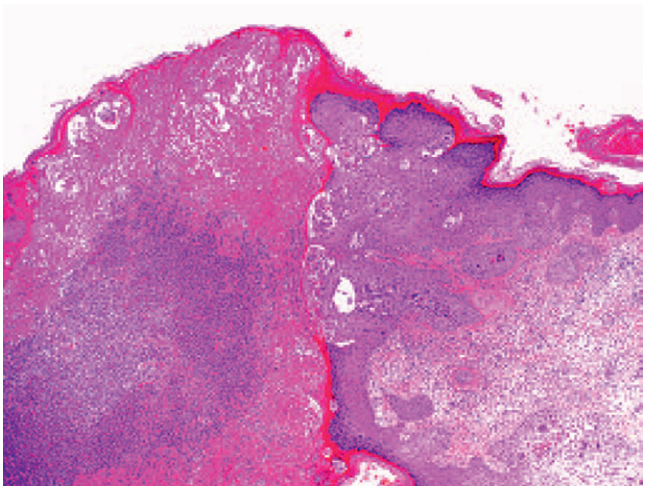

FIGURE 4

Varicella zoster. At low power there is pronounced submucosal edema and epithelial hyperplasia. Ulceration is inconspicuous.

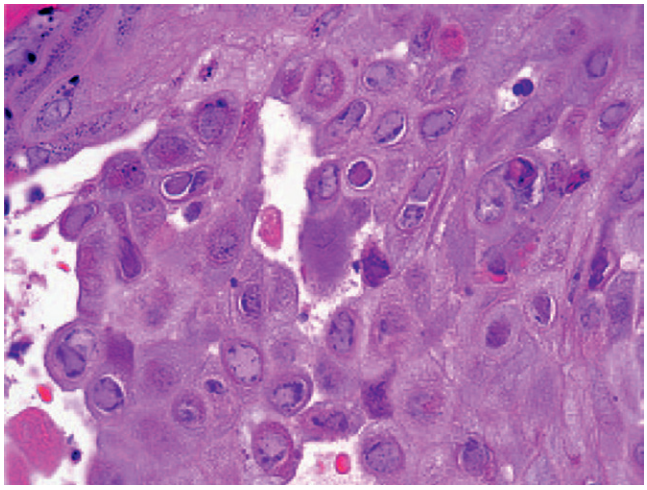

FIGURE 5

Inclusions are conspicuous at higher power, similar in appearance to herpes simplex.

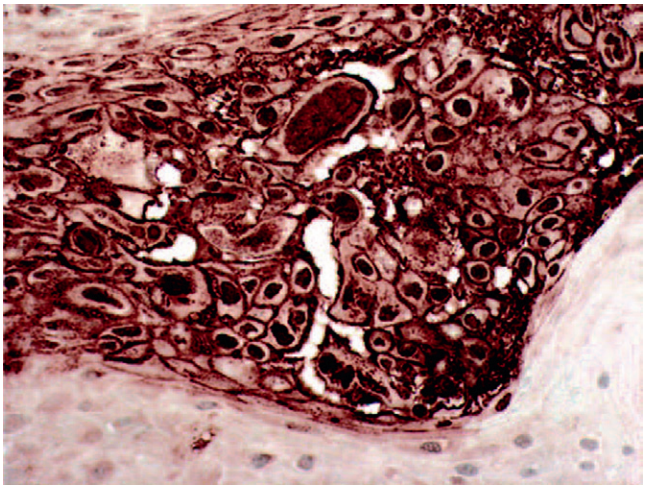

FIGURE 6

Immunohistochemical staining for zoster will discriminate this from herpes simplex.

BARTHOLIN'S DUCT CYST

Definition—Cyst formation follows occlusion of Bartholin's duct, which drains Bartholin's glands.

Clinical Features

Epidemiology

- Common lesions that happen in all age groups.

Presentation

- May present as mass lesions with or without tenderness based on accompanying inflammation (or abscess formation).
- Cysts are located in the posterior introitus around the orifices of the ducts that drain Bartholin's glands.

Prognosis and Treatment

- Excellent.
- The majority of the lesions can be treated by catheter insertion and marsupialization, the latter of which is not recommended in abscesses.
- Antibiotics may be utilized for accompanying cellulitis.

Pathology

Histology

- Variable-sized cysts lined by squamous-, mucinous-, or transitional-type epithelium in varying proportions.
- An adjacent Bartholin's gland may be present.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Skene's duct cyst—periurethral location.
- Epidermal inclusion cyst—subepithelial, no accompanying Bartholin's gland.
- Mucous cyst—usually vaginal in location.
- Benign adnexal tumors—hidradenoma and syringoma, may be confused clinically.
- Soft-tissue tumors—may be confused clinically.
- Bartholin's adenoma/carcinoma—may be confused clinically.

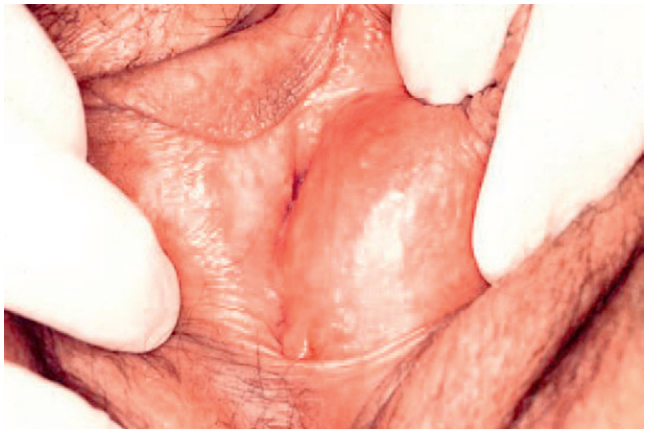

FIGURE 1

Clinical appearance of Bartholin's duct cyst. *(From Marzano DA, Haefner HK: The barthol gland cyst: past, present and future, J Low Genit Tract Dis 8(3):195-204, 2004.)*

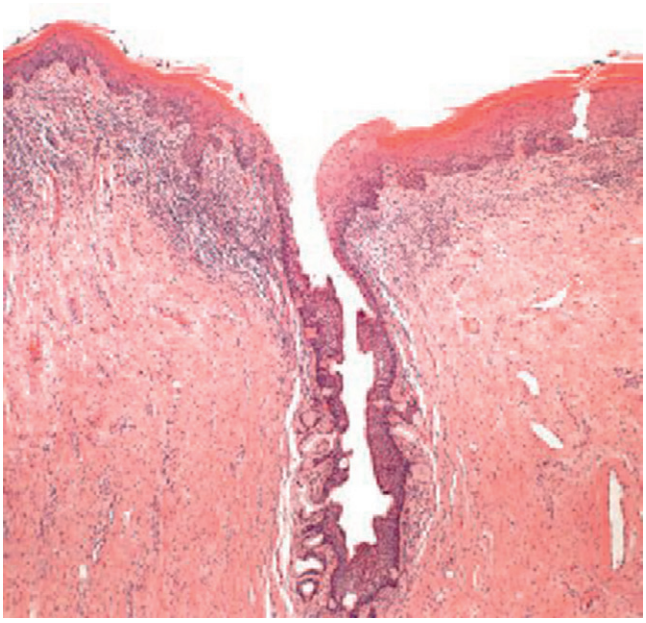

FIGURE 2

Bartholin's duct cyst. Low-power microphotography illustrating the transitional epithelium.

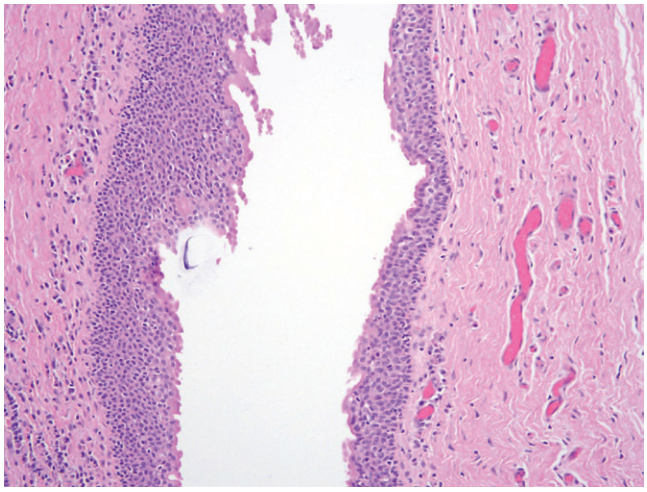

FIGURE 3

Higher magnification of a prominent cyst with transitional epithelium.

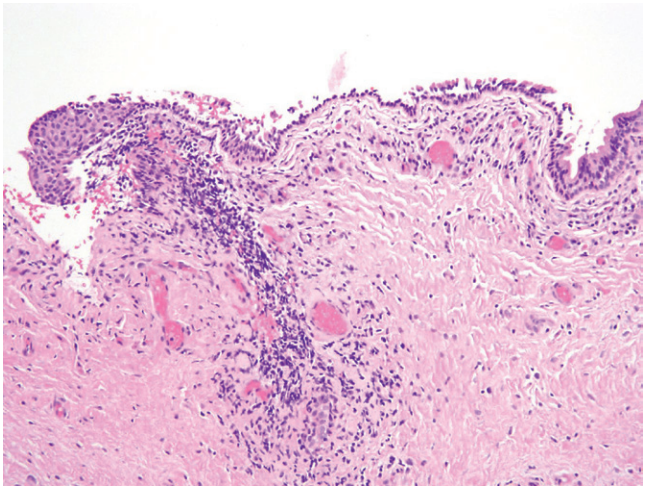

FIGURE 4

Bartholin's duct cyst. In this image there is attenuation of the epithelium and some underlying inflammation.

MUCOUS CYST OF THE VAGINA

Definition—Vaginal cyst of müllerian origin.

Clinical Features

Epidemiology

- Relatively uncommon.
- Derived from müllerian remnants.
- Wide age range with a median in the fourth decade.

Presentation

- Lateral and posterior wall.
- Patient may notice a swelling and experience dyspareunia and stress incontinence.

Prognosis and Treatment

- Excision is curative.

Pathology

Histology

- Variable size lined by müllerian (endocervical-type) mucinous epithelium.
- Squamous metaplasia is common.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Skene's duct cyst—periurethral location.
- Epidermal inclusion cyst—squamous epithelium that may be confused with squamous metaplasia, but keratinaceous debris is more typical.
- Benign adnexal tumors—hidradenoma and syringoma may be confused clinically but are more typically situated in the vulva.
- Gartner's duct cyst—cuboidal lining and no mucin.

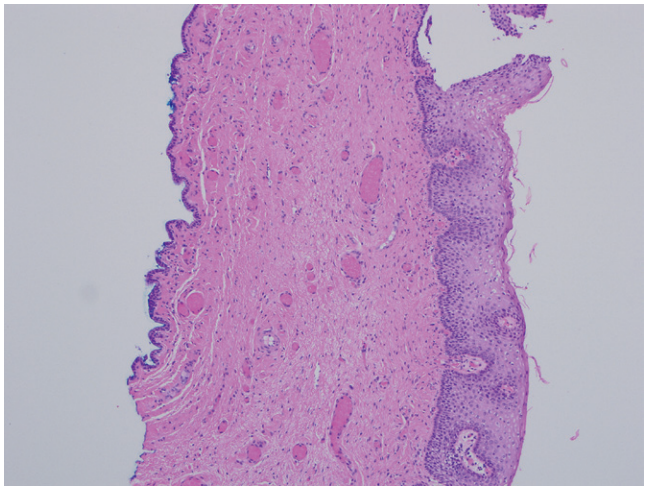

FIGURE 1

Mucous cyst lined by a low columnar mucin-producing epithelium. Surface squamous mucosa is on the right.

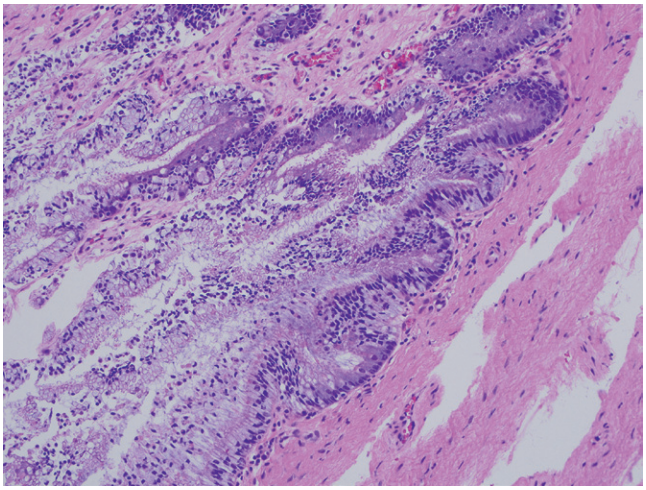

FIGURE 2

Mucous cyst. Abundant mucin-producing epithelium.

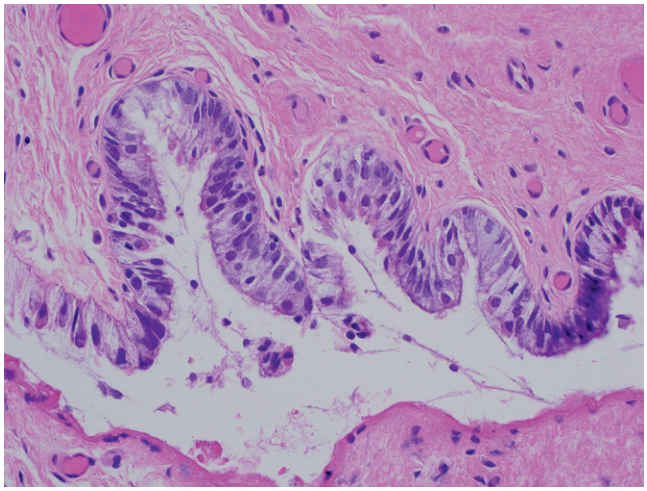

FIGURE 3

Mucous cyst. Note the resemblance to endocervical epithelium.

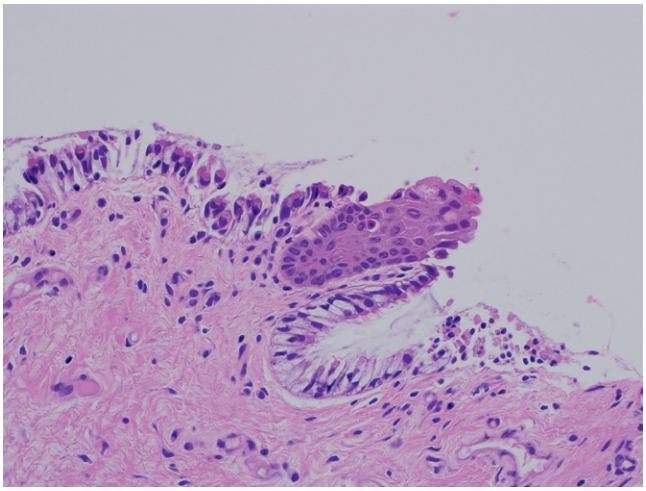

FIGURE 4

Mucinous cyst with focal squamous differentiation.

ECTOPIC BREAST TISSUE

Definition—Adnexal tissue with mammary differentiation in the vulvar region.

Clinical Features

Epidemiology

- Rare.
- The most popular theory is that it reflects a rudiment of caudal mammary buds (in the "milk line") that did not completely regress during development.
- Other theories include mammary-like anogenital glands that concentrate in the labial sulcus and give rise to "ectopic breast tissue."

Presentation

- Typically presents as a smooth well-circumscribed mass resembling a Bartholin's duct cyst or hidradenoma. May be seen during pregnancy.

Prognosis and Treatment

- Excision is curative.

Pathology

Histology

- Appearance is that of normal breast tissue.
- Glandular epithelium including ducts and lobules.

Immunopathology (Including Immunohistochemistry)

- Usually noncontributory; but in less discrete cases, p63 immunostaining will highlight basal–reserve cells confirming a benign process.

Main Differential Diagnosis

- No diagnostic problems are expected on histology. However, the lesion may clinically be confused with adnexal cysts or benign tumors.
- Fibroadenomas and other neoplasms can arise in the breast tissue (see fibroadenoma).

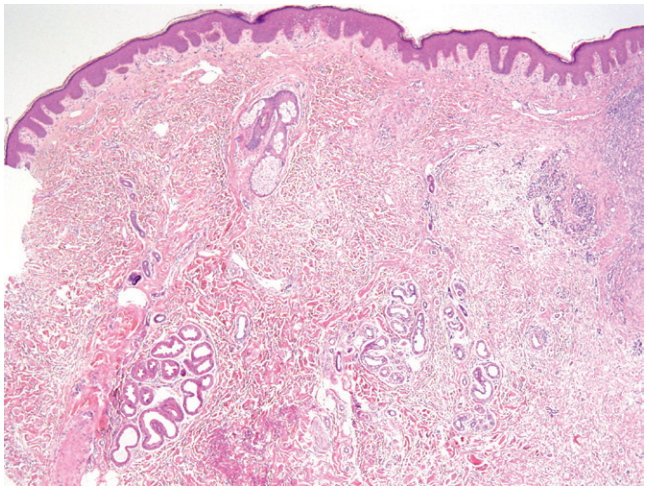

FIGURE 1

Ectopic breast tissue. Mammary differentiation is seen with small ducts and acini, including a focus with apocrine metaplasia *(lower left)*.

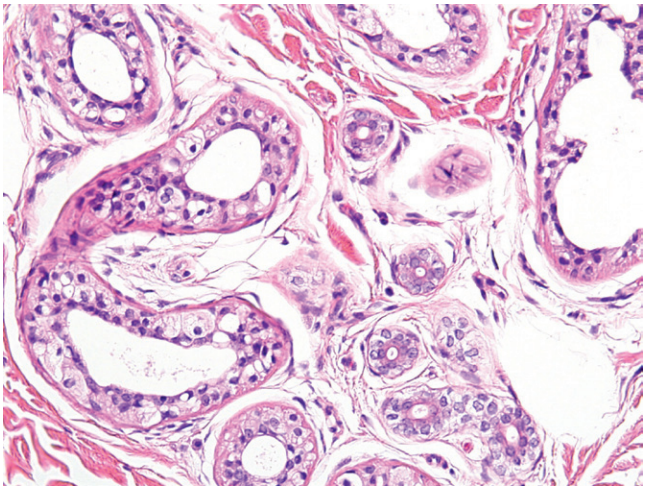

FIGURE 2

Ectopic breast tissue. Higher magnification depicts ductal structures.

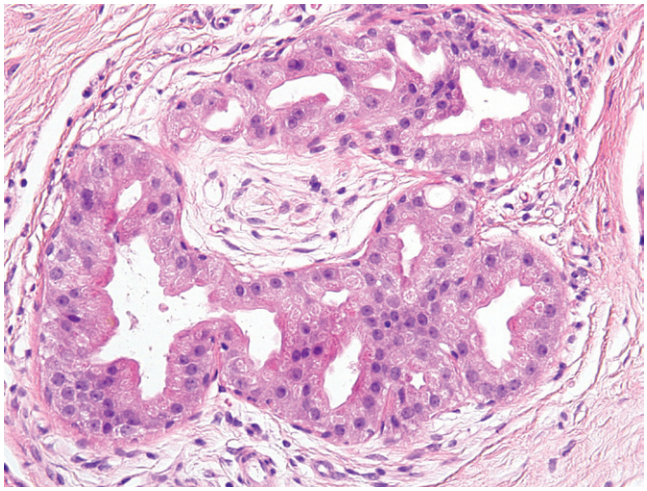

FIGURE 3

Ectopic breast tissue. Apocrine differentiation.

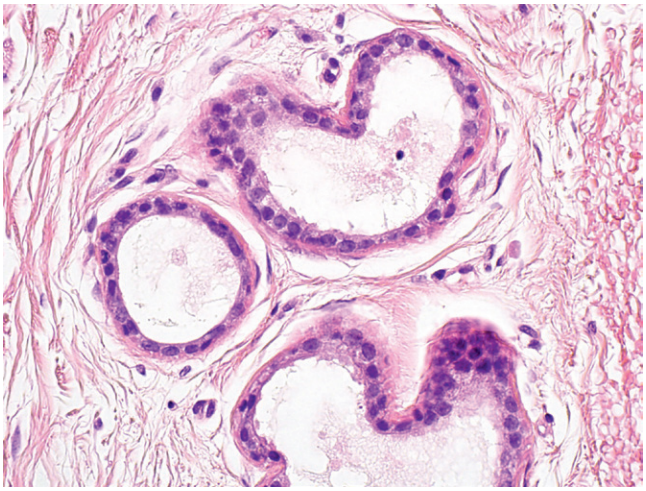

FIGURE 4

Small ectatic ducts in ectopic breast tissue.

FIBROADENOMA

Definition—Tumor of mammary phenotype arising in ectopic breast tissue.

Clinical Features

Epidemiology

- Rare.
- The most popular theory is that this tumor arises in a rudiment of mammary tissue (in the "milk line") that did not completely regress during development.

Presentation

- Young patients typically.
- Typically presents as a smooth well-circumscribed mass resembling an adnexal duct cyst or hidradenoma. May be seen during pregnancy.

Prognosis and Treatment

- Excision is curative.

Pathology

Histology

- May be associated with recognizable normal breast tissue.
- Glandular epithelium including ducts and lobules within a characteristic benign appearing fibromatous stroma.
- Some glandular proliferation may be seen.
- Some fibroadenomas may appear complex, raising the possibility of a phyllodes tumor. However, stroma cells are usually not atypical.

Immunopathology (Including Immunohistochemistry)

- Usually noncontributory; but in less discrete cases, p63 immunostaining will highlight basal–reserve cells confirming a benign process.

Main Differential Diagnosis

- Hidradenoma—this may exhibit similar differentiation but exhibits the characteristic acinar/papillary architecture without the more typical concentric fibrous component of a fibroadenoma.

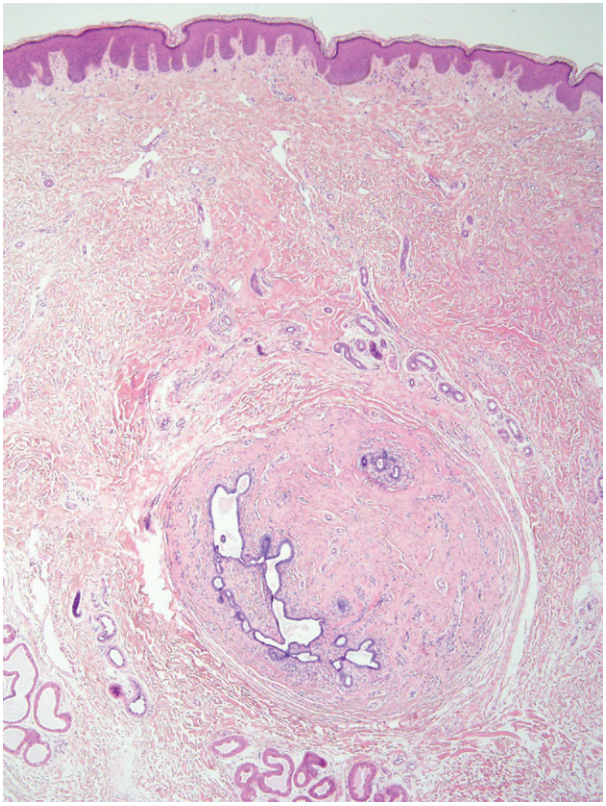

FIGURE 1

Ectopic breast tissue with fibroadenoma. Note the central fibrous nodule with mild glandular hyperplasia.

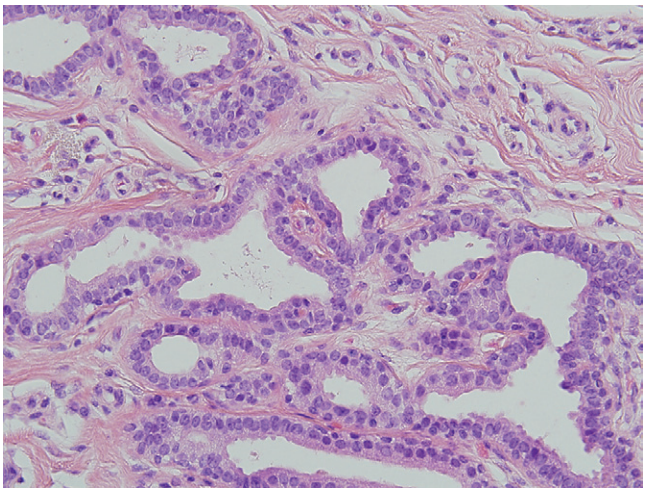

FIGURE 2

Ectopic breast tissue with fibroadenoma. There is some mild increase in glandular proliferation.

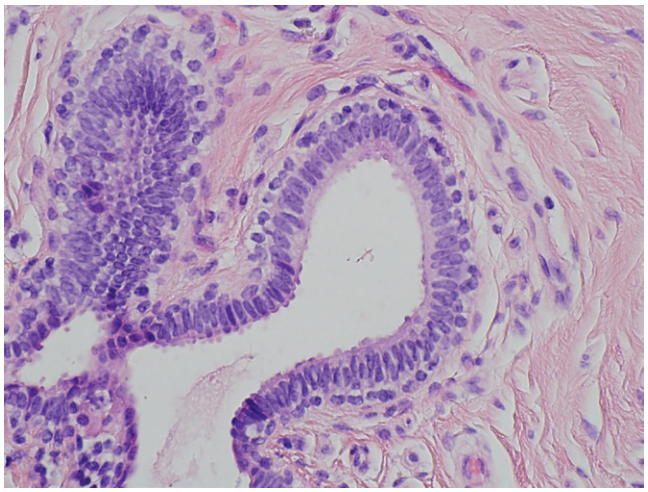

FIGURE 3

Ectopic breast tissue with fibroadenoma. Note the benign cytologic features.

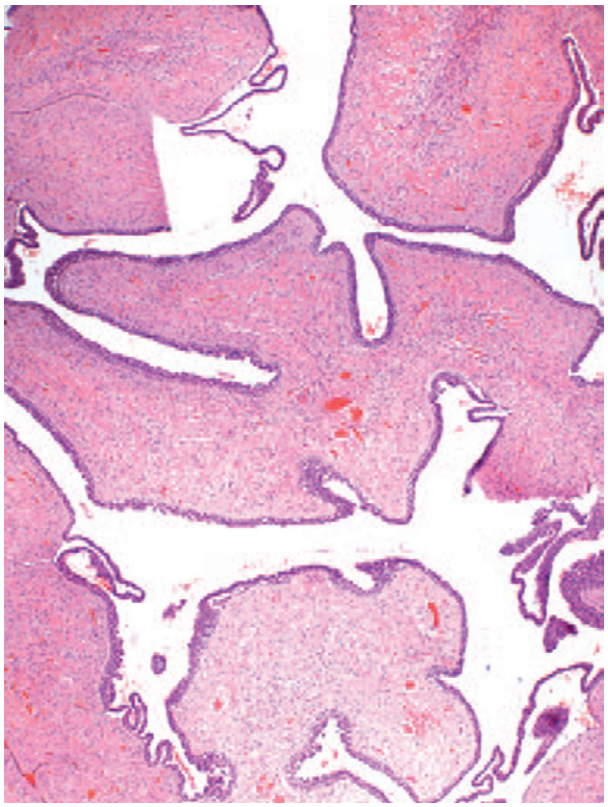

FIGURE 4

Mildly complex fibroadenoma. Note the somewhat phyllodiform appearance. There is no stromal atypia.

HIDRADENOMA

PITFALL

Definition—An unusual benign adnexal tumor that exhibits both apocrine and eccrine differentiation and occurs almost exclusively in the vulva.

Clinical Features

Epidemiology

- Uncommon.
- Nearly always seen in postpubertal, but premenopausal, adult women.
- More frequent in Caucasians.

Presentation

- A small- to medium-sized (<2 cm), discrete, painless nodule located in the sulcus between the labium minus and majus.

Prognosis and Treatment

- Excision is curative.

Pathology

Histology

- Most are well-circumscribed papillary-to-cribriform proliferation of glandular epithelium.
- The characteristic two-layer epithelium has a strikingly uniform appearance.
- The surface epithelial cells exhibit distinctive "decapitation secretion."
- Myoepithelial cells and fibrovascular cores are evident.
- Overlying acanthosis is occasionally prominent.
- Beware occasional cases that are not discrete and may be intermixed with fibrosis, mimicking malignancy.
- Some will exhibit prominent apocrine differentiation.

Immunopathology (Including Immunohistochemistry)

- Usually noncontributory; but in less discrete cases, p63 immunostaining will highlight basal–reserve cells confirming a benign process.

Main Differential Diagnosis

- Adenocarcinoma (such as metastatic endometrioid) when gland proliferation is prominent.
- Infiltrating adenocarcinoma when fibrosis with gland entrapment occurs (exclude with staining for p63).
- Mesenchymal neoplasms (clinical).

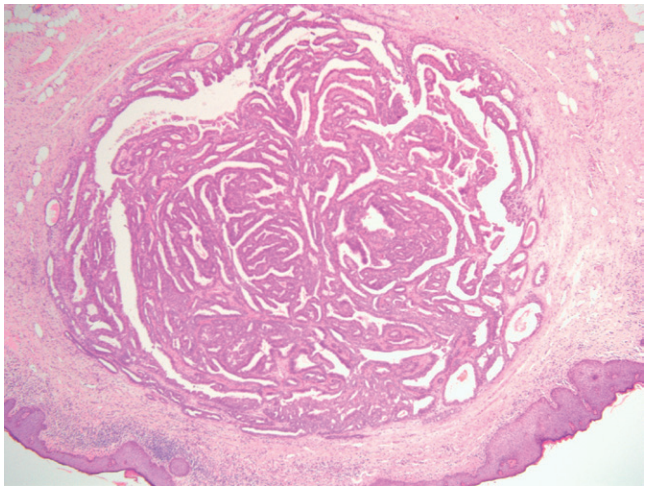

FIGURE 1

Hidradenoma papilliferum (HP). A well-circumscribed nodule of glandular epithelium.

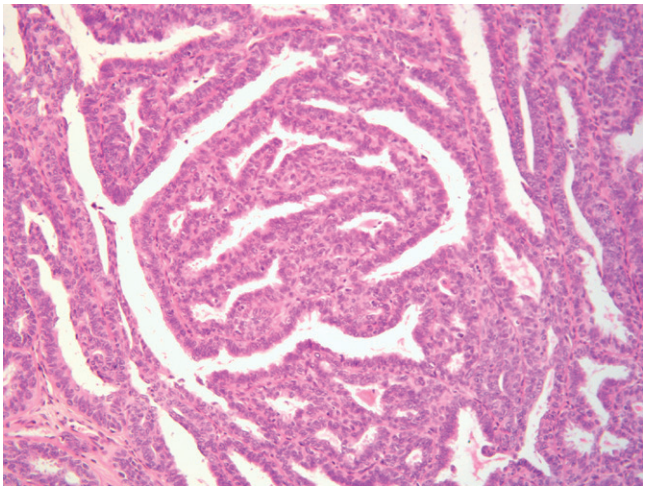

FIGURE 2

HP. Higher magnification depicts regularly arranged but variable lumens.

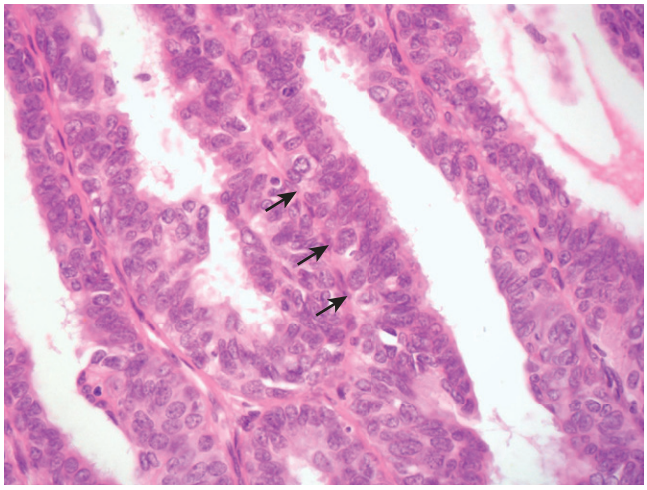

FIGURE 3

HP. Uniform cells arranged focally into conspicuous two cell layers *(arrows).*

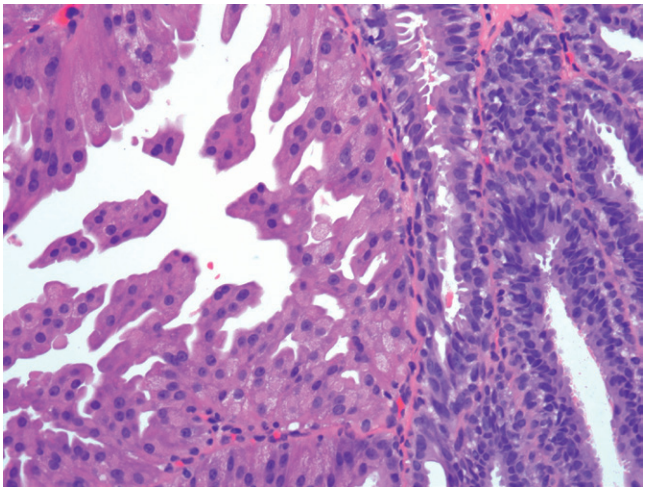

FIGURE 4

Apocrine differentiation in HP.

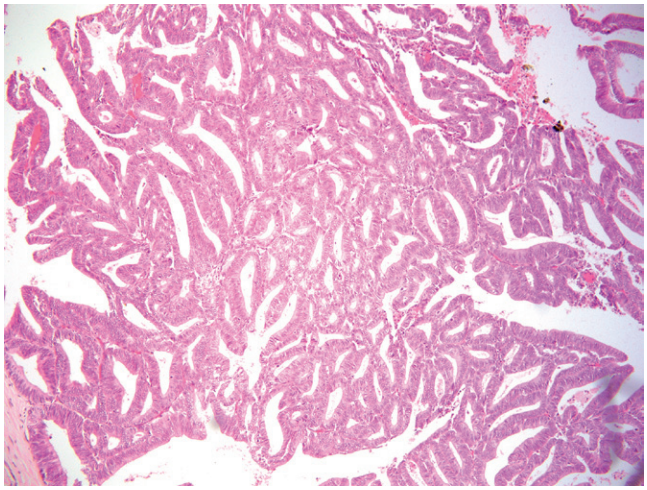

FIGURE 5
Metastatic endometrioid carcinoma for comparison.

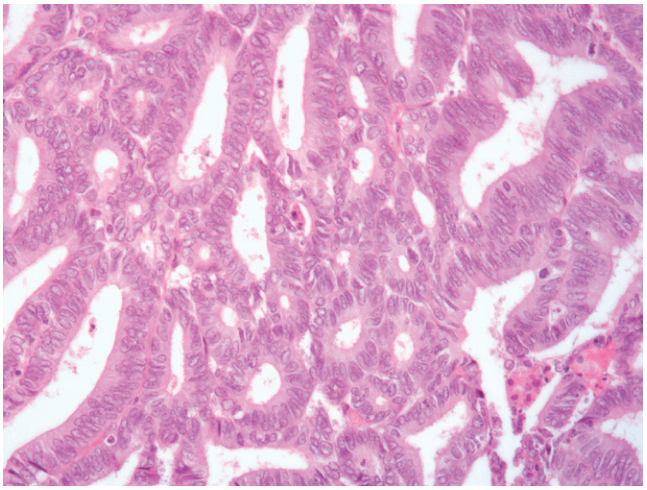

FIGURE 6
At higher magnification, metastatic carcinoma with a single neoplastic cell type devoid of two cell layers.

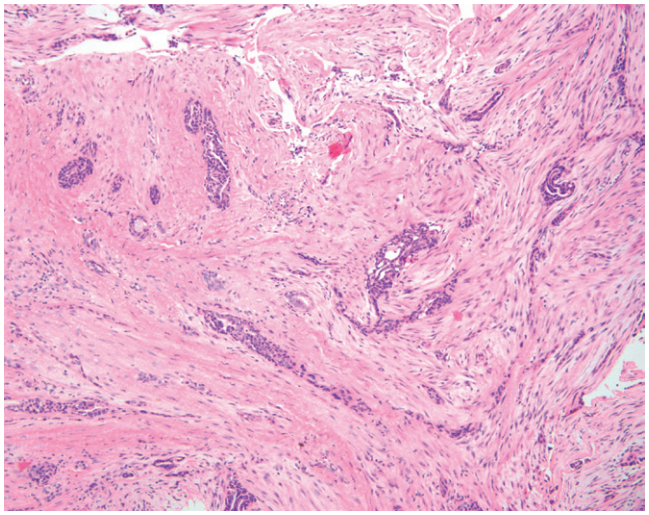

FIGURE 7
Sclerotic HP mimicking an infiltrative carcinoma.

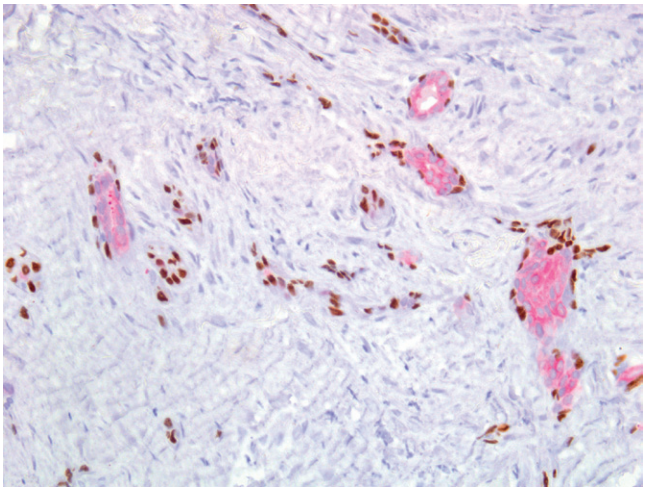

FIGURE 8
p63 immunostaining of field in Figure 7 highlights reserve cell layer, confirming a benign HP and excluding invasive carcinoma.

SYRINGOMA

Definition—A benign adnexal tumor with eccrine differentiation.

Clinical Features

Epidemiology

- Higher incidence in women and Asians.
- More frequently identified in trisomy 21 patients.

Presentation

- Small (<4 mm) flesh-colored papules with a symmetrical distribution.
- Most commonly found on the lower eyelid but can also affect the vulva.
- Often appear around puberty.
- Can be pruritic, which is exacerbated by pregnancy and warm weather.

Prognosis and Treatment

- Excellent.
- For symptomatic lesions, laser ablation has been used.

Pathology

Histology

- Intersecting epithelial strands and ducts forming comma-shaped structures (tadpoles) set within an eosinophilic fibrous stroma.
- The ductlike structures are characterized by two cell layers.
- The nuclei are bland, and mitoses are infrequent.

Immunopathology (Including Immunohistochemistry)

- Not needed, although p63 highlights the basal epithelial layer.

Main Differential Diagnosis

- Fox-Fordyce disease.

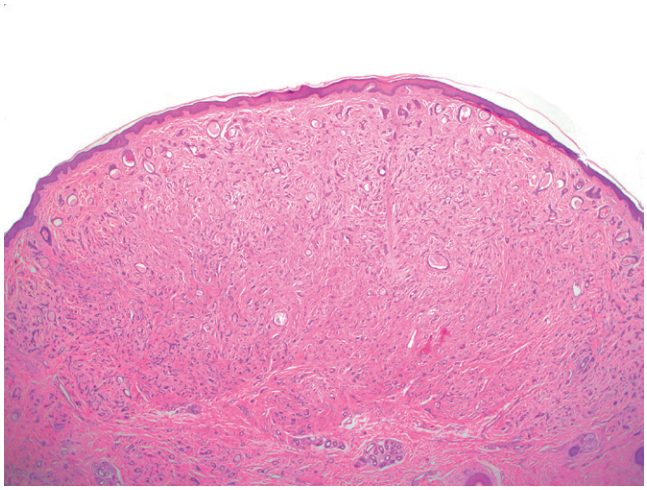

FIGURE 1
Syringoma, seen here at low magnification as a well-circumscribed lesion.

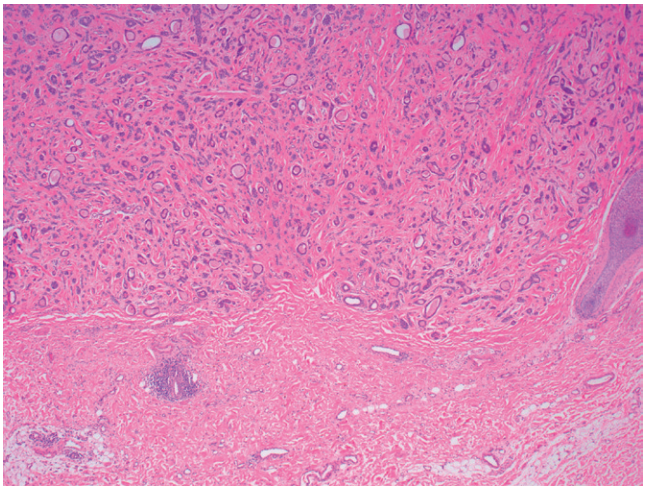

FIGURE 2
Syringoma. The lesion–stromal interface is uniformly demarcated.

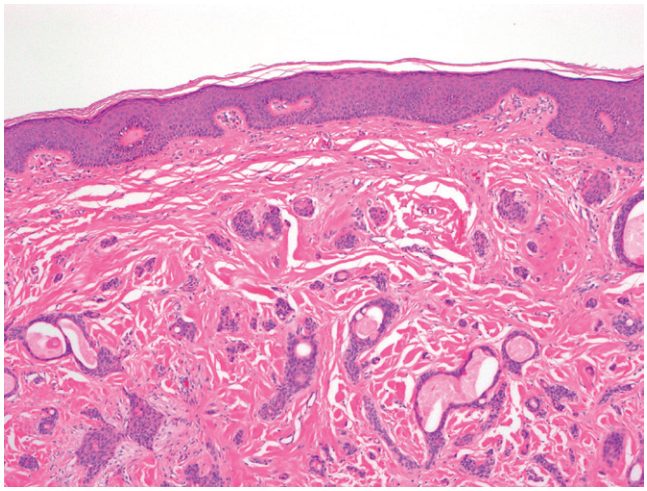

FIGURE 3
Syringoma. Note the angulated comma-shaped epithelial structures.

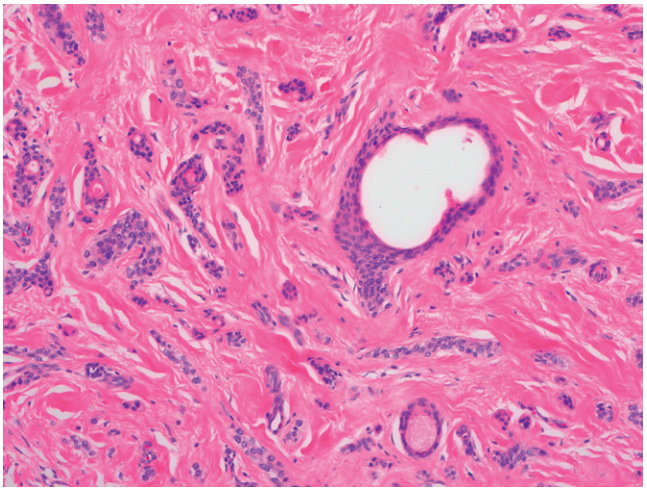

FIGURE 4
Syringoma. Some ectatic ductal structures are admixed with the others.

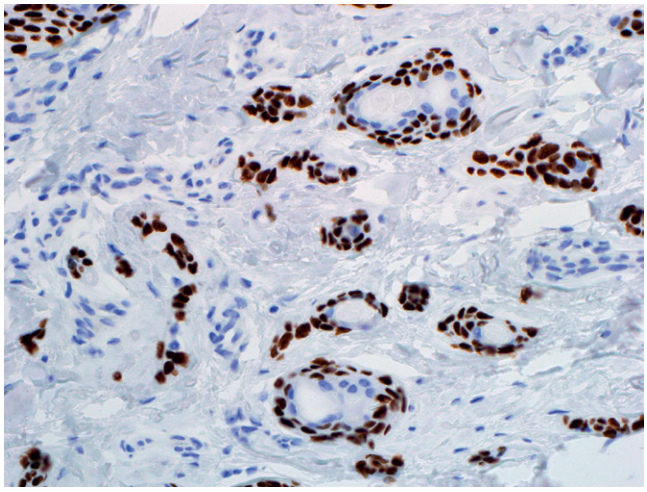

FIGURE 5
Syringoma. A p63 immunostain highlights the basal cells in a two-cell-layered epithelium.

HYPERPLASIA OF BARTHOLIN'S GLAND

Definition—An increase in the number of Bartholin's glands with preservation of normal architecture.

Clinical Features

Epidemiology

- Seen in a wide age range.
- Hyperplasia of Bartholin's glands generally occurs at a younger age than adenoma.

Presentation

- May present as a mass-forming lesion.

Prognosis and Treatment

- Excellent prognosis.
- Cured by excision.

Pathology

Histology

- A general increase in the number of Bartholin's glands.
- Ductal and acinar architecture are preserved.
- Coexisting inflammation and squamous metaplasia may also be present.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Bartholin's duct cyst or abscess—may be confused clinically.
- Bartholin's gland adenoma—loss of gland to duct orientation.

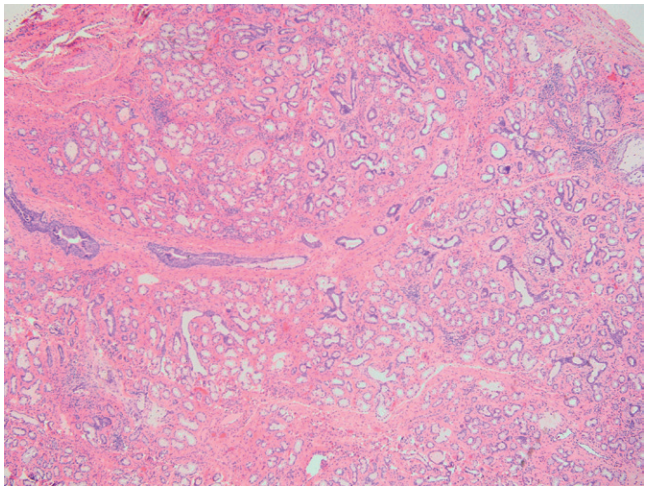

FIGURE 1

Bartholin's gland hyperplasia. Increased numbers of mucinous Bartholin's glands can be seen. There is a preservation of the normal lobular architecture.

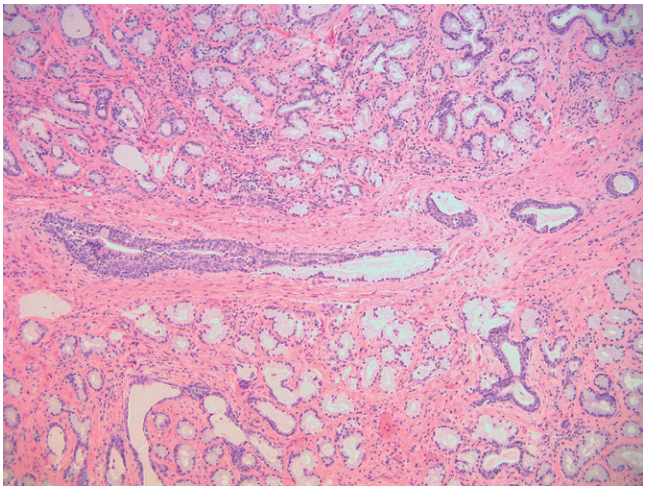

FIGURE 2

Bartholin's gland hyperplasia. At higher power, emphasizing the preservation of the ducts (centrally).

BARTHOLIN'S ADENOMA

Definition—An increase in the number of Bartholin's glands with a generalized loss of architecture.

Clinical Features

Epidemiology

- Occurs across a wide age range; however, adenomas generally occur at an older age.
- Very rare.

Presentation

- May present as a mass-forming lesion, mimicking a Bartholin's gland cyst.
- May also present with pain.

Prognosis and Treatment

- Favorable prognosis.
- The majority of lesions are cured by excision.
- Rare cases have been associated with a concomitant malignancy (adenocarcinoma).

Pathology

Histology

- Increased numbers of Bartholin's glands with a loss of the normal architecture (i.e., haphazard growth pattern).
- As in hyperplasia, squamous metaplasia and inflammation may be present.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Bartholin's duct cyst or abscess—may be confused clinically. Gland structures will be seen in the wall of the cyst.
- Bartholin's gland hyperplasia—duct structures are preserved.
- Malignancy (clinically).

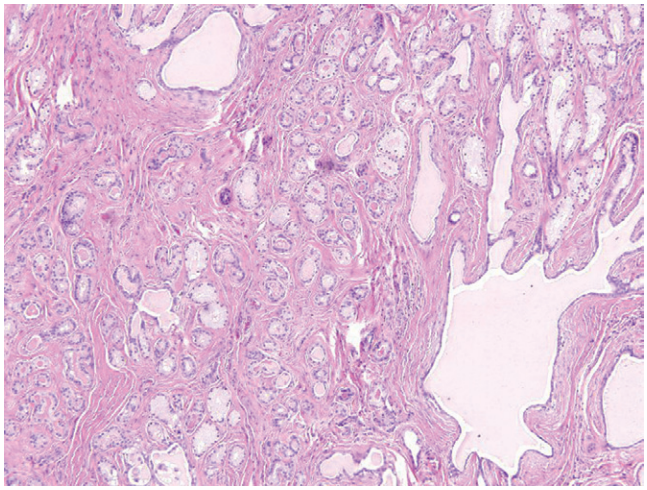

FIGURE 1

Bartholin's gland adenoma. Medium-magnification view of numerous, haphazardly arranged glands comprising a Bartholin's adenoma.

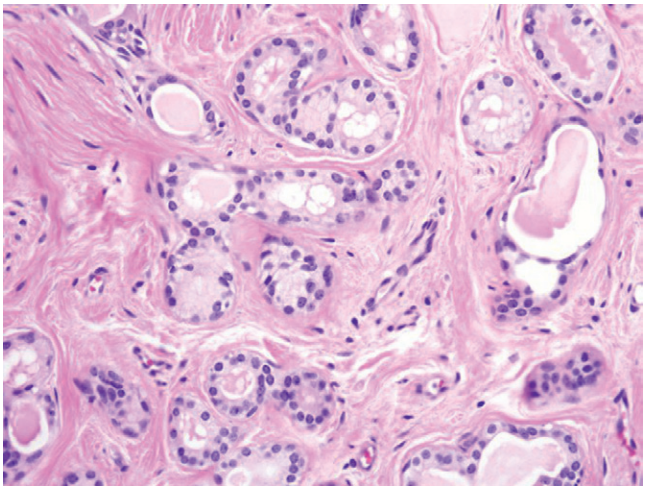

FIGURE 2

Bartholin's gland adenoma. Disorganized glands with abundant eosinophilic cytoplasm and innocuous, regular nuclei.

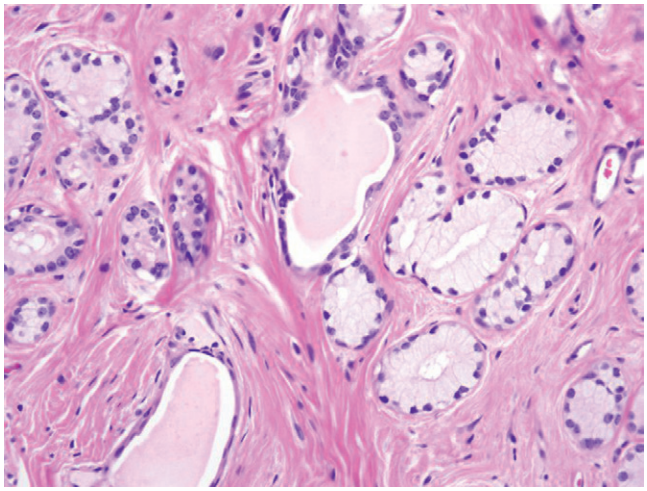

FIGURE 3

Bartholin's gland adenoma. Occasional glands may show cystic dilatation and irregular contours.

ADENOID CYSTIC CARCINOMA

Definition—A slow-growing/indolent malignancy derived from the Bartholin's gland with a tendency for late metastasis.

Clinical Features

Epidemiology

- Very rare.
- Accounts for less than 1% of vulvar malignancies.
- Wide age range, with an average age in the fourth decade.

Presentation

- Mass-forming lesion in the area of the Bartholin's gland.
- Slow growing, may be present for months or years.

Prognosis and Treatment

- Treatment includes wide local excision.
- Slow growth, frequent recurrence, and a tendency toward late distant metastases to lymph nodes and lung.
- Reported 5-year survival is 70%.

Pathology

Histology

- At low power the tumor fills and expands the background Bartholin's gland ducts and is composed of small, bland cells arranged in two patterns.
- The first pattern is a cribriform or microcystic pattern in which nests of cells form small pseudoduct-like spaces with thin, delicate septae.
- The second pattern is characterized by nests, cords, or reticular arrangements of small blue cells set in an eosinophilic hyaline matrix.

Immunopathology (Including Immunohistochemistry)

- Luminal secretions are periodic acid–Schiff (PAS) positive.

Main Differential Diagnosis

- Hidradenoma (will exhibit two cell layers with p63+ basal cells).
- Adenoid variant of basal cell carcinoma (located superficial rather than deep).
- Myoepithelioma (benign mixed tumor).
- Poorly differentiated basaloid carcinomas—usually seen in the vagina and cervix.
- Adnexal or apocrine carcinoma—superficial, exhibits marked atypia.

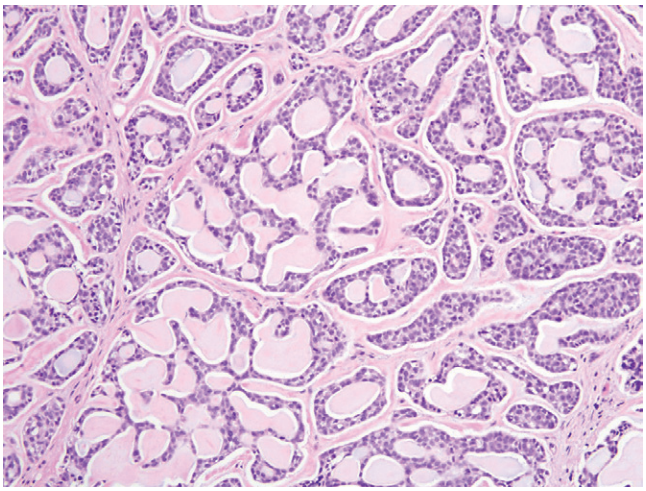

FIGURE 1

Adenoid cystic carcinoma. Adenoid cystic carcinoma showing a predominantly cribriform architecture, marked by large nests of monomorphic tumor cells with pseudoglandular spaces.

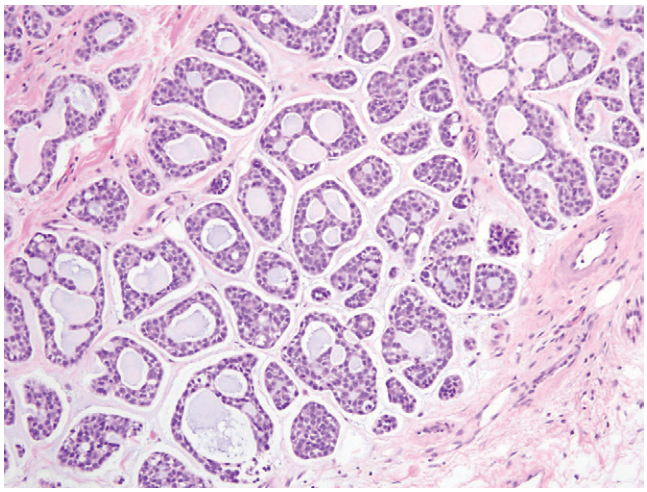

FIGURE 2

Adenoid cystic carcinoma. Small nests of cells without pseudoglandular spaces may be appreciated in the lower half of this photomicrograph.

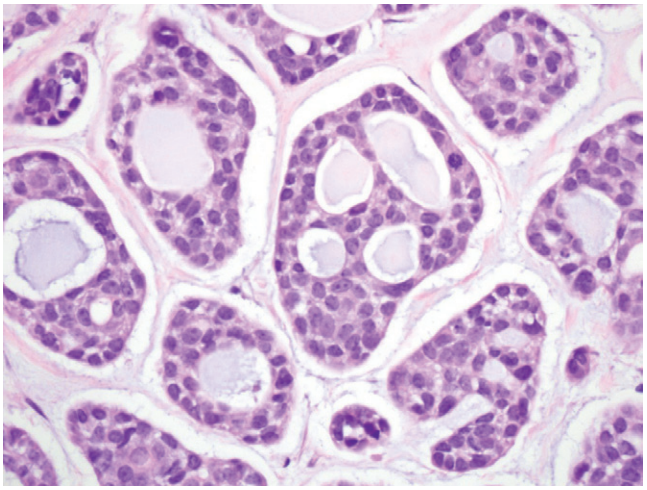

FIGURE 3

Adenoid cystic carcinoma. High-power detail of nests of tumor cells with monomorphic cells with bland nuclei. Note the hazy, amphophilic luminal secretions that will stain positive with PAS.

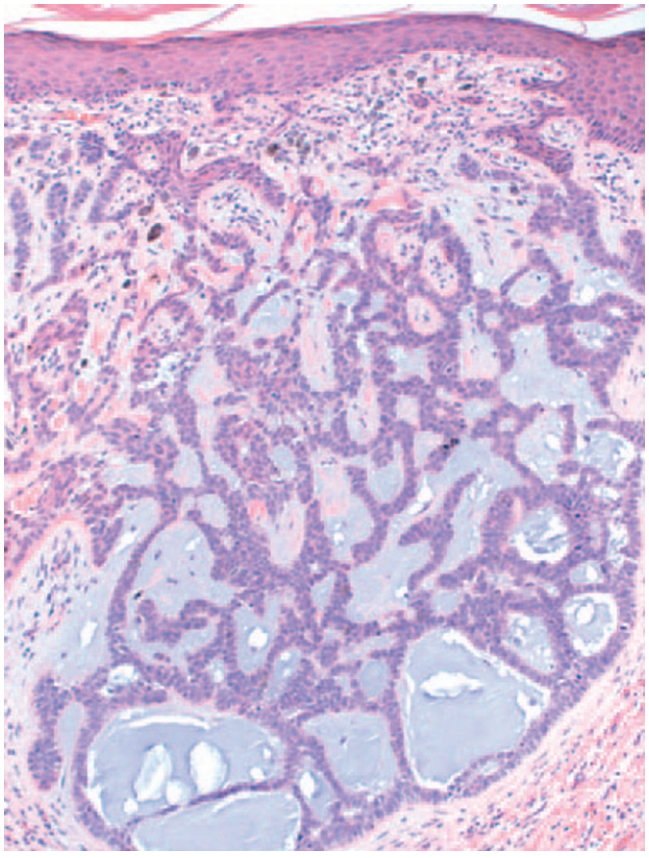

FIGURE 4

Basal cell carcinoma, adenoid variant. This is superficially situated.

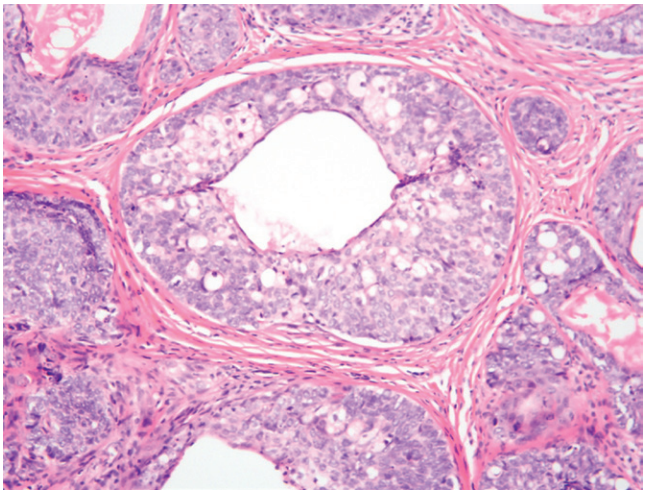

FIGURE 5

Adenocarcinoma with apocrine features. Note the high-grade nuclei.

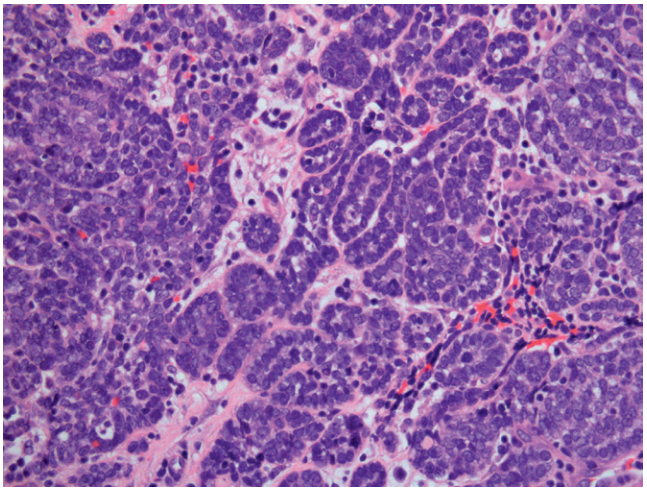

FIGURE 6

Basaloid carcinoma. This tumor consists of a primitive-appearing population of simple glands. It is typically seen in the apex of the vagina or cervix.

BARTHOLIN'S GLAND CARCINOMA

Definition—A malignancy arising in the Bartholin's glands or ducts.

Clinical Features

Epidemiology

- Very rare.
- Incidence of approximately one per million.
- Approximately 75% are squamous carcinomas, and the remainder include adenoid cystic carcinoma; adenocarcinoma, not otherwise specified (NOS); epithelial–myoepithelial carcinoma; and neuroendocrine carcinoma.

Presentation

- Typically present as a mass that may be slow growing.

Prognosis and Treatment

- Excision and node dissection, similar to other forms of vulvar carcinoma.
- Prognosis is dependent on stage and tumor type, with neuroendocrine carcinomas having a poor prognosis and most patients dying within 2 years.

Pathology

Histology

- At low power the tumor fills and expands the background Bartholin's gland ducts and is composed of small, bland cells arranged in two patterns.
- The first pattern is a cribriform, or microcystic, pattern in which nests of cells form small pseudoduct-like spaces with thin, delicate septae.
- The second pattern is characterized by nests, cords, or reticular arrangements of small blue cells set in an eosinophilic hyaline matrix.

Immunopathology (Including Immunohistochemistry)

- Luminal secretions are periodic acid–Schiff (PAS) positive.

Main Differential Diagnosis

- Hidradenoma (will exhibit two cell layers with p63+ basal cells).
- Adenoid variant of basal cell carcinoma (located superficial rather than deep).
- Myoepithelioma (benign mixed tumor).
- Poorly differentiated basaloid carcinomas—usually seen in the vagina and cervix.
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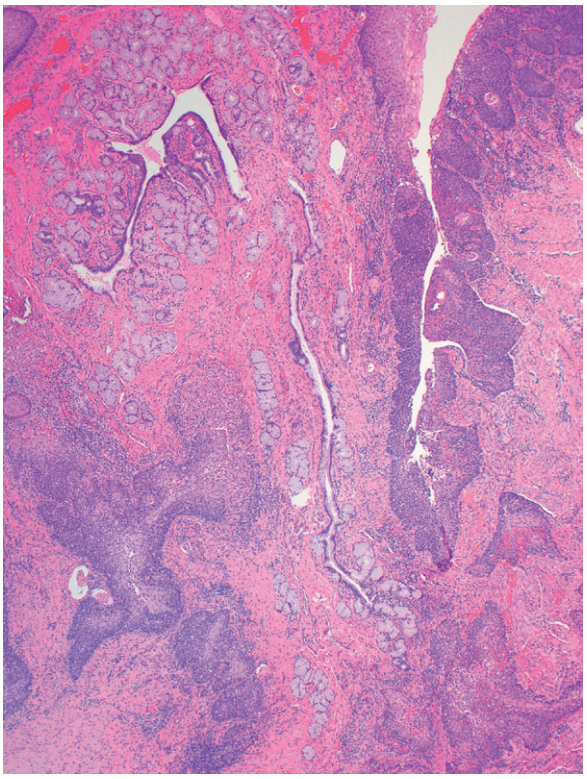

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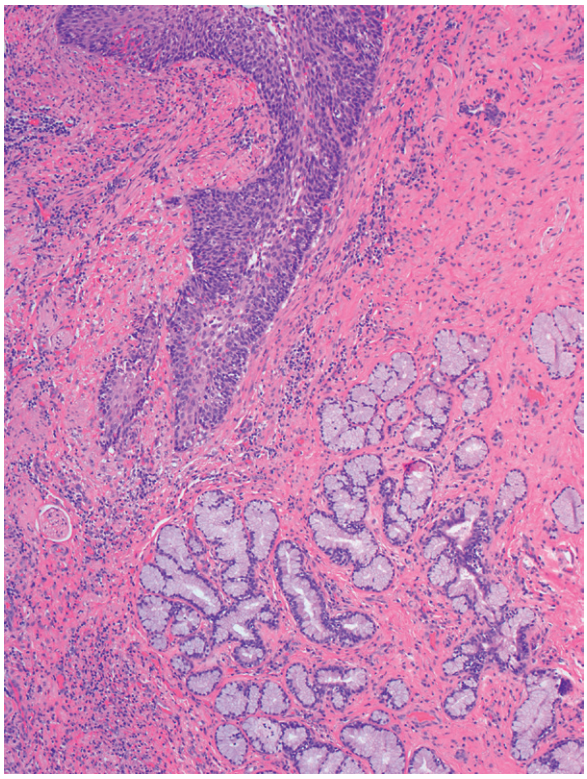

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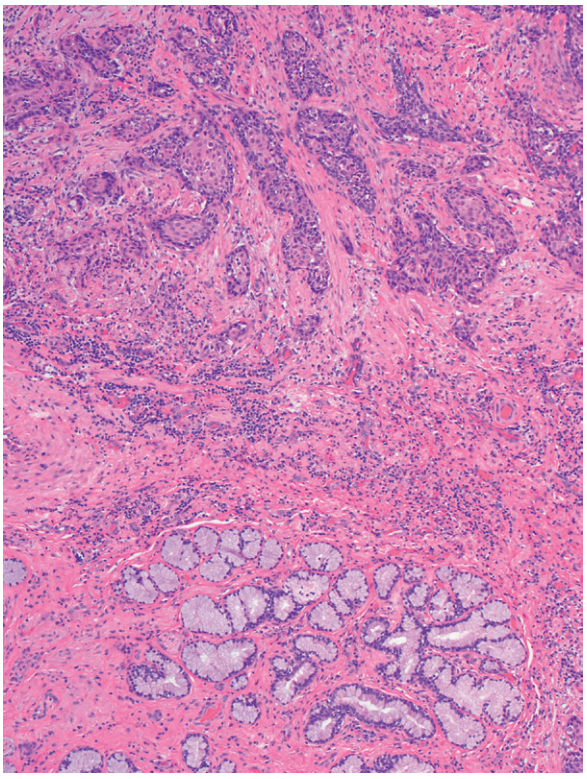

FIGURE 3

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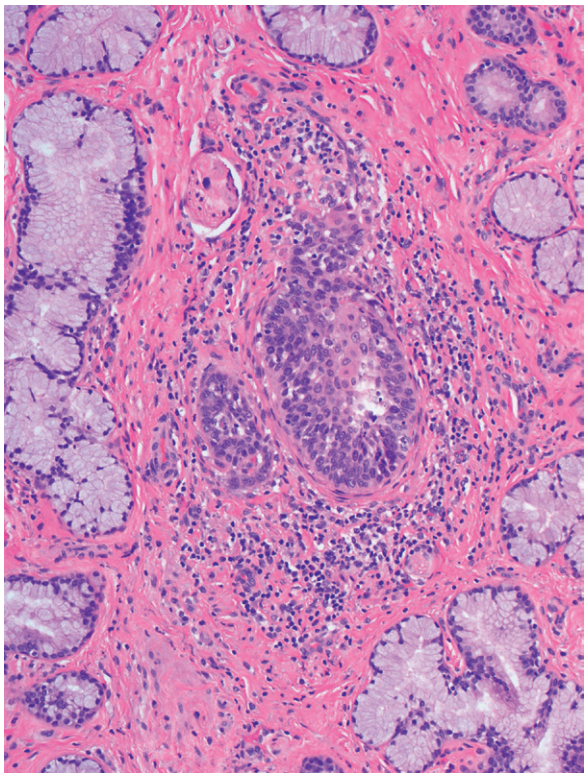

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Basal cell carcinoma, adenoid variant. This is superficially situated.

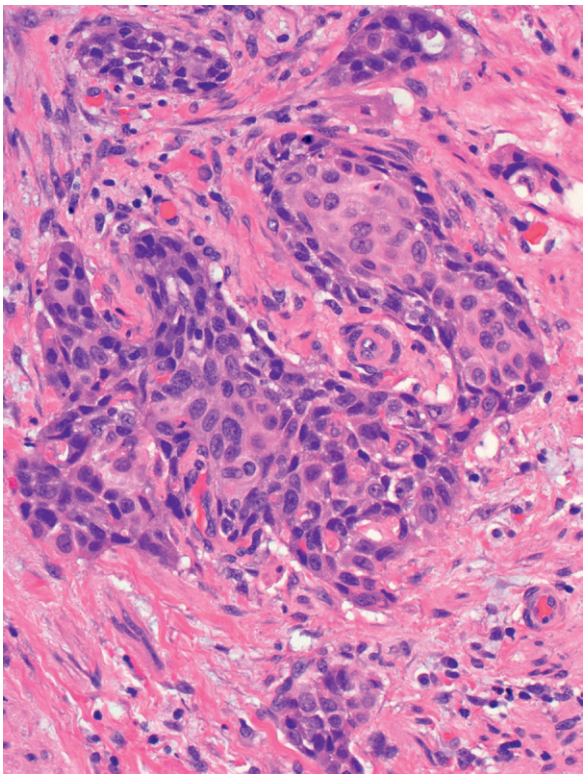


FIGURE 5

Adenocarcinoma with apocrine features. Note the high-grade nuclei.

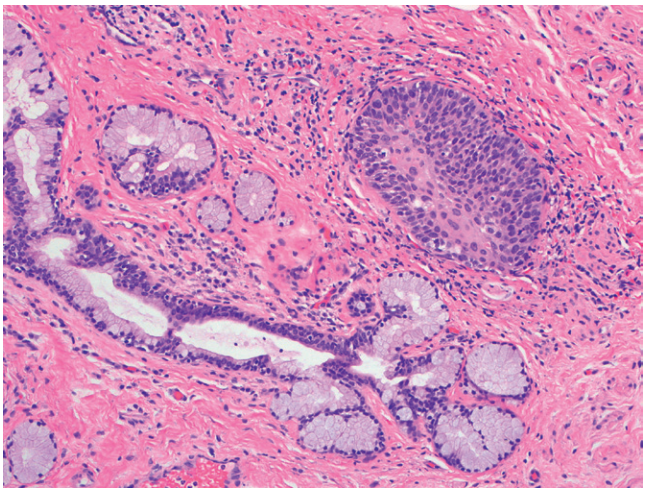


FIGURE 6

Basaloid carcinoma. This tumor consists of a primitive-appearing population of simple glands. It is typically seen in the apex of the vagina or cervix.

CONDYLOMA

Definition—Benign squamous tumors caused by infection of human papillomavirus (HPV). In this chapter condyloma includes two verruciform variants: classic condyloma and fibroepithelial papilloma. A third, seborrheic, keratosis-like condyloma will be discussed separately.

Clinical Features

Epidemiology

- Very common sexually transmitted tumors that are most commonly (~80%) caused by infection of HPV 6 or 11.
- Approximately one million women are affected each year. Disease is most common in young, sexually active women.

Presentation

- Presentation may range from small macules or papules to large lesions that affect the entire vulva.
- Smaller lesions may coalesce.

Prognosis and Treatment

- Excellent; the majority of lesions in patients regress in 6 weeks or less.
- Lesions that progress may be treated with fluorouracil (5-FU), Aldara, cryotherapy, or carbon dioxide laser.

Pathology

Histology

- Classic lesions consist of papillary, "spirelike" proliferations of stratified squamous epithelium supported by fibrovascular stroma.
- Typically acanthosis, parakeratosis, hyperkeratosis, and superficial koilocytosis are present.
- Many lesions, however, will have little to no cytopathic (koilocytic) changes, often termed fibroepithelial papillomas.
- Many "condylomas" will closely resemble seborrheic keratoses seen on skin.
- The combination of papillomatosis and acanthosis is strongly suggestive of the diagnosis of a condyloma.

Immunopathology (Including Immunohistochemistry)

- Ki-67 will show increased proliferative activity in the upper epidermal layers, but it may be subtle.
- Staining with p16 is patchy (as opposed to strong, diffuse staining in high-grade lesions associated with high-risk HPVs).
- In situ hybridization for HPV (low risk) will show nuclear reactivity.

Main Differential Diagnosis

- Fibroepithelial papilloma and seborrheic keratoses are managed (at least in premenopausal women) as variants of condyloma.
- Pseudobowenoid papulosis—an unusual variant of HPV infection (presumably low risk) that manifests with many apoptotic cells.
- Fibroepithelial stromal polyp—lacks the verruciform acanthosis of condyloma.
- Verruciform lichen simplex chronicus—lacks the characteristic cytopathic effect seen in condyloma.
- Vulvar acanthosis with altered differentiation—surface epithelial pallor instead of cytopathic effect.
- Verrucous carcinoma—an important differential when faced with large lesions. Beware the diagnosis of verrucous carcinoma in a young woman.
- Verruciform squamous cell carcinoma—marked atypia is the rule.
- Keratoacanthoma—a cup-shaped acanthosis.
- Classic vulvar intraepithelial neoplasia (VIN)—prominent atypia in at least the basal two thirds of the epithelium.
- Papillary squamous cell carcinoma—high proliferative index and atypia.

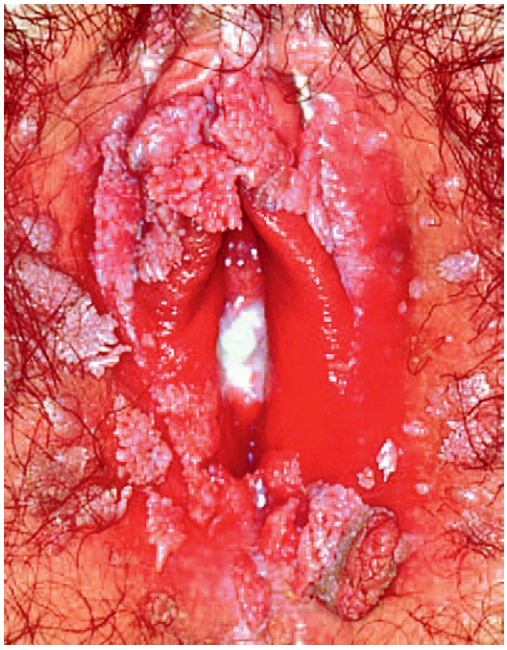


FIGURE 1

Condyloma acuminatum. Multiple small white lesions at the introitus. *(Courtesy Alex Ferenczy.)*

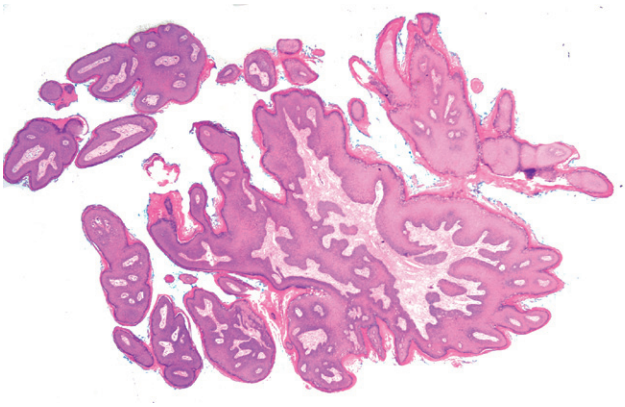


FIGURE 2

Low-power scanning image details the acanthosis and papillomatosis of multiple condylomata.

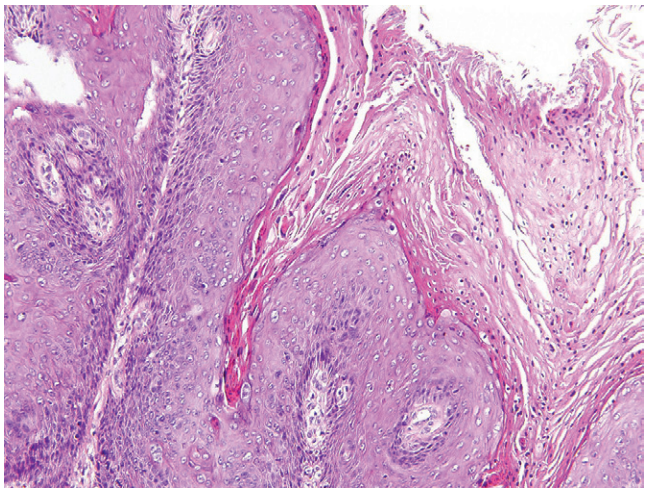


FIGURE 3

Condyloma acuminatum. Prominent "spirelike" projections are present, along with marked acanthosis, hyperkeratosis, and hypergranulosis. Note the lack of conspicuous parabasal nuclear atypia.

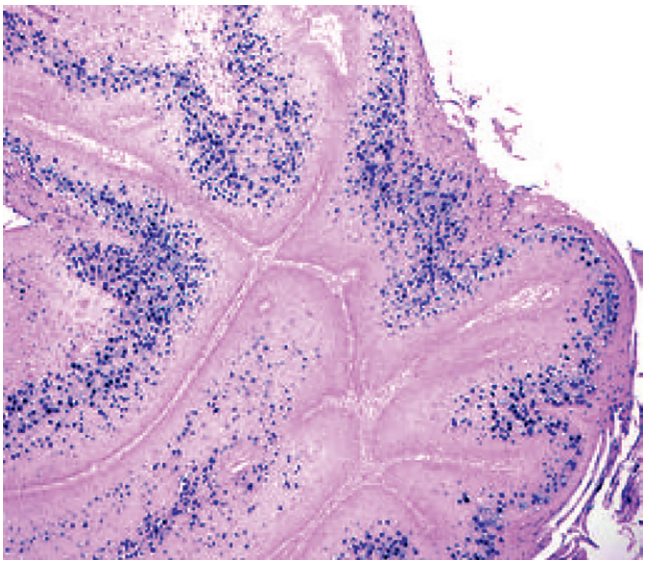


FIGURE 4

Condyloma acuminatum depicting strong nuclear staining for low-risk (corresponding to HPV 6) HPV nucleic acids. *(Courtesy Lisa Jensen-Long, Ventana Medical Systems.)*

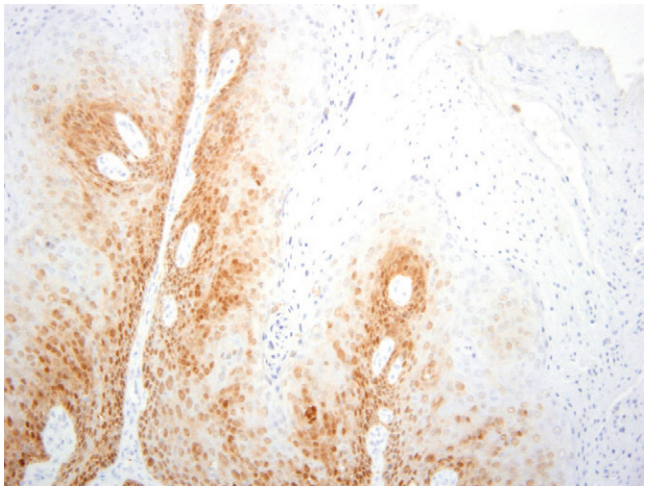


FIGURE 5

Condyloma acuminatum with immunostaining for p16. Note the patchy basal positivity.

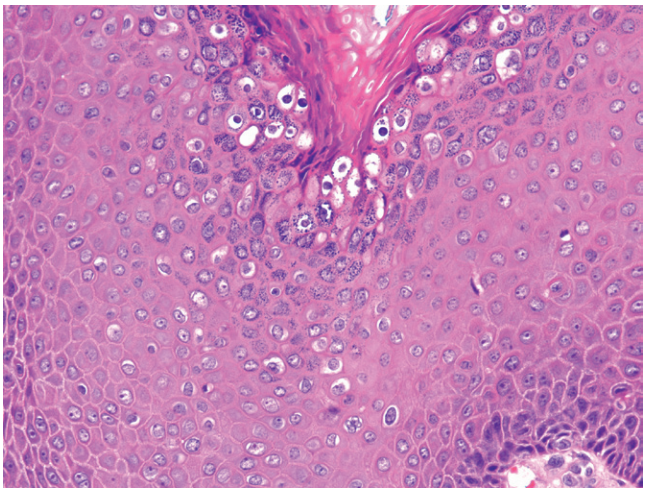


FIGURE 6

This condyloma contains less striking koilocytotic atypia. The acanthosis and papillomatosis are the key features in the diagnosis, since atypia will vary.

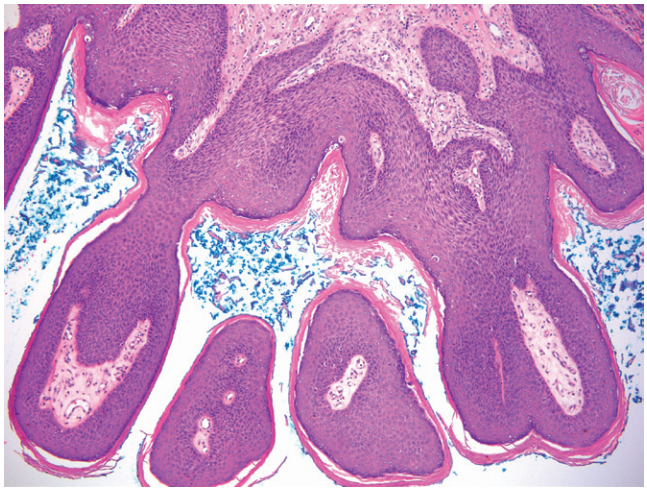


FIGURE 7

Nonkoilocytotic variant of condyloma (fibroepithelial papilloma).

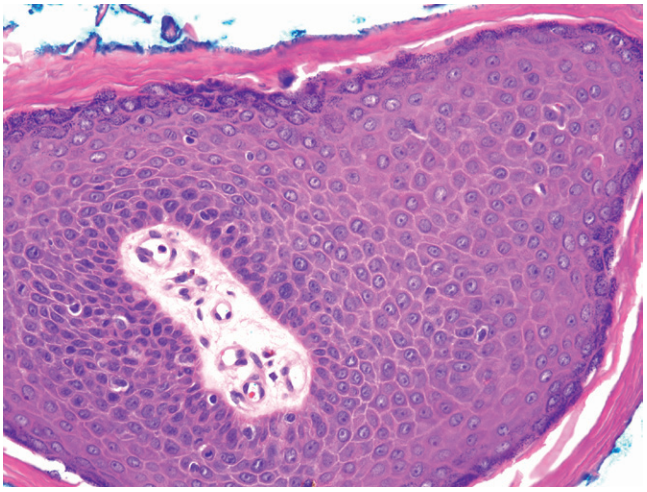


FIGURE 8

At higher magnification, fibroepithelial papilloma displays no atypia. Nonetheless, in this setting it is synonymous with condyloma.

VERRUCIFORM XANTHOMA

Definition—Verruciform xanthoma is a solitary benign verrucous lesion of the vulva that contains foamy histiocytes in the lamina propria.

Clinical Features

- Middle-aged women.
- Solitary wartlike growth on the genital area.
- No relationship to human papillomavirus (HPV).

Pathology

Histology

- Uniform repetitive verruciform architecture.
- Superficial dyskeratosis with variable acute inflammatory changes, resembling but not quite the same as parakeratosis.
- The hallmark is numerous foamy histiocytes in the stroma of the papillae.
- Absence of koilocytosis or surface atypia.

Immunohistochemistry

- Not applicable.

Differential Diagnosis and Pitfalls

- Condyloma acuminatum, including seborrheic keratosis variants. This entity will manifest with surface atypia.
- Verruciform lichen simplex chronicus—prominent keratohyalin granules and absence of xanthoma cells.
- Candida infection due to the focal surface inflammatory exudate, foam cell absent.
- Psoriasis due to the small plaques of dyskeratotic epithelial cells, foam cell absent.
- Granular cell myoblastoma. This lesion may be associated with epithelial hyperplasia, but the granular cells can easily be distinguished from foamy histiocytes.
- Verrucous carcinoma and its precursor verruciform acanthosis are usually more irregular in growth and lack the foamy histiocytes.

Clinical Management/Outcome

- Verruciform xanthoma is a benign condition that is not infectious and in rare cases will recur following removal.

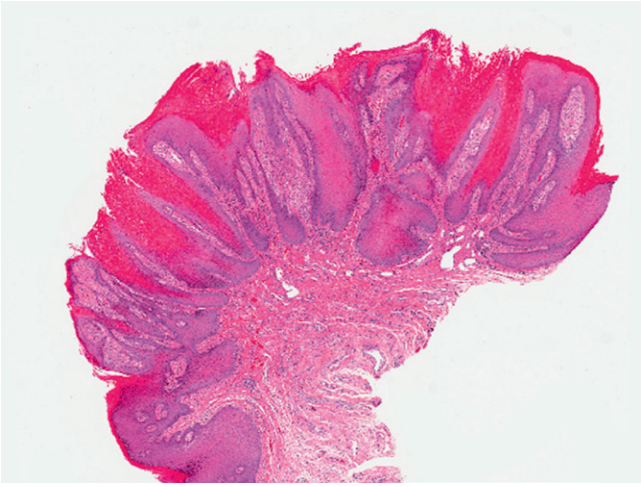


FIGURE 1

Verruciform xanthoma at low magnification. Note the regularity of the verrucous architecture and eosinophilic layers of pseudoparakeratosis (dyskeratosis) on the surface.

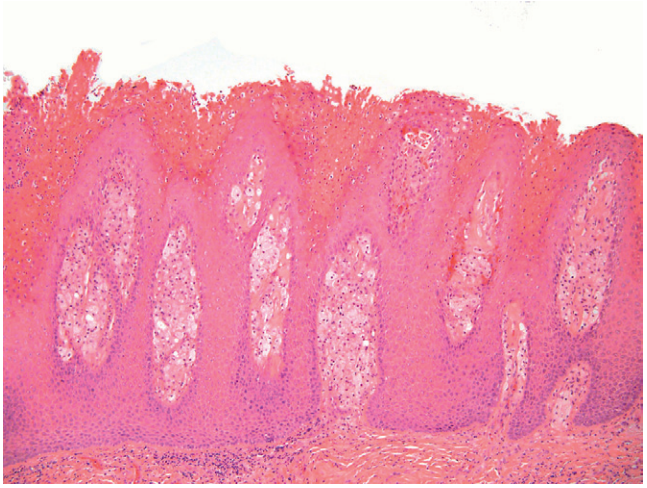


FIGURE 2

At medium magnification the dense layer of surface dyskeratosis is visible, resembling that seen in psoriasis.

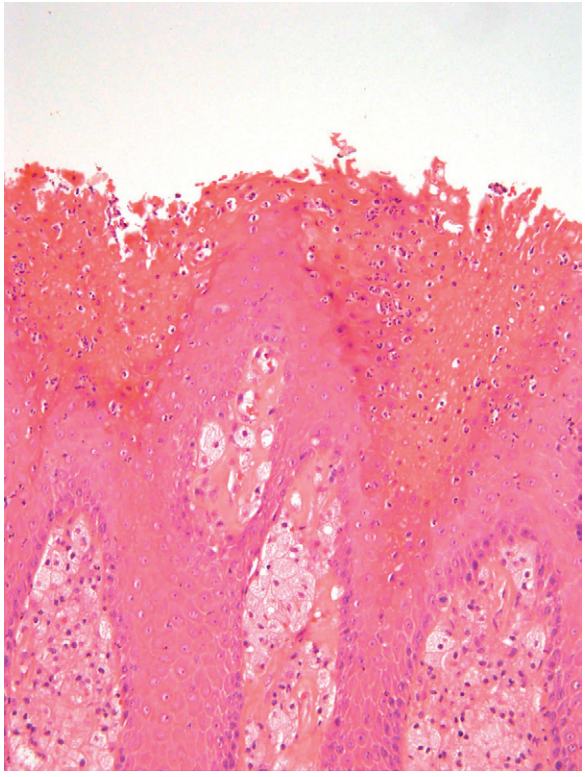


FIGURE 3

At higher magnification the foamy histiocytes in the dermis can be seen.

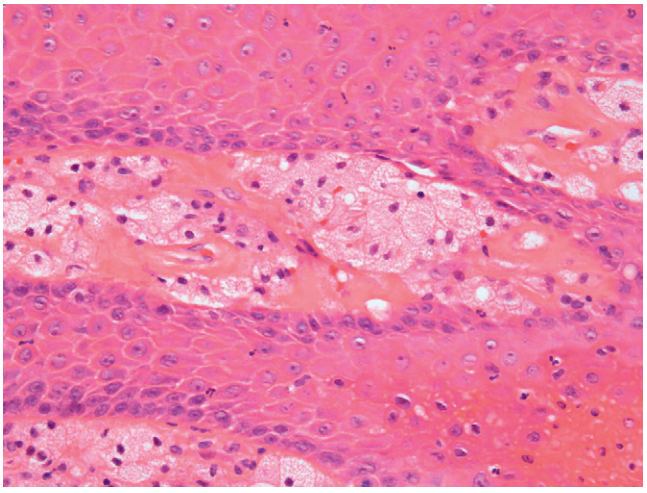


FIGURE 4

High magnification of the foamy histiocytes.

WARTY DYSKERATOMA

Definition—A solitary acanthotic and dyskeratotic epidermal proliferation.

Clinical Features

Epidemiology

- Rare disease, most often seen in the head and neck regions.
- Very rarely involves the vulva.
- Not an inherited condition (as opposed to Darier's disease).

Presentation

- Solitary keratotic papule or nodule.
- May be umbilicated.

Prognosis and Treatment

- Prognosis is excellent as these are benign lesions.
- Excision is adequate treatment.

Pathology

Histology

- Acanthotic and hyperkeratotic plaques.
- Dyskeratosis is frequently present, presenting as corps ronds.
- Parakeratosis with retained nuclei (grains of Darier) may be present as well.
- Acantholysis can occasionally lend a prominent pseudopapillary architecture.
- Warty dyskeratoma frequently has a more pronounced papillary architecture than Darier's disease.

Immunopathology (Including Immunohistochemistry)

- Immunofluorescence is negative.

Main Differential Diagnosis

- Darier's disease—multiple lesions, familial.
- Acantholytic hyperkeratosis—does not have the prominent grains of Darier.
- Verruciform vulvar intraepithelial neoplasia (VIN)—exhibits marked atypia.
- Viral warts (condyloma)—lack the prominent grains of Darier and acantholysis.

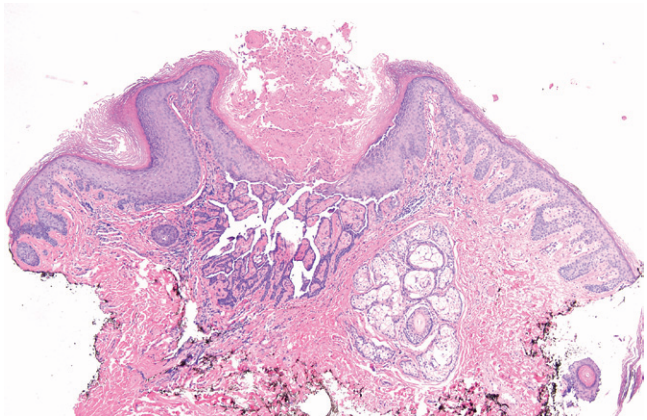


FIGURE 1

Low magnification of a warty dyskeratoma. Note the cup-shaped lesion with dense hyperkeratosis.

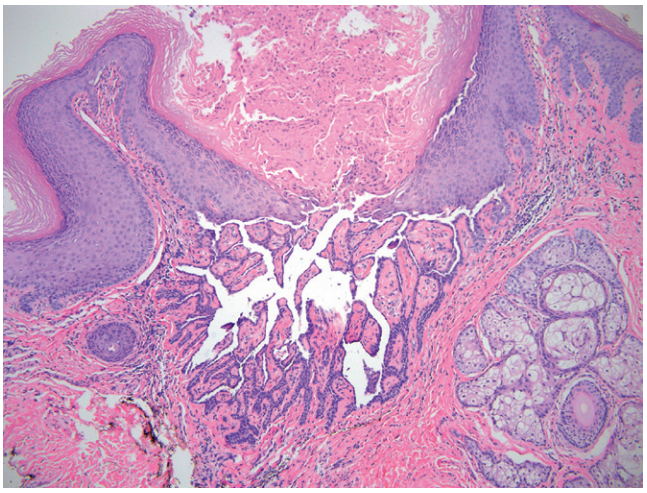


FIGURE 2

Higher magnification reveals the striking acantholysis, revealing the bare dermal papillae in a pseudopapillary conformation.

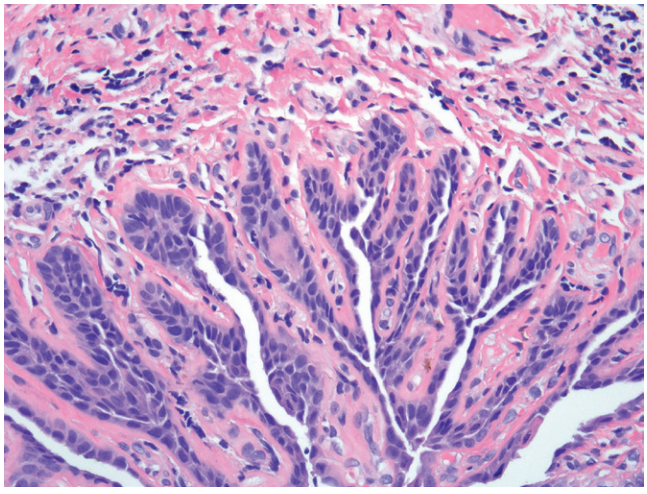


FIGURE 3

Higher magnification of the pseudopapillary appearance at the interface of the acantholysis.

FIBROEPITHELIAL STROMAL POLYP

Definition—Benign polypoid vulvovaginal lesions of young- to middle-aged women with a striking array of histologic appearances, often associated with pregnancy.

Clinical Features

Epidemiology

- Young- to middle-aged women.
- Multiple lesions are associated with pregnancy.
- Very rare before menarche.

Presentation

- Pedunculated, polypoid, or occasionally fronded lesion(s) of the vulva, vagina, or (occasionally) the cervix.
- Size varies considerably from small (<1 cm) to very large (>10 cm).

Prognosis and Treatment

- Excellent.
- Complete excision is advised as lesions may recur if incompletely excised.

Pathology

Histology

- Bland overlying squamous epithelium.
- Central fibrovascular core, with thick-walled medium-sized vessels.
- Stellate multinucleate stromal cells that are particularly prominent at the stromal–epithelial interface and a margin that blends imperceptibly with surrounding soft tissue.
- Particularly during pregnancy, the stroma may be more cellular, with strikingly pleomorphic stromal cells and atypical mitotic figures (pseudosarcoma botryoides).

Immunopathology (Including Immunohistochemistry)

- Desmin positive; estrogen and progestin receptors are variable.

Main Differential Diagnosis

- Aggressive angiomyxoma—these are deeper lesions with a zone of normal tissue separating the mucosa, plus a distinct vascular pattern.
- Condyloma—there should be acanthosis and variable verruciform epithelial growth.

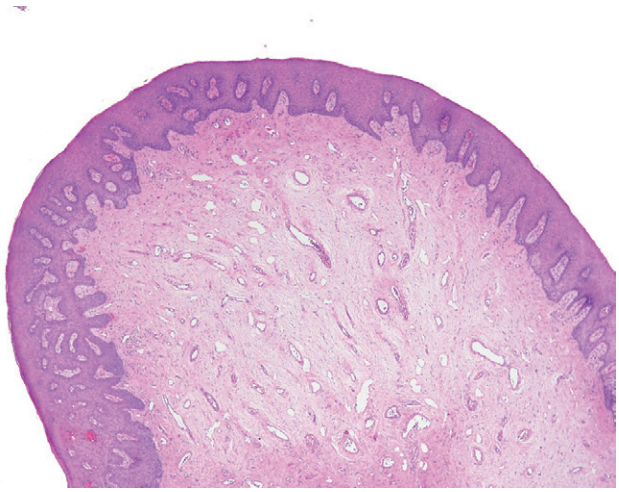


FIGURE 1

Fibroepithelial stromal polyp. A polypoid projection with an unremarkable, albeit acanthotic, squamous lining. The stroma is relatively hypocellular, and there are numerous small- to medium-sized vessels present.

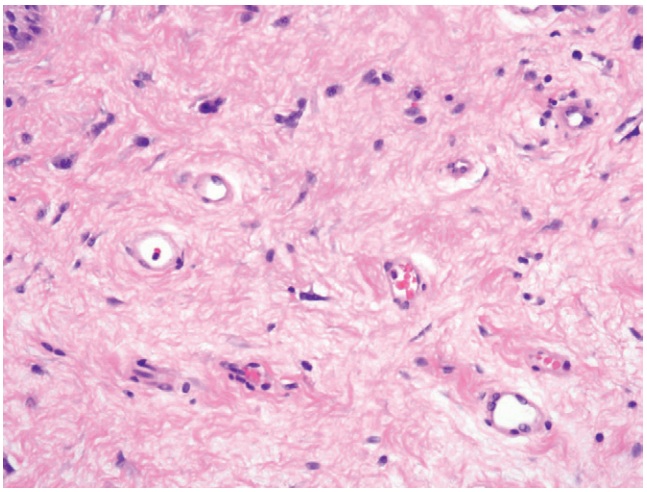


FIGURE 2

Fibroepithelial stromal polyp. Paucicellular stroma with small, bland, stromal cells. Numerous small vessels are present.

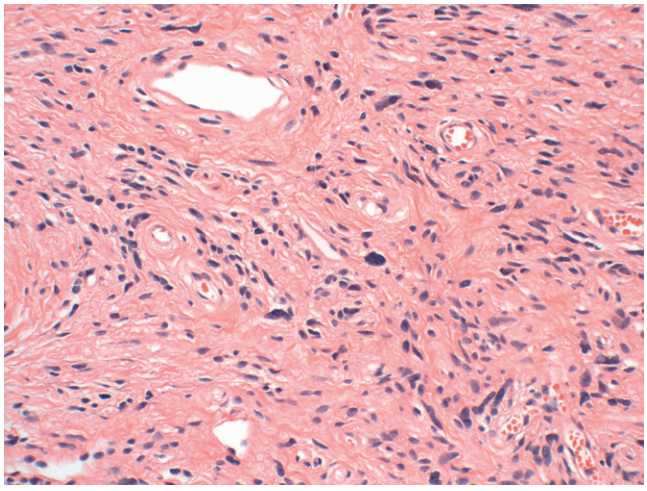


FIGURE 3

Fibroepithelial stromal polyp. Occasional polyps may be more hypercellular or contain atypical stromal cells. These are not signs of malignancy.

SEBORRHEIC KERATOSIS

Definition—A benign, warty proliferation of keratinocytes that is frequently pigmented and often associated with low-risk human papillomavirus (HPV) (types 6 and 11).

Clinical Features

Epidemiology

- Can be seen in all age groups.
- A large percentage are associated with HPV types 6 and 11, implying a variant of condyloma (or low-grade squamous intraepithelial lesion). Presumably a subset of HPV-negative lesions also exists.

Presentation

- Maculopapular lesions that appear "stuck on."
- Seborrheic keratosis (SK) may be skin colored or hyperpigmented.
- Usually asymptomatic, although some patients report pruritus or irritation.
- Lesions range in size from several millimeters to several centimeters.

Prognosis and Treatment

- Excellent prognosis.
- Conservative excision is curative but not required.

Pathology

Histology

- A benign epidermal proliferation characterized by acanthosis with hyperkeratosis and pseudohorn cysts, which are invaginations of the epithelial surface.
- The lesions appear raised and are thickened compared with the adjacent normal epithelium.
- The base is flat and exhibits the so-called string sign; one can imagine holding a piece of string taut along the base.
- There is a variable amount of melanin pigment; in hyperpigmented examples most of the pigment has been taken up by the lesional keratinocytes.
- A range of epithelial architectural patterns have been identified in SK, including clonal, reticular, hyperkeratotic, and verrucous. These variants are important only to recognize the variety of appearances possible in SK.
- Reactive epithelial changes are common in traumatized lesions and can include reactive cytologic atypia, dyskeratosis, spongiosis, and increased mitoses.

Diagnostic terms: In younger individuals where the lesion presents as a presumed condyloma the diagnosis of "condyloma with features of SK" is appropriate. For SKs presenting with minimal acanthosis or wartlike features, a diagnosis of unqualified "SK" is appropriate.

Immunopathology (Including Immunohistochemistry)

- p16 immunostains will be patchy or negative, in keeping with low-risk HPV.
- KI67 (MIB1) stains will usually highlight cells in the upper epithelial layers similar to other variants of condyloma.

Main Differential Diagnosis

- Condyloma—typically contains koilocytotic atypia but overlaps etiologically with SK.
- Nevus (epidermal)—linear in distribution and can be seen in young patients.
- Vulvar intraepithelial neoplasia, low grade (VIN I) or "bowenoid dysplasias"—some bland-appearing HPV 16 infections of the vulva may overlap with SK. Typically staining for p16 will be strongly positive in such lesions in contrast to SK.

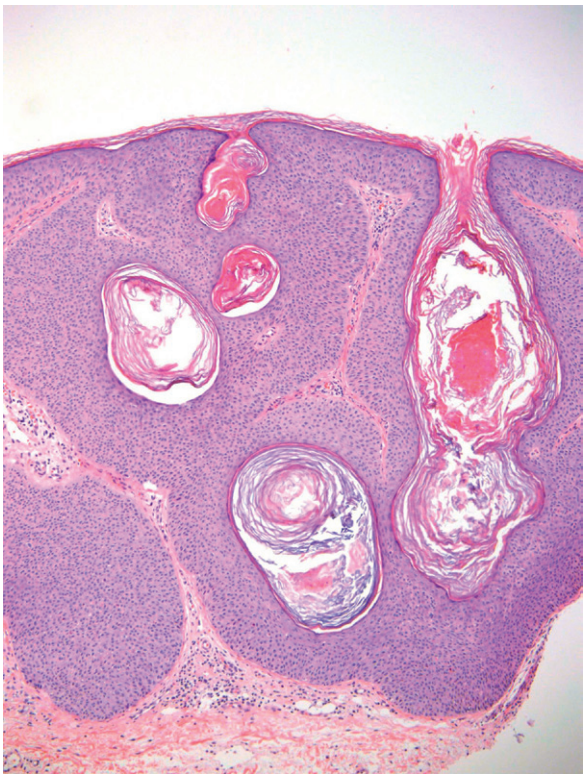


FIGURE 1

Seborrheic keratosis. Prominent acanthosis with pseudohorn cysts.

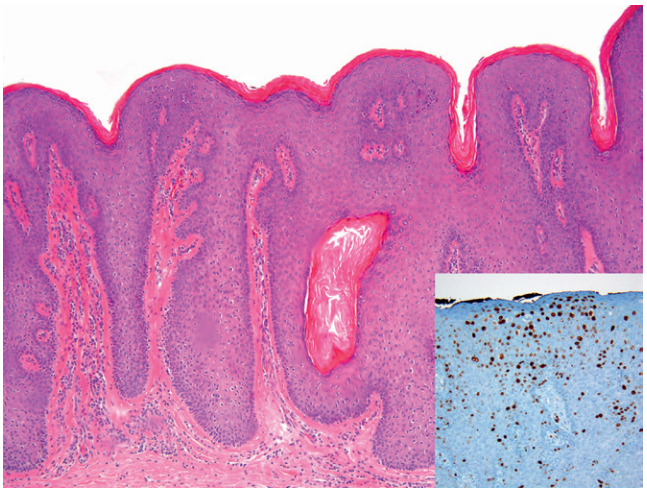


FIGURE 2

Seborrheic keratosis. Slightly more subtle variant but discrete acanthosis. MIB1 immunostaining *(inset)* depicts numerous positive nuclei in the upper epithelial layers.

PSEUDOBOWENOID PAPULOSIS

PITFALL

Definition—An unusual variant of condyloma that is marked by a striking increase in apoptosis in the upper epithelial layers.

Clinical Features

Epidemiology

- Occurs in the same demographic groups as typical condyloma; however, disease is secondary to more uncommon variants of human papillomavirus (HPV) such as types 13 and 32.

Presentation

- Small to large macular or papular lesions.

Prognosis and Treatment

- Favorable, similar outcome as seen in traditional condyloma acuminata.

Pathology

Histology

- The upper epithelial layers display a striking increase in apoptotic cells.
- These cells are in different stages of degeneration, ranging from chromatin dispersal (which may appear similar to a mitotic figure [i.e., pseudomitoses]) to small hypereosinophilic (degenerated) keratinocytes.
- Koilocytic atypia is usually not seen.

Diagnostic terminology: Low-grade squamous intraepithelial lesion (condyloma/VINI).

Immunopathology (Including Immunohistochemistry)

- Ki-67 may be increased in the upper epidermis.
- Staining for p16 is patchy.

Main Differential Diagnosis

- Fibroepithelial papilloma or condyloma—these lesions do not contain apoptosis.
- Seborrheic keratosis—may resemble pseudobowenoid papulosis but lacks apoptosis and pseudomitoses.
- Classic vulvar intraepithelial neoplasia (VIN)—overlaps histologically because of the apoptosis, but the remainder of the keratinocytes will display atypia, unlike pseudobowenoid papulosis.

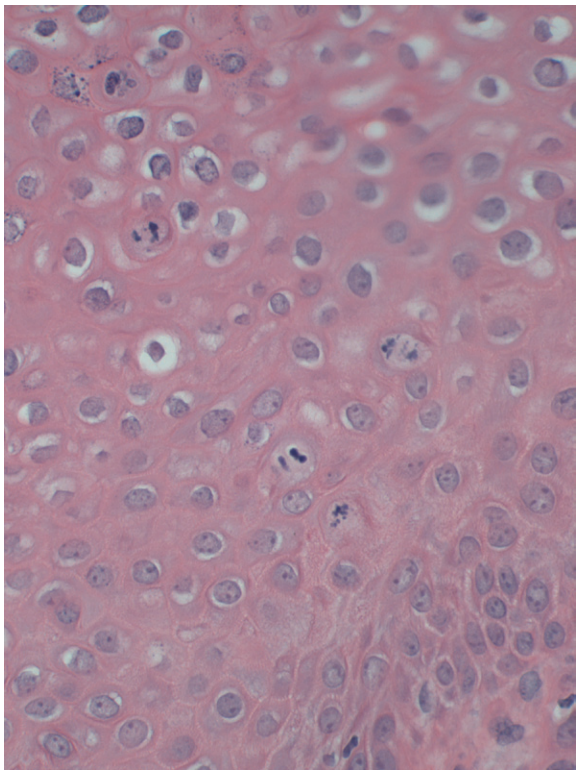


FIGURE 1

Pseudobowenoid papulosis. Note the presence of some koilocytes interspersed with pseudomitoses. The remainder of the epithelial cells show minimal atypia.

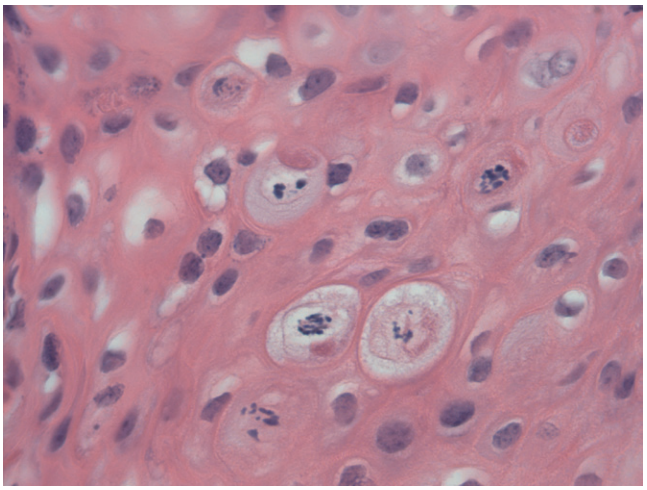


FIGURE 2

Pseudobowenoid papulosis. Apoptotic bodies in different stages of degradation, some of which resemble mitotic figures. The centrally clumped chromatin is surrounded in some by a collapsing cell membrane with another space between the membrane and the interface with the adjacent cells. This creates a targetlike appearance.

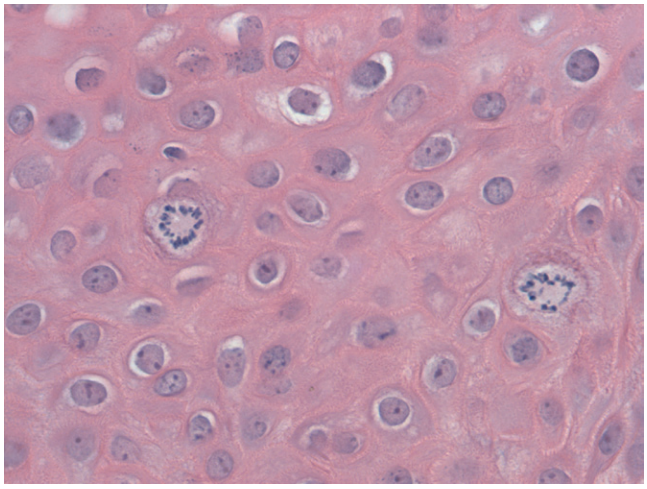


FIGURE 3

Pseudobowenoid papulosis. A few apoptotic cells with uniformly circumferentially dispersed chromatin.

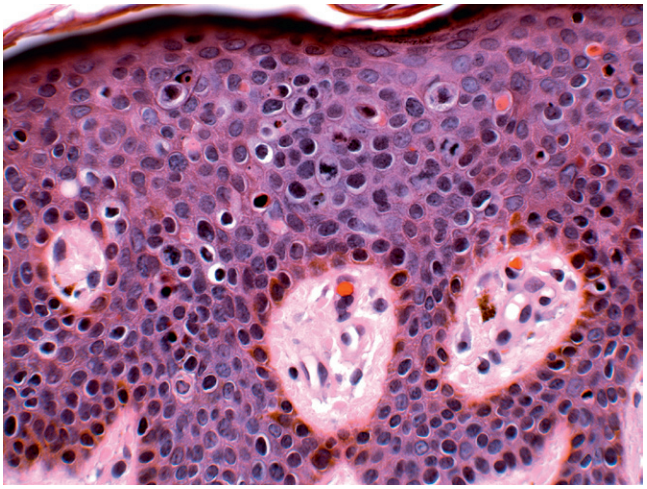


FIGURE 4

This variant of VIN contains a mild to moderate degree of diffuse nuclear atypia with some apoptotic cells in the upper layers and may be confused with the pseudobowenoid papulosis variant of condyloma.

FLAT CONDYLOMA (VIN1)

Definition—Flat condyloma is defined as a macular variant of condyloma that falls within the category of low-grade squamous intraepithelial lesion (LSIL) and displays an identical distribution of atypia as its exophytic counterpart. In contrast to exophytic condylomas, these flat lesions are more likely to be associated with high-risk human papillomavirus (HPV) types, although the majority do not contain HPV 16 and the regression rate is presumably high. Another term for these lesions has been "VIN1," although this term is somewhat problematic. Currently they are under the category of LSILs of the vulva, similar to exophytic condylomas and their variants.

Clinical Features

- Reproductive age, sexually active women.
- Small papular or raised vulvar lesions, similar to condyloma.
- Acetowhite.

Pathology

Histology

- Discrete acanthosis.
- Variable cytopathic effect (koilocytosis).
- Mild to moderate hypercellularity in the lower epithelial cell layers.
- In some instances cytopathic effect is minimal, and the lesion resembles a macular seborrheic keratosis.

Immunohistochemistry/Molecular Findings

- Ki-67 expression is moderate, and staining in the upper epithelial layers is present due to expression of viral genes in superficial (koilocytotic) cell nuclei.
- p16ink4 expression is variable and not helpful diagnostically.
- A wide range of HPVs, with HPV 16 present in less than 15%.

Differential Diagnosis and Pitfalls

- Koilocytotic (warty) vulvar intraepithelial neoplasia II (VIN II) will have greater atypia in the lower epithelial layers.

Clinical Management/Outcome

- Most flat condylomas are managed conservatively by observation or with topical (Aldara) therapy.

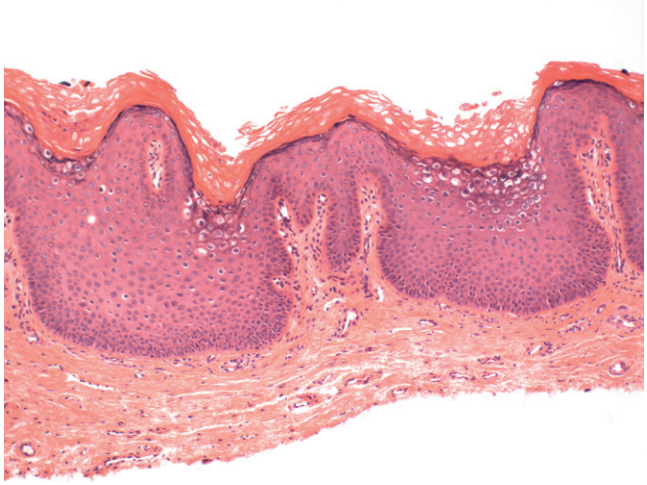


FIGURE 1

Flat condyloma (LSIL) with koilocytotic atypia. Note the basal hypercellularity without appreciable atypia.

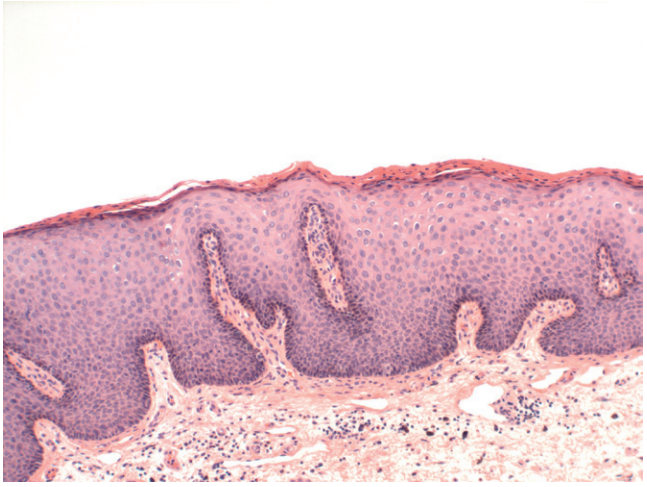


FIGURE 2

A flat condyloma (LSIL) with no evidence of koilocytotic atypia. There is prominent hypercellularity, as well as parakeratosis, present within the basal aspect.

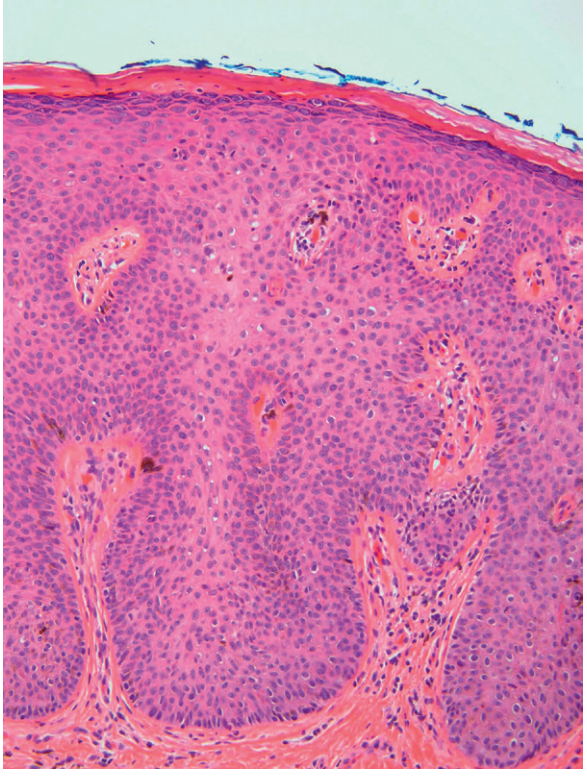


FIGURE 3

A flat lesion resembling seborrheic keratosis, also within the category of LSIL.

CLASSIC (USUAL) VULVAR INTRAEPITHELIAL NEOPLASIA

Definition—Classic (usual) high-grade squamous intraepithelial lesions of the vulva are defined as full-thickness or near full-thickness atypias associated with high-risk or carcinogenic human papillomavirus (HPV) infections, principally HPV 16.

Clinical Features

- A wide age range, from second to eighth decade, predominating in the fourth and fifth decades.
- From papular to verrucous in presentation, pigmented or nonpigmented.
- Increased frequency in immunosuppressed women.
- Acetowhite in the mucosal surfaces.

Clinical Management/Outcome

- Outcome is strongly associated with age, with the risk of both progression and coexistence of invasion (20%) associated with postmenopause.
- Spontaneous regression is associated with pigmented lesions, younger age, and pregnancy.
- Smoking and immunosuppression both are associated with persistence and resistance to therapy.
- Local excision is preferred, followed by laser or in small lesions topical imiquimod (Aldara).

Pathology

Histology

- Increased cellularity with hyperchromasia and a high cell density.
- Anisokaryosis, polychromasia, and coarse chromatin, usually involving at least the lower two thirds of the epithelial thickness.
- Variable maturation ranging from minimal (basaloid) to conspicuous with pseudokoilocytosis (warty).
- Abnormal mitoses (multipolar, irregular, dispersed).
- Pigmentation (variable).

Diagnostic terminology: High-grade squamous intraepithelial lesion (vulvar intraepithelial neoplasia [VIN] II and III).

Immunohistochemistry

- Ki-67 expression is usually near full thickness due to loss of cell cycle control throughout the epithelium but may be less pronounced in some cases.
- p16ink4 expression is usually diffuse and linear in the immature component and typically both cytoplasmic and nuclear.
- p53 staining is negative or patchy (nuclear).

Differential Diagnosis and Pitfalls

- Seborrheic keratosis—minimal nuclear atypia, negative for p16.
- Pseudobowenoid papulosis—apoptotic cells (pseudomitoses) may mimic mitotic activity, but basal layers exhibit minimal atypia, negative for p16.
- Multinucleate atypia—polynucleation, which is uncommon in classic VIN; low proliferative index; negative for p16.

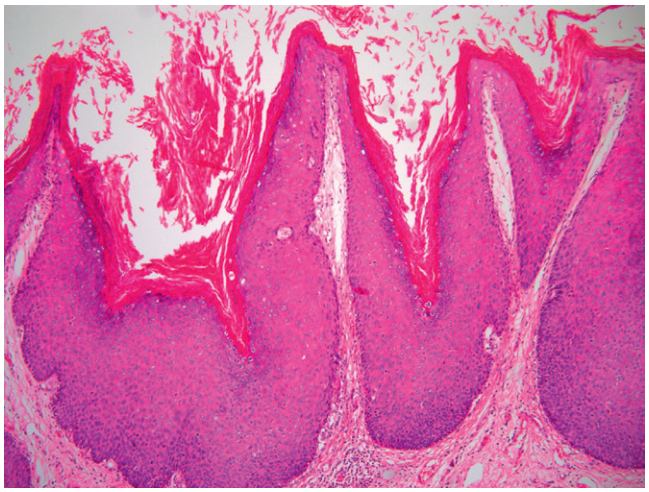


FIGURE 1
Classic VIN. This case exhibits a verruciform or warty pattern.

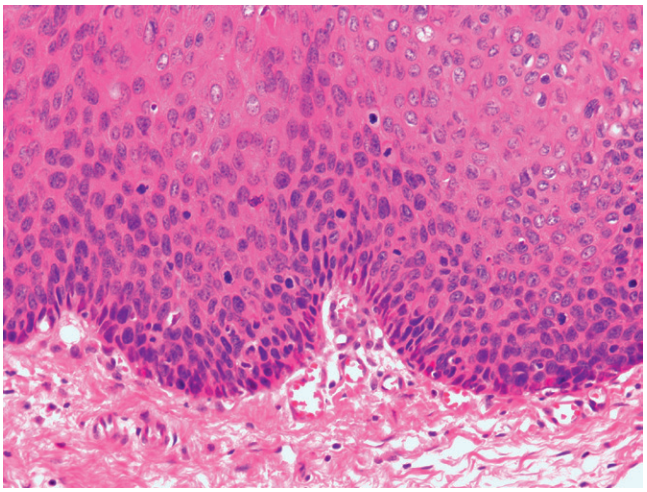


FIGURE 2
Classic VIN. At higher magnification the immature cells show marked atypia.

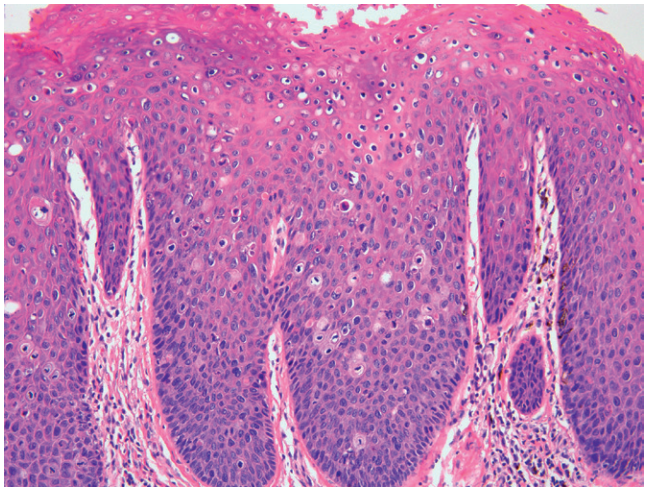


FIGURE 3
Classic VIN. This is a slightly less mature variant of classic VIN.

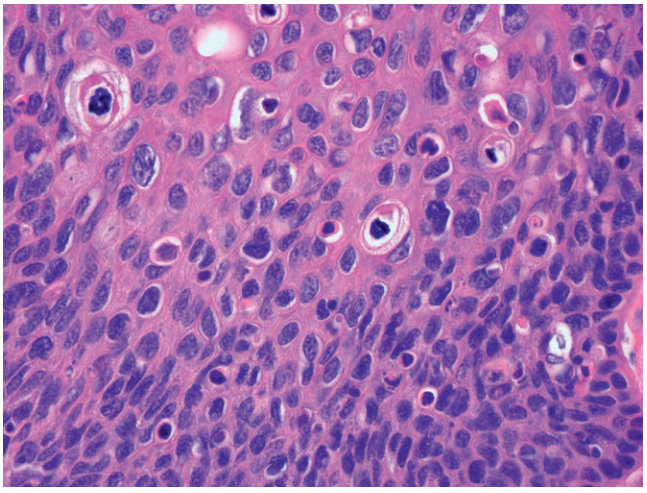


FIGURE 4
Classic VIN. Note the prominent apoptosis and individual cell keratinization.

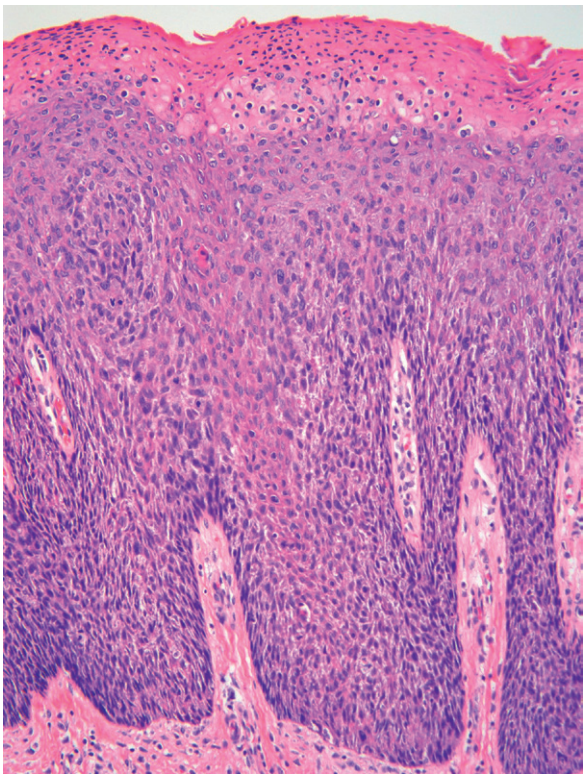


FIGURE 5

Classic VIN. This variant is rather homogeneous in appearance.

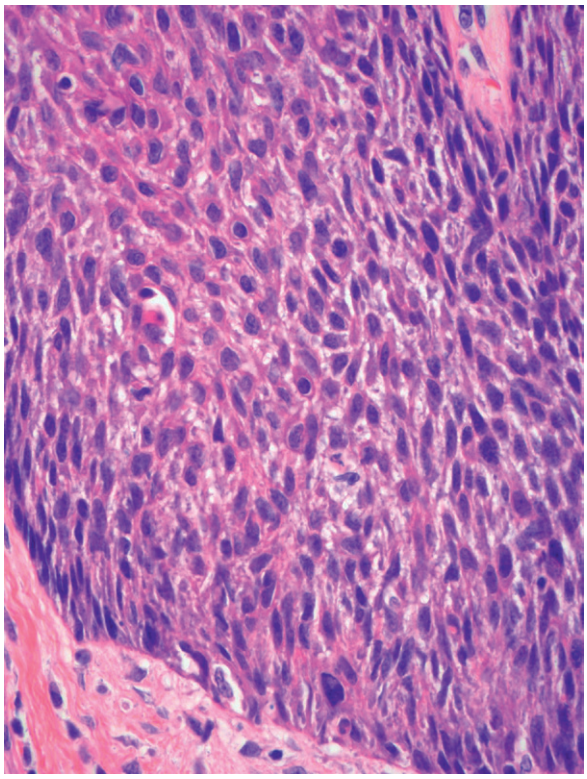


FIGURE 6

Classic VIN. At high power the cells are uniform but in this case uniformly abnormal.

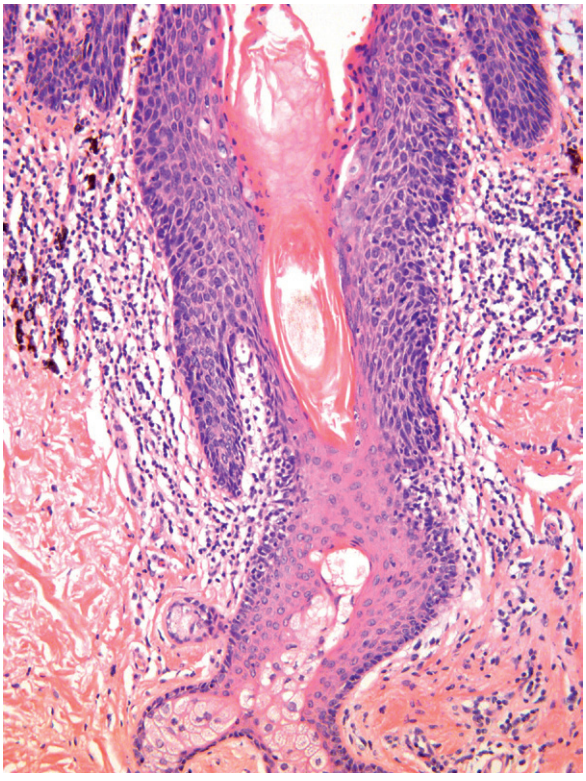


FIGURE 7

Classic VIN. An example of adnexal involvement.

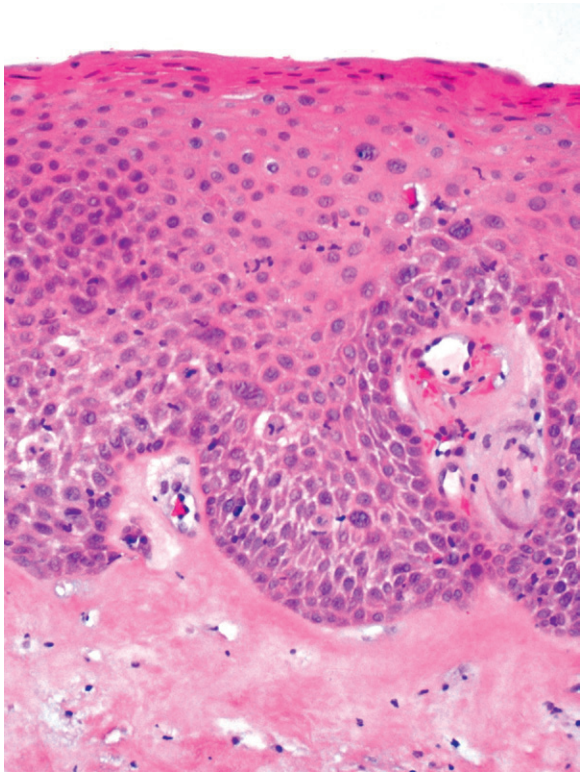


FIGURE 8

Classic VIN. This HPV 16–positive example was associated with lichen sclerosus.

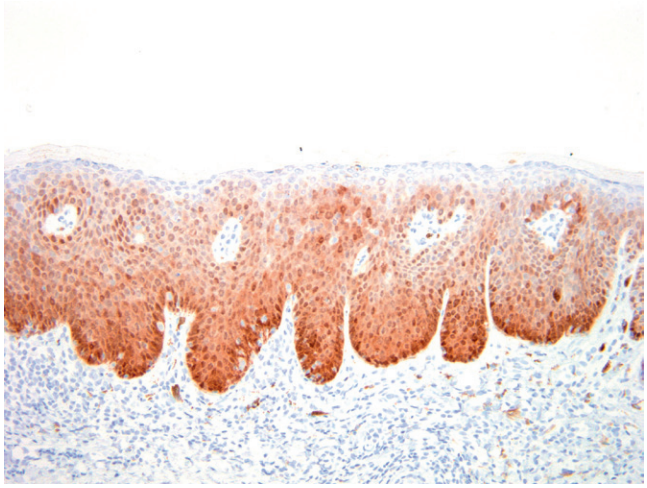


FIGURE 9

Classic VIN. Immunohistochemical staining for p16 shows both nuclear and cytoplasmic positivity in the immature component.

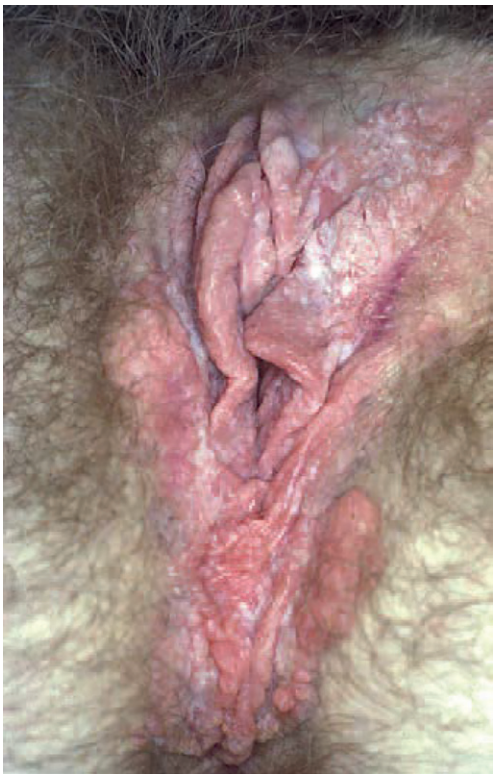


FIGURE 10

Classic VIN presenting as raised, thickened mucosa with hyperkeratosis.

CLASSIC VULVAR INTRAEPITHELIAL NEOPLASIA WITH LICHEN SIMPLEX CHRONICUS

PITFALL

Definition—Human papillomavirus (HPV)-associated squamous intraepithelial lesion (SIL) with superimposed changes of lichen simplex chronicus (LSC).

Clinical Features

Epidemiology

- Affects a fraction of the patients with classic vulvar intraepithelial neoplasia (VIN).

Presentation

- Similar to that of classic VIN.
- The plaques, papules, and scaly skin changes seen in LSC are invariably present.

Prognosis and Treatment

- Similar to that of classic VIN.

Pathology

Histology

- Acanthosis with parakeratosis and prominent keratohyalin granules may initially present some confusion because it will be associated with reduced atypia in the upper epithelial layers.
- Variable amounts of chronic inflammatory cells are present within the dermis.
- Squamous cell atypia is mild to moderate and typically more basal in location, mimicking the findings seen in differentiated VIN. In some cases the degree of atypia may be quite subtle.
- Areas with histology more typical of classic VIN are variably present.

Diagnostic terminology: High-grade squamous intraepithelial lesion (HSIL) (or low-grade squamous intraepithelial lesion [LSIL]) with superimposed LSC. If uncertain as to lesion grade, simply classify as SIL with superimposed LSC and comment that the lesion is of intermediate grade (VIN I–VIN II).

Immunopathology (Including Immunohistochemistry)

- p16 will stain cells diffusely within the basal compartment, with maturing cells in the upper epidermal layers showing a lack of staining.
- Ki-67 demonstrates increased labeling but will be more prominent in the basal epithelial layers.
- p53 immunostains will be weak and patchy.

Main Differential Diagnosis

- LSC—prominent basal atypia is not seen.
- Differentiated VIN—can be more difficult. Immunostaining for p16 (strong) and p53 (weak) may be helpful.

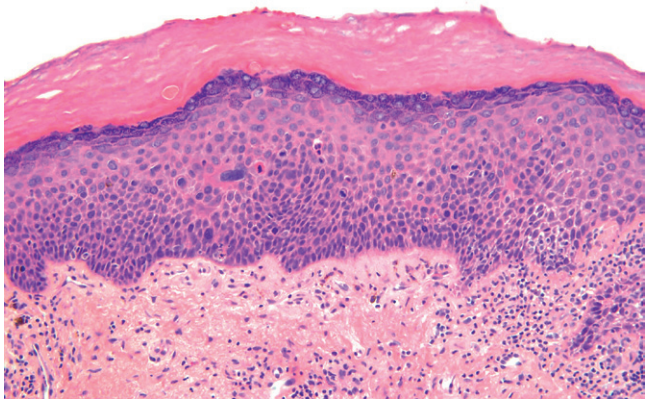


FIGURE 1

Classic VIN with superimposed LSC. Conspicuous hyperkeratosis and hypergranulosis are often present. Expansion of the basal layer and prominent atypia are similar to classic VIN in this case, which would be easily distinguished from differentiated VIN or LSC alone. Note the dermal inflammatory infiltrate.

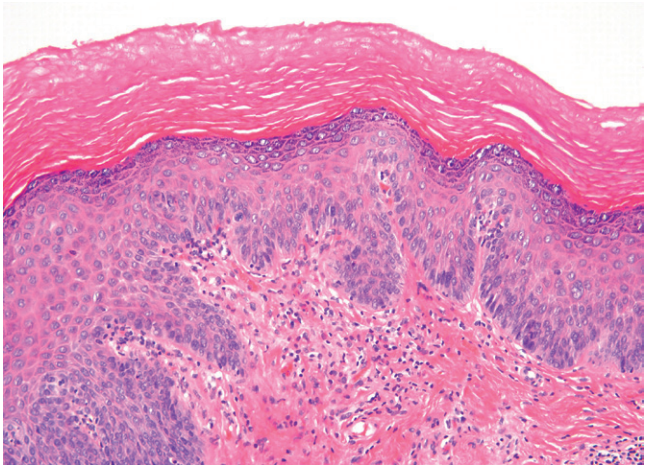


FIGURE 2

A more subtle example of classic VIN with superimposed LSC. Note how much more subtle the atypia is in this case. There is prominent hypergranulosis.

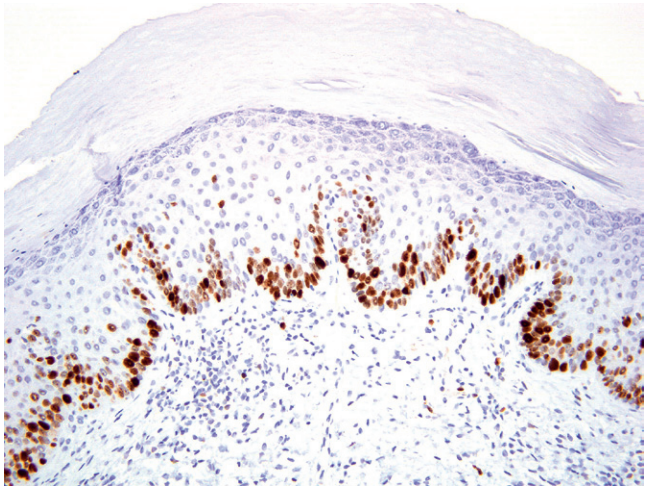


FIGURE 3

MIB-1 immunostain of the case in Figure 2. Note the confinement of the positive cells to the basal portion of the epithelium, similar to LSC.

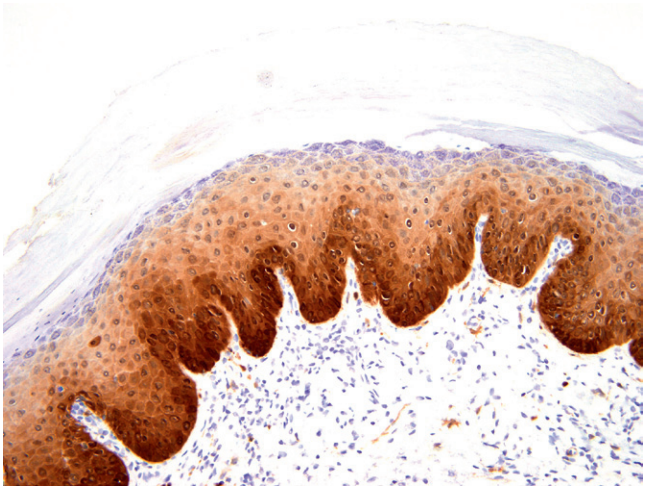


FIGURE 4

Immunostaining for p16 of the above case (in Figure 2) shows intense nuclear and cytoplasmic positivity in the lower half of the epithelium, in keeping with a variant of classic VIN.

CLASSIC VULVAR INTRAEPITHELIAL NEOPLASIA (BOWENOID DYSPLASIA)

Definition—Classic or "usual-type" vulvar intraepithelial neoplasia (VIN) with full-thickness atypia similar to that seen in bowenoid papulosis but with milder atypia.

Clinical Features

Epidemiology

- Consists of a fraction of the patients with classic VIN.
- May be seen in younger women.

Presentation

- Similar to that of classic VIN.

Prognosis and Treatment

- Similar to that of classic VIN. Might temporize on management if lesions are small.

Pathology

Histology

- This variant of classic VIN is problematic by virtue of its milder atypia. It overlaps with bowenoid papulosis (i.e., classic VIN).
- Atypia is full thickness but mild.
- An expanded population of basaloid keratinocytes.

Terminology: Squamous intraepithelial lesion, intermediate grade (VIN I-VIN II).

Immunopathology (Including Immunohistochemistry)

- P16 staining should be diffuse.
- Ki-67 demonstrates increased labeling, including cells in the upper epidermis.

Main Differential Diagnosis

- Seborrheic keratosis—p16 stains will be patchy.
- Pseudobowenoid papulosis—similar population of immature keratinocytes. Should be distinguished by the p16 stain.
- Seborrheic keratosis-like condyloma—similar cell population but less atypia; p16 patchy or negative.

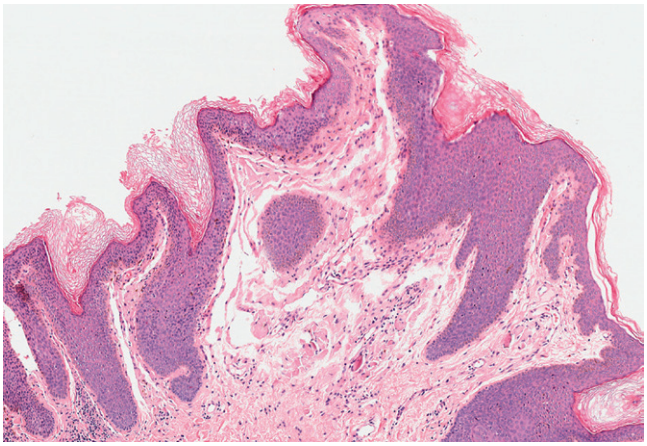


FIGURE 1

Bowenoid dysplasia. Low-power view showing full-thickness loss of maturation but the degree of atypia is mild. Must be distinguished from seborrheic keratosis or pseudobowenoid papulosis.

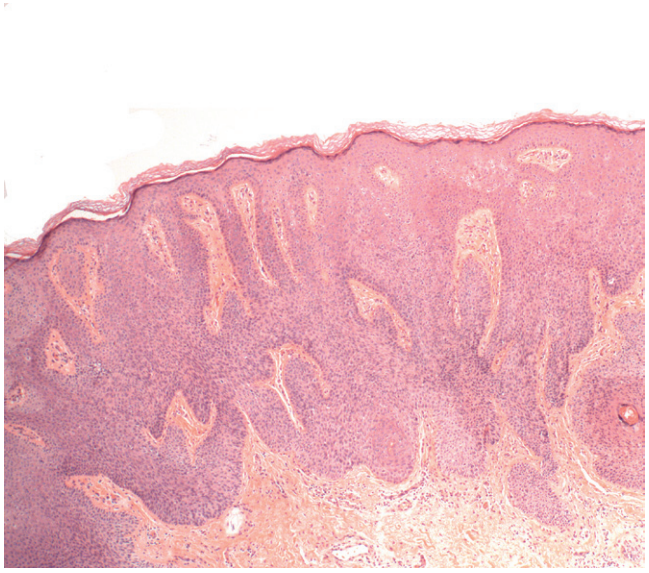


FIGURE 2

Bowenoid dysplasia associated with HPV 16. Another case with acanthosis and monotonous population of immature keratinocytes.

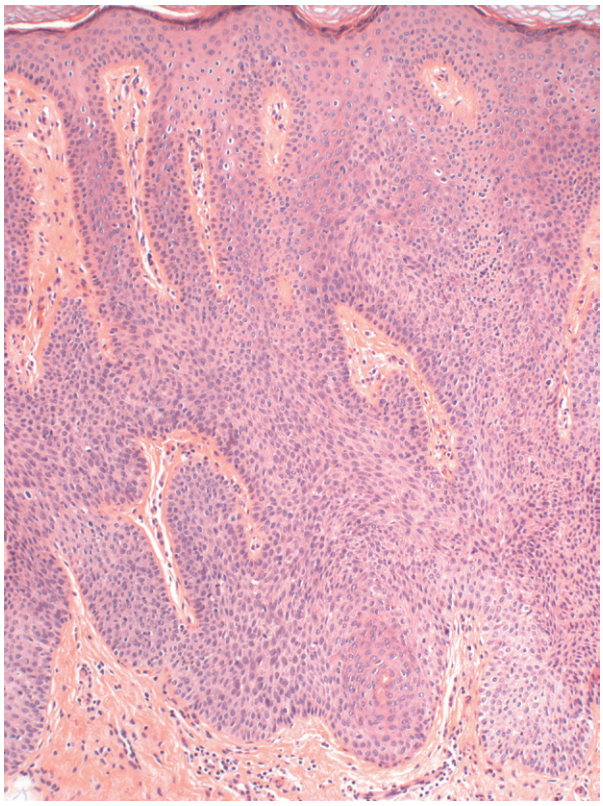


FIGURE 3

Bowenoid dysplasia associated with HPV 16. Note the resemblance to seborrheic keratosis.

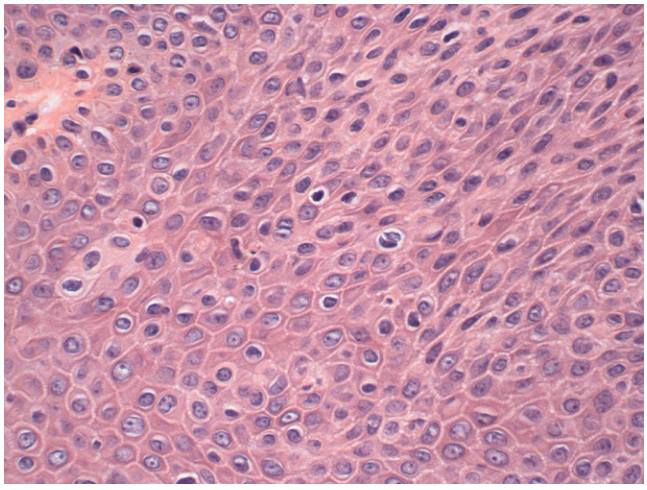


FIGURE 4

Bowenoid dysplasia. At high magnification there is modest variation in nuclear size.

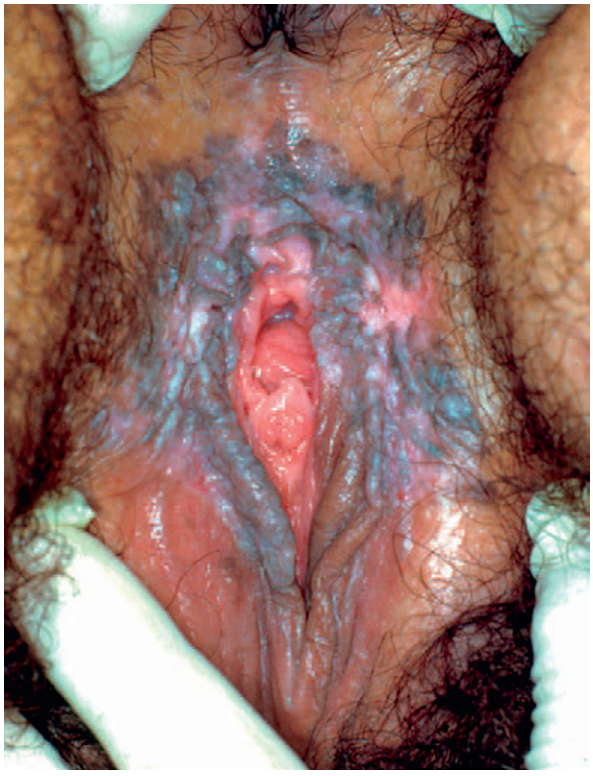


FIGURE 5

Pigmented bowenoid VIN in a reproductive-age woman.

PAGETOID VULVAR INTRAEPITHELIAL NEOPLASIA

PITFALL

Definition—An unusual variant of vulvar intraepithelial neoplasia (VIN) in which the more poorly differentiated cells invade the overlying mature squamous epithelium.

Clinical Features

Epidemiology

- Rare, affects a small fraction of the patients with classic VIN.

Presentation

- Similar to that of classic VIN.

Prognosis and Treatment

- Similar to that of classic VIN.

Pathology

Histology

- The less-differentiated cells invade the overlying, mature, squamous epithelium.
- The migrating cells may be seen as single cells or clusters admixed with the mature keratinocytes.
- The distribution of the affected cells mimics that of Paget's disease.

Immunopathology (Including Immunohistochemistry)

- p16 stains the abnormal immature cells in both the basal and upper epidermal layers.
- Ki-67 demonstrates increased labeling, including cells in the upper epidermis.

Main Differential Diagnosis

- Paget's disease (histologically).

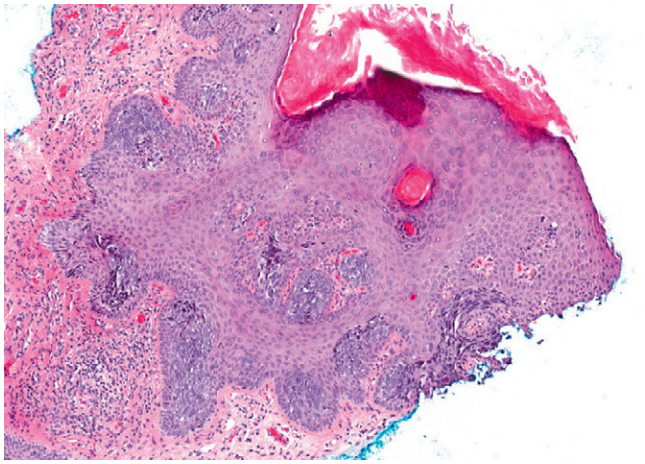


FIGURE 1

Pagetoid VIN. This biopsy specimen depicts discontinuous nests of basophilic cells in the lower epithelium.

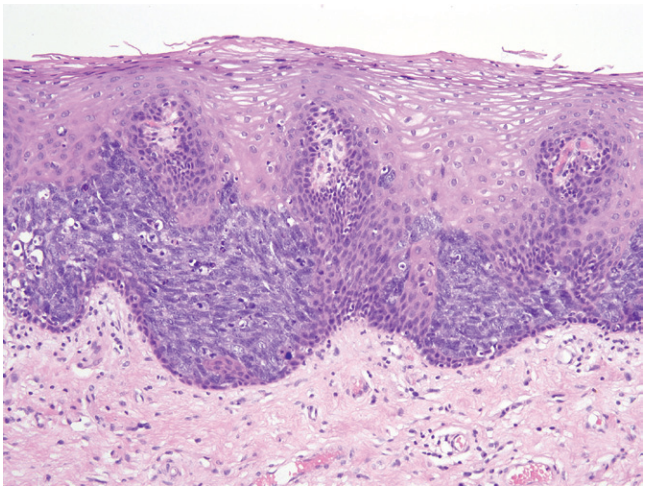


FIGURE 2

Pagetoid VIN. Another pagetoid VIN showing the discontinuous nests of neoplastic squamous cells at higher magnification.

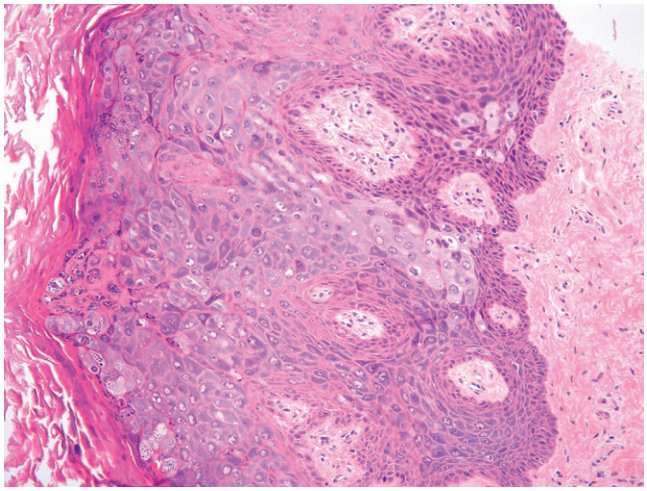


FIGURE 3

A third case of pagetoid VIN showing dyskeratosis in the neoplastic cells.

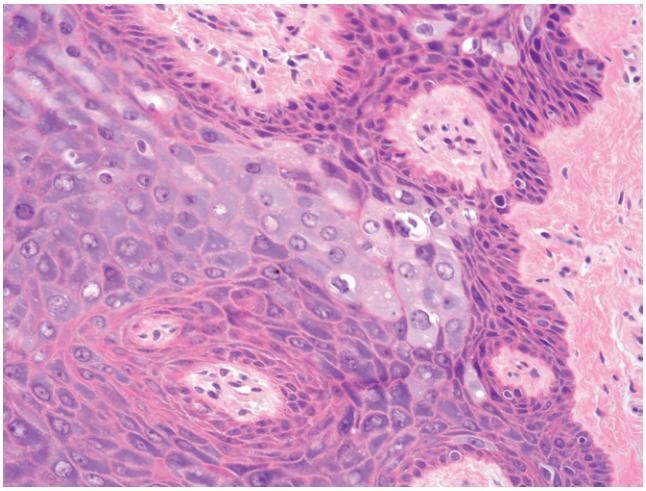


FIGURE 4

Dyskeratotic pagetoid squamous cells at higher magnification.

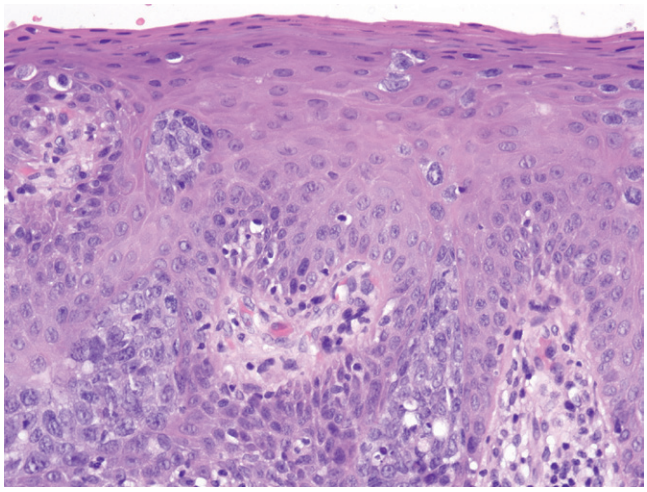


FIGURE 5

Small clusters of neoplastic squamous cells situated higher in the epidermis.

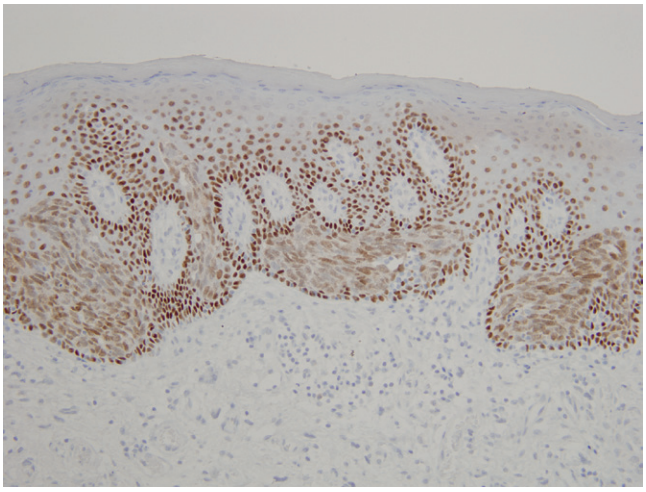


FIGURE 6

This stain for p63 highlights both the normal basal squamous cells and the neoplastic nests, distinguishing them from columnar-derived cells of conventional Paget's disease. The lighter-staining pagetoid squamous cells contrast sharply with the normal basal keratinocytes.

VULVAR INTRAEPITHELIAL NEOPLASIA WITH COLUMNAR DIFFERENTIATION

PITFALL

Definition—A rare variant of vulvar intraepithelial neoplasia (VIN) with lesional columnar (i.e., mucinous) cells.

Clinical Features

Epidemiology

- Rare, affects a small fraction of the patients with classic VIN.

Presentation

- Similar to that of classic VIN.

Prognosis and Treatment

- Similar to that of classic VIN.

Pathology

Histology

- Atypical mucinous columnar epithelial cells admixed with typical squamous cells.
- The columnar cells may show only mild pleomorphism.
- May cause diagnostic confusion with Paget's disease or extension from a urothelial carcinoma.

Immunopathology (Including Immunohistochemistry)

- p16 stains the immature cells in both the basal and upper epidermal layers.
- Ki-67 demonstrates increased labeling, including cells in the upper epidermis.
- Mucicarmine highlights mucin-containing cells in difficult cases.

Main Differential Diagnosis

- Paget's disease (histologically).
- Urothelial carcinoma (histologically).

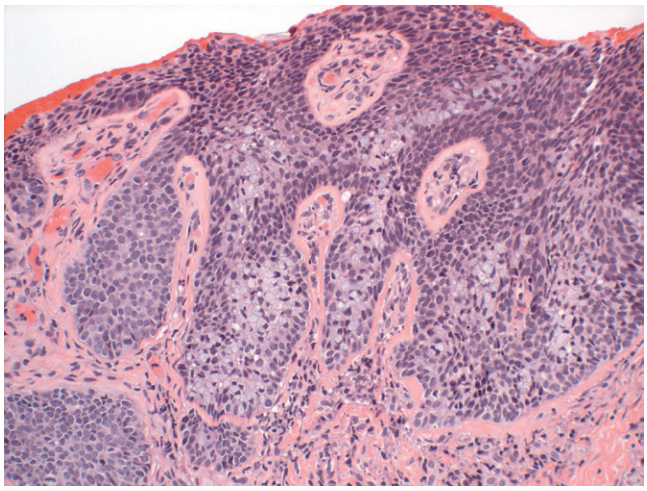


FIGURE 1

Classic VIN with columnar differentiation. Classic, high-grade, basaloid VIN with admixed mucin-containing cells.

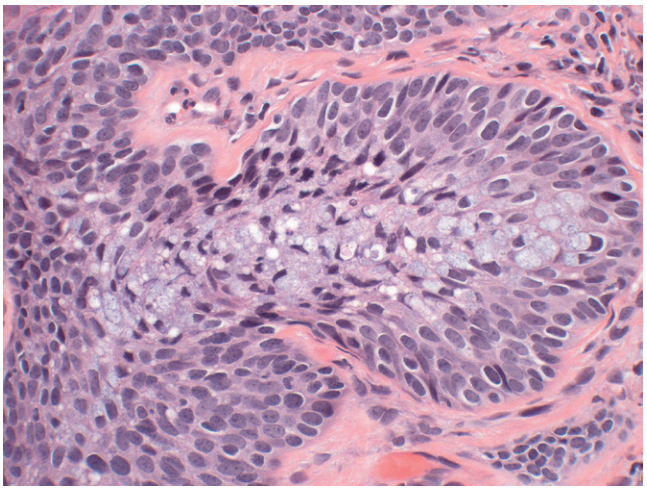


FIGURE 2

Classic VIN with columnar differentiation. Immature, dysplastic squamous cells with admixed mucinous cells. Note the pale blue cytoplasm.

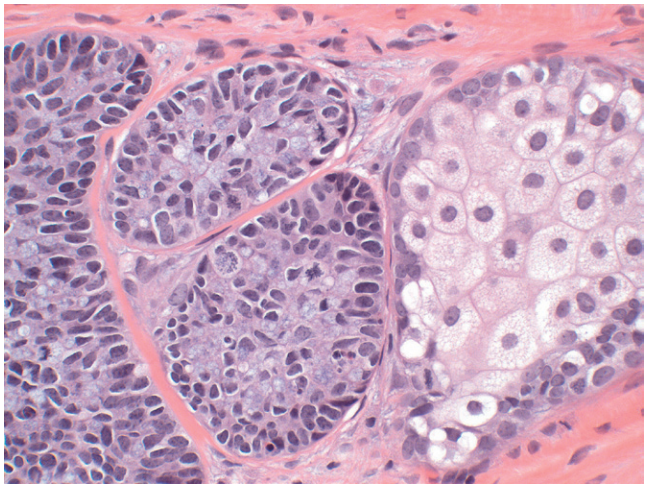


FIGURE 3

Classic VIN with columnar differentiation. In this example the mucinous cells are the predominant component. Increased mitotic figures are present.

EPIDERMODYSPLASIA VERRUCIFORMIS–LIKE ATYPIA

PITFALL

Definition—A variant of epithelial atypia associated with gamma papillomaviruses, classically associated with epidermodysplasia verruciformis (EDV) but now appreciated in immunosuppressed (including human immunodeficiency virus [HIV]–infected) patients and involves the vulva.

Clinical Features

- A wide age range.
  - Multiple plaque or papular to verrucous in presentation, pigmented or nonpigmented.
  - May resemble condyloma, seborrheic keratosis, or psoriasis.
- Increased frequency in HIV-infected or immunosuppressed women.
- Can be seen on any cutaneous or mucosal site.

Clinical Management/Outcome

- Conservative local excision or topical Aldara is the rule.
- Treatment of the underlying immune suppression although it may or may not ameliorate the disorder.
- Risk of progression to malignancy is low.

Pathology

Histology

- Enlarged keratinocytes in the upper epidermis with gray-blue cytoplasm.
  - Enlarged, round nuclei with pale chromatin, and one or multiple nucleoli.
- Basal atypia variable.

Immunohistochemistry

- Ki-67 expression is usually near full thickness due to loss of cell cycle control throughout the epithelium but may be less pronounced in some cases.
- p16ink4 expression may vary. Diffuse staining is not the rule.
- p53 staining is negative or patchy (nuclear).

Differential Diagnosis and Pitfalls

- Seborrheic keratosis—minimal nuclear atypia, negative for p16.
- Pseudobowenoid papulosis—apoptotic cells (pseudomitoses) may mimic mitotic activity, but basal layers exhibit minimal atypia, negative for p16.
- Multinucleate atypia—polynucleation, which is uncommon in classic vulvar intraepithelial neoplasia (VIN); low proliferative index; negative for p16.

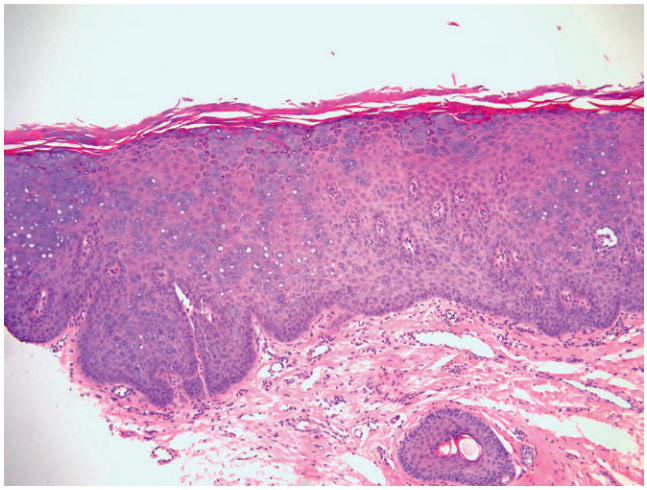


FIGURE 1

EDV-like atypia in an immunosuppressed patient. There is mild hyperkeratosis, and the acanthotic epithelium is punctuated by basophilic clusters of maturing keratinocytes.

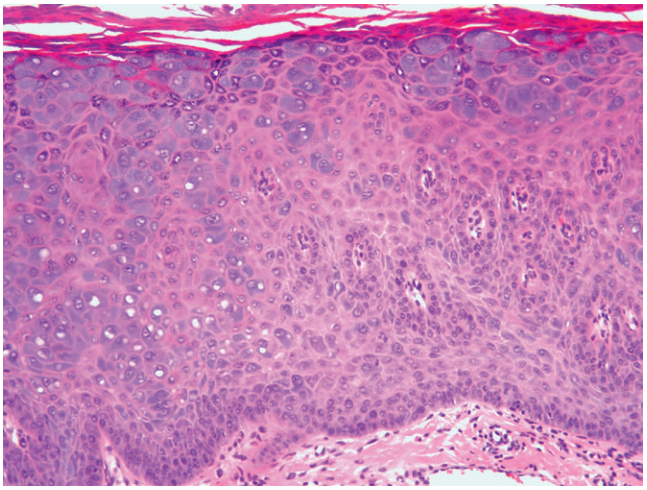


FIGURE 2

EDV-like atypia. At higher magnification of Figure 1, note the clustered groups with basophilia. Note the lower third of the epithelium exhibits minimal crowding or atypia in this field.

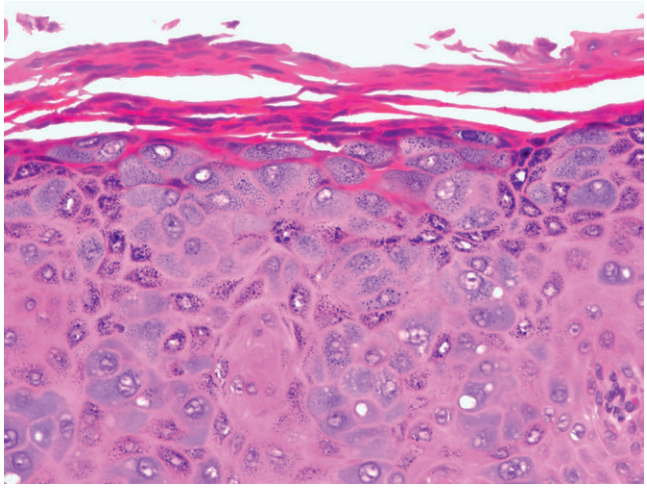


FIGURE 3

Higher magnification of the surface cell layers. The cytoplasm is punctuated by fine keratohyalin granules.

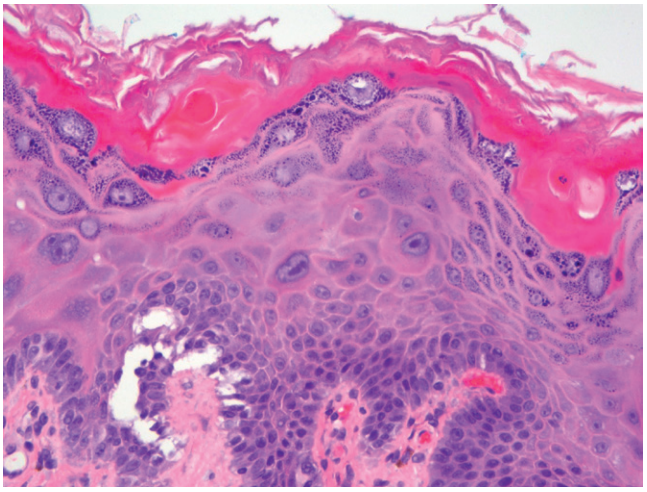


FIGURE 4

In this field there is focal nuclear enlargement, suspended in the middle of the epithelium with prominent nucleoli.

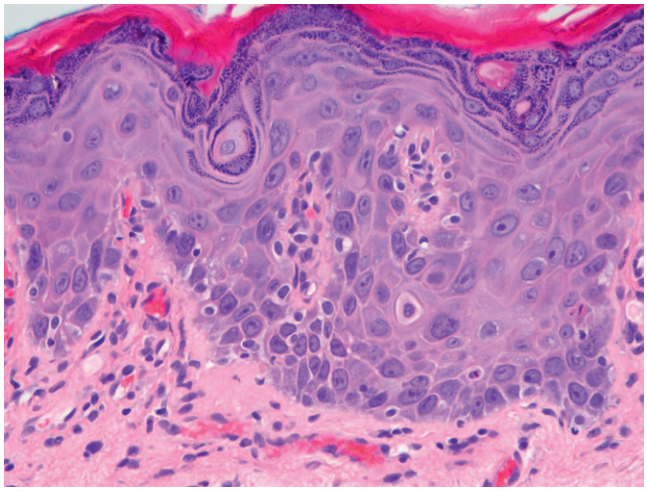


FIGURE 5

This field more closely resembles a classic VIN except for the prominent nucleoli.

POLYNUCLEATED ATYPIA OF THE VULVA

Definition—A reactive epithelial process seen in skin or vulva characterized by a cytoskeletal defect with accumulation of nuclei in individual cells (multinucleation).

Clinical Features

Epidemiology

- No particular demographic other than an association with nonspecific, chronic, irritative, or inflammatory changes in the vulva. Similar changes can be seen in cutaneous dermatoses.

Presentation

- Flesh-colored mucocutaneous papules. Lesions may be pruritic or painful in keeping with the underlying condition.

Prognosis and Treatment

- A benign condition likely superimposed on a dermatosis. Management of the dermatological condition will suffice. The impact of this entity lies in its potential misdiagnosis as a condyloma or vulvar intraepithelial neoplasia (VIN).

Pathology

Histology

- Mild acanthosis, normal maturation, and no appreciable nuclear enlargement.
- Keratinocytes in the lower to middle epithelium exhibit multiple nuclei.
- The nuclei are normochromatic and identical in size to those in the normal surrounding cells.
- As many as a dozen nuclei may be seen in a single cell.

Diagnostic Terminology: Benign squamous mucosa with reactive epithelial changes.

Immunohistochemistry

- Not necessary, but Mib-1 and p16ink4 stains will be negative (normal distribution). These cells are human papillomavirus (HPV) negative.

Main Differential Diagnosis

- Condyloma—these have superficial nuclear atypia, and there is nuclear enlargement.
- VIN II and III—these lesions may have multinucleation but like condyloma the nuclei are abnormal, as is the rest of the epithelium.
- Viral (herpetic) changes—characteristic viral cytopathic effect with inclusions.

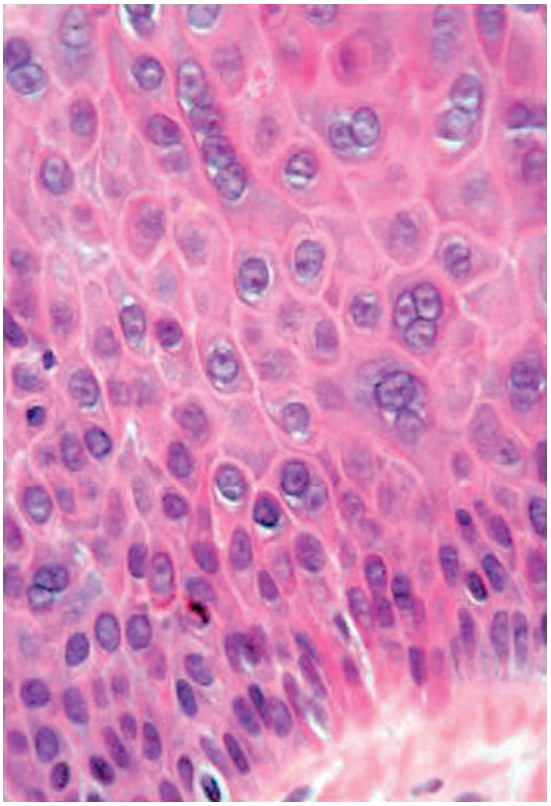


FIGURE 1

Multinucleated atypia of the vulva (MAV). Note the presence of keratinocytes in the lower and middle epithelial layers with two or more nuclei. Note also the lack of chromatin abnormalities and similarities in size to the adjacent normal mononuclear cells.

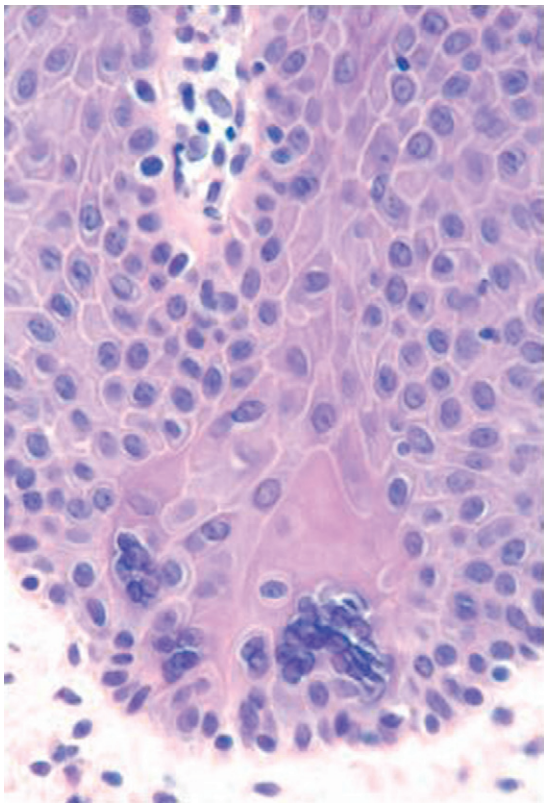


FIGURE 2

MAV. One basal-oriented cell in particular contains numerous nuclei.

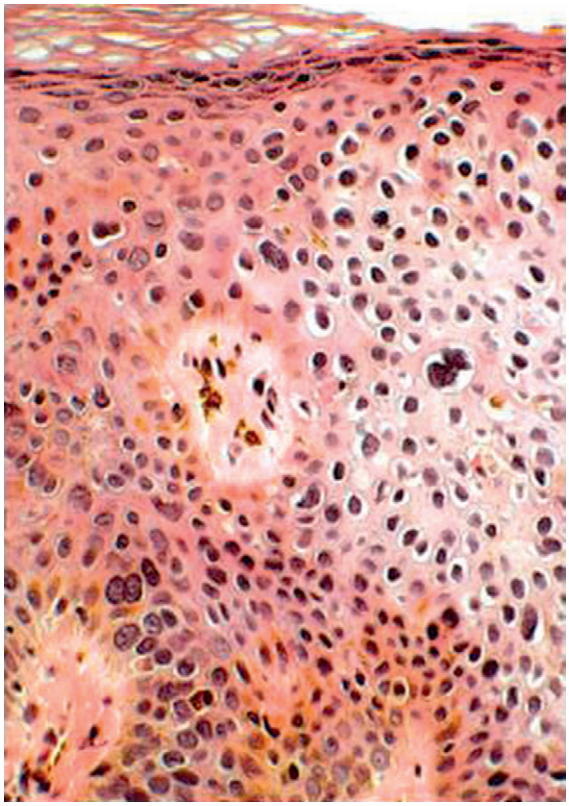


FIGURE 3

VIN with multinucleation. This should be easily distinguished from MAV by the additional nuclear abnormalities.

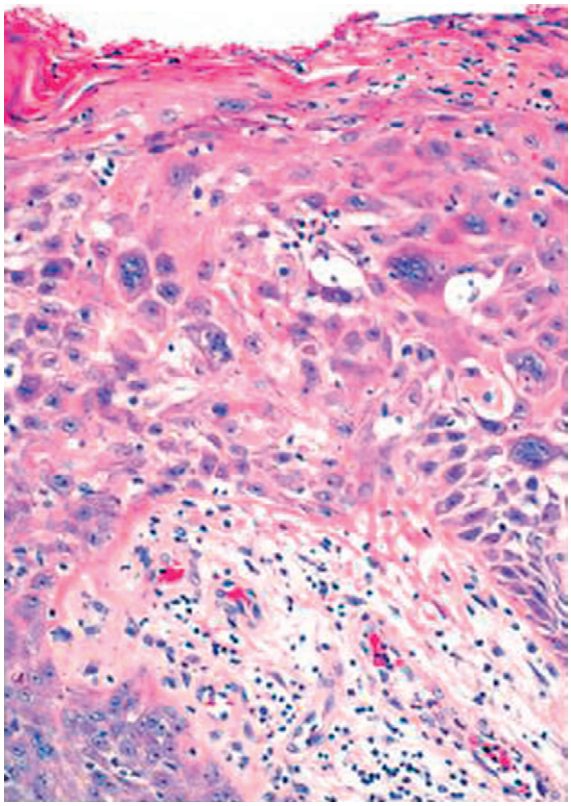


FIGURE 4

Herpetic infections of the vulva can also manifest with multinucleation but are distinguished by the characteristic presentation (usually with inflammation and ulceration) and viral inclusions.

DIFFERENTIATED VULVAR INTRAEPITHELIAL NEOPLASIA

Definition—Vulvar intraepithelial neoplasia (VIN) that likely is secondary to a series of host gene alterations that are discrete from those involved in classic VIN.

Clinical Features

Epidemiology

- Occurs in postmenopausal women but can be seen earlier.
- Associated with less than 5% of all diagnosed cases of VIN.
- Typically associated with chronic vulvar inflammatory disease (lichen sclerosus or lichen simplex chronicus).

Presentation

- Typically presents with symptoms and signs associated with lichen sclerosus and lichen simplex chronicus.
- Lesions tend to be less conspicuous clinically.

Prognosis and Treatment

- Most differentiated VINs (DVINs) are found in association with keratinizing squamous cell carcinomas. Outcome of isolated cases is uncertain, but they are approached as cancer precursors.
- Conservative excision of lesions and biopsy of new and/or suspicious lesions in patients with DVIN are recommended.
- Most are not typically managed with topical therapy due to the severity of the underlying vulvar inflammatory process.

Pathology

Histology

- Best appreciated as variable and sometimes subtle forms of atypia, and there is no sharp cutoff between lichen simplex chronicus and DVIN.
- Basal atypia is the rule and is characterized by variable hyperchromasia, nuclear enlargement, and nucleoli.
- Foci of accentuated keratinization.
- Foci of prominent spongiosis or acantholysis often present.
- Occasional variants demonstrate expansion of the basal cell layer and may mimic classic VIN.

Immunopathology (Including Immunohistochemistry)

- p53 staining is often, if not invariably, diffuse and moderate to marked in degree. Depending on the degree of basal cell expansion, involved cell layers will be from one to several and occasionally near full thickness.
- Ki-67 may also be focally increased in the basal layers but will parallel the degree of immaturity and is not a reliable marker.
- p16 staining is typically negative or patchy, distinguishing DVIN from classic VIN.

Main Differential Diagnosis

- Psoriasis—similar architecture but lacks the basal atypia.
- Spongiotic dermatitis—basal cells will display minimal atypia.
- Candida vulvitis—may mimic a hypertropic DVIN but lacks atypia.
- Lichen sclerosus and lichen simplex chronicus—can be distinguished by degree of atypia. p53 immunostaining might help in making the distinction.

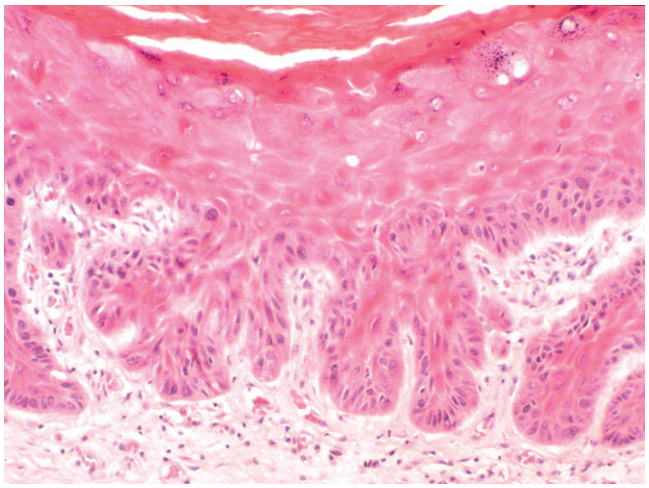


FIGURE 1

DVIN. Striking basal atypia consisting of hyperchromasia and irregular nuclear contours is seen in the first two to three cell layers.

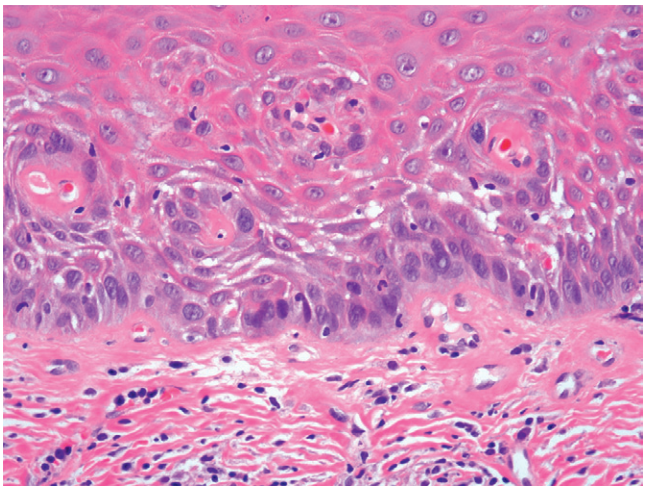


FIGURE 2

DVIN. This DVIN exhibits a more subtle but definite basal atypia.

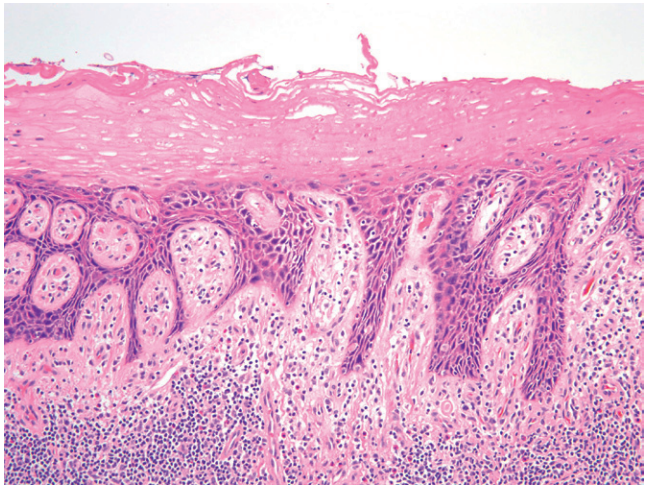


FIGURE 3

DVIN. This example has an expanded basal layer with conspicuous atypia.

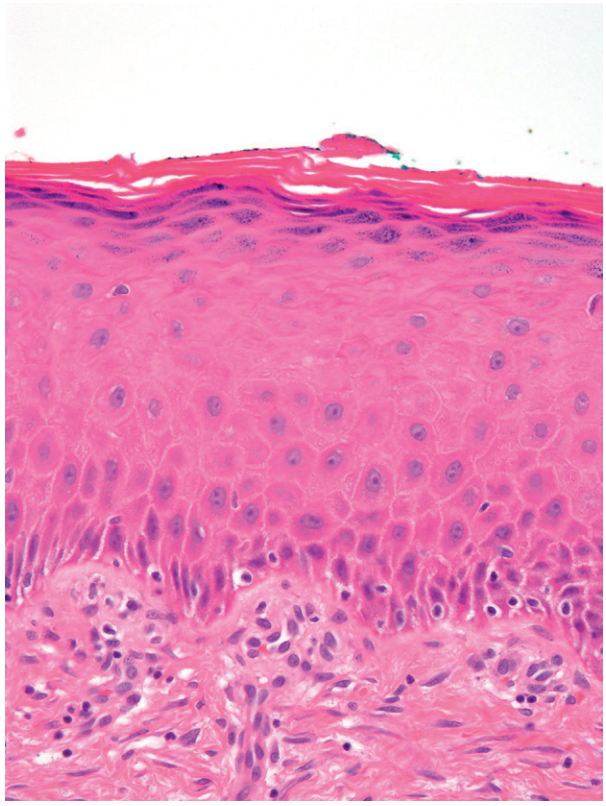


FIGURE 4

Nonneoplastic squamous mucosa for comparison.

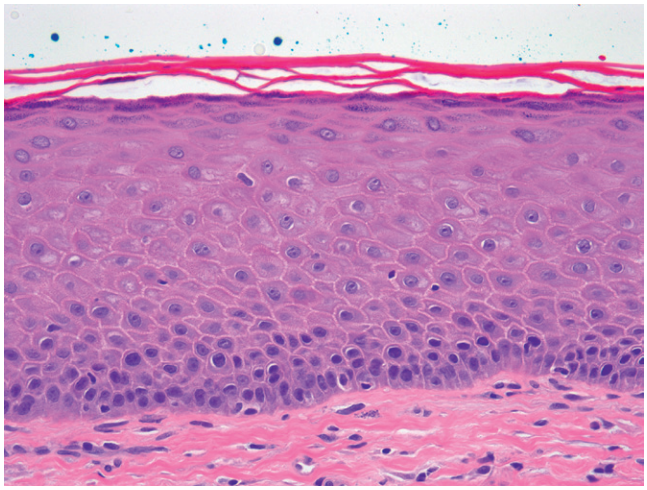


FIGURE 5

First of a series of biopsy specimens from the same patient. This is below the threshold for DVIN.

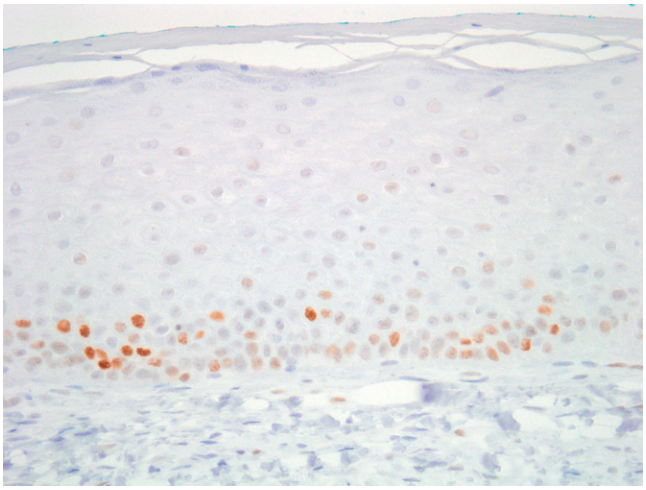


FIGURE 6

Immunostaining of Figure 5 for p53 shows sporadic staining.

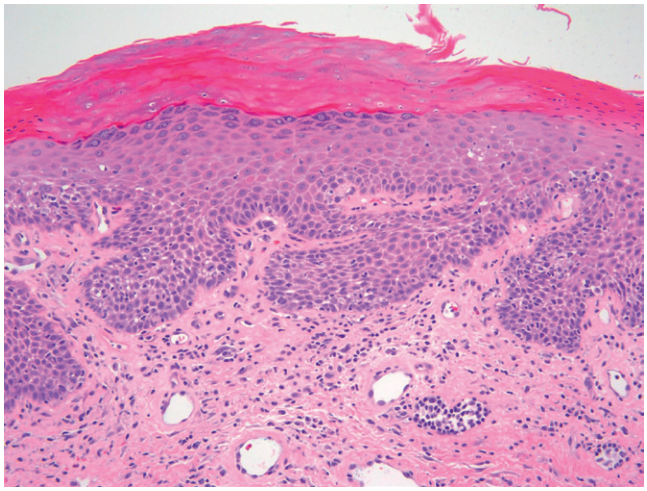


FIGURE 7

An adjacent field shows slightly higher accentuation of the basal layer.

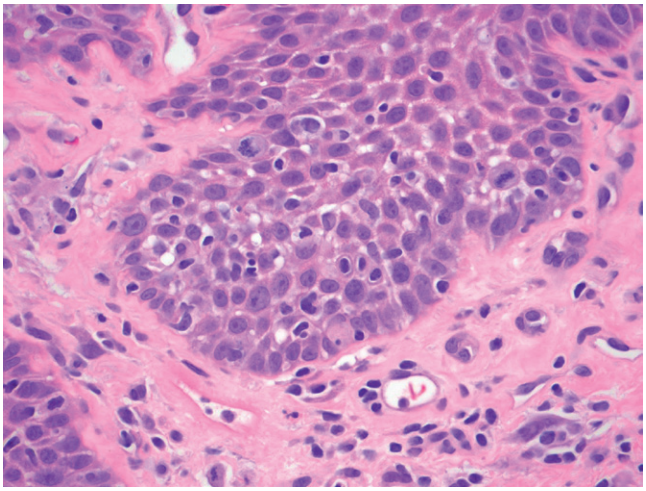


FIGURE 8

At higher magnification the basal cells display subtle enlargement with prominent nucleoli.

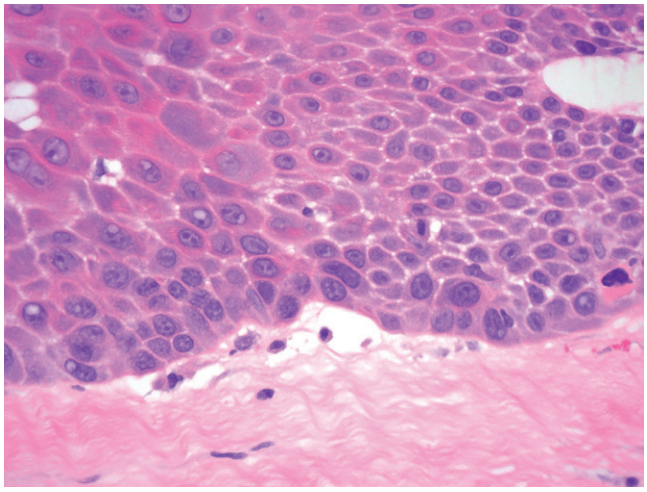


FIGURE 9

An adjacent field displays even greater basal atypia. Note the abnormal keratinization in the upper left of the panel.

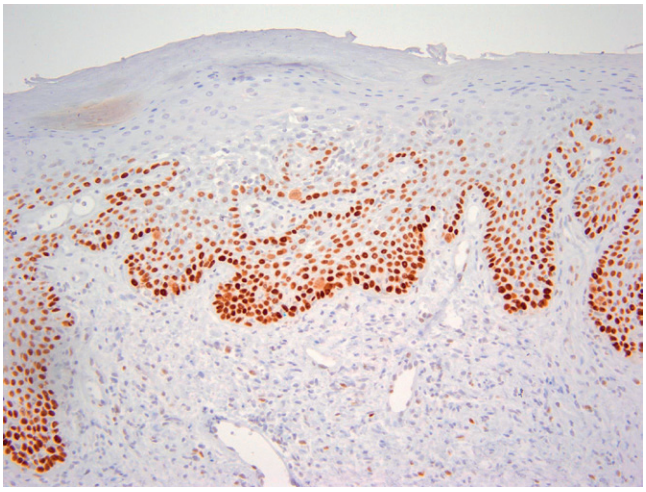


FIGURE 10

A p53 stain of this area (in Figures 7 to 9) shows strong multilayered p53 staining.

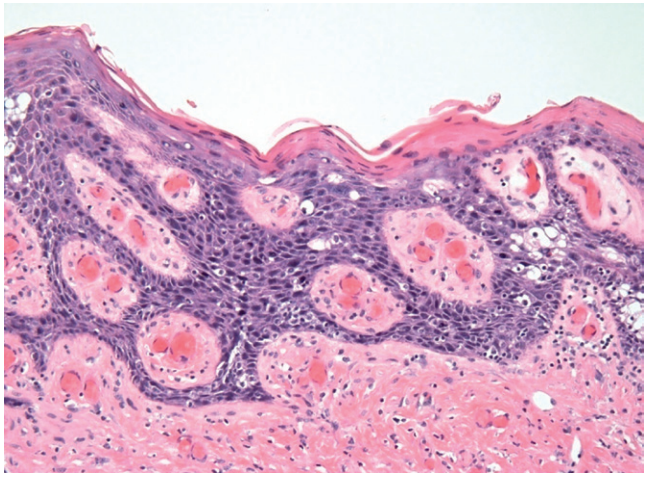


FIGURE 11

Prominent basal cell expansion in a DVIN mimics classic VIN.

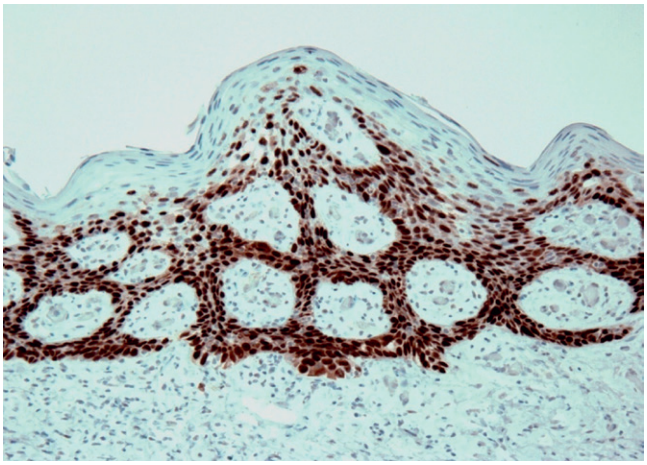


FIGURE 12

A p53 stain is strong in all layers. In essence, the distribution of p53 parallels the degree of basal cell expansion. The latter appears to increase as a function of lesion severity.

VERRUCIFORM LICHEN SIMPLEX CHRONICUS

Definition—A clinical and pathologic response to continued physical trauma comprised of markedly thickened skin with verruciform changes along with erythema and plaquelike scaling.

Clinical Features

Epidemiology

- Seen in all demographic groups; however, has been associated with vulvar cancer and verrucous carcinoma.

Presentation

- Patients typically present with a history of irritation/pruritus. Clinically the skin is markedly thickened with surrounding erythema and overlying plaquelike scale. Excoriation is frequently present. Normal physiologic skin markings may be exaggerated.

Prognosis and Treatment

- Prognosis—can be associated with vulvar carcinoma, and regular follow-up (especially in older patients) is warranted.
- Treatment—breaking of the irritant/trauma cycle with or without topical steroids. Patient education and behavioral modification. Close clinical follow-up.

Pathology

Histology

- Acanthosis with hyperkeratosis and hypergranulosis is present in varying degrees. A variable mononuclear cell infiltrate is present in the superficial dermis.
- Verruciform features may mimic other verruciform lesions.

Immunopathology (Including Immunohistochemistry)

- Usually noncontributory, although p53 immunostains should be negative with heterogeneous staining in the lower epithelial layers.

Main Differential Diagnosis

- Verrucous carcinoma—there is less hypergranulosis, with superficial epithelial pallor and bulbous downgrowth (blunt invasion).
- Fungal infection (tinea cruris)—may overlap with verruciform lichen simplex chronicus (LSC). Fungal stains should be considered in the appropriate clinical context.
- Differentiated vulvar intraepithelial neoplasia (VIN)—verruciform variants exist and overlap with verruciform LSC. p53 immunostaining may help (but not always) make this distinction.

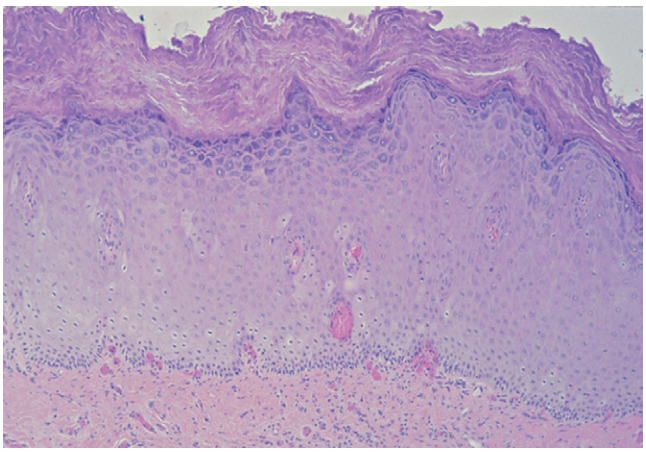


FIGURE 1

Verruciform LSC. There is mild verruciform architecture with hypergranulosis. No atypia is seen.

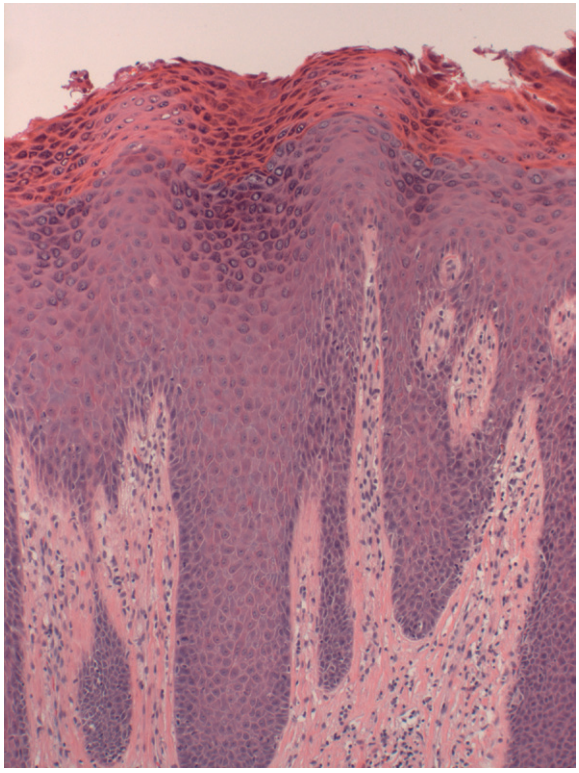


FIGURE 2

Verruciform LSC. There is mild elongation of the rete.

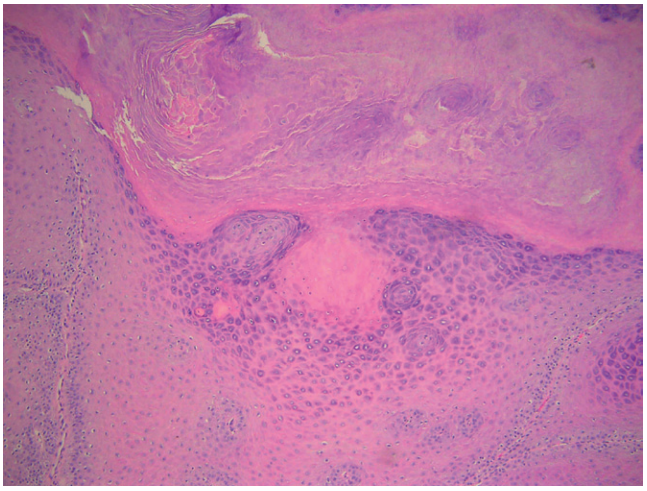


FIGURE 3

Verruciform LSC. Note the thickening of the epithelium with some verruciform architecture and slight papillomatosis.

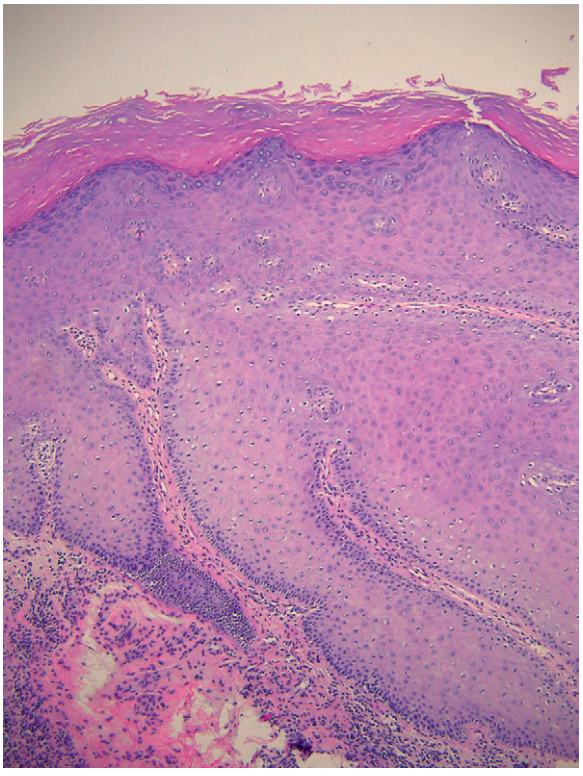


FIGURE 4

Verruciform LSC. Again note the absence of basal atypia.

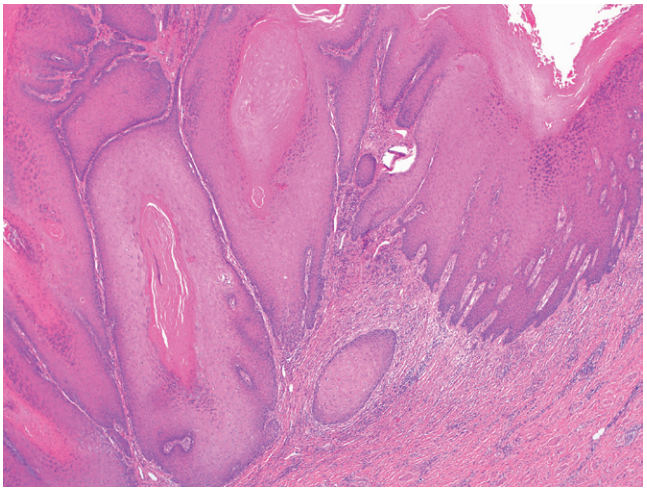


FIGURE 5

Verruciform LSC *(right)* merging with a verrucous carcinoma *(left)*.

VULVAR ACANTHOSIS WITH ALTERED DIFFERENTIATION (ATYPICAL VERRUCIFORM HYPERPLASIA)

Definition—Vulvar acanthosis with altered differentiation (VAAD) is defined as vulvar acanthosis with variable verruciform architecture that lacks the nuclear atypia characteristic of vulvar intraepithelial neoplasia (VIN) but exhibits abnormalities in keratinocyte differentiation. It is classed as a risk factor for squamous carcinoma. For the purposes of this discussion, we will address this entity and potential mimics.

Clinical Features

Epidemiology

- Menopausal and postmenopausal women.
- Associated with lichen sclerosus, lichen simplex chronicus (LSC), and verruciform LSC.

Presentation

- Patchy verruciform or exophytic growth on the vulva.

Prognosis and Treatment

- VAAD may be associated with verrucous carcinoma or well-differentiated squamous carcinoma.
- Conservative removal and follow-up, with attention to any new lesions.

Pathology

Histology

- Acanthosis.
- Variable verruciform architecture.
- Layers of parakeratosis.
- Epithelial cytoplasmic pallor near the surface.
- Limited downward elongation of the rete pegs.
- Virtually no interface atypia.

Terminology: Either epithelial hyperplasia or acanthosis with altered differentiation, with the proviso that this is not considered a precancer (no nuclear atypia) but merits follow up with biopsy of any new or suspicious lesions.

Immunohistochemistry

- Ki-67, p16, and p53 staining will be unremarkable.

Differential Diagnosis and Pitfalls

- Differentiated VIN will exhibit *interface atypia*.
- Verrucous carcinoma will demonstrate similar features but will exhibit *blunt invasion*.
- Classic VIN will exhibit conspicuous and usually near full-thickness atypia (excepting classic VIN with superimposed LSC).
- Verruciform LSC will contain prominent keratohyalin granules and does not contain prominent parakeratosis and epithelial pallor.
- Pseudoepitheliomatous hyperplasia lacks either nuclear or cytoplasmic atypia.
- Inverted keratosis—a regular pattern of pearl-like formation without atypical cytoplasmic differentiation (squamous eddies).
- Verruciform xanthoma—foamy macrophages in the lamina propria, pseudoparakeratosis.

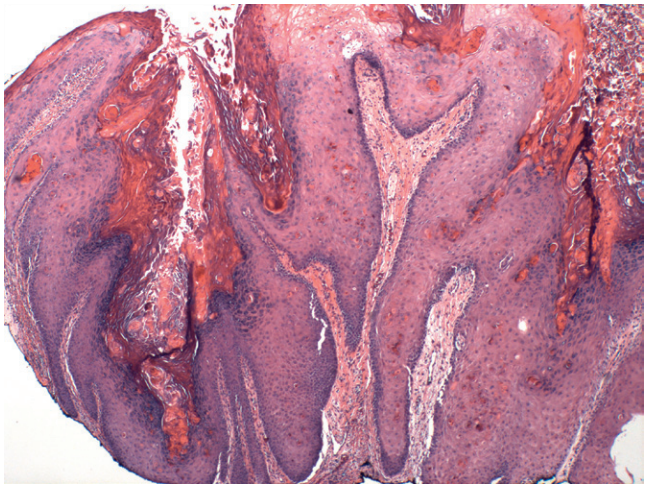


FIGURE 1

VAAD. This low-power image illustrates acanthosis with verruciform architecture.

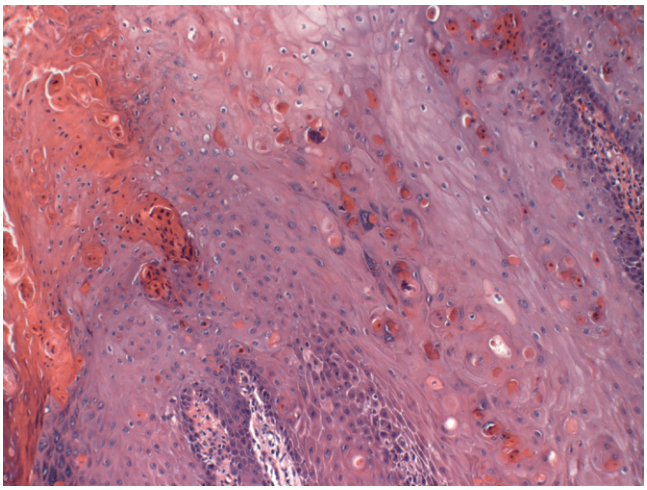


FIGURE 2

Higher magnification of VAAD. Note the prominent dyskeratosis and lack of atypia.

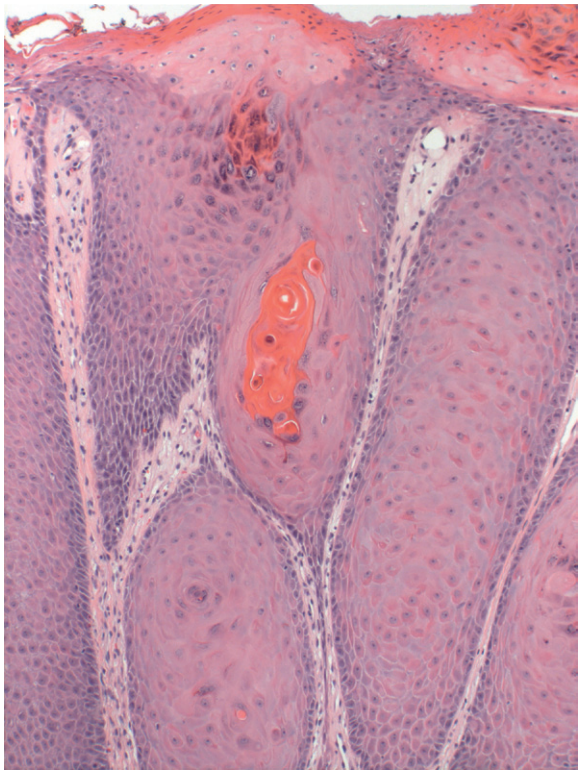


FIGURE 3

VAAD showing some abnormalities in superficial cytoplasmic differentiation with epithelial cell pallor and parakeratosis. This is not specific for this entity because similar changes can be seen in reactive epithelia.

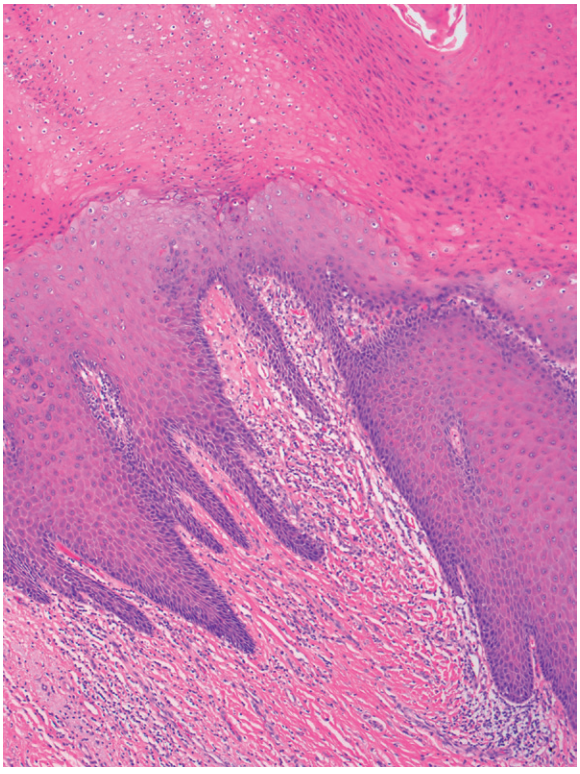


FIGURE 4

VAAD. Note the surface epithelial pallor and parakeratosis.

EARLY INVASIVE SQUAMOUS CELL CARCINOMA

Definition—Invasion less than 2 cm in diameter and to a depth of less than 1 mm below the highest epithelial–stromal interface.

Epidemiology

- A wide age range, from second to eighth decade, predominating in the fifth and sixth decades.
- Patients typically present with vulvar intraepithelial neoplasia (VIN). Approximately 20% of VINs in older women harbor areas of early invasion.

Clinical Management/Outcome

- Risk of metastases is essentially zero for lesions that fulfill the criteria for "microinvasion."
- Wide local excision is preferred. Regional lymph node sampling may be done if there is regional lymph node enlargement or other clinical concerns, such as multiple foci of invasion or uncertainty regarding lymphovascular invasion (LVI).
- Lesions invading greater than 1 mm or with LVI have an appreciable (5% to 10%) risk of lymph node metastases.

Pathology

Histology

Patterns of early invasion include

- Confluent growth with an irregular epithelial–stromal interface.
- Discrete tongues of neoplastic epithelium with desmoplasia.
- Irregular intersecting nests with variable size and conformation, as seen with basaloid growth.
- Bulbous pushing invasion. This can be difficult to distinguish from noninvasive adnexal involvement.

Diagnostic Terminology: Superficially invasive squamous cell carcinoma, well, moderate, or poorly differentiated. The lesion measures (numeric value) mm in length and invades to a depth of (numeric value) mm beneath the highest epithelial–stromal interface. LVI is present/absent. The invasive focus is (numeric value) mm from the deep margin, and a minimum of (numeric value) mm from the lateral (radial) margins.

Immunohistochemistry

- Usually noncontributory.

Differential Diagnosis and Pitfalls

- Appendage involvement by VIN.
- Pseudoepitheliomatous hyperplasia (in VIN).
- Tangential sectioning.
- Traumatic displacement of neoplastic epithelium in stroma.
- Basal cell carcinoma.

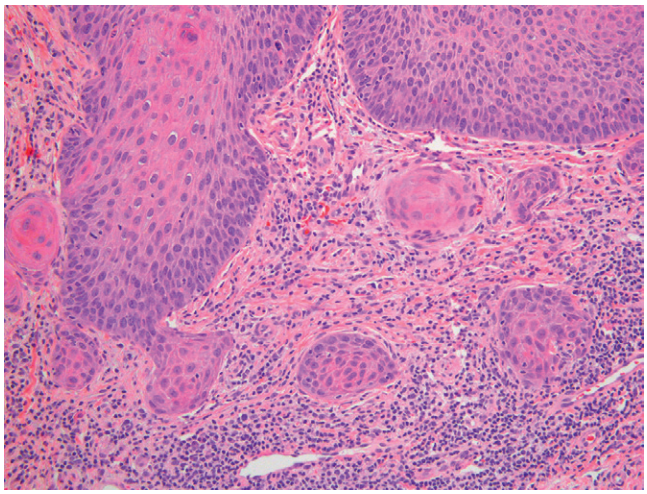


FIGURE 1

Superficially invasive squamous cell carcinoma. Note the small nests beneath the epithelial–stromal interface with a subtle loss of epithelial polarity. One nest is budding from the overlying epithelium.

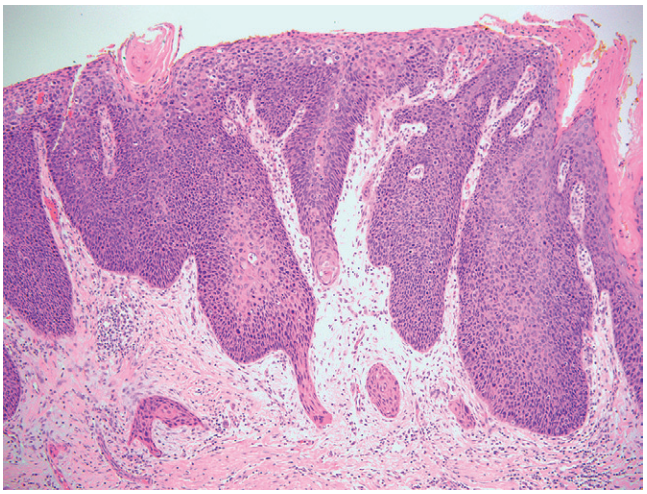


FIGURE 2

Superficially invasive squamous cell carcinoma. These invasive nests are more conspicuous by their irregular shapes, prominent maturation, and desmoplasia.

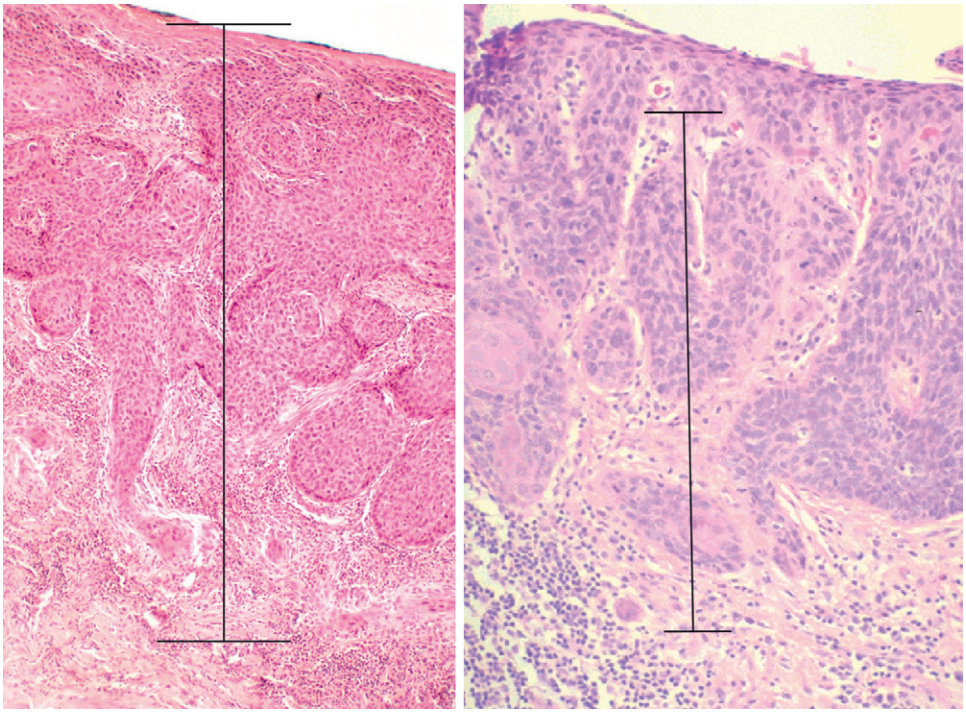


FIGURE 3

Superficially invasive squamous cell carcinoma. Depth is measured, if possible, from the highest adjacent epithelial–stromal interface. If this is not possible a measurement of thickness is sufficient.

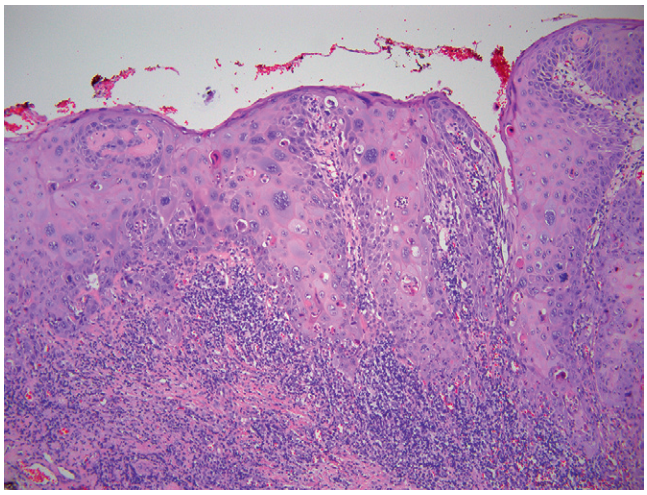


FIGURE 4

Superficially invasive squamous cell carcinoma. This neoplastic epithelium is more difficult to assess because of the inflammation. However, note the obvious loss of epithelial polarity at the base.

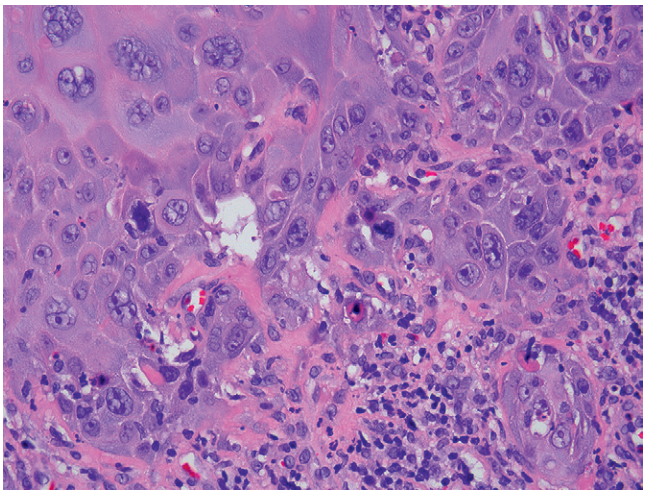


FIGURE 5

Superficially invasive squamous cell carcinoma. The obvious loss of epithelial polarity at the base in Figure 4 is seen at higher power here.

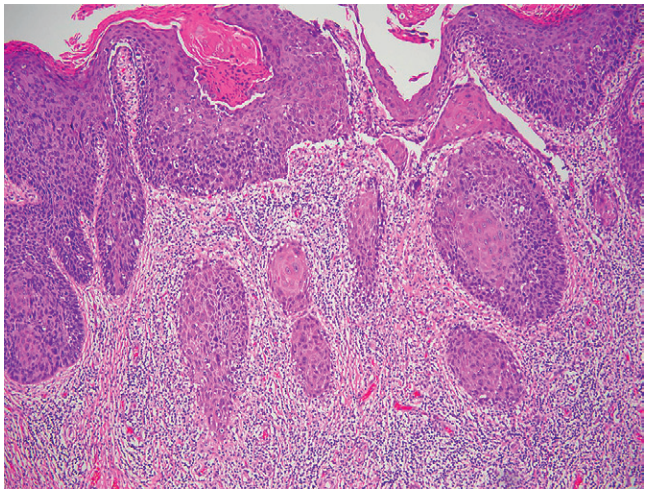


FIGURE 6

Mimic of early invasion. Marked inflammation is present but the nests exhibit a uniform contour.

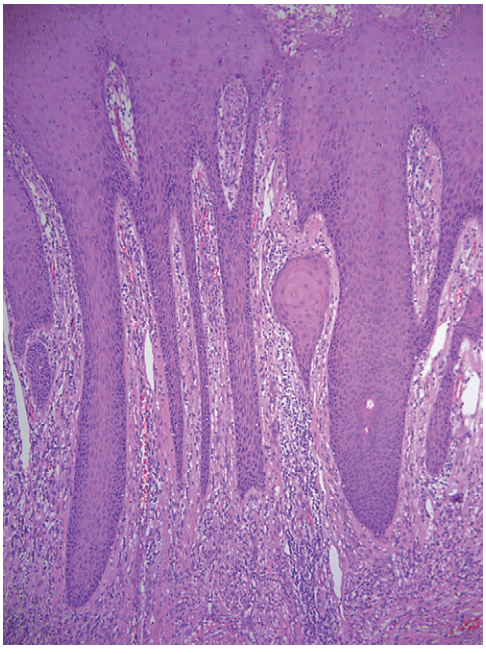


FIGURE 7

Mimic of early invasion. Small foci of dysmaturation within epithelial hyperplasia.

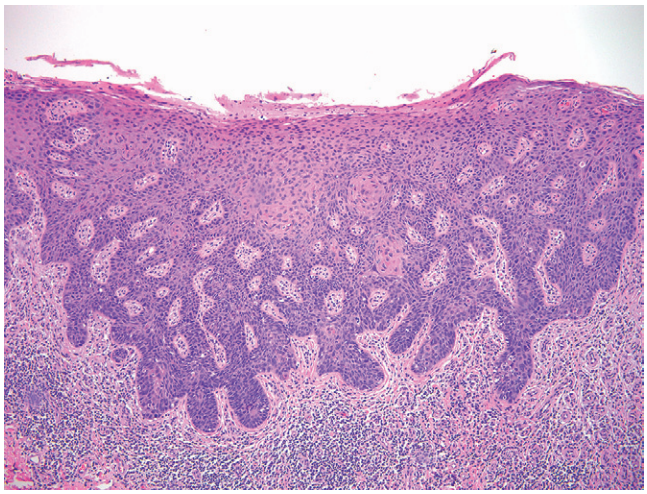


FIGURE 8

Mimic of early invasion. Tangential sectioning of VIN. Note the uniform network of interconnecting basal epithelium.

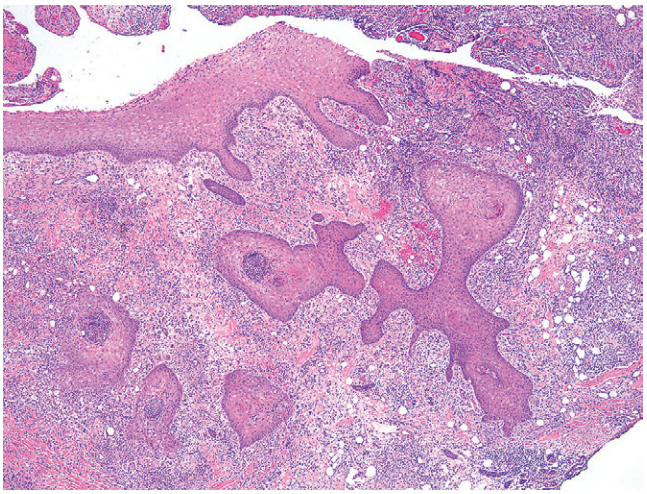


FIGURE 9

Mimic of early invasion. Pseudoepitheliomatous hyperplasia in an inclusion cyst.

VULVAR SQUAMOUS CARCINOMA: BASALOID AND WARTY PATTERNS

Definition—Invasive epithelial neoplasm composed of keratinocytes involving the vulva. Comprise tumors associated with classic vulvar intraepithelial neoplasia (VIN).

Clinical Features

Epidemiology

- Typically affects women in their sixth decade but can be seen in women under 40 who are immunocompromised.
- Strong association with human papillomavirus (HPV), particularly HPV 16.
- Usually found associated with classic VIN.
- Some patients present with no history of vulvar neoplasia.
- Strong association with smoking.
- Association with other lesions in the lower genital tract (cervix, vagina).
- Risk increases with increasing age.

Presentation

- May be seen in the clinical context of classic VIN symptoms (pruritus, pain, or bleeding).
- Will often complicate VIN in women aged over 50.

Prognosis and Treatment

- Guarded, patients with localized, resectable disease have a variable recurrence rate.
- Patients with documented nodal spread at the time of first treatment have a recurrence rate of 30% to 70% if they do not receive adjuvant radiation therapy.
- Recurrence in the groin carries a mortality of about 90% even if the groin was not treated at the time of initial diagnosis.
- Localized recurrence may be treated with re-excision or radiation.
- Surgical resection with lymph node dissection is the most common treatment approach.
- There is increasing interest in sentinel lymph node excision to decrease morbidity.
- Tumors that are papillary without stromal penetration have an excellent prognosis.

Pathology

Histology

Invasion criteria

- Differentiating invasive disease from high-grade VIN may be difficult, especially in cases with extensive inflammation.
- Classic features of invasion include irregular epithelial profiles in the stroma, desmoplasia, loss of cellular polarity, and vascular space invasion.
- In addition, the following patterns are strongly suggestive of invasion (and warrant further sampling if invasion is not found):
  1. Cohesive "intraepithelial-like" invasive patterns (associated with classic VIN).
  2. Linear pavementlike clusters of poorly differentiated epithelium with a discrete epithelial–stromal interface but excessive architectural complexity.
  3. Well-differentiated, infiltrative-appearing patterns with high nuclear grade.
  4. Well-differentiated cohesive clusters with a moderate to high nuclear grade.

Differentiation patterns

- Well to poorly differentiated cohesive growth patterns (warty or basaloid) with well-circumscribed nests of tumor cells. These nests frequently have smooth, undulating borders and resemble intraepithelial neoplasia (intraepithelial like).
- Papillary carcinomas with striking similarity to papillary squamous cell carcinomas in the cervix. These show exophytic, filiform papillae that are lined by a well-polarized squamous epithelium. These may be difficult to distinguish from high-grade squamous intraepithelial

lesions (HSIL) (VIN2 and VIN3) and may display a sharply defined epithelial–stromal interface.

Immunopathology (Including Immunohistochemistry)

- p16 staining may be helpful in discriminating HPV-associated carcinomas from those that are HPV negative. However, special stains are not routinely used.

Main Differential Diagnosis

- Tangential sectioning of VIN—the nests are regular in contour with preserved polarity.
- Adnexal involvement—similar to tangential sectioning.
- Pseudoepitheliomatous hyperplasia—fine threadlike strands interconnect nests of benign-appearing epithelium. However, similar changes can occur in VIN.
- Artifactual displacement of tumor by trauma/iatrogenic—look for other evidence of trauma, markedly dilated vessels suggesting anesthetic injection, disaggregated fragments of tumor rather than more rounded smooth-bordered tumor conforming to the vessel wall.
- Keratoacanthoma—always a difficult distinction and one that should be made with caution.

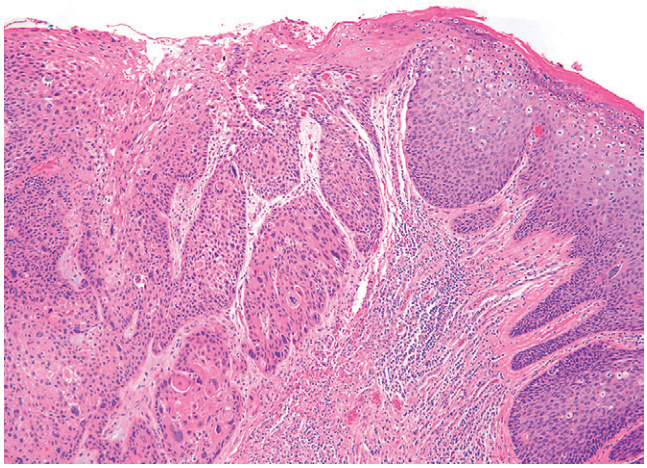


FIGURE 1

Vulvar squamous cell carcinoma. An HSIL on the right merges with an invasive carcinoma at the left.

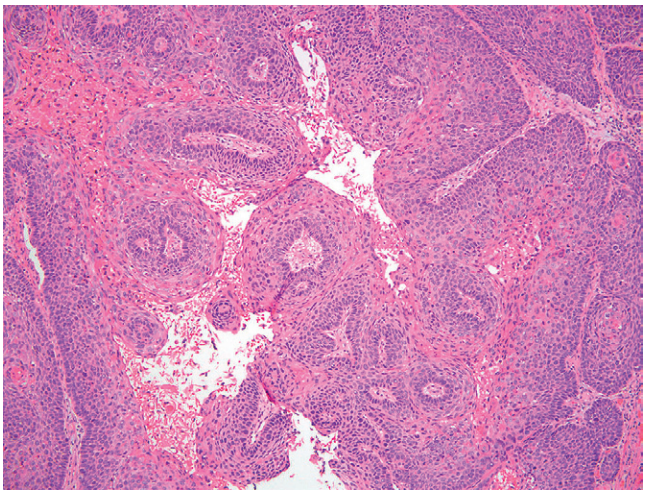


FIGURE 3

Vulvar squamous cell carcinoma. Irregular ill-defined papillary architecture with abnormal parakeratosis lends a warty appearance to this tumor.

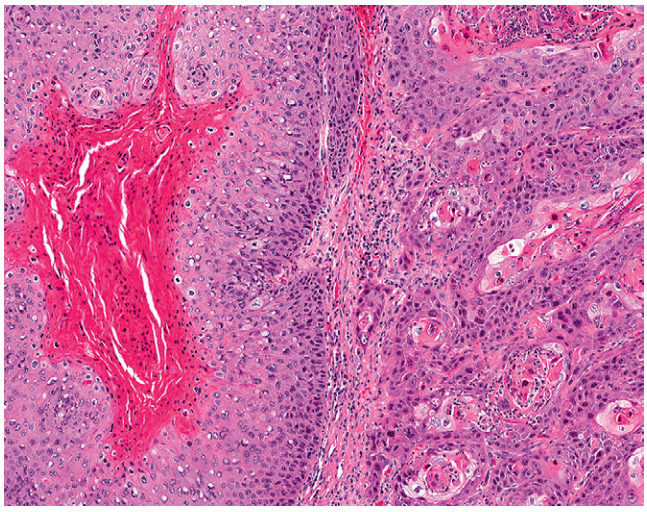


FIGURE 2

Vulvar squamous cell carcinoma. Irregular nests of invasive carcinoma at the right beneath an intraepithelial lesion (VIN, left).

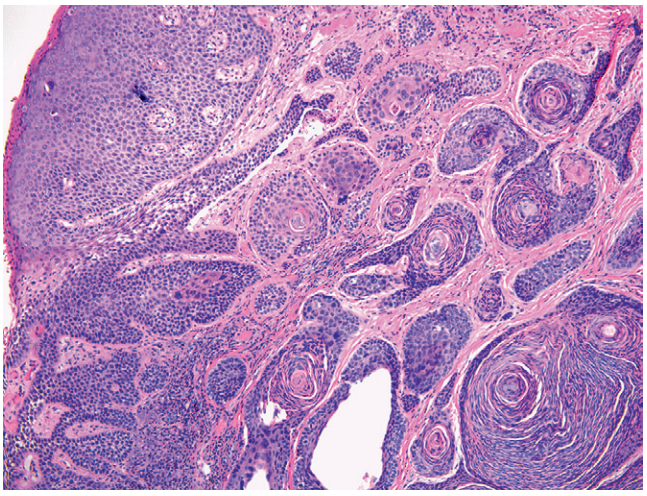


FIGURE 4

Vulvar squamous cell carcinoma. An HSIL (upper left) overlays poorly differentiated infiltrating (basaloid) squamous carcinoma. Note the similarity of the invasive component to the HSIL (intraepithelial like).

VULVAR SQUAMOUS CARCINOMA: KERATINIZING PATTERN

Definition—Invasive epithelial neoplasm composed of keratinocytes involving the vulva. Human papillomavirus (HPV) negative.

Clinical Features

Epidemiology

- Typically affects women in their seventh and eighth decades and is usually found associated with inflammatory dermatosis (differentiated vulvar intraepithelial neoplasia [VIN]).
- Some patients present with no history of vulvar neoplasia.
- Not associated with HPV and not associated with squamous neoplasms of the cervix.

Presentation

- Typically emerges in the background of vulvar inflammatory disease.
- Often not preceded by a diagnosis of differentiated VIN.
- May develop rapidly as a nodule.

Prognosis and Treatment

- Guarded, patients with localized, resectable disease have a variable recurrence rate.
- Patients with documented nodal spread or recurrence in the groin have a mortality of 85% to 100%.
- Localized recurrence may be treated with re-excision or radiation.
- Surgical resection with or without lymph node dissection is the most common treatment approach.
- There is increasing interest in sentinel lymph node excision to decrease morbidity.

Pathology

Histology

- Tumors that demonstrate maturation and keratinization toward the epithelial surface (or in the center of invasive nests of tumor).
- Mild to moderate nuclear atypia is usually present in the basal layers as these tumors are often associated with differentiated VIN or inflammatory dermatoses.
- Invasive nests of tumor may range from large, blunt, cohesive cell nests with conspicuous keratinization to small, angular nests of malignant cells.
- Single, invasive, eosinophilic cells may be noted as well.

Diagnostic terminology: Well/moderately/poorly differentiated keratinizing squamous cell carcinoma.

Immunopathology (Including Immunohistochemistry)

- p16 staining will be negative or patchy, therefore is not helpful.
- p53 staining will typically be strong in the immature epithelial layers.
- Lesions will be HPV negative by in situ hybridization or other HPV detection techniques.

Main Differential Diagnosis

- Tangential sectioning of differentiated VIN: This can be highly subjective.
- Pseudoepitheliomatous hyperplasia (PEH): Differentiation from keratinizing cancer can be difficult. Important is the lack of atypia with PEH.
- Inverted keratosis: Lack of atypia at the epithelial stromal interface.

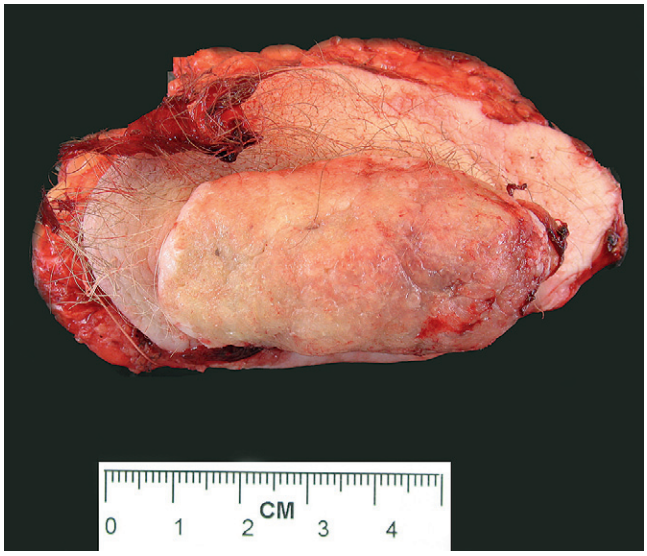


FIGURE 1

Keratinizing vulvar squamous cell carcinoma. A discrete plaquelike tumor on this wide excision.

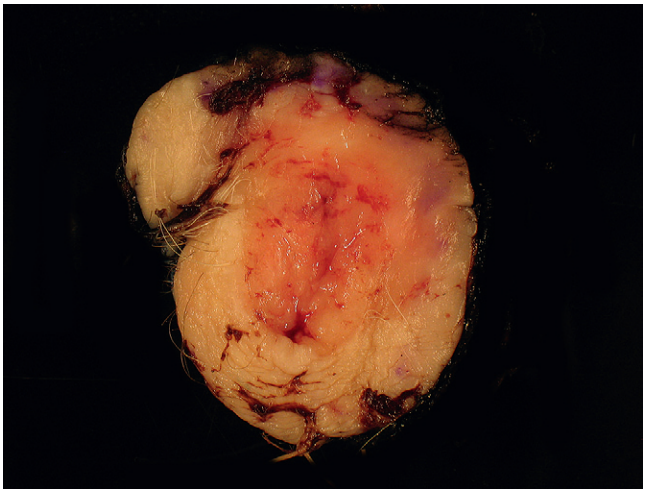


FIGURE 3

Keratinizing vulvar squamous cell carcinoma. This tumor presents as a flat shallow ulcer without exophytic growth.

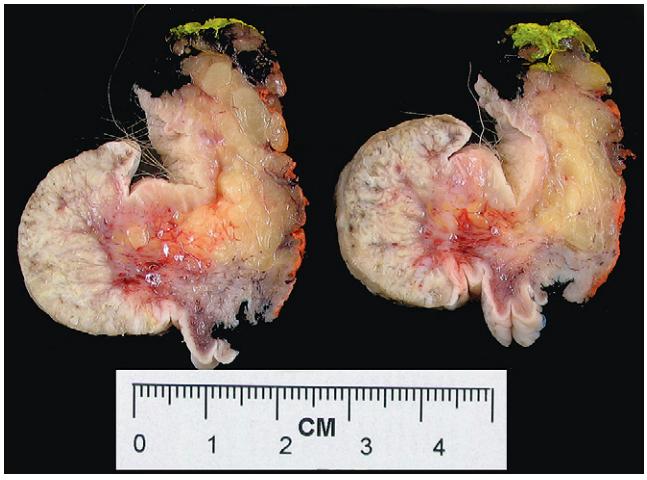


FIGURE 2

Keratinizing vulvar squamous cell carcinoma. Sectioning of the tumor in Figure 1 shows a raised warty or exophytic appearance.

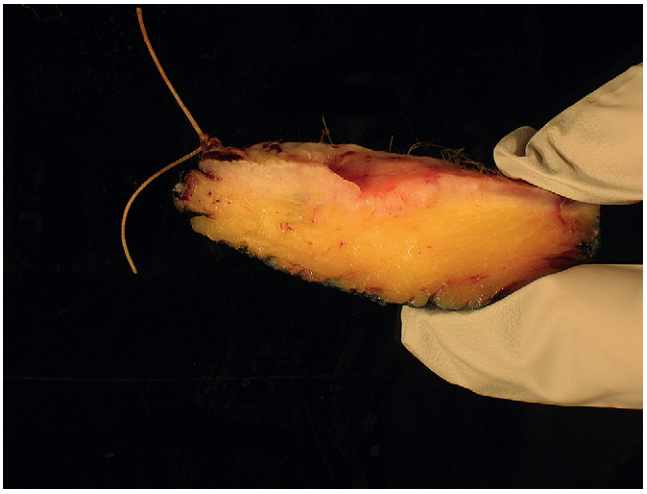


FIGURE 4

Keratinizing vulvar squamous cell carcinoma. Sectioning of the tumor in Figure 3 shows the shallow ulcer with vertical growth into the stroma. This can appear to happen rather quickly in some cases.

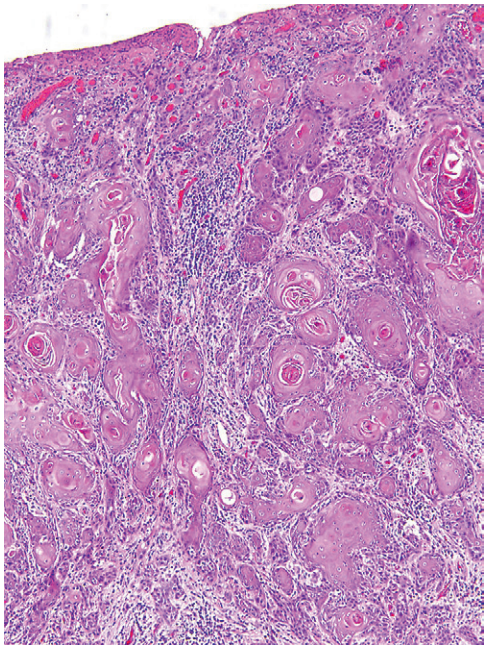


FIGURE 5

Keratinizing vulvar squamous cell carcinoma. Confluent, disorganized tumor nests of variable sizes penetrate the stroma, with focal keratinization.

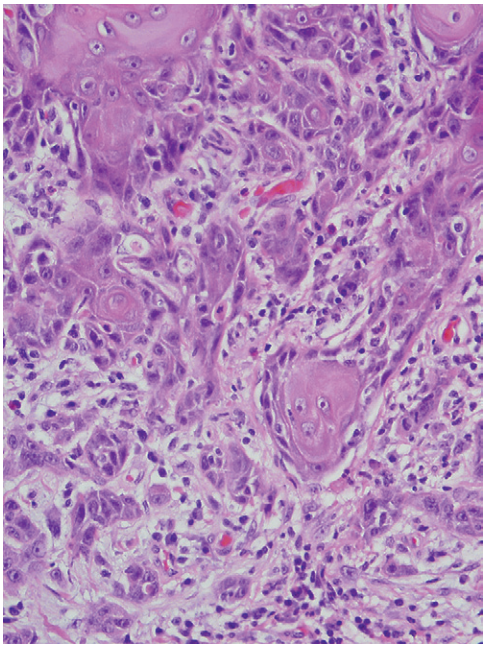


FIGURE 6

Keratinizing vulvar squamous cell carcinoma. Tumor stromal interfaces with conspicuous atypia.

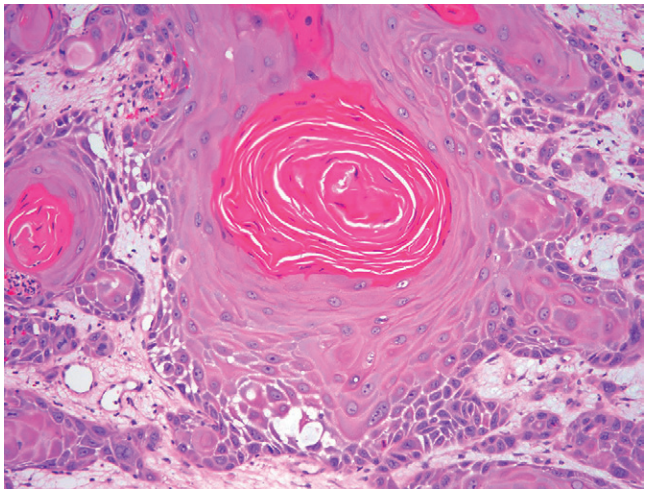


FIGURE 7

Keratinizing vulvar squamous cell carcinoma. Note the sharp transition from basal atypia to a blander mature keratinizing epitheium.

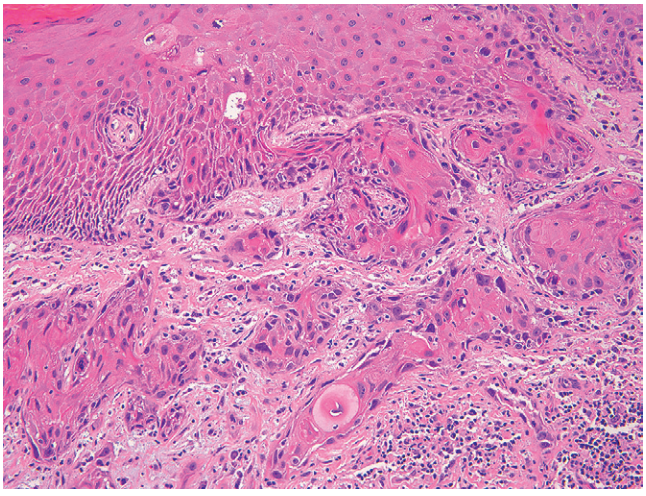


FIGURE 8

Keratinizing vulvar squamous cell carcinoma. The prominent nuclear atypia distinguishes this from pseudoepitheliomatous hyperplasia or tangentially sectioned reactive epithelial changes.

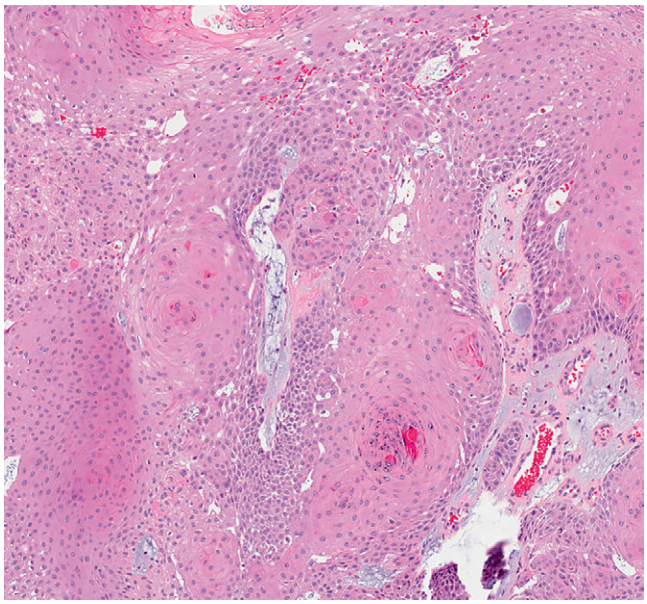


FIGURE 9

Inverted keratosis. This will present an appearance of disorganized keratinizing epithelium. However, note the lack of atypia.

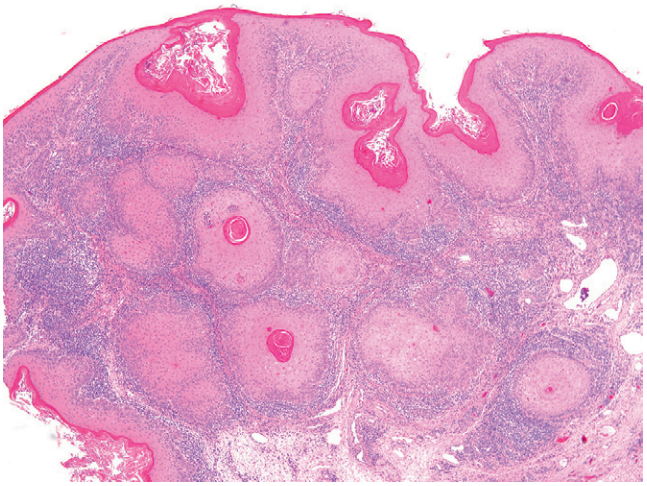


FIGURE 10

PEH with a dense lymphoplasmacytic infiltrate. This may mimic keratinizing carcinoma but raises the possibility of syphilis, which must be excluded.

VERRUCOUS SQUAMOUS CELL CARCINOMA

Definition—Invasive epithelial neoplasm composed of keratinocytes involving the vulva. Exhibits a distinct histology and invasive pattern that is nonmetastasizing.

Clinical Features

Epidemiology

- Typically affects women in their seventh and eighth decades and is usually found associated with inflammatory dermatosis. May be associated with atypical verruciform hyperplasia.
- Human papillomavirus (HPV) negative and not linked to other gynecologic (cervical) squamous lesions.

Presentation

- Usually elderly, long-standing inflammatory dermatosis, such as lichen simplex chronicus (LSC) or lichen sclerosus et atrophicus (LSA) may be present with an associated mass lesion.

Prognosis and Treatment

- Good prognosis if resectable and not associated with conventional carcinoma.
- Localized recurrence may be treated with re-excision; radiation to be avoided.
- Surgical resection with or without lymph node dissection is the most common treatment approach.

Pathology

Histology

Cardinal histologic features
- Large verruciform mass.
- The absence of atypia in the superficial layers and at the stromal interface.
- Bulbous, blunt pattern of invasion.
- Some inflammation or necrosis common.
- The large lesions must be extensively sampled to rule out concurrent conventional squamous cell carcinoma.

Diagnostic terminology: Extremely well-differentiated squamous carcinoma (verrucous carcinoma [VC]) (with measurements and margins). Comment: This form of squamous carcinoma is not typically associated with lymph node metastases. However, clinical correlation is advised.

Immunopathology (Including Immunohistochemistry)

- p16 staining will be patchy or negative at the stromal interface.
- Ki-67 labeling is not increased, confined to the basal layers.
- p53 immunostaining should be weak and sporadic.
- HPV negative.

Main Differential Diagnosis

- Large (giant) condylomas. These can be seen at all ages including older women. Key features are an exophytic growth pattern without appreciable extension into the underlying stroma and normal keratinocyte maturation relative to VC.
- Deceptively bland keratinizing squamous carcinomas. These will differ from VC by the more irregular interface. Look closely for interface atypia.
- Keratoacanthoma.

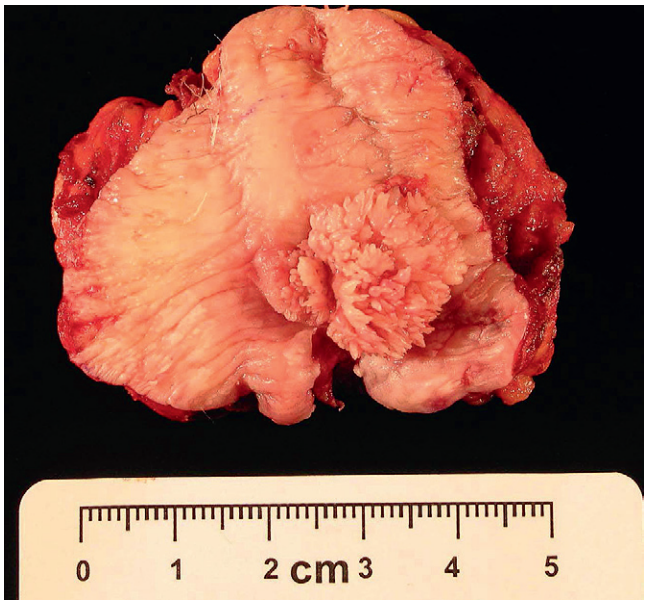


FIGURE 1
VC. Gross photo of a fungating discrete mass on the vulva.

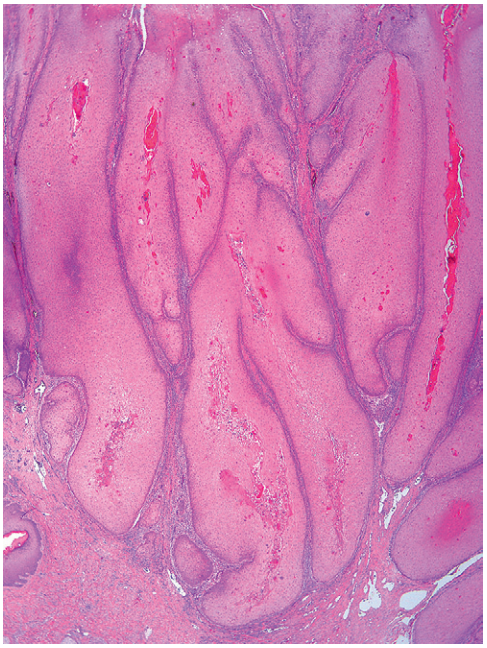


FIGURE 2
Low magnification depicts the bulbous growth pattern.

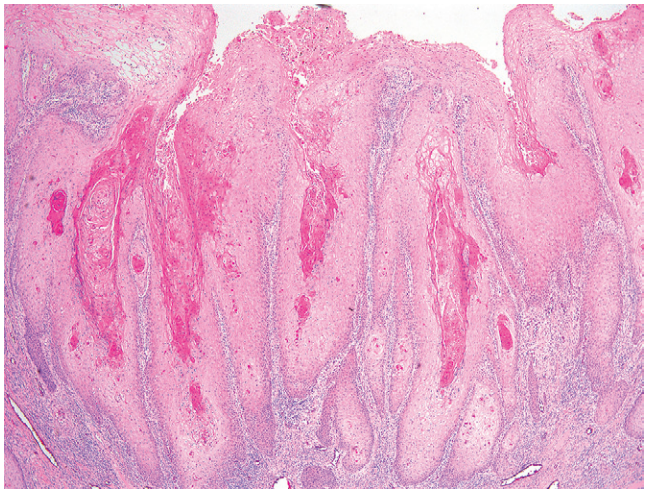


FIGURE 3
This low-power image of a VC illustrates a more narrow growth pattern.

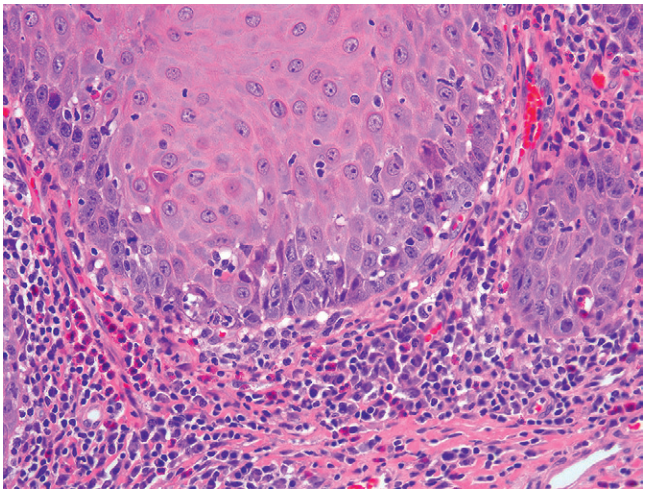


FIGURE 4
At high magnification the basal cells are uniform, albeit with prominent nucleoli.

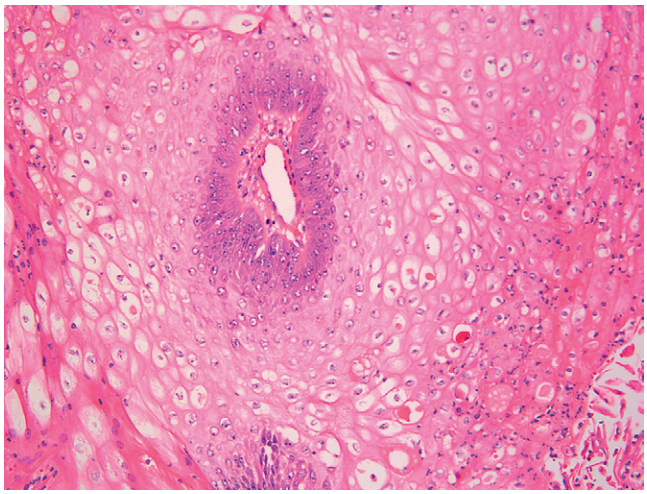


FIGURE 5

The absence of superficial atypia characterizes VC.

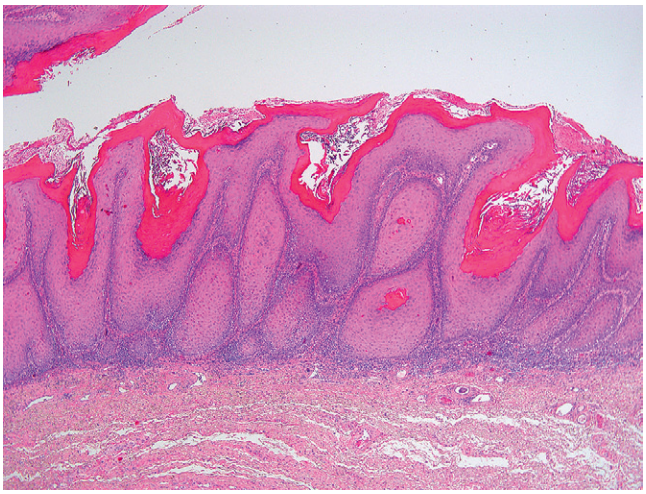


FIGURE 6

An earlier noninvasive component of a VC, adjacent to the main tumor mass.

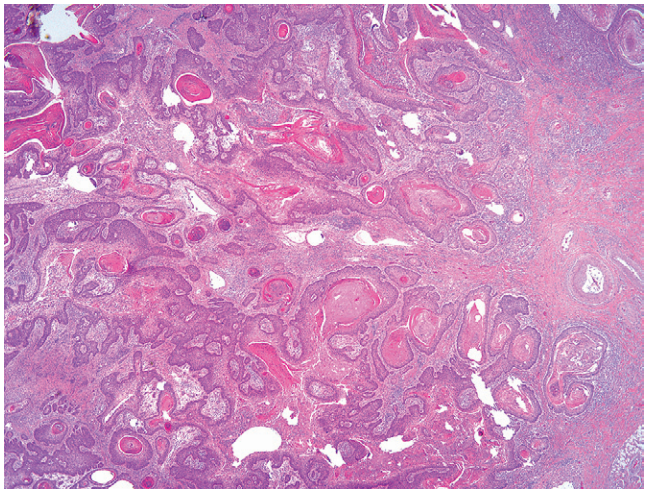


FIGURE 7

Low magnification of a well-differentiated conventional squamous carcinoma.

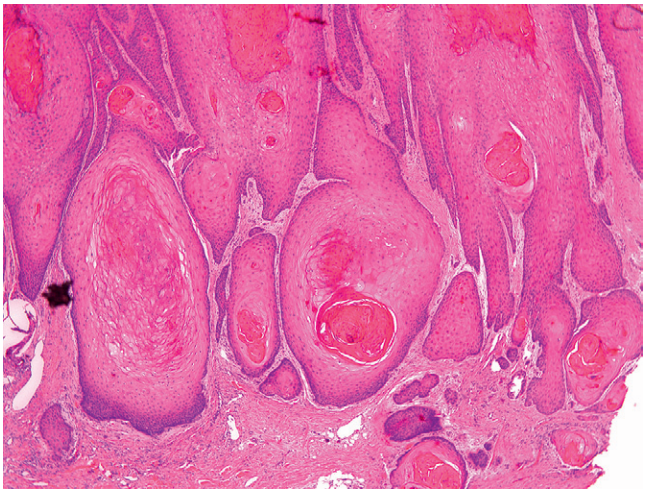


FIGURE 8

This low-power view of a well-differentiated vulvar squamous carcinoma resembles VC but depicts more irregular, angulated invasive epithelium.

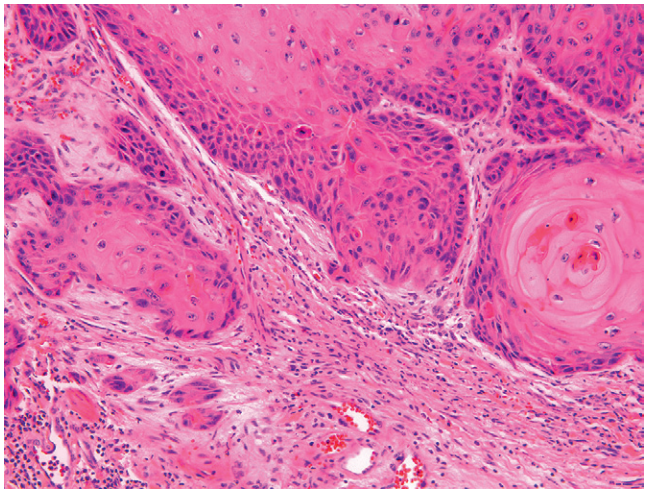


FIGURE 9

A different field of the case in Figure 8 confirms interface atypia and invasion by small groups of cells.

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (VULVAR INTRAEPITHELIAL NEOPLASIA III) WITH CONFLUENT PAPILLARY GROWTH

Definition—A papillary exophytic squamous lesion similar in morphology to vulvar intraepithelial neoplasia (VIN) III but with risk of underlying invasion.

Clinical Features

Epidemiology

- Identical to that of a classic or usual high-grade VIN. May be associated with an invasive carcinoma. Human papillomavirus (HPV) positive, usually HPV 16. Predominating in the fifth and sixth decades of age.

Presentation

- Raised, verruciform- or condyloma-like lesions, may be erythematous and hyperkeratotic.

Prognosis and Treatment

- Managed by excision and lymph node dissection if invasion is present or strongly suspected. If not, wide excision alone will suffice. Risk of lymph node involvement is minimal if there is no invasion.

Pathology

Histology

- High-grade histology, in keeping with a VIN III. Confluent or complex intraepithelial growth pattern with "reduplication" and exophytic features. Confluent growth pattern resembles a carcinoma but may not breach the basal lamina.

Immunohistochemistry

- Not necessary if the histology is characteristic of a high-grade lesion, but Mib-1 and p16ink4 stains will be positive (diffuse distribution). These cells are usually HPV positive (high-risk types mostly HPV 16).

Main Differential Diagnosis

- Condyloma—these might be confused with carcinoma if markedly inflamed or very large.
- Unclassified papillary neoplasms with moderate atypia—this entity is not well defined but falls between condyloma and a papillary carcinoma.
- Verruciform VIN II and III—the epithelial architecture is preserved, and "reduplication" is not seen.
- Verrucous carcinoma—these are very well differentiated.

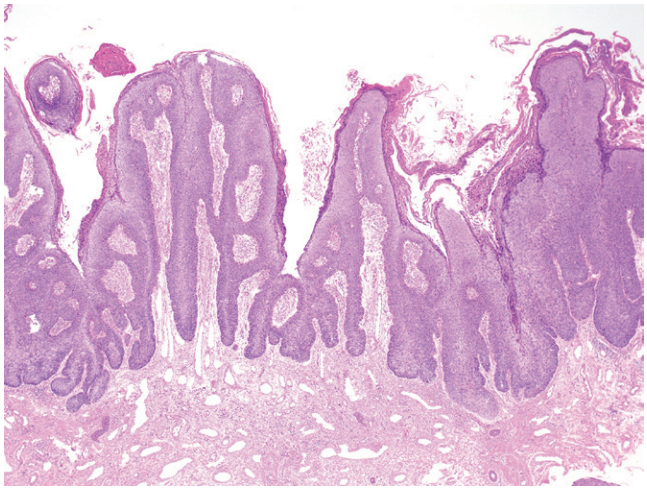


FIGURE 1

Papillary high-grade squamous intraepithelial lesion (HSIL). This is a typical HSIL of the vulva. There is no confluence of papillary growth.

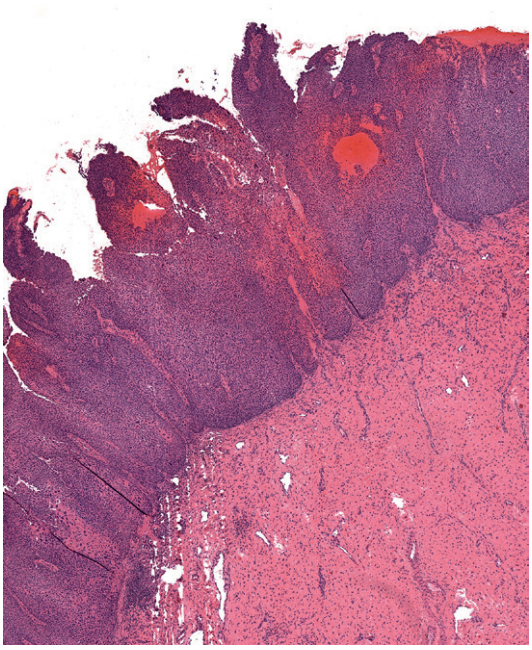


FIGURE 2

Papillary HSIL. There is focal confluence of papillae but the degree is still within the range accepted for an HSIL.

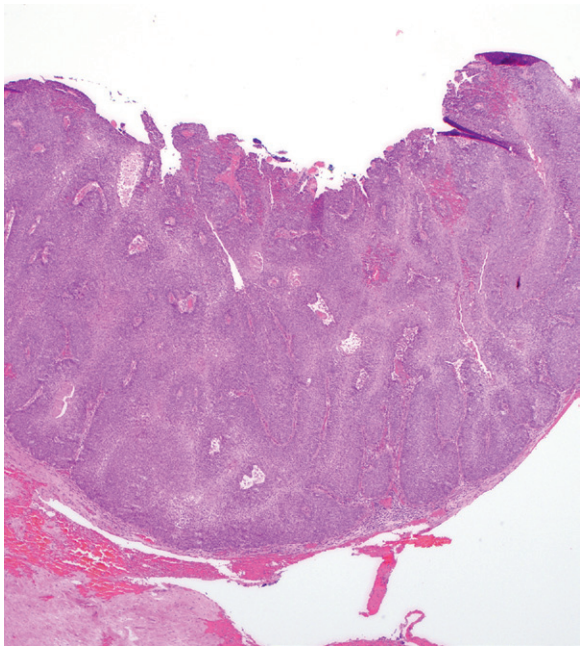


FIGURE 3

HSIL with confluent papillary growth. This is analogous to papillary carcinoma; however, there is no stromal invasion.

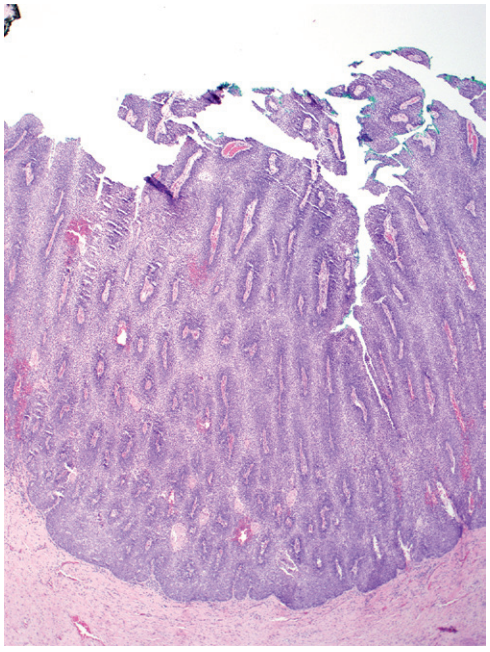


FIGURE 4

HSIL with confluent papillary growth. This is analogous to papillary carcinoma; however, there is no stromal invasion.

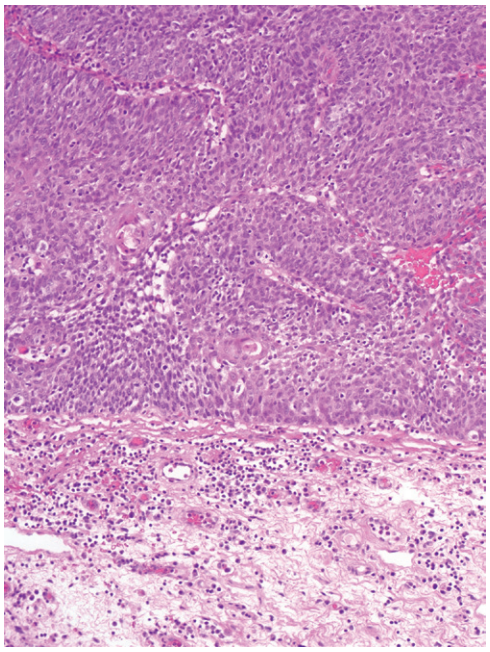


FIGURE 5
Uniform epithelial–stromal interface in a papillary HSIL with complex growth.

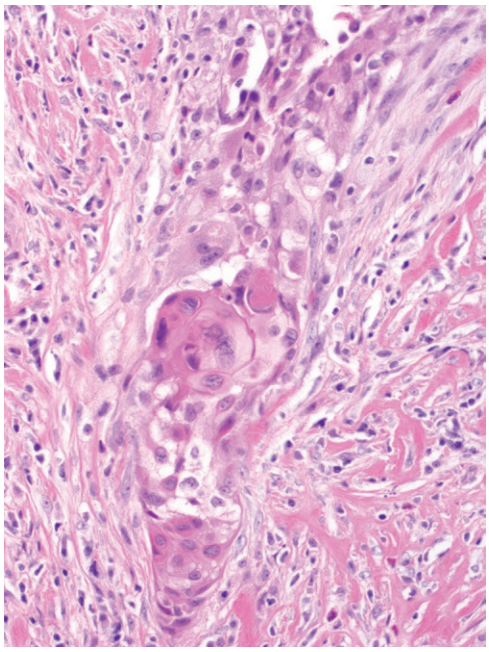


FIGURE 6
A focus of invasion confirms malignancy.

GIANT CONDYLOMA OF THE EXTERNAL GENITALIA

PITFALL

Definition—A papillosquamous lesion of significant size, histologically indistinguishable from generic condyloma.

Clinical Features

Epidemiology

- A rare entity that most commonly affects young men.
- Seen more commonly in immunosuppressed patients (human immunodeficiency virus [HIV] positive).
- Can also be seen in older women and may be human papillomavirus (HPV) negative.

Presentation

- Large, diffuse, papillary lesions resembling typical condyloma, with a much more extensive distribution.

Prognosis and Treatment

- Topical and surgical treatments are available; however, the disease has a high local recurrence rate, especially in immunocompromised individuals.
- In elderly patients close follow-up is advised to exclude progression to a more aggressive entity (such as verrucous carcinoma or keratinizing squamous carcinoma).

Pathology

Histology

- Papillary squamous hyperplasia.
- Koilocytosis is variable and may be absent in older women.
- These lesions are differentiated from verrucous carcinoma in that they have uniform cell maturation and lack of fingerlike projections into the underlying stroma.
- Inflammation may be present.

Diagnostic terminology: Extensive (giant) condyloma.

Immunopathology (Including Immunohistochemistry)

- Mib-1 and p16 staining are patchy and not dramatically increased.
- p53 staining will be weak or patchy.
- HPV testing should reveal HPV 6 or 11 in many cases, but some will score negative, suggesting an alternative pathogenesis.

Main Differential Diagnosis

- Condyloma—smaller, has more conspicuous koilocytosis or keratohyalin granules.
- Verrucous carcinoma—bulbous downward growth, epithelial pallor.

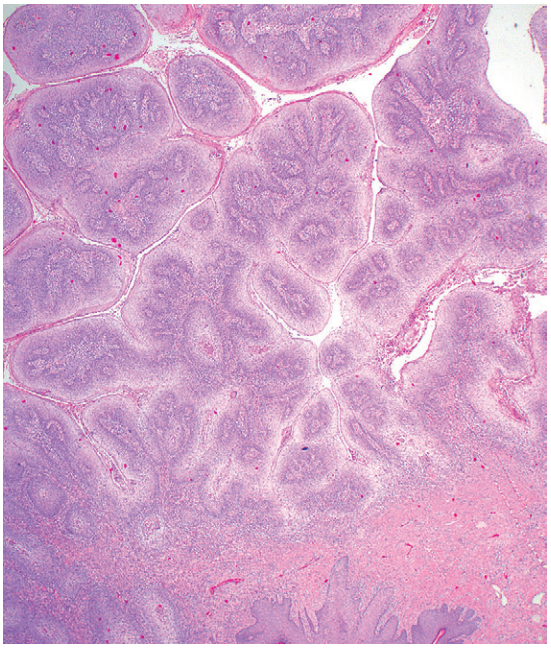


FIGURE 1

Giant condyloma. A large lesion with broad verrucopapillary projections.

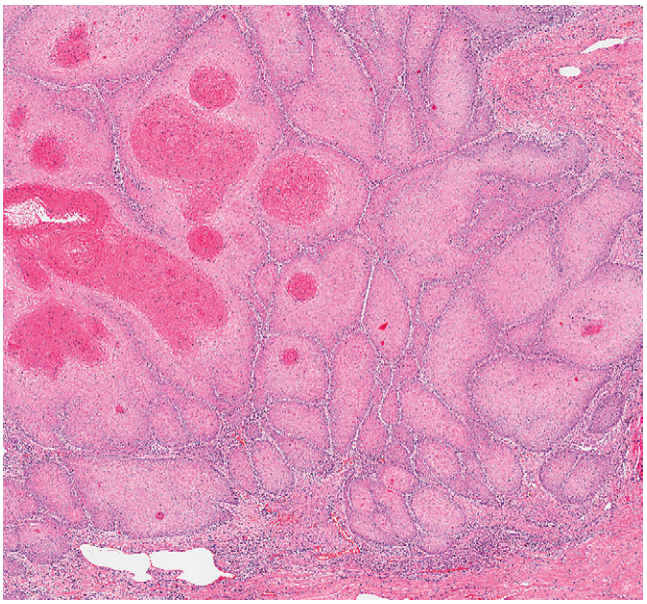


FIGURE 2

Verrucous carcinoma for comparison. Note the numerous rounded epithelial nests penetrating the underlying stroma.

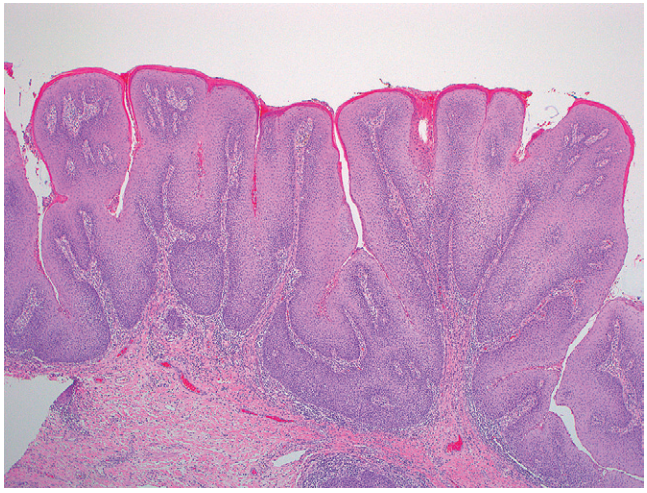


FIGURE 3

Giant condyloma. A less dramatic verrucous growth in this area.

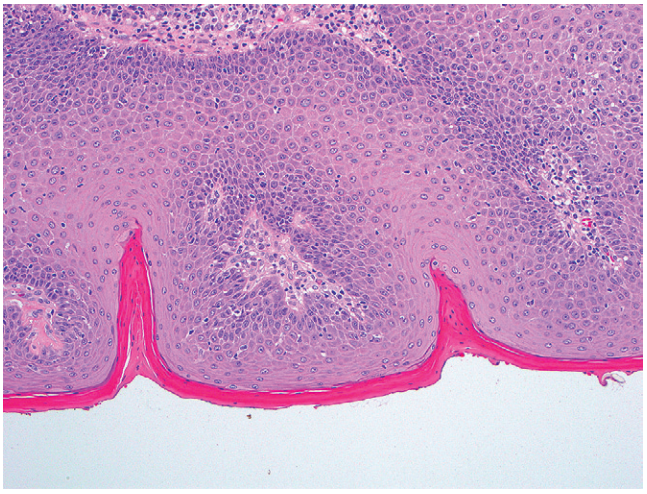


FIGURE 4

Giant condyloma. Superficial growth with uniform maturation. However, note the lack of koilocytotic atypia.

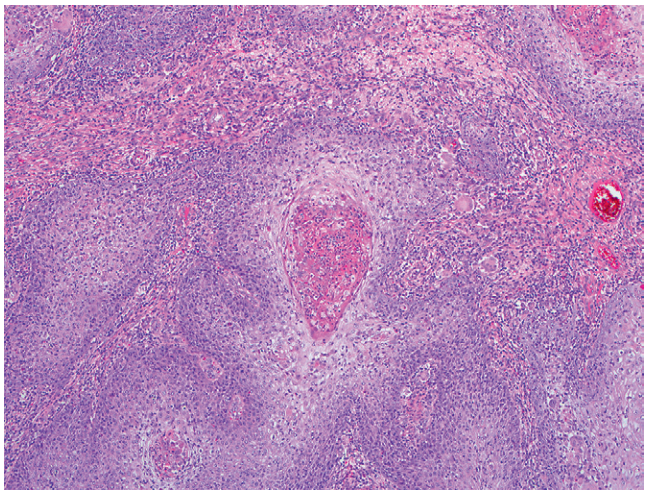


FIGURE 5
Giant condyloma. Note the inflammation at the epithelial stromal interface.

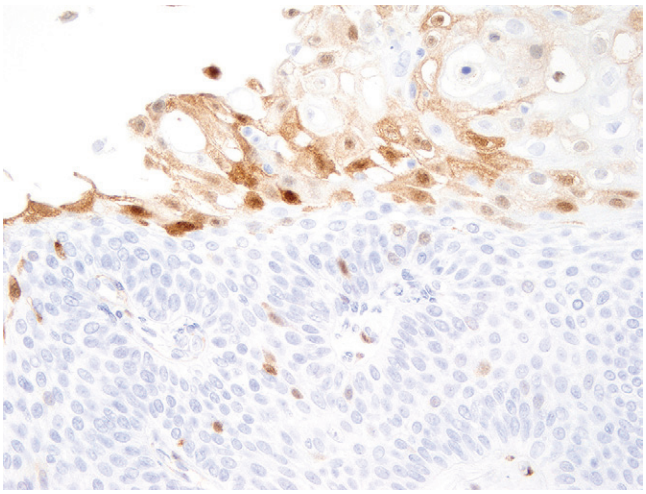


FIGURE 6
Giant condyloma. p16 staining is weak or patchy.

PSEUDOEPITHELIOMATOUS HYPERPLASIA

PITFALL

Definition—A reactive condition marked by acanthosis and irregular epithelial architecture.

Clinical Features

Epidemiology

- Noncontributory.

Presentation

- Thickening of the skin, coexisting conditions are usually present (occasionally, granular cell tumor)

Prognosis and Treatment

- Noncontributory.

Pathology

Histology

- Acanthosis with an irregular dermal/epidermal junction.
- Traditionally there is a lack of atypia, and the dermal component consists of thin, irregular squamous projections that frequently have pointed tips.
- Underlying conditions such as a granular cell tumor or inflammatory process should be sought out.

Immunopathology (Including Immunohistochemistry)

- Noncontributory although staining for both p16 and p53 should be negative if there is no coexisting vulvar intraepithelial neoplasia (VIN).

Main Differential Diagnosis

- Squamous cell carcinoma with or without invasion.
- A syphilitic lesion can also present this way (look for abundant plasma cells and do appropriate tests if concerned).
- Rarely, associated with an underlying granular cell tumor.

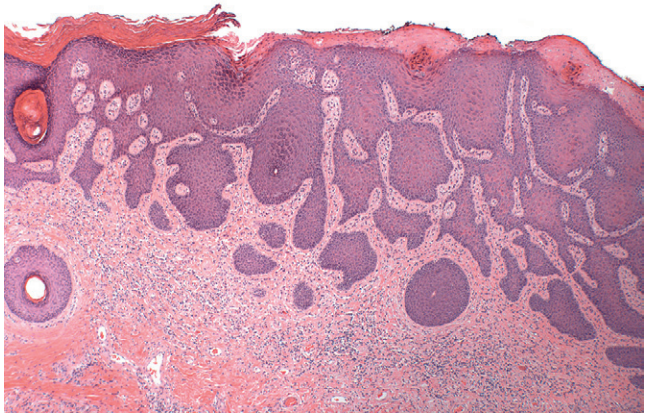


FIGURE 1

Pseudoepitheliomatous hyperplasia (PEH). There are numerous subsurface epithelial nests, connected by thin septae. There may be an element of tangential sectioning in this case.

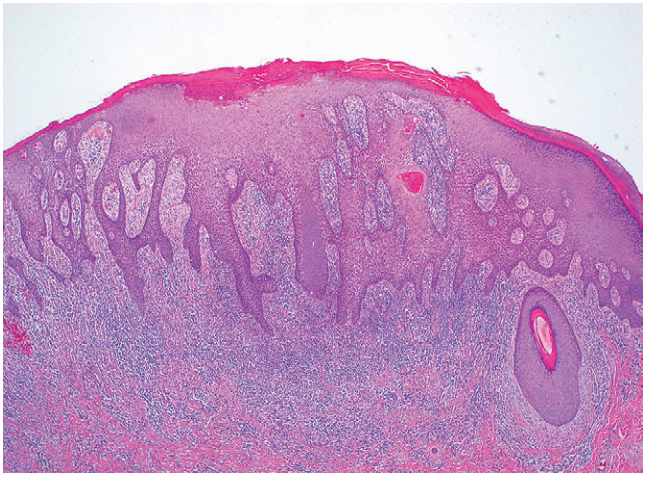


FIGURE 2

PEH. Marked acanthosis with irregular, pointed epithelial projections into the stroma. Abnormal keratinization may be present and is not a sign of malignancy.

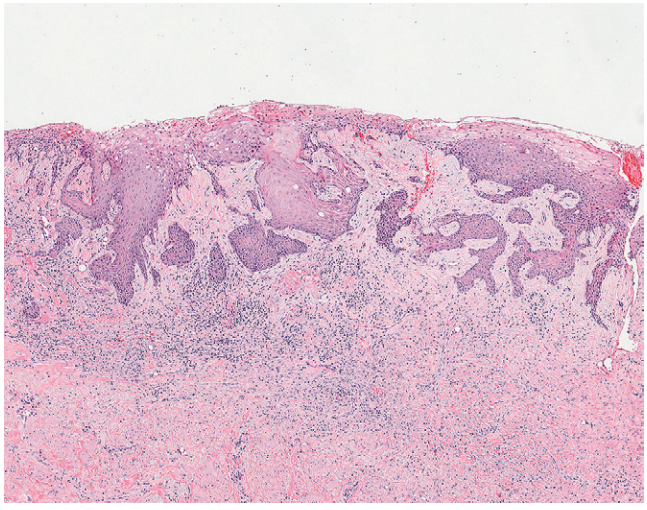


FIGURE 3

PEH. This is a more challenging case and might elicit some controversy as to whether this is PEH or invasive carcinoma. This patient was irradiated for a prior squamous carcinoma. Note the oddly angulated subsurface nests and the *absence* of atypia, loss of polarity, and desmoplasia.

KERATOACANTHOMA

PITFALL

Definition—A neoplastic proliferation of keratinocytes arising in follicular epithelium.

Clinical Features

Epidemiology

- Typically occurs in the middle aged to elderly.
- Suspected causes include ultraviolet light, immunosuppression, genetic alterations, chemical exposure, viruses, and trauma.

Presentation

- Papular masses with central umbilication and keratin accumulation form rapidly.

Prognosis and Treatment

- The prognosis is good.
- Most cases left untreated will spontaneously regress; however, rare cases of metastasis have been noted.
- Surgery is curative in the vast majority of cases.

Pathology

Histology

- A discrete, inverted, cup-shaped lesion with central keratin accumulation.
- In general the basal keratinocytes lack atypia when compared with traditional squamous cell carcinoma.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Traditional squamous cell carcinoma—conspicuous atypia is the norm but not invariable.
- Pustular folliculitis.

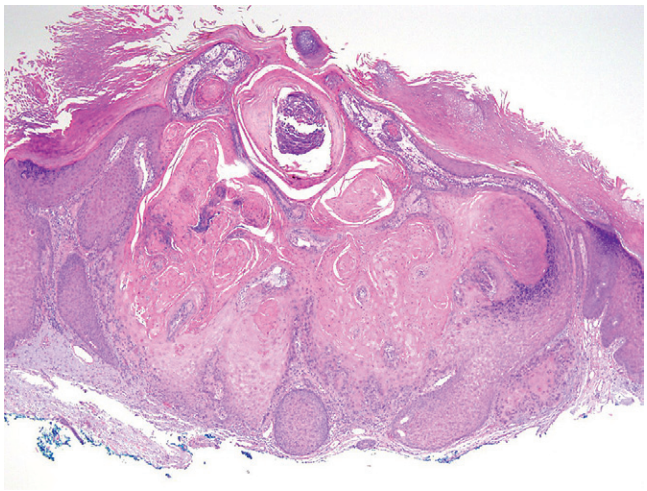


FIGURE 1

Keratoacanthoma. Low-power examination reveals a cup-shaped lesion with pushing borders and central keratinization.

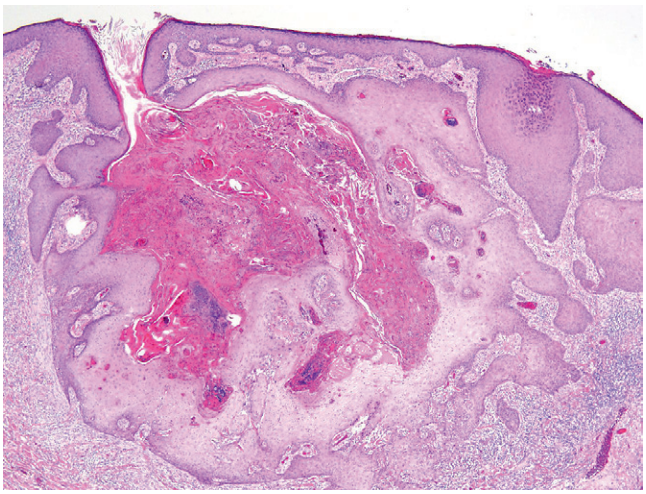


FIGURE 2

Keratoacanthoma. Prominent keratinization may be seen in the center of the lesion. Note the irregular epithelial stromal interface.

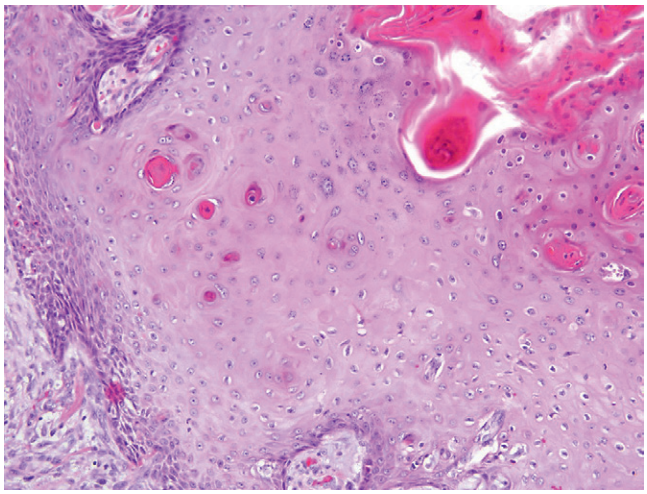


FIGURE 3

Keratoacanthoma. The squamous cells lack conspicuous atypia.

BASAL CELL CARCINOMA

Definition—An uncommon, nonmetastasizing (usually!) but locally destructive carcinoma of basal keratinocytes with characteristic peripheral nuclear palisading.

Clinical Features

Epidemiology

- Rare.
- Not human papillomavirus (HPV) associated.
- Elderly women in their 70s and 80s.

Presentation

- Typically a raised, sometimes ulcerated, discoid vulvar lesion.
- Occasionally presents as a polypoid mass.

Prognosis and Treatment

- Wide local excision is appropriate,
- These carcinomas are nonmetastasizing but have a propensity for destructive local recurrence.
- Rare reports of nodal metastases exist.
- May be a candidate for Mohs' surgery.

Pathology

Histology

- Vulvar tumors have the same histologic features as lesions at other sites.
- These carcinomas are characterized by a monotonous, cohesive population of small blue cells with a high nuclear-to-cytoplasmic ratio.
- Cells may be arranged in rounded or elongated nests with peripheral nuclear palisading (classic pattern), or as infiltrative cords and strands set in a myxoid matrix with a reticular architecture (adenoid pattern).
- Nests often show characteristic clefting between tumor cells and surrounding stroma.
- The tumor cells lack significant nuclear atypia, and mitotic figures are rare.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Basaloid squamous cell carcinoma—higher nuclear grade, irregular growth pattern, associated vulvar intraepithelial neoplasia (VIN).
- Pagetoid VIN—discrete foci of neoplastic epithelium but intraepithelial and does not extend into stroma.
- Differentiated VIN with parabasal expansion—nesting is less discrete.
- Adenoid cystic carcinoma—mimicked by adenoid variant of basal cell carcinoma (BCC).
- Syringoma—bland-appearing nests may suggest BCC at low power.

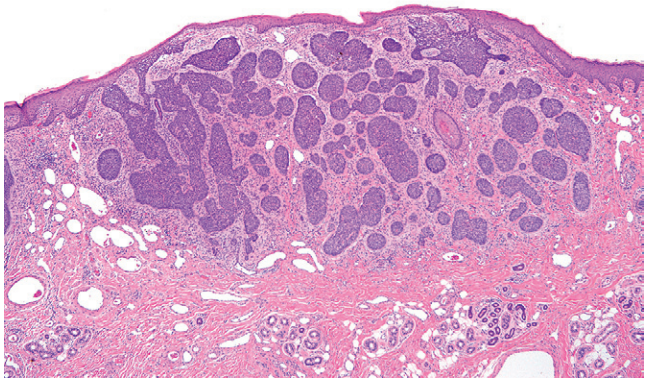


FIGURE 1

BCC. At low power, nests of darkly staining cells are emanating from abnormal basal cells at the epithelial–stromal interface, forming a nodular mass.

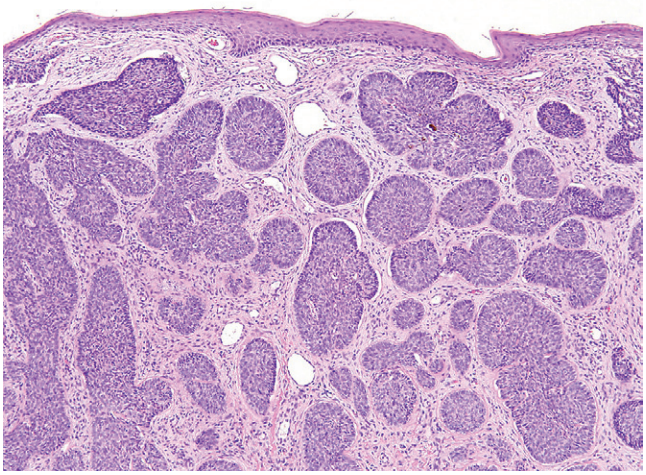


FIGURE 2

At higher magnification, the discrete nests are regularly arranged with minimal stromal reaction.

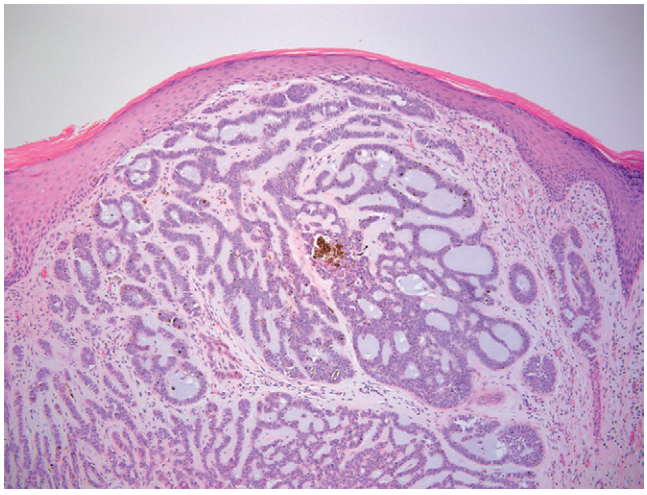


FIGURE 3

BCC with an adenoid pattern with delicate anastomosing strands of neoplastic epithelium. Note the pigment in the center.

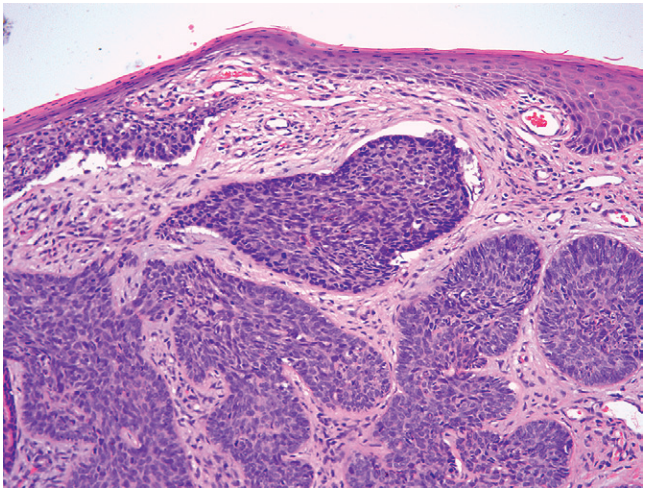


FIGURE 4

BCC. BCC with discrete nests of neoplastic basal cells and minimal stromal reaction in the dermis.

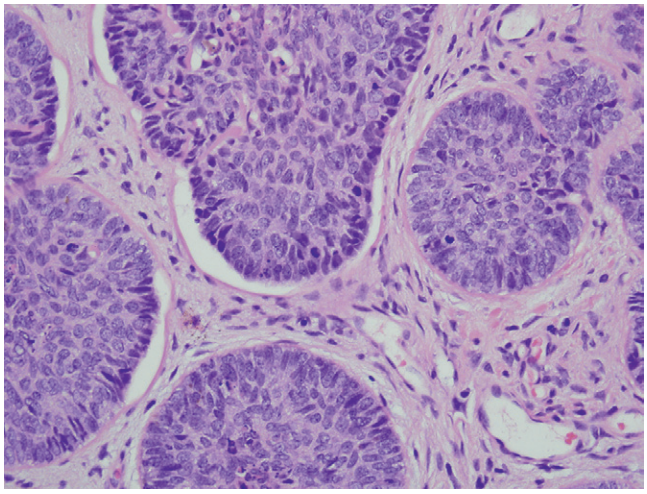


FIGURE 5

BCC at higher power, showing uniformly polarized neoplastic cells and apoptosis.

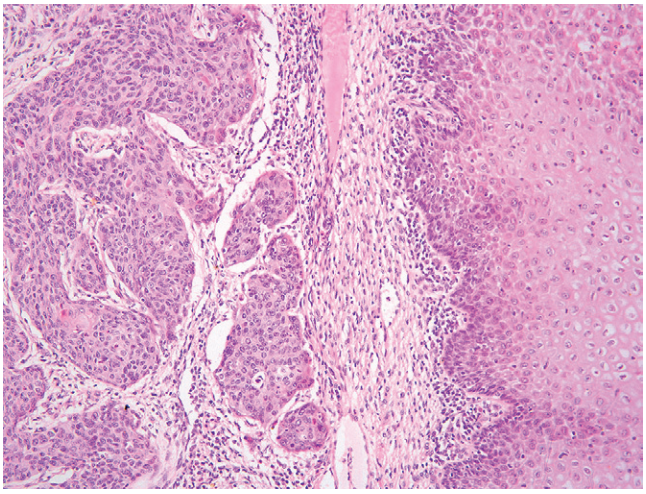


FIGURE 6

Basaloid squamous carcinoma (HPV positive), for comparison, shows an irregular growth pattern and cellular heterogeneity.

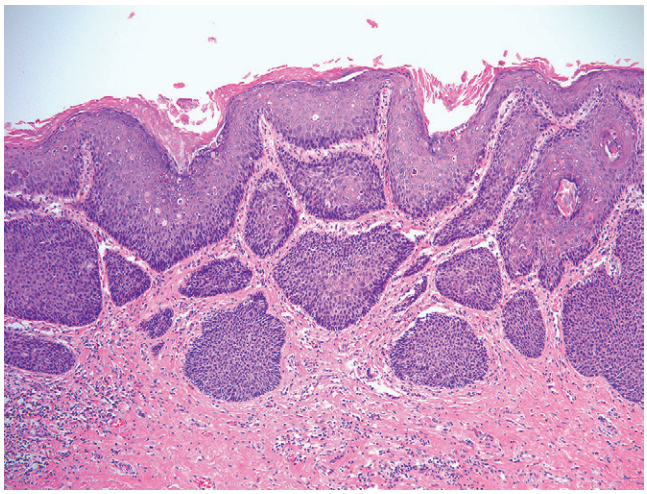


FIGURE 7

Classic VIN, with appendage involvement, for comparison.

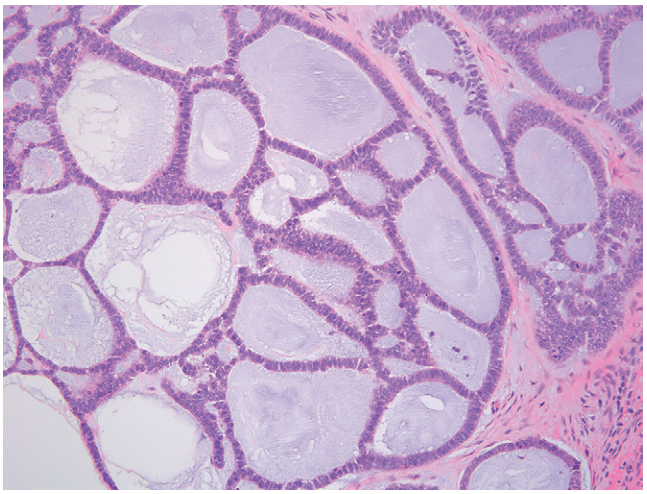


FIGURE 8

High magnification of adenoid BCC of the vulva. Contrast with adenoid cystic carcinoma (see page 74).

ADENOSQUAMOUS CARCINOMA

Definition—An aggressive variant of squamous cell carcinoma with conspicuous glandular differentiation.

Clinical Features

Epidemiology

- Uncommon.
- Mean age at diagnosis is 65 to 70 years.
- Associated with chronic vulvar inflammatory disease.
- Human papillomavirus (HPV) link is unclear but likely when coexisting with basaloid carcinomas.

Presentation

- Vulvar mass involving the labium majus and occasionally the minus; may also arise in the Bartholin's duct or gland.
- The majority of patients present with late-stage disease.

Prognosis and Treatment

- A few reports suggest that outcomes are worse than for conventional squamous cell carcinoma.
- The extent of surgical excision depends heavily on disease extent; small lesions (< 2 cm in diameter and 1 mm thickness) may be treated with wide excision and 1 cm margins.
- For larger lesions, partial radical vulvectomy and ipsilateral groin lymphadenectomy or sentinel node sampling is required.
- For nonsurgical (late-stage) disease, combination chemoradiation is the standard of care.

Pathology

Histology

- This tumor is characterized by a blend of squamous and glandular differentiation.
- The squamous component typically exhibits acanthosis and desquamation of dyskeratotic cells into glandular spaces.
- The glandular component is admixed with the squamous and composed of medium-sized to small acinar glandular spaces.
- The glands are lined by one- to two-cell layer of low columnar to cuboidal cells.
- In most cases the tumor is deeply invasive and involves adjacent perineal structures or the vagina.
- In metastatic lesions the dual squamous and glandular differentiation pattern is retained.

Immunopathology (Including Immunohistochemistry)

- p16ink4 immunostaining, when diffuse and strong, would favor if not guarantee an HPV etiology.

Main Differential Diagnosis

- Conventional invasive squamous cell carcinoma with acantholysis.
- Invasive Paget's disease.
- Amelanotic melanoma.
- Sweat gland carcinoma.

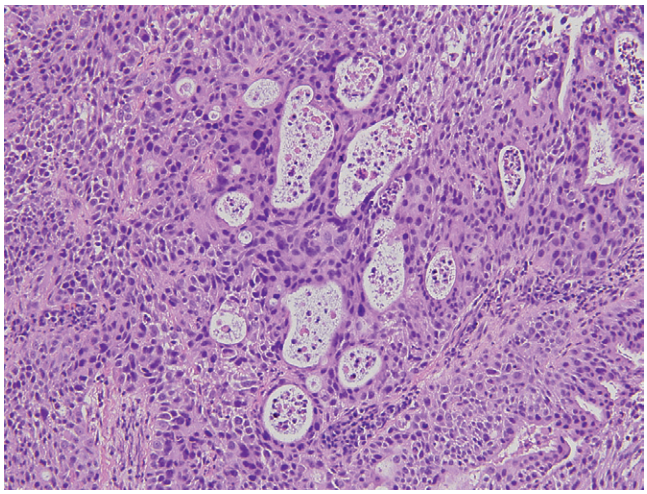


FIGURE 1

Adenosquamous carcinoma. Squamous carcinoma showing acantholysis and desquamation into luminal-like spaces.

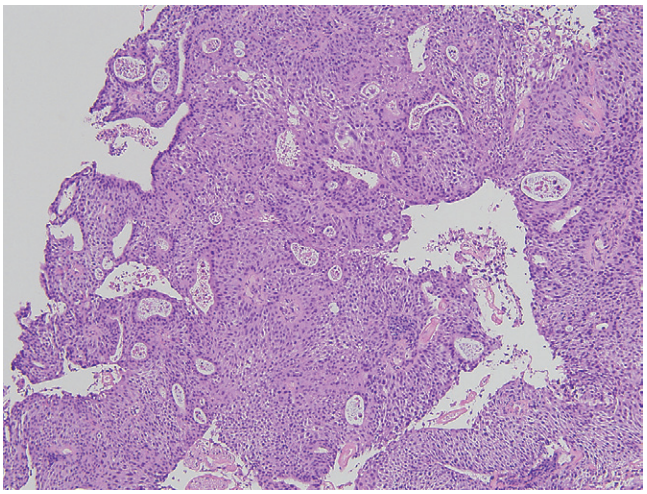


FIGURE 2

Adenosquamous carcinoma. Alternating areas of squamous and glandular differentiation. The glands are frequently lined by low cuboidal epithelium.

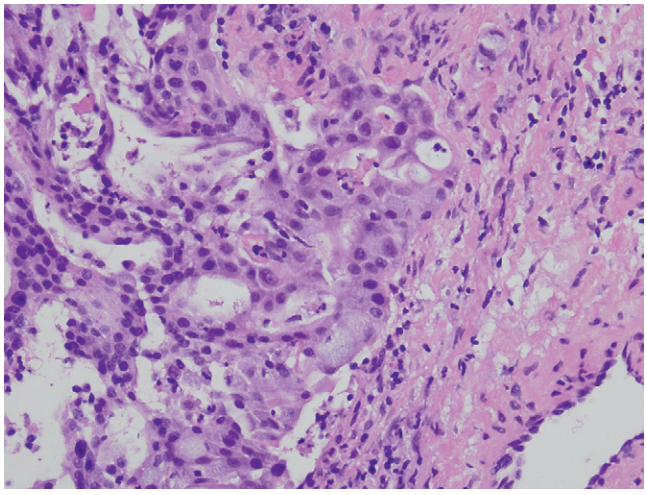


FIGURE 3

Adenosquamous carcinoma. High-power detail of area of adenocarcinoma within an adenosquamous carcinoma. Note the cribriforming glandular spaces lined by low cuboidal to columnar epithelium.

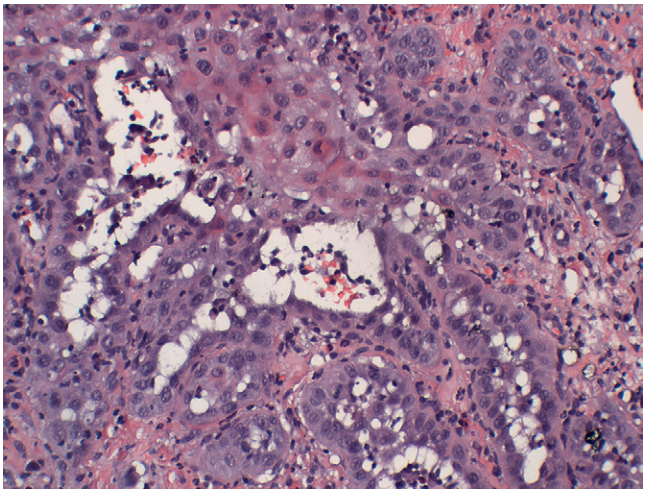


FIGURE 4

Adenosquamous carcinoma. Both carcinoma and adenocarcinoma can be seen here, with the areas of squamous carcinoma denoted by their deeply eosinophilic cytoplasm (keratinization).

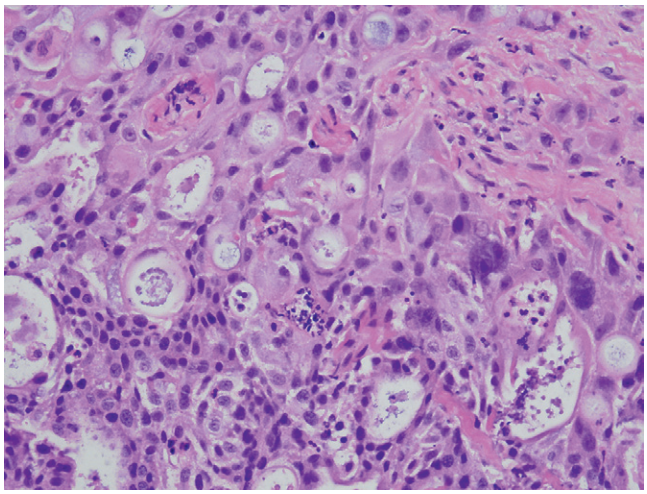


FIGURE 5

Adenosquamous carcinoma. Marked nuclear pleomorphism.

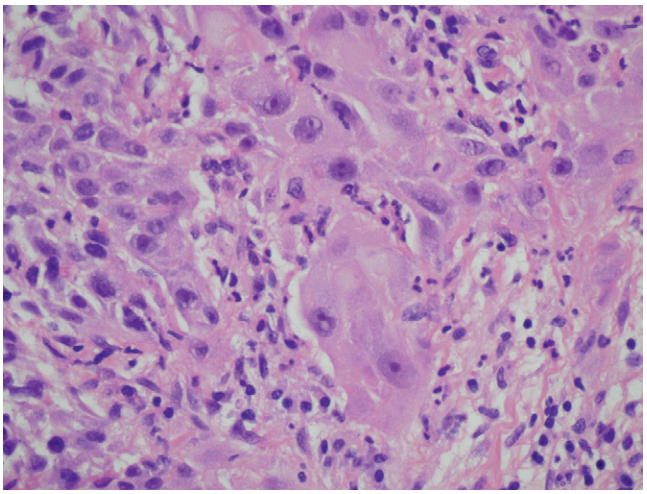


FIGURE 6

Adenosquamous carcinoma. Large keratinizing squamous cells.

PAGET'S DISEASE OF THE VULVA

Definition—Infiltration of the squamous epithelium by mucin-producing neoplastic cells.

Clinical Features

Epidemiology

- Uncommon; represents only 1% to 2% of vulvar malignancies.
- The average age at presentation is 65 years; the majority of patients are over 50 years.

Presentation

- Vulvar pruritus is the most common symptom.
- Ill-defined, erythematous plaques on the labium (majus or minus), perineum, or anus.
- Involved skin may exhibit eczematous changes or ulceration.

Prognosis and Treatment

- Radical excision is the treatment of choice and often requires reconstruction.
- Close follow-up is necessary; disease recurs in up to 50% of patients, even with negative margins.
- If stromal invasion is present, recurrence and metastases to distant sites and lymph nodes may occur.
- An associated internal malignancy (e.g., colorectal carcinoma) has been reported in up to 25% of cases.

Pathology

Histology

- Nests and single cells percolate through the epidermis, frequently extending into adnexal structures.
- The neoplastic cells are large, often with abundant pale blue cytoplasm, large vesicular nuclei, and small conspicuous nucleoli.
- Rarely Paget cells may form glands within the epidermis.
- A basal keratinocyte is often present between the Paget's cells and the basement membrane.
- Stromal invasion by Paget's cells may be difficult to distinguish from adnexal involvement.
- The associated squamous epithelium may show benign changes including acanthosis, hyperkeratosis, or papillomatous hyperplasia.

Immunopathology (Including Immunohistochemistry)

- Positive for CK7 and mucin.
- Negative for CK5/6 (positive in squamous epithelium), CK20, S100, and p63.

Main Differential Diagnosis

- Melanoma.
- Urothelial carcinoma (via direct extension).
- Pagetoid vulvar intraepithelial neoplasia.
- Candidal infection (clinically).

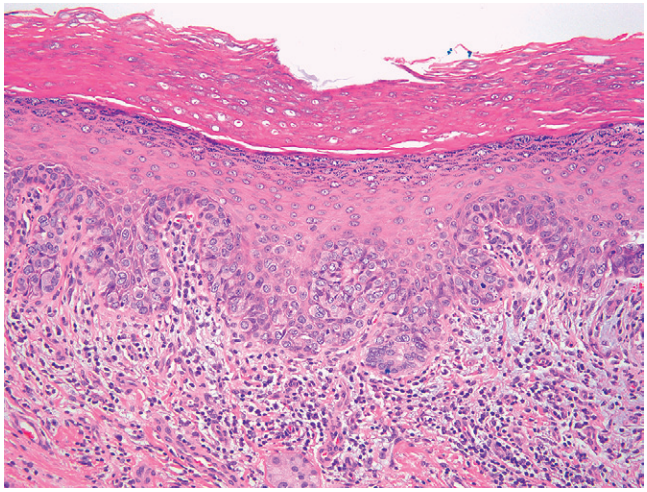


FIGURE 1

Paget's disease. Basal involvement by large cells with abundant hazy blue cytoplasm.

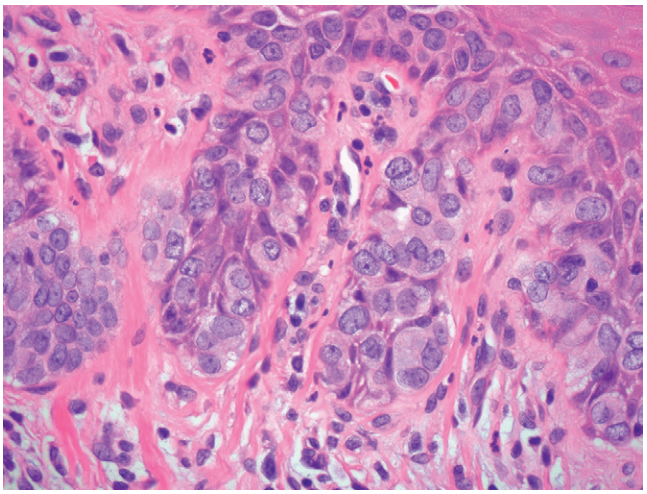


FIGURE 2

Paget's disease. Large cells with abundant blue cytoplasm, large nuclei, and pinpoint nucleoli.

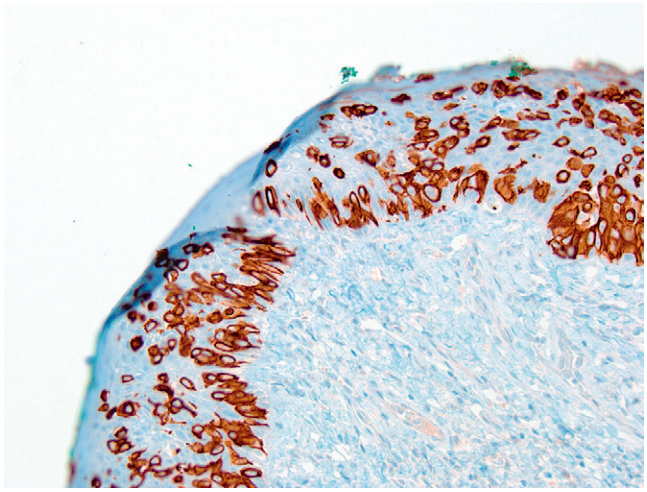


FIGURE 3

Paget's disease. Immunohistochemical staining with CK7, highlighting the neoplastic cells.

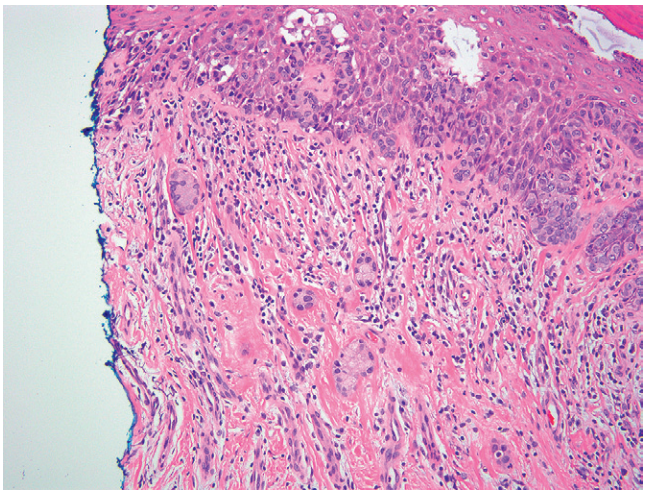


FIGURE 4

Paget's disease. Nests of Paget's disease cells within the dermis.

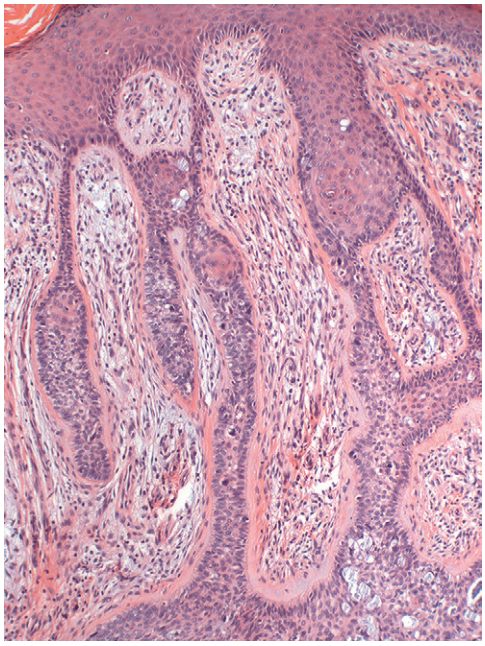


FIGURE 5

Paget's disease. Pseudoepitheliomatous hyperplasia associated with Paget's disease.

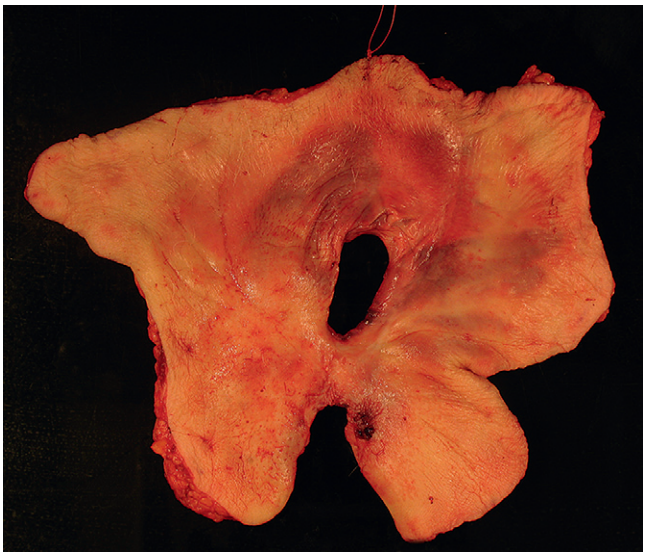


FIGURE 6

Paget's disease. Gross specimen displaying Paget's disease. Note the ill-defined, erythematous plaques.

MERKEL CELL CARCINOMA

Definition—A malignant mucocutaneous neuroendocrine neoplasm.

Clinical Features

Epidemiology

- Very rare (~12 per year in the United States).
- Vulvar tumors account for about 3% of all Merkel cell carcinomas.
- Risk factors include age (>60 years) and sun exposure.

Presentation

- Nonspecific.
- Submucosal nodules or papules.

Prognosis and Treatment

- Poor; even early-stage lesions have a 10% mortality rate.
- Wide local excision with at least 2.5 cm margins and lymphadenectomy or sentinel node sampling.
- Radiation therapy seems to have survival benefit; tumors are chemosensitive, but chemotherapy may not increase survival.

Pathology

Histology

- At low power the tumor is composed of sheets and nodules of cells with a high nuclear-to-cytoplasmic ratio and geographic tumor necrosis.
- The tumor frequently undermines the overlying epithelium.
- At high power the cells are monotonous and undifferentiated with nuclear molding, prominent crush artifact, and a high mitotic index.

Immunopathology (Including Immunohistochemistry)

- Low-molecular-weight keratins (Cam5.2, AEl/AE3), including CK20, are positive in a characteristic dotlike perinuclear pattern.
- Chromogranin and synaptophysin are positive.
- S100 is negative.

Main Differential Diagnosis

- Metastatic pulmonary small cell carcinoma.
- Ewing's sarcoma (primitive neuroectodermal tumor [PNET]).
- Melanoma.
- Lymphoma.

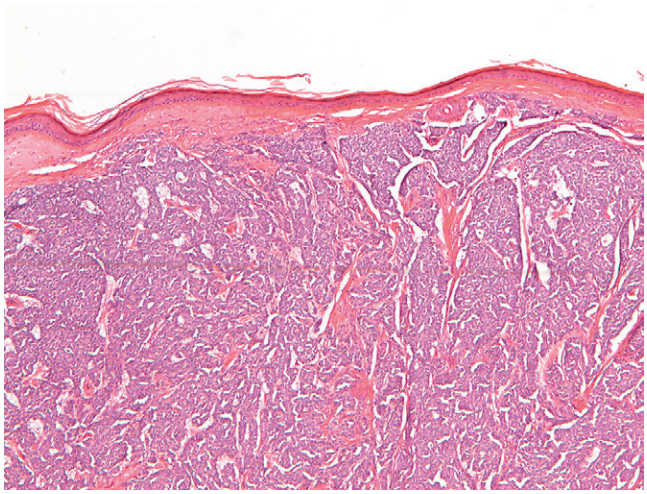


FIGURE 1

Merkel cell carcinoma. Nests of malignant cells filling the dermis. Note the trabecular and nested architecture.

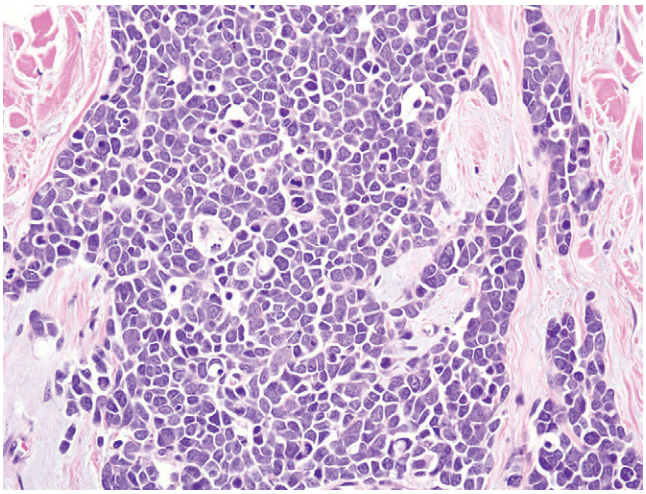


FIGURE 2

Merkel cell carcinoma. Pleomorphic cells with amphophilic cytoplasm, nuclear molding (suggestive of neuroendocrine differentiation).

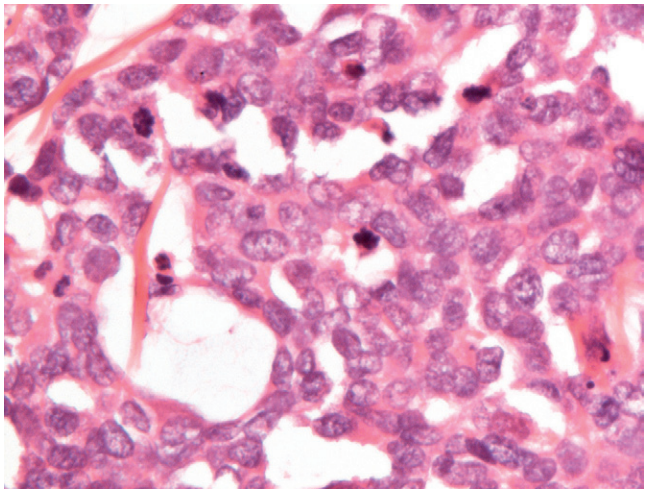


FIGURE 3

Merkel cell carcinoma. Vesicular chromatin with numerous mitotic figures and apoptotic debris.

CLOACOGENIC NEOPLASIA

Definition—"Ectopic," colonic-type neoplasia (adenoma/carcinoma) arising in the vaginal or vulvar mucosa.

Clinical Features

Epidemiology

- Origin is in colonic-type epithelium, presumably incorporated into the vaginal or vulvar region following formation of the urorectal septum in early development.
- Another possible scenario is intestinal metaplasia of vaginal adenosis as rare cases have been reported in diethylstilbestrol (DES)–exposed women.
- Typically seen in adults, implying an age-related transformation of colonic-type epithelium to form these neoplasms.

Presentation

- Patients may present with vaginal bleeding or discharge.
- An exophytic or pedunculated polyp is found in the vagina.

Prognosis and Treatment

- Outcome depends on the extent and grade of the disease.
- A favorable outcome is expected for most, although some may recur locally.

Pathology

Histology

- Squamous mucosa is replaced by a lesion closely resembling adenoma with a pseudostratified columnar cell lining with goblet cells.
- Glands may be predominantly tubular, reminiscent of a tubular adenoma, or exhibit prominent villous architecture as seen in villous adenomas.
- Adenocarcinomas arising in either of the above are typically intestinal.

Diagnostic terminology: Cloacogenic polyp, adenoma, and carcinoma.

Immunopathology (Including Immunohistochemistry)

- Tumors are typically CK20 positive and CK7 negative.
- Some studies have demonstrated *O*-acetylated sialomucin, considered a specific marker of large intestinal differentiation.

Main Differential Diagnosis

- Metastatic colonic carcinoma.
- Rectovaginal fistula.

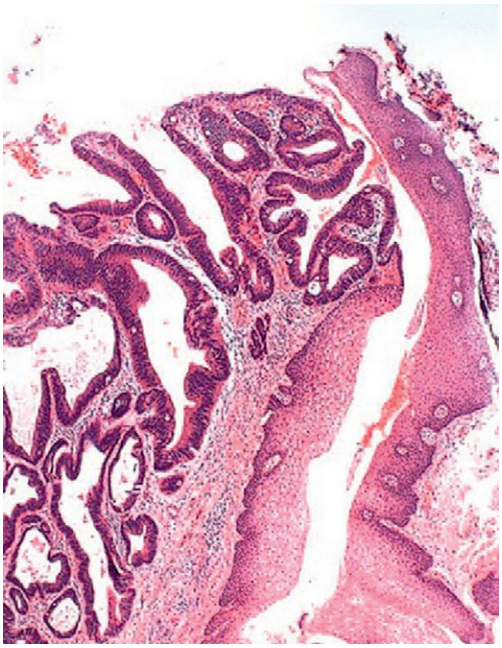


FIGURE 1

Cloacogenic neoplasia of the vagina with merging of normal squamous mucosa *(right)* and a lesion closely resembling a villous adenoma of the colon *(left)*. *(From Crum CP, Nucci MR, Lee KR, editors. Diagnostic Gynecologic and Obstetric Pathology. 2nd ed. Philadelphia: Elsevier; 2011, Fig. 12-17A.)*

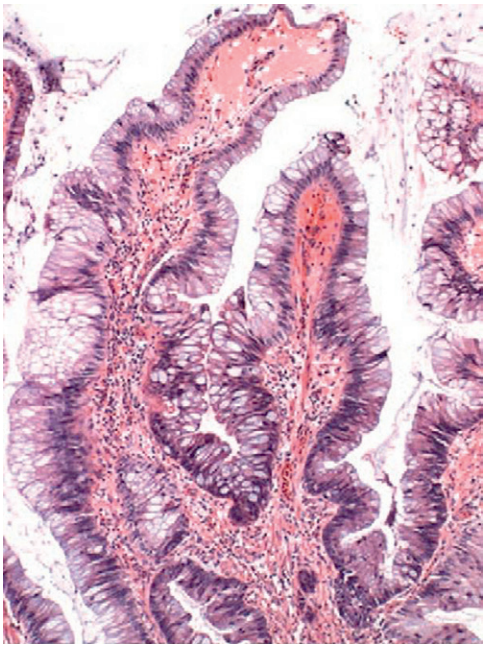


FIGURE 2

Well-differentiated villous architecture in a cloacogenic neoplasm. *(From Crum CP, Nucci MR, Lee KR, editors. Diagnostic Gynecologic and Obstetric Pathology. 2nd ed. Philadelphia: Elsevier; 2011, Fig. 12-17B.)*

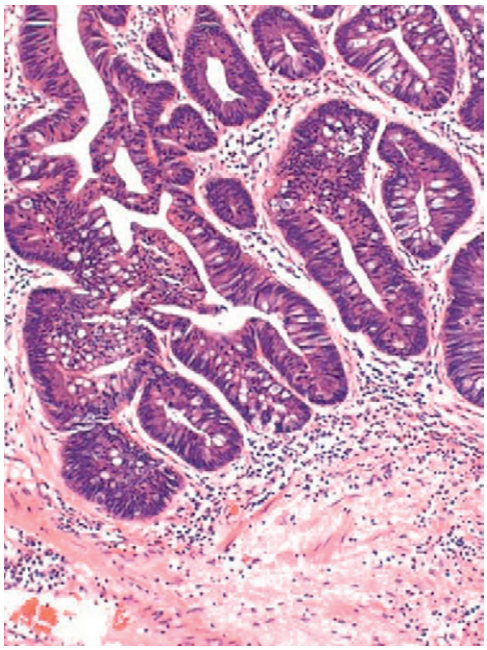


FIGURE 3

Colonic-type glands in a cloacogenic adenoma. *(From Crum CP, Nucci MR, Lee KR, editors. Diagnostic Gynecologic and Obstetric Pathology. 2nd ed. Philadelphia: Elsevier; 2011, Fig. 12-17C.)*

METASTATIC CARCINOMA OF THE VULVA

Definition—Secondary involvement of the vulva by metastatic carcinoma.

Clinical Features

Epidemiology

- Rare.
- Accounts for 5% to 8% of vulvar malignancies.

Presentation

- Mass lesion.
- Erythema or other skin changes.

Prognosis and Treatment

- Poor, as metastasis generally suggests late-stage disease.

Pathology

Histology

- Resembles the primary tumor; anogenital, urothelial, breast, lung, and endometrial carcinomas are the most commonly encountered.
- The metastatic carcinoma may form a tumoral mass within the dermis or subcutaneous tissue or may be present as single cells or small nests within lymphatic spaces.

Immunopathology (Including Immunohistochemistry)

- Varies with primary tumor site.
- Urothelial carcinoma is GCDFP negative and CK7 and CK20 positive.

Main Differential Diagnosis

- Paget's disease (particularly with urothelial carcinoma)
- Melanoma. This should be considered for any poorly differentiated epithelioid or spindle cell neoplasm involving the vulva.
- Breast carcinoma arising in ectopic breast tissue.

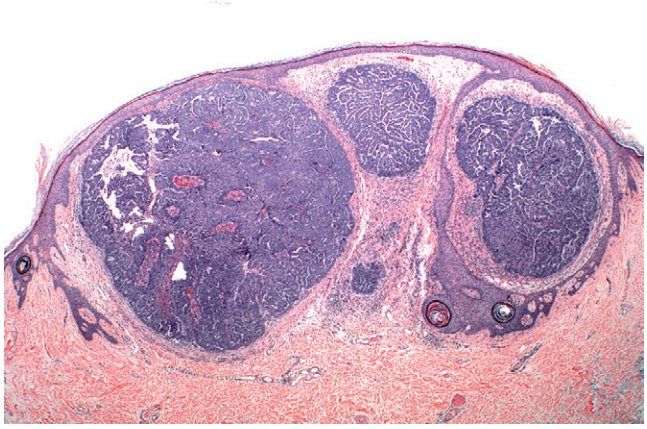


FIGURE 1

Vulvar metastasis. A nodular mass within the dermis. Note the attenuated, uninvolved overlying epidermis.

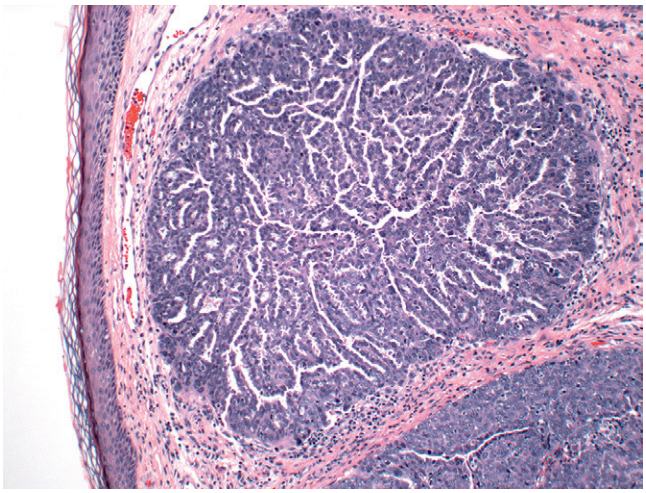


FIGURE 2

Vulvar metastasis. A nodule of metastatic tumor composed of serous carcinoma.

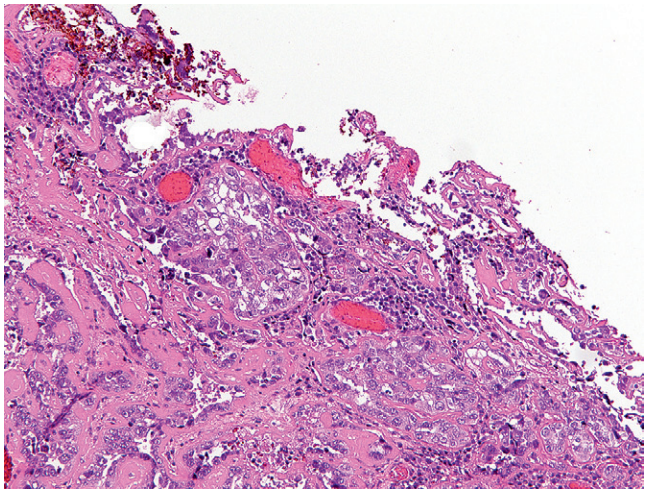


FIGURE 3

Vulvar metastasis. Metastatic clear cell carcinoma with ulceration and loss of the overlying epithelium.

LENTIGO

Definition—Benign pigmented lesion of mucosal surfaces.

Clinical Features

Epidemiology

- No distinct demographic associations.
- Increased numbers may be seen in Carney complex.

Presentation

- Most commonly seen as a well-circumscribed, small (<1 cm), flat brown patch, occurring anywhere on genital mucosa.
- Occasionally presents as a large, darkly pigmented, asymmetrical lesion with irregular borders.

Prognosis and Treatment

- Excellent.

Pathology

Histology

- Cytologically benign melanocytes evenly spaced as single cells within the basal layers.
- Mild acanthosis of the epidermis with hyperpigmentation of basal keratinocytes, particularly at the tips of rete ridges.
- Pigment-laden macrophages (melanophages) may be prominent in the papillary dermis.

Immunopathology (including immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Lentiginous nevus—enlarged, irregularly spaced melanocytes.

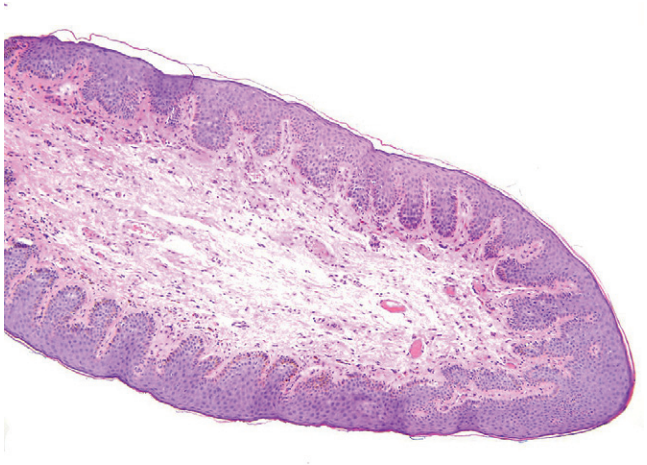


FIGURE 1

Mucosal lentigo. A continuous band of pigment can be seen at low power. Note the absence of visible nests of melanocytes.

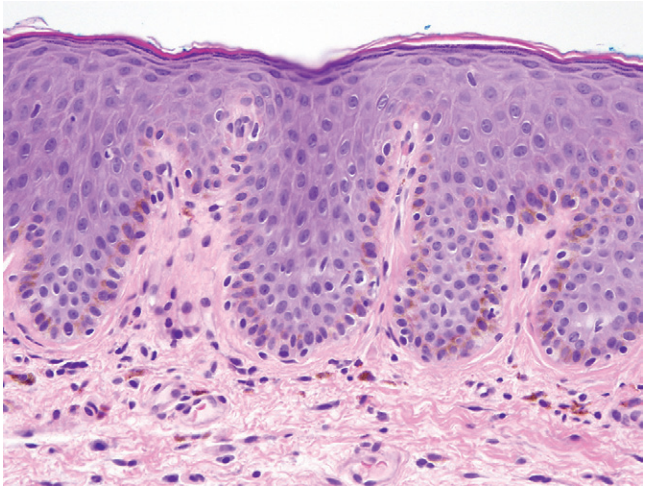


FIGURE 2

Mucosal lentigo. Basal pigmentation, scattered melanocytes, and dermal macrophages with pigment.

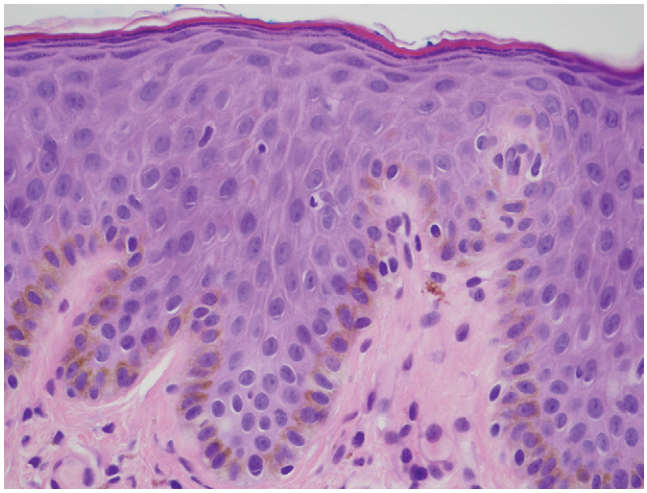


FIGURE 3

Mucosal lentigo. A closer view of the basal pigmentation.

GENITAL-TYPE NEVUS

Definition—A melanocytic proliferation seen in locations with redundant skin, characterized by large junctional melanocyte nests and transepidermal elimination of nests.

Clinical Features

Epidemiology

- Uncommon; estimated prevalence of 2.3% in women.
- Young women, most often in the third decade of life.

Presentation

- Most lesions are seen on the labia (majus or minus).
- Seen clinically as small (<1 cm), heavily pigmented, irregular lesions.

Prognosis and Treatment

- Overall prognosis is excellent.
- If significant atypia is present, complete excision is recommended as biologic potential is not well understood.

Pathology

- May be junctional or compound, symmetrical or asymmetrical, and flat or papillomatous.
- A lentiginous and nested proliferation with characteristically large junctional nests at the sides and tips of the rete with prominent retraction artifact.
- Transepidermal elimination of nests of melanocytes is common (but not epidermal pagetoid spread).
- Only focal atypia should be present.
- Dermal component resembles a typical nevus with basal maturation.

Histology

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Dysplastic nevus. Look for more pronounced melanocyte atypia at the interface.
- Melanoma.

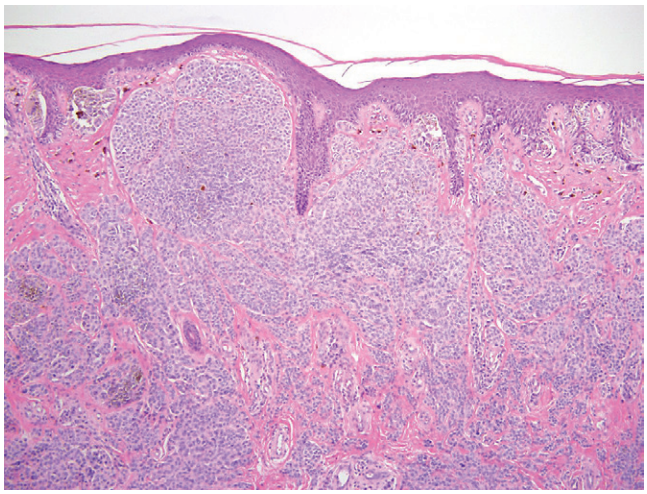


FIGURE 1

Genital-type nevus. Junctional nevus with large nests of melanocytes.

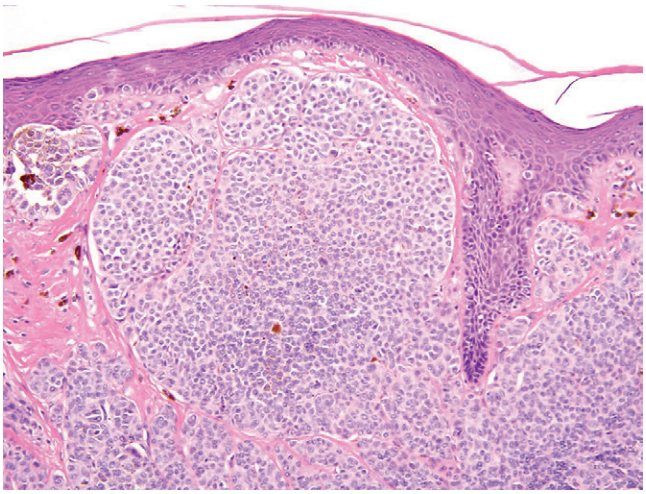


FIGURE 2

Genital-type nevus. Melanocytes composing the nests are regular and lack significant atypia.

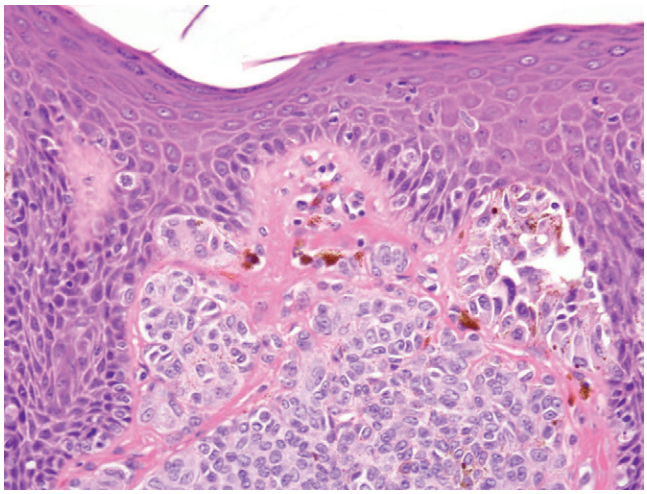


FIGURE 3

Genital-type nevus. Pigment incontinence may be present, especially in a traumatized nevus. Note the lack of atypia and mitotic activity.

DYSPLASTIC NEVUS

Definition—A melanocytic proliferation with architectural, cytologic, and clinical features that are intermediate between those seen in common nevi and melanoma.

Clinical Features

Epidemiology

- Patients have a higher risk of melanoma.
- Patients with first-degree relatives who have melanoma have an extremely high risk of developing melanoma (dysplastic nevus syndrome).

Presentation

- Larger than typical nevi and often asymmetrical with irregular borders.

Prognosis and Treatment

- Complete excision is advised.

Pathology

Histology

- Architectural atypia: Variably sized and shaped junctional nests that stream from rete to rete (bridging), a prominent lentiginous growth pattern, and extension of the epidermal component beyond the dermal component (a "shoulder").
- Cytologic atypia: Large nuclei (as compared with adjacent keratinocytes), coarse chromatin, irregular nuclear outlines, and variably prominent nucleoli.
- The pigment is often a gray-brown (dishwater) color.
- Stromal changes include eosinophilic lamellar fibrosis of the papillary dermis.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Melanoma.
- Genital type nevus.

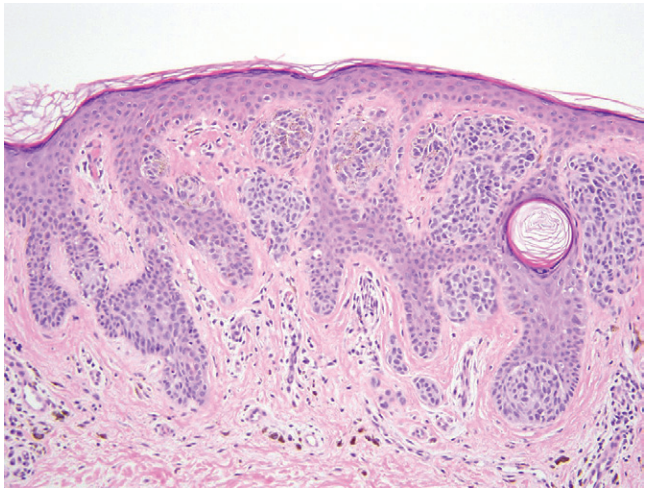


FIGURE 1

Dysplastic nevus. Nests of melanocytes with varying size and shape present in the dermis.

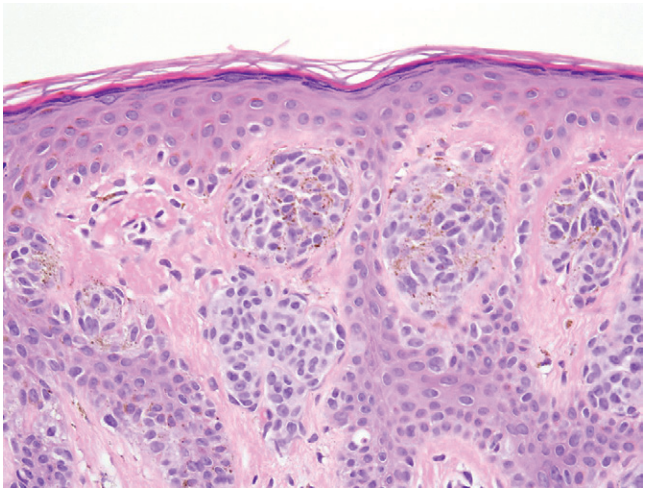


FIGURE 2

Dysplastic nevus. Irregularity of the melanocytes and lamellar fibrosis.

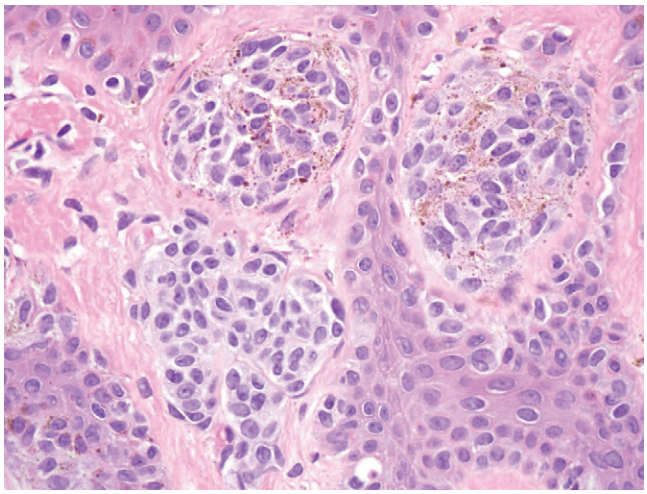


FIGURE 3

Dysplastic nevus. Atypical melanocytes displaying nuclear enlargement and prominent nucleoli. Note the absence of mitotic activity.

MELANOMA

Definition—A highly malignant tumor of dermal melanocytes.

Clinical Features

Epidemiology

- Rare.
- Accounts for approximately 3% of all melanomas in women.
- The second most common vulvar malignancy.
- Most often in patients in their sixth decade of life.
- May be more common in patients with a BRCA2 mutation.

Presentation

- A polypoid mass is present in one third of cases.
- Bleeding, ulceration, discomfort, and other nonspecific symptoms may be encountered.
- Flat pigmented lesions are the classic presentation, but amelanotic lesions are not uncommon.
- Labia majora and minora lesions account for approximately 50% of cases, and periclitoral tumors account for another 30%; other sites are less common.

Prognosis and Treatment

- Varies tremendously with extent of disease; Breslow's depth is the single most predictive factor.
- Five-year survival for vulvar melanoma is lower than at nongenital sites, with studies showing a range from 15% to 50%; vaginal melanoma has a 5-year survival of less than 20%.
- Standard treatment includes local excision with 1 to 2 cm margins and sentinel lymph node biopsy.

Pathology

Histology

- The epidermal component is composed of single cells and nests of monotonous, severely atypical melanocytes with irregular chromatin and prominent nucleoli.
- Effacement of the dermal-epidermal junction is common, resulting in a "moth-eaten" appearance.
- The dermal component is most often composed of epithelioid cells with a similar histology to those present in the overlying epidermis and without "maturation."
- Melanoma is known for its variable morphology, and the spectrum is broad; cases range from the epithelioid tumors described earlier to a malignant spindle cell proliferation that can be confused with a sarcomatoid squamous cell carcinoma or a mesenchymal neoplasm.

Immunopathology (Including Immunohistochemistry)

- S100 positive.
- MART1, HMB45, and Melan-A are generally positive but may be lost in poorly differentiated tumors.

Main Differential Diagnosis

- Paget's disease—strongly CK7 positive.
- Squamous cell carcinoma.
- Melanoma in situ.

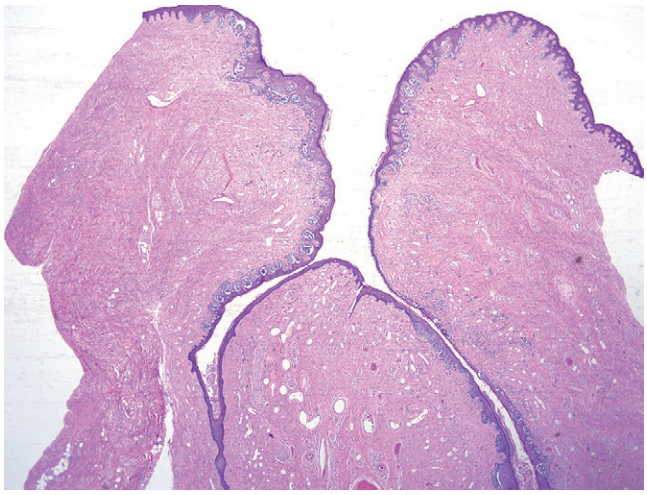


FIGURE 1

Vulvar melanoma. Nests of melanocytes can be seen at low power. Note the bridging of the rete by the theques.

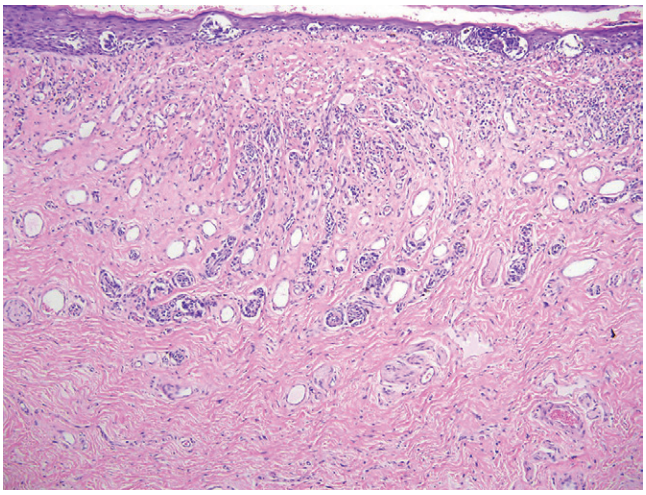


FIGURE 2

Vulvar melanoma. Malignant cells infiltrate into the dermis. There is no maturation of the deep cells when compared with the melanocytes in the junctional component.

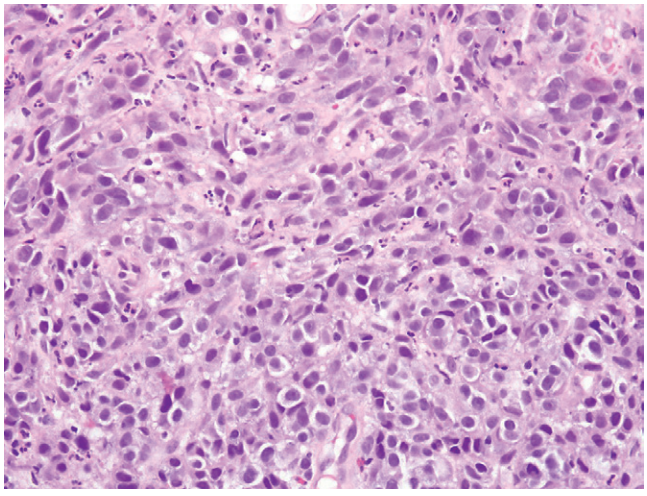


FIGURE 3

Vulvar melanoma. Malignant melanocytes displaying nuclear pleomorphism.

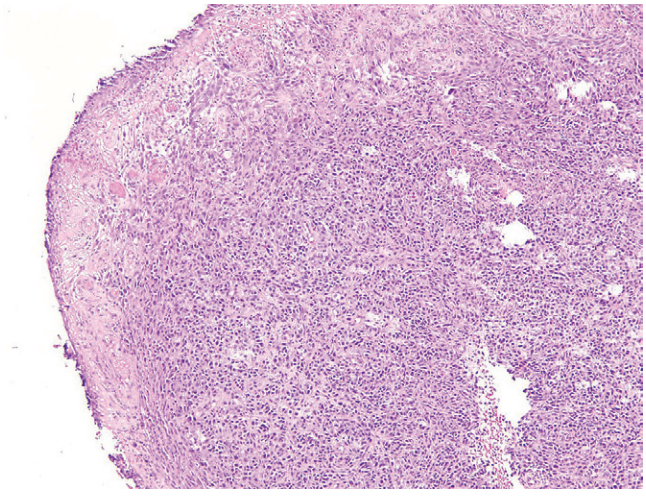


FIGURE 4

Vulvar melanoma. Nodular melanoma composed of sheets of melanocytes.

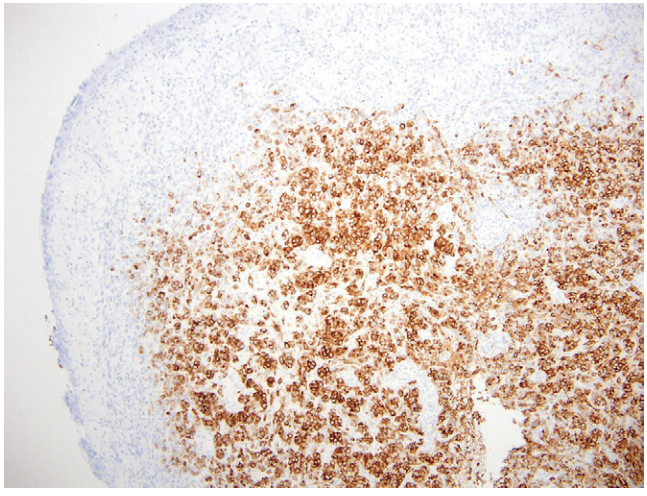


FIGURE 5

Vulvar melanoma. Positive immunohistochemical staining with MART1.

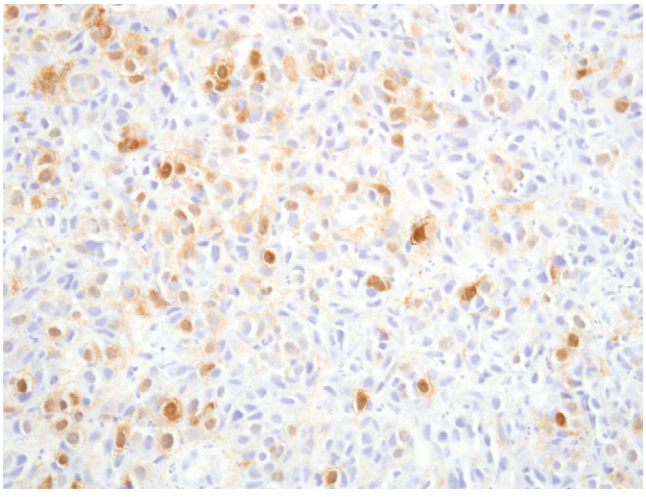


FIGURE 6

Vulvar melanoma. Positive (patchy) staining with S100.

ANGIOMYOFIBROBLASTOMA

Definition—A benign, nonrecurring spindle cell lesion of the vulvovaginal region, characterized by alternating hypercellular and hypocellular areas.

Clinical Features

Epidemiology

- Reproductive-age women.
- Uncommon.

Presentation

- Bartholin's gland "cyst," usually smaller than 5 cm.

Prognosis and Treatment

- Excellent.
- There has been one case report of sarcomatous transformation and recurrence.
- Complete excision with negative margins is advised.

Pathology

Histology

- Well circumscribed, with alternating hypercellular and hypocellular areas.
- The stromal cells may be plump and spindled (especially in postmenopausal women) to strikingly epithelioid, and tend to cluster around small capillary-sized vessels.
- Plasmacytoid and multinucleate stromal cells are common.

Immunopathology (Including Immunohistochemistry)

- Desmin positive; smooth muscle actin is variable.

Main Differential Diagnosis

- Aggressive angiomyxoma.
- Asymmetrical vulvar hypertrophy.
- Superficial angiomyxoma.

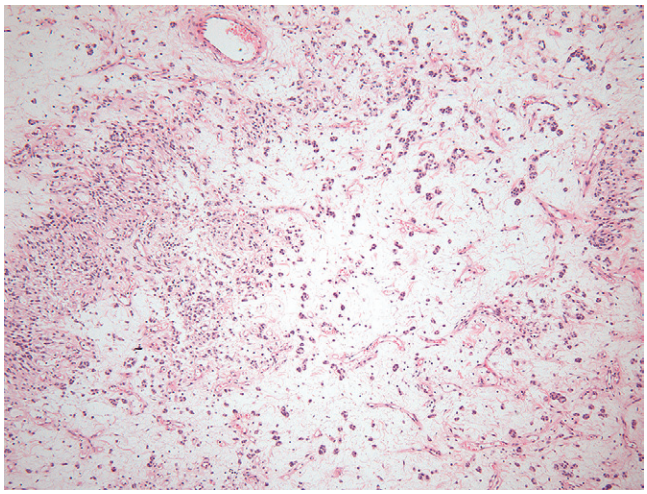


FIGURE 1

Angiomyofibroblastoma. At low power, alternating hypercellular and hypocellular areas can be appreciated. Note the numerous, delicate capillaries present.

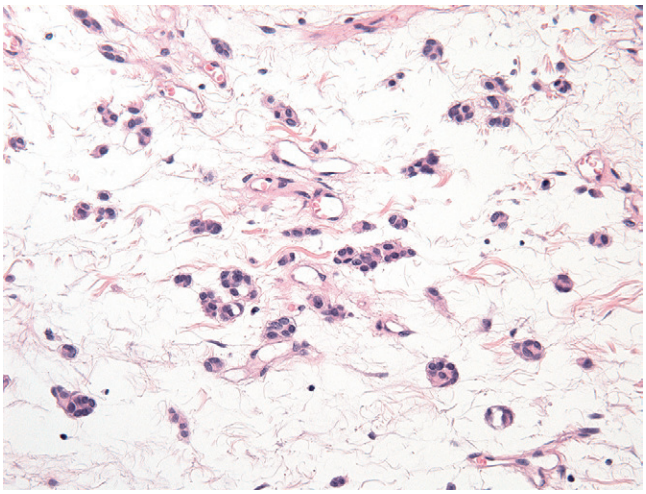


FIGURE 2

Angiomyofibroblastoma. Small, capillary-sized vessels with surrounding clusters of cells with a plasmacytoid appearance. Several multinucleated cells are present.

AGGRESSIVE ANGIOMYXOMA

PITFALL

Definition—A bland, hypocellular, spindle cell lesion of the vulvar/perineal region with a tendency for local infiltration and recurrence.

Clinical Features

Epidemiology

- Reproductive-age women in their 30s.
  - Uncommon.

Presentation

- Commonly presents as a labial or Bartholin's gland "cyst."

Prognosis and Treatment

- Nonmetastasizing, but locally destructive.
- Recurrence occurs in 30% to 40% of cases, sometimes years after initial excision.
- Complete excision with negative margins (at least 1 cm).

Pathology

Histology

- Poorly circumscribed, paucicellular neoplasm with inconspicuous infiltration into surrounding soft tissue.
- Bland spindle cells set within a copious myxoid matrix.
- Fibrillary collagen and eosinophilic smooth muscle cells often condense around blood vessels.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Superficial angiomyxoma.
- Angiomyofibroblastoma.

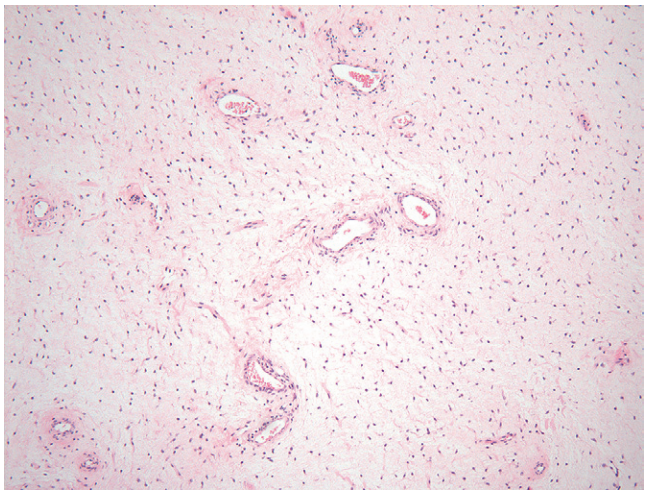


FIGURE 1

Deep aggressive angiomyxoma. Low-power examination reveals a paucicellular, myxoid neoplasm. Note the cellular condensation around the blood vessels.

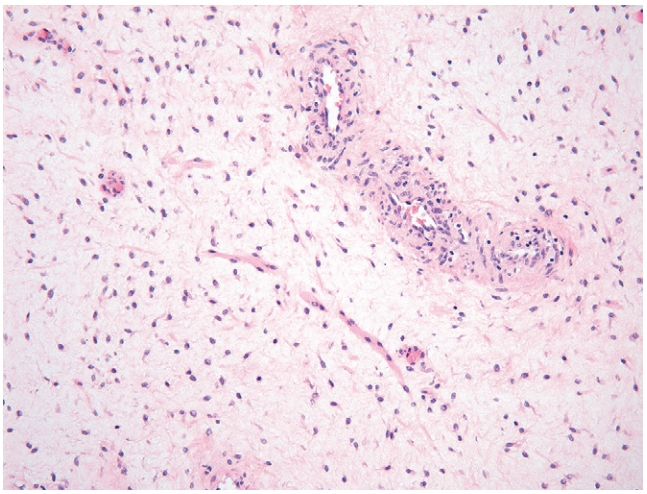


FIGURE 2

Deep aggressive angiomyxoma. The cells comprising the lesion are small, bland, and spindled. Smooth muscle cells and collagen bundles can be seen condensing around the blood vessel.

SUPERFICIAL ANGIOMYXOMA

Definition—A benign pedunculated myxoid soft tissue neoplasm with a tendency toward local recurrence.

Clinical Features

Epidemiology

- Rare.
- Occasionally occurs in the vulva.
- Most frequently seen in reproductive-age women in their 30s.

Presentation

- Solitary, slow-growing, painless polypoid or pedunculated mass.
- Usually less than 5 cm in size.

Prognosis and Treatment

- Complete excision with negative margins.
- Propensity for local recurrence in up to 30% to 40% of cases.

Pathology

Histology

- Well-demarcated and multilobulated superficial angiomyxoma (SAM) is superficial and situated in the subcutis.
- The lobules are strikingly hypocellular and myxoid, with slender stellate spindle cells and thin-walled vessels admixed with polymorphonuclear cells.
- Perivascular hyalinization is not appreciated.
- The tumor cells are small and bland; nuclear atypia is not appreciated.
- Atypical mitotic figures are not seen.
- An epithelial component, usually a squamous-lined cyst, is occasionally present.

Immunopathology (Including Immunohistochemistry)

- Immunohistochemical staining for SMA, desmin, and S100 is negative.

Main Differential Diagnosis

- Deep aggressive angiomyxoma. Deeply situated with the classic vascular pattern.

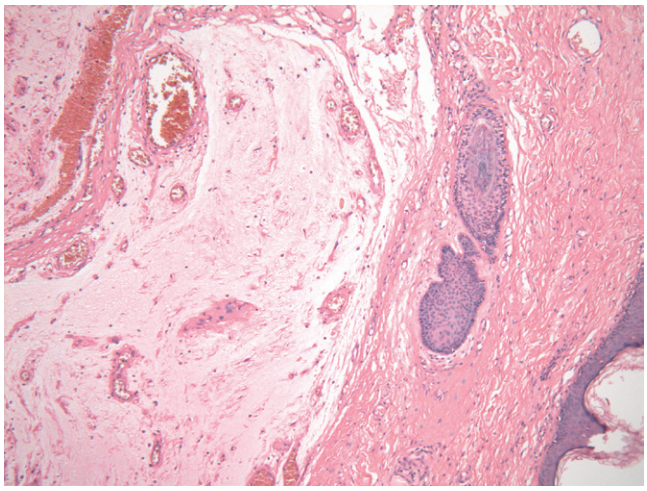


FIGURE 1

SAM. A dermally situated, multilobulated, myxoid mass with well-demarcated borders.

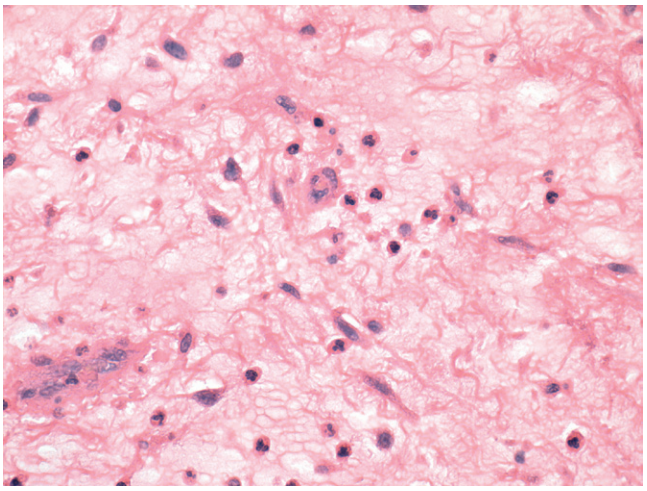


FIGURE 2

SAM. Bland stellate spindle cells set within a myxoid stroma, admixed with neutrophils.

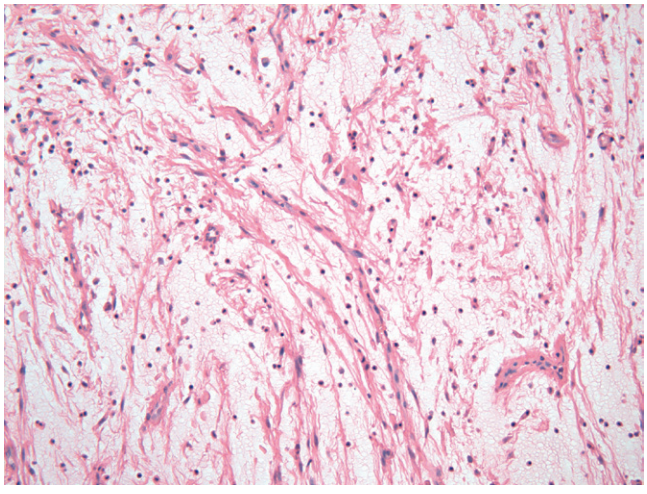


FIGURE 3

SAM. Thin-walled curvilinear vascular structures.

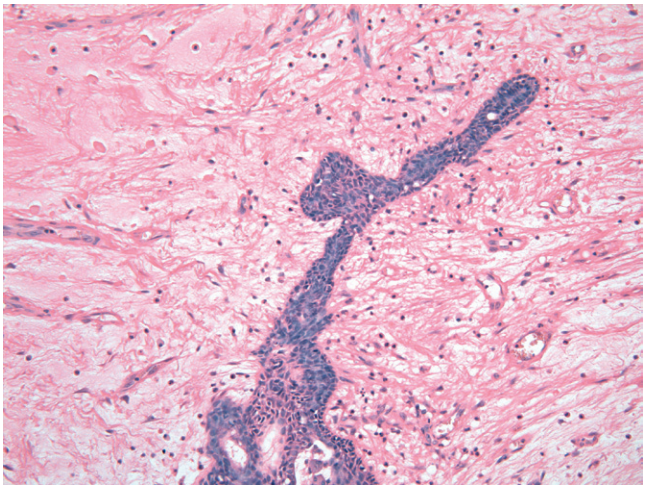


FIGURE 4

SAM. Benign epithelial elements, a squamous-lined cyst, within the tumor.

CELLULAR ANGIOFIBROMA

Definition—A benign subcutaneous neoplasm composed of short fascicles of spindle cells with prominent small, thick-walled, blood vessels.

Clinical Features

Epidemiology

- Uncommon.
  - Typically seen in middle-aged women (mean age ~55 years).

Presentation

- Small (<3 cm), painless, subcutaneous vulvovaginal or perineal mass.

Prognosis and Treatment

- Benign.
  - Complete excision is advised as incompletely removed tumors may regrow.

Pathology

Histology

- Well-demarcated proliferation of short fascicles of bland spindle cells with interspersed wispy collagen bundles.
- Prominent vasculature composed of small round vessels with thick, densely hyalinized, eosinophilic walls.
- Entrapped fat or nerve is often present at the periphery.

Immunopathology (Including Immunohistochemistry)

- Variably positive for CD34 and SMA; occasionally desmin positive.
- Negative for S100.

Main Differential Diagnosis

- Solitary fibrous tumor.
  - Angiomyofibroblastoma.
  - Deep aggressive angiomyxoma (when edematous).
- Fibroepithelial stromal polyp—pedunculated, lacks the high vessel density of cellular angiofibroma.

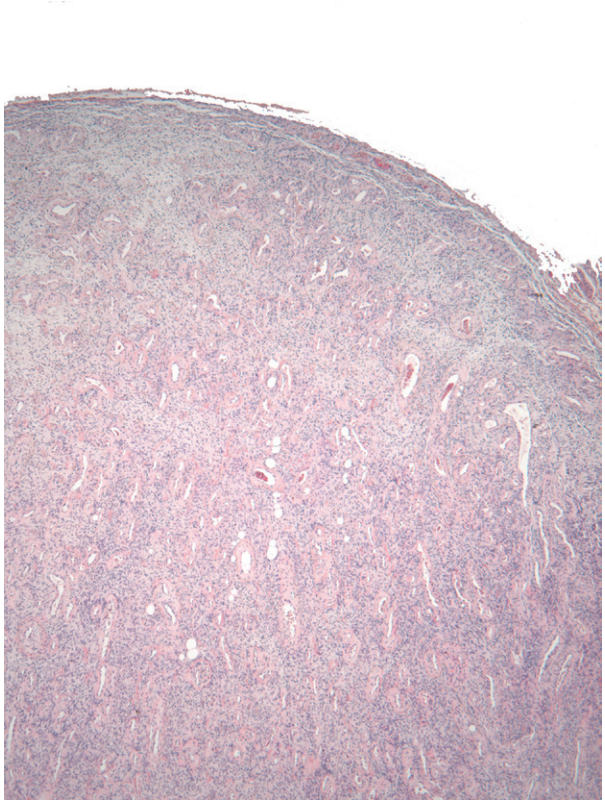


FIGURE 1

Cellular angiofibroma. At low magnification a highly cellular proliferation admixed with numerous small- to medium-sized vessels can be seen.

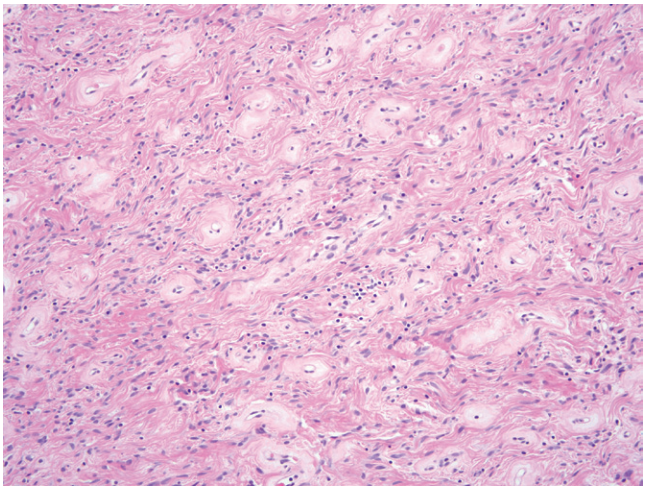


FIGURE 2

Cellular angiofibroma. Fascicles of bland, spindled cells admixed with numerous small vessels with prominent hyalinization.

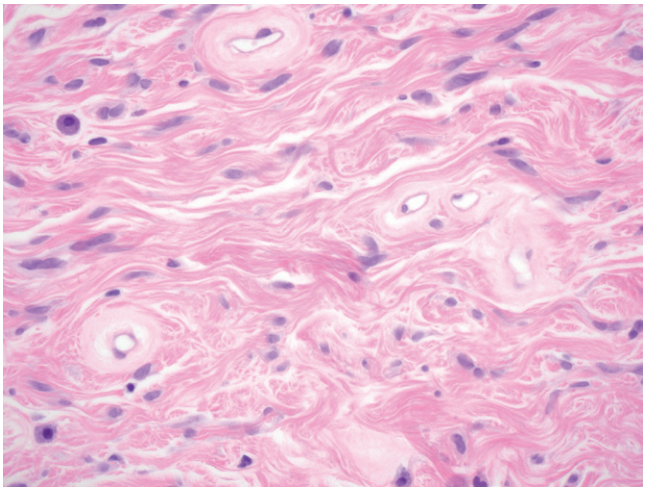


FIGURE 3

Cellular angiofibroma. Bland spindle cells with hyalinized vessels. Note the occasional mast cells.

DERMATOFIBROMA (FIBROUS HISTIOCYTOMA)

Definition—A benign fibrohistiocytic tumor of dermal stroma, composed of spindle cells with a storiform (pinwheel) growth pattern.

Clinical Features

Epidemiology

- Occurs in adults.

Presentation

- Papules, plaques, or nodules in the vulva.
- Lesions may be flesh colored or pigmented.

Prognosis and Treatment

- Excellent.
- Excision is adequate treatment.
- For some types (deep, cellular, atypical, aneurysmal), at least marginal excision is advised as these variants are more likely to recur.

Pathology

Histology

- Classical dermatofibroma is a well-circumscribed dermal proliferation of bland spindle cells arranged in a storiform pattern, with trapping of dermal collagen at the edges.
- The overlying epidermis is often hyperplastic (pseudoepitheliomatous hyperplasia).

Immunopathology (Including Immunohistochemistry)

- CD34 is variable.

Main Differential Diagnosis

- Dermatofibrosarcoma protuberans. Typically more cellular and infiltrates subcutaneous fat.

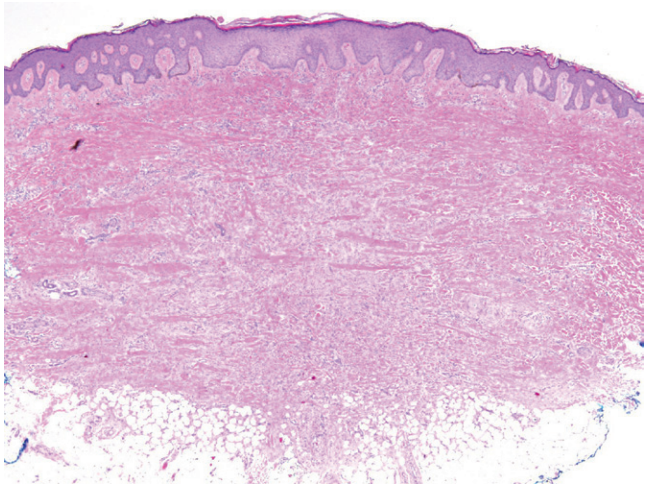


FIGURE 1

Dermatofibroma. A well-circumscribed dermal mass with overlying epidermal (pseudoepitheliomatous) hyperplasia.

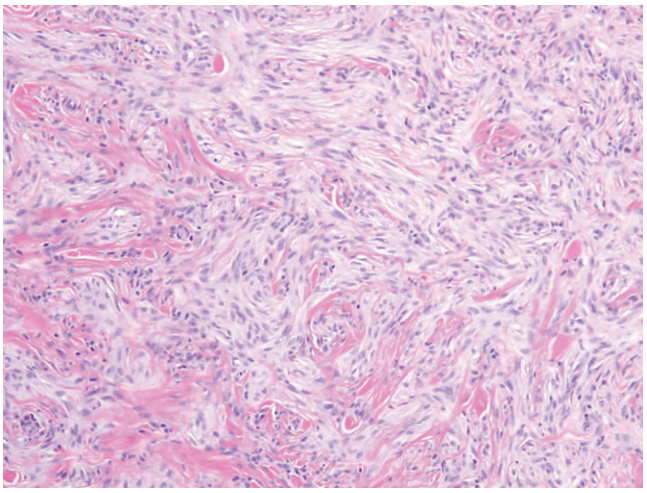


FIGURE 2

Dermatofibroma. Bland, spindled cells with entrapped collagen bundles.

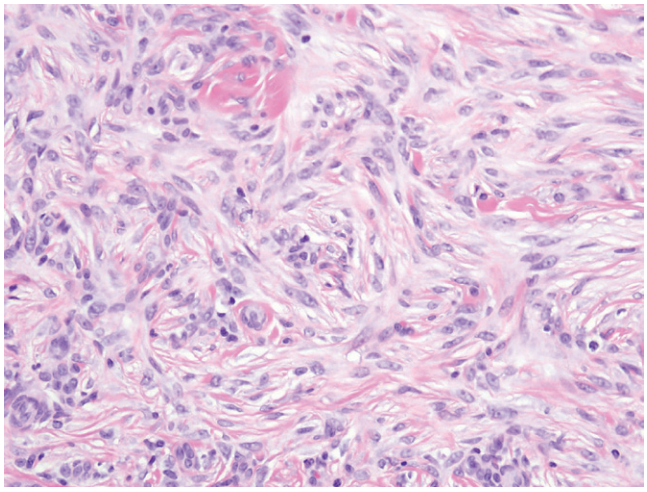


FIGURE 3

Dermatofibroma. Spindle cells arranged in a storiform pattern. Delicate strands of entrapped collagen are present.

DERMATOFIBROSARCOMA PROTUBERANS

Definition—A subcutaneous, locally aggressive spindle cell neoplasm with a storiform growth pattern and honeycomb-like infiltration into adipose tissue.

Clinical Features

Epidemiology

- Dermatofibrosarcoma protuberans involving the vulva is rare; however, cases have been reported.

Presentation

- A nodule, plaque, or large multinodular growth in the groin.
- Vulvar lesions are uncommon.

Prognosis and Treatment

- Local recurrence is common; metastases are infrequent.
- Fibrosarcomatous lesions have a higher rate of metastases (up to 15%).
- Complete excision with negative margins is advised.

Pathology

Histology

- A poorly circumscribed mass with a honeycomb pattern of infiltration into subcutaneous adipose tissue.
- A monomorphic, storiform proliferation of spindled cells separated from the overlying atrophic epithelium by a rim of normal stroma (grenz zone).
- Fibrosarcomatous change is identified by its herring-bone growth pattern, increased mitotic rate, and hypercellularity.

Immunopathology (Including Immunohistochemistry)

- CD34 is usually diffusely positive.

Main Differential Diagnosis

- Dermatofibroma—less cellular, lacks the deep dermal infiltration into adipose tissue.

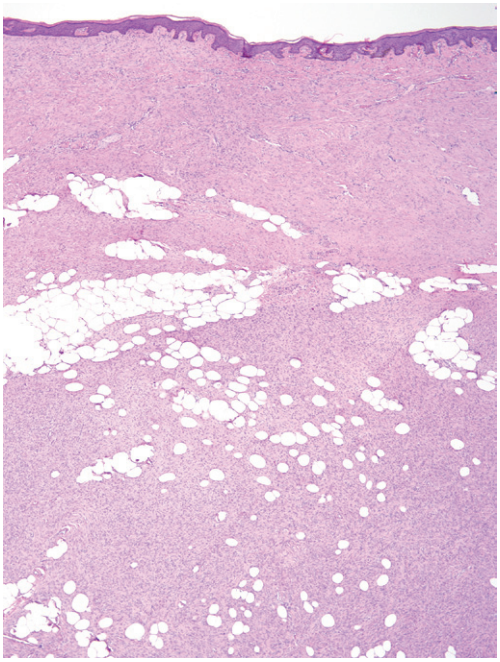


FIGURE 1

Dermatofibrosarcoma protuberans. A poorly circumscribed mass involving the deep dermis and extending into the subcutaneous tissue. Note the absence of pseudoepitheliomatous hyperplasia seen in dermatofibroma and the presence of a grenz zone.

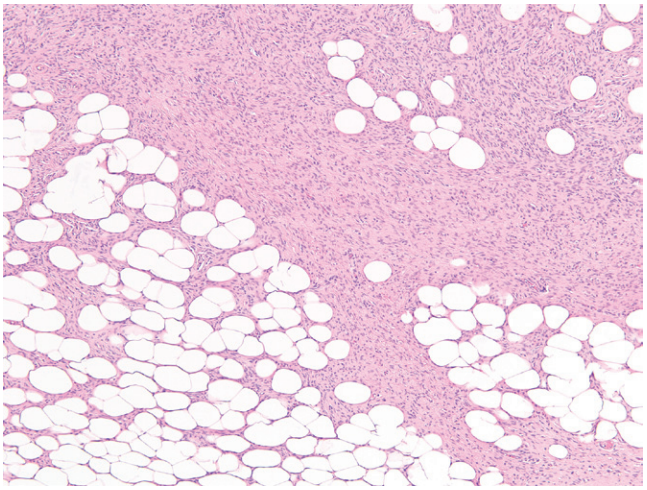


FIGURE 2

Dermatofibrosarcoma protuberans. Infiltration of the spindled cells between fat cells in the subcutaneous tissue creates a honeycomb pattern.

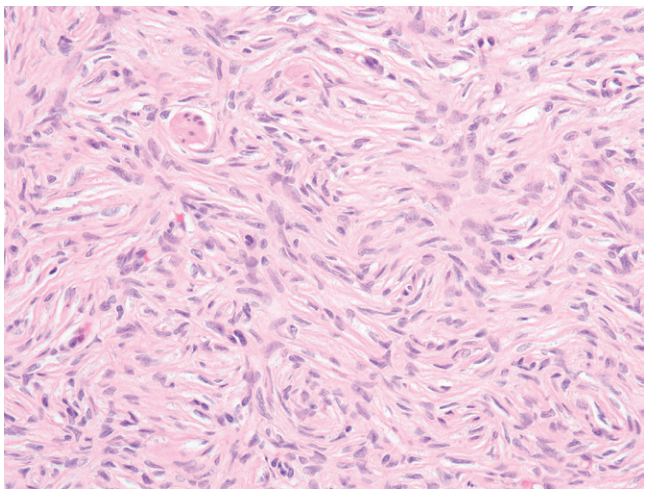


FIGURE 3

Dermatofibrosarcoma protuberans. Bland, spindled cells arranged in a storiform growth pattern.

LOW-GRADE FIBROMYXOID SARCOMA

Definition—A painless, deep-seated, and slow-growing tumor with a deceptively bland histologic appearance and a propensity for local recurrence.

Clinical Features

Epidemiology

- Low-grade fibromyxoid sarcoma (LGFMS) is uncommon.
- Most often identified in children and young to middle-aged adults.
- The third and fourth decades of life are the most common age at presentation.

Presentation

- Presents as a slow-growing, painless mass involving the vulva, perineum, or pelvic region.
- May be asymptomatic if deep seated or may present as a palpable mass.

Prognosis and Treatment

- Metastases are uncommon, but local recurrence is frequent.
- Wide local excision is the treatment of choice.

Pathology

Histology

- Grossly, LGFMS ranges in size from 1 to 20 cm, although most are smaller than 10 cm.
- On cut section these tumors are slightly soft, infiltrate into surrounding soft tissues, and are white to yellow with gelatinous glistening areas.
- At low power the tumor is composed of bland spindle cells arranged in alternating hypocellular and hypercellular tongues and nodules.
- The tumor cells are small, with oval to stellate hyperchromatic nuclei, variably prominent small nucleoli, and moderate amounts of indistinct wispy eosinophilic cytoplasm.
- The tumor cells are set in variably fibrous to myxoid-appearing stroma.
- The transitions between the fibrous areas and the myxoid, more hypocellular, areas are abrupt.
- The vasculature is characterized by a proliferation of delicate curvilinear capillary-sized vessels that are most prominent in the myxoid zones.
- Some lesions have prominent collagen rosettes; this pattern was formerly known as "hyalinizing spindle cell tumor with giant rosettes."

Immunopathology (Including Immunohistochemistry)

- Immunohistochemical staining is positive for EMA and MUC4.
- These tumors are characterized cytogenetically by a *FUS/CREB* fusion, which can be detected using a break-apart FISH probe for the *FUS* gene on chromosome 7.

Main Differential Diagnosis

- Nodular fasciitis.
- Deep aggressive angiomyxoma.
- Angiomyofibroblastoma.

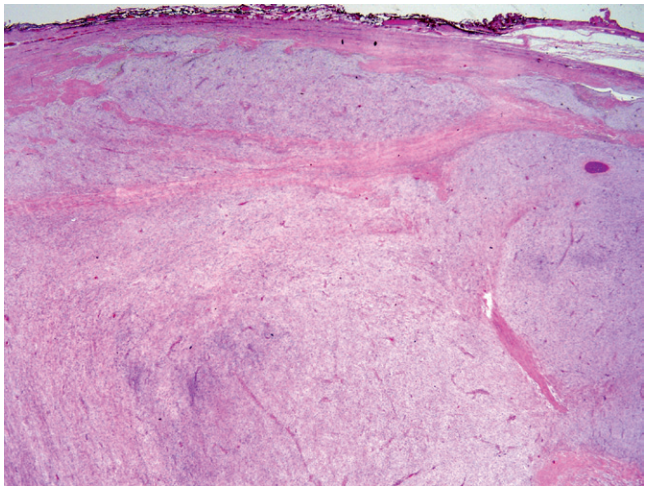


FIGURE 1

LGFMS. Low power showing a spindle cell proliferation with abrupt transition between myxoid and fibrous zones.

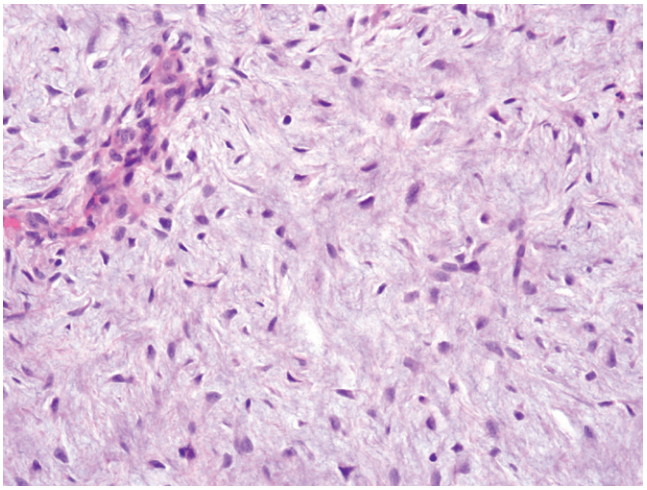


FIGURE 2

LGFMS. Myxoid zone at high power showing bland, oval to stellate tumor cells with indistinct cytoplasm. A small, delicate capillary-sized vessel is present.

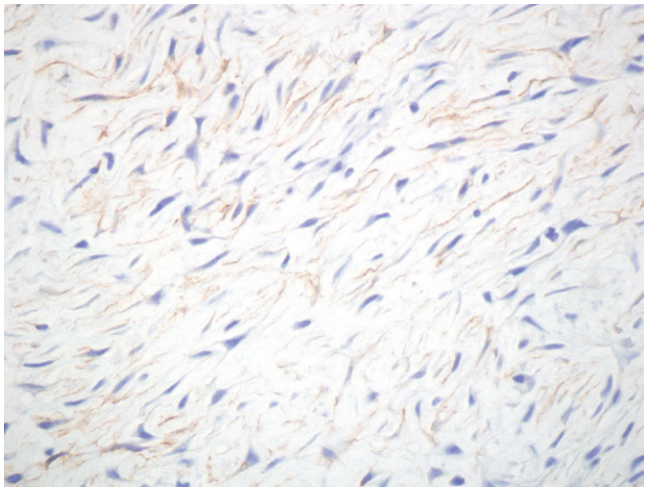


FIGURE 3

LGFMS. Immunohistochemical stain for EMA is positive.

LIPOMA

Definition—A benign adipocytic neoplasm.

Clinical Features

Epidemiology

- Rarely encountered in the vulva.

Presentation

- Slow-growing mass in the labium majus.
- Large lesions may be pedunculated.

Prognosis and Treatment

- Excellent.
- Excision is curative.

Pathology

Histology

- Well-circumscribed proliferation of mature adipose tissue.

Immunopathology (Including Immunohistochemistry)

- MDM2 and CDK4 are negative.

Main Differential Diagnosis

- Well-differentiated liposarcoma.

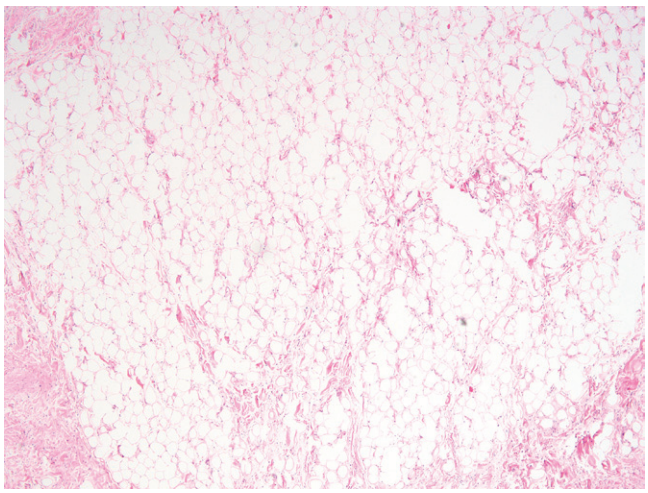


FIGURE 1
Vulvar lipoma. Well-circumscribed mass of mature adipose tissue.

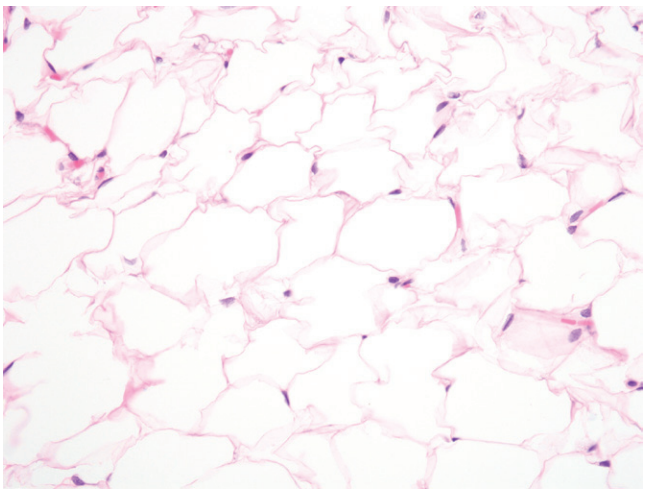


FIGURE 2
Vulvar lipoma. Mature adipocytes. No lipoblasts should be identified.

LIPOSARCOMA

Definition—A malignant neoplasm of adipocytes.

Clinical Features

Epidemiology

- Rare.
- Most commonly encountered in middle-aged women.

Presentation

- Vulvar mass or cyst.

Prognosis and Treatment

- If amenable to wide local excision, excellent (in these cases the term *atypical lipomatous tumor* is more appropriate).
- If not completely excised, there is a tendency for destructive local recurrence.
- Distant metastases are extremely rare.

Pathology

Histology

- Well-differentiated liposarcoma is characterized by sheets of adipocytes of varying sizes, cellular fibrous septa containing atypical nuclei, and occasional lipoblasts.
- Occasionally, well-differentiated vulvar liposarcoma may be composed of bland-appearing spindle cells admixed with adipocytes and numerous bivacuolated lipoblasts.
- Dedifferentiated liposarcoma is a spindle cell sarcoma and is recognized by its proximity to a more well-differentiated component.
- Myxoid liposarcoma, as at other sites, is identified by its characteristic thin-walled "chicken-wire" vasculature, mucin pools, and very occasional lipoblasts.

Immunopathology (Including Immunohistochemistry)

- MDM2 and CDK4 are positive in well-differentiated/dedifferentiated liposarcoma.
- Immunohistochemistry is noncontributory for myxoid liposarcoma.

Main Differential Diagnosis

- Lipoma.
- Lipoma with extensive fat necrosis.
- Spindle cell lipoma.
- Angiomyofibroblastoma.

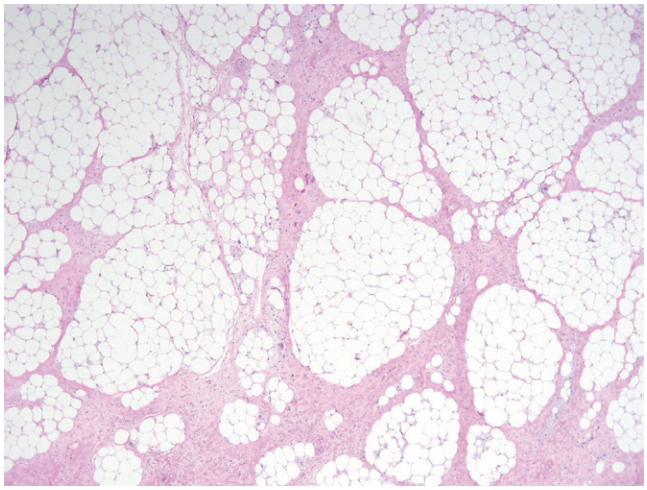


FIGURE 1

Liposarcoma. Nodules of adipose tissue are separated by thick fibrous septa.

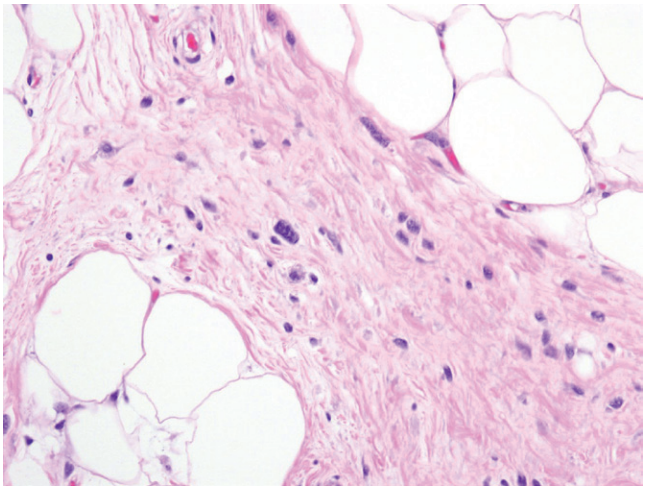


FIGURE 2

Liposarcoma. Atypical stromal cells can be identified within the fibrous bands.

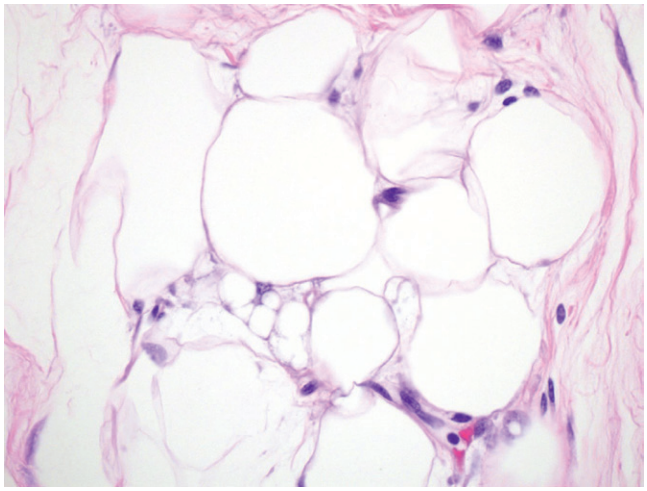


FIGURE 3

Liposarcoma. An example of a lipoblast. Lipoblasts can be identified by the presence of multiple fat vacuoles within the cytoplasm and the distinctive scalloped nuclear contours they create.

SYNOVIAL SARCOMA OF THE VULVA

PITFALL

Definition—A malignant frequently biphasic tumor of soft tissue.

Clinical Features

Epidemiology

- Rare.
- Encountered in all age groups, mostly in the second and third decades.
- t(X:18) translocation (representing a fusion of SYT [at 18q11] with either SSX1 or SSX2 [at Xp11]) linked to pathogenesis and prognosis.

Presentation

- Vulvar mass.

Prognosis and Treatment

- Known for high recurrence rate.
- Prognosis depends to some degree on tumor grade, mitotic index, age, size (5-cm cutoff), and resectability.
- Standard is resection if possible; radiation and chemotherapy of uncertain benefit.
- Five-year survival approximately 60%, disease-free survival approximately 30%.
- Adverse outcome linked to older age, high mitotic/proliferative index, monophasic tumors, tumors over 5 cm in diameter, and/or incompletely excised.
- More complex genomes have been linked to adverse outcomes.

Pathology

Histology

- Classic biphasic synovial sarcoma shows a mixture of spindle and epithelial cell components. However, the epithelial component can predominate in the presence of bland-appearing spindled cells.
- Spindle cell component can be rather bland and distinct from, but closely admixed with, the epithelial component.
- Monophasic tumors exhibit spindle cell morphology; epithelial component may be less conspicuous, consisting of eosinophilic cells scattered through the mesenchymal component.
- Myxoid areas may be seen.

Immunopathology (Including Immunohistochemistry)

- PAX8 negative, ER/PR negative.
- TLE-1 strong positivity is highly specific for synovial sarcoma if not exclusive to this tumor.

Main Differential Diagnosis

- Carcinosarcoma—the mesenchymal component will typically be more poorly differentiated; the epithelial component should be PAX8 positive in most cases and TLE-1 negative.
- Endometrioid adenocarcinoma with a spindle cell component—may closely resemble synovial sarcoma. Should be PAX8 positive and TLE-1 negative.
- Spindle cell epithelioma—a benign spindle cell tumor with focal epithelial differentiation. Should be negative for TLE-1.
- Extrarenal Wilms' tumor—this tumor is rarely found in the vulvar region. The epithelial component is typically more primitive in appearance, composed of small tubular structures within blastema.

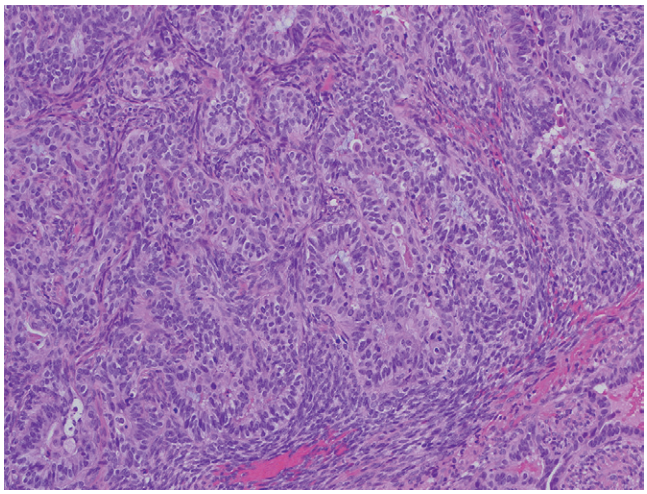


FIGURE 1

Synovial sarcoma. In this field the epithelial component predominates.

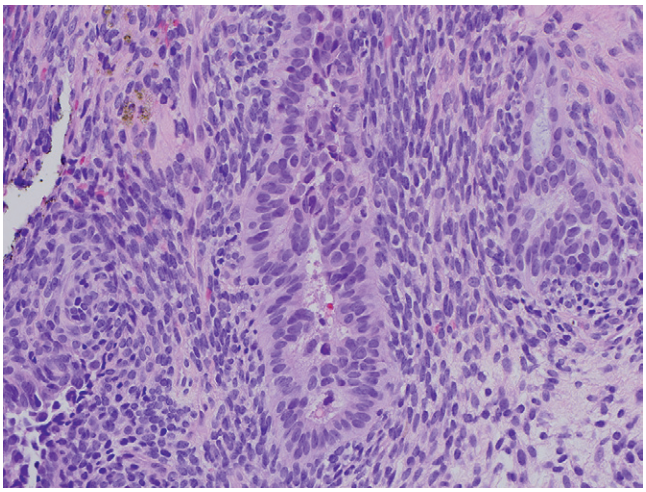


FIGURE 2

Synovial sarcoma. There is a juxtaposed epithelial component *(center)* and adjacent spindle cell component.

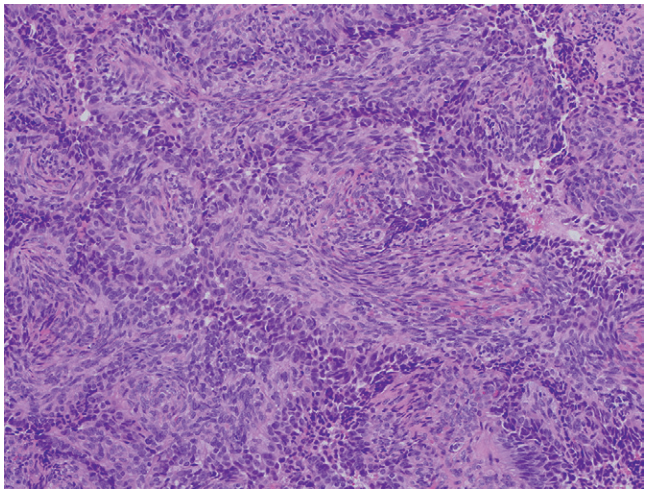


FIGURE 3

Synovial sarcoma. In this field the epithelial nests are more spindled (squamoid) and the mesenchymal component consists of narrow bands of more poorly differentiated spindled cells.

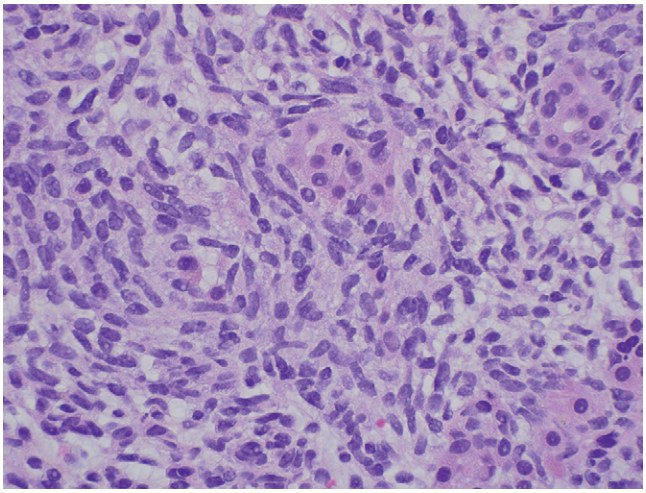


FIGURE 4

This synovial sarcoma is predominantly mesenchymal, with interlacing spindled cells punctuated by a few pink glandlike structures.

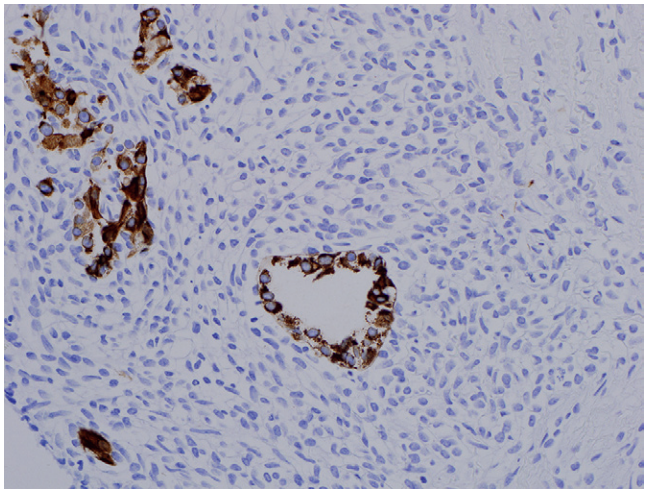


FIGURE 5

An AE1/AE3 immunostain highlights both glandlike and less organized epithelial cells within the sarcomatous stroma.

RHABDOMYOMA

Definition—A solitary, benign, polypoid lesion of the vagina composed of bland rhabdomyoblasts.

Clinical Features

Epidemiology

- Middle-aged women.

Presentation

- Solitary polypoid lesion, usually smaller than 3 cm.
- Vagina is the most common site, followed by vulva and cervix.

Prognosis and Treatment

- Excellent.
- Complete excision is curative.

Pathology

Histology

- An irregular and vaguely vascular submucosal proliferation of bland rhabdomyoblasts.
- The rhabdomyoblasts are brightly eosinophilic, spindle to strap shaped, with visible cytoplasmic cross striations.
- Nuclear atypia is absent, and mitotic activity is low.
- Subepithelial condensation (cambium layer) is not present.

Immunopathology (Including Immunohistochemistry)

- Desmin, myogenin, and Myf-4 are positive (skeletal muscle markers).
- S100 is negative, differentiating from a granular cell tumor.

Main Differential Diagnosis

- Embryonal rhabdomyosarcoma—look for smaller, more primitive mesenchymal cells, including a cambium layer.
- Granular cell tumor—typically seen on the vulva. S-100 positive, and often associated with pseudoepitheliomatous hyperplasia.
- Spindle cell epithelioma (mixed tumor)—lacks the prominent eosinophilic cytoplasm and cross-striations of a rhabdomyoma.

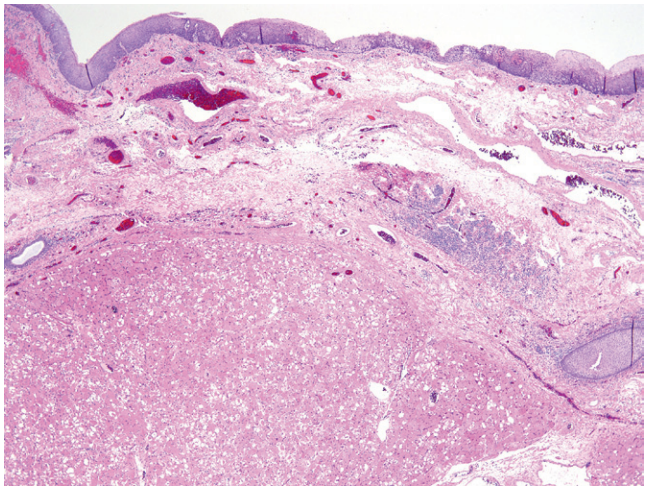


FIGURE 1

Genital rhabdomyoma. Well-circumscribed mass within the submucosa. Note the irregular borders. Brightly eosinophilic cells are evident at low power.

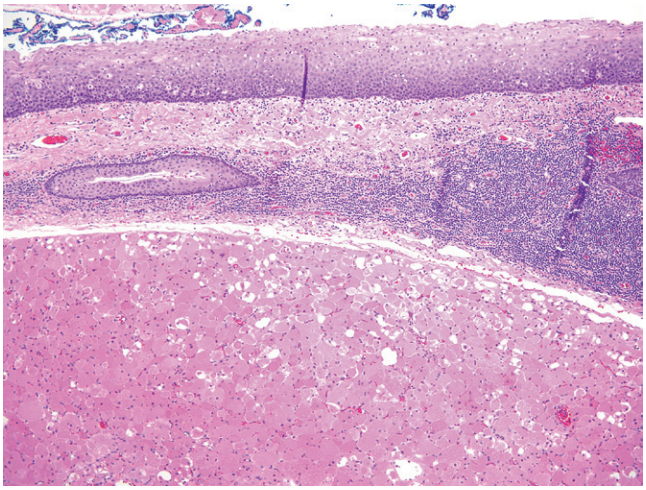


FIGURE 2

Genital rhabdomyoma. Large eosinophilic cells with small nuclei.

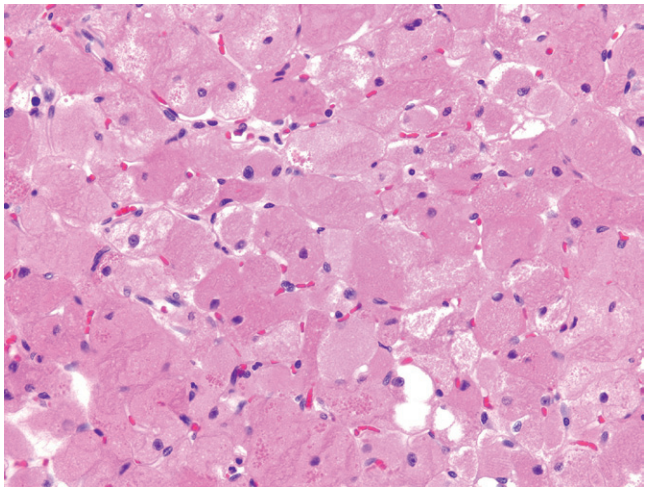


FIGURE 3

Genital rhabdomyoma. Large, polygonal eosinophilic cells with occasional striations. The nuclei are small, round, and regular.

ANGIOKERATOMA

Definition—A discrete vascular ectasia with overlying epidermal hyperplasia.

Clinical Features

Epidemiology

- Typically seen in women under age 50.
- Typically sporadic but also associated with Fabry's disease (deficiency of lysosomal alpha-galactosidase).

Presentation

- Generally asymptomatic but may present with bleeding or pain.
- Papular, occasionally warty lesions (<1 cm in size) of the vulva.
- May be solitary or multiple (including angiokeratoma corporis diffusum).

Prognosis and Treatment

- Prognosis is excellent.
- Observation is adequate; if symptomatic, excision or ablation may be required.

Pathology

Histology

- Dilated blood-filled spaces in the papillary dermis, closely apposed to the epidermis.
- The epidermis exhibits prominent acanthosis with hyperkeratosis and occasionally papillomatosis.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Squamous papilloma/condyloma—dilated vascular spaces are not typical in condyloma, and koilocytes are not present in angiokeratoma.
- Hemangioma—should be situated more deeply in the dermis.

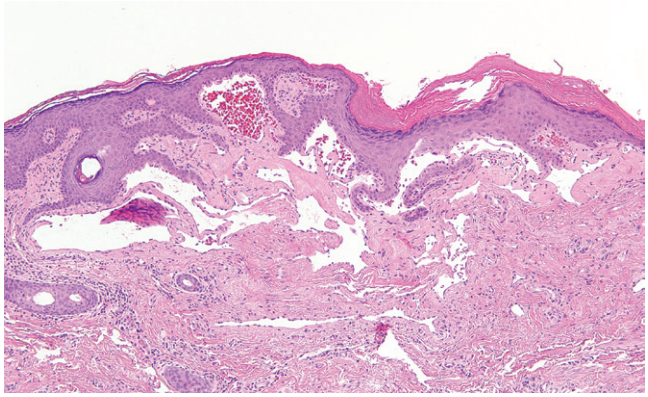


FIGURE 1

Angiokeratoma. Ectatic vessels can be seen in the dermis, several of which contain red blood cells. Even at low power the hyperkeratosis and hypergranulosis are evident.

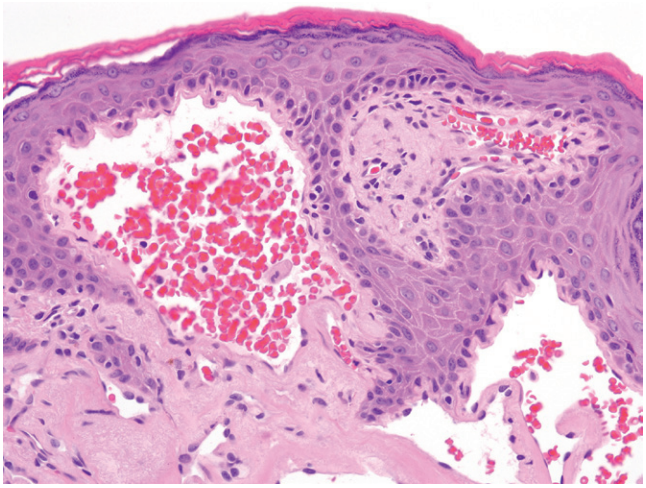


FIGURE 2

Angiokeratoma. Dilated vascular spaces with a bland endothelial lining.

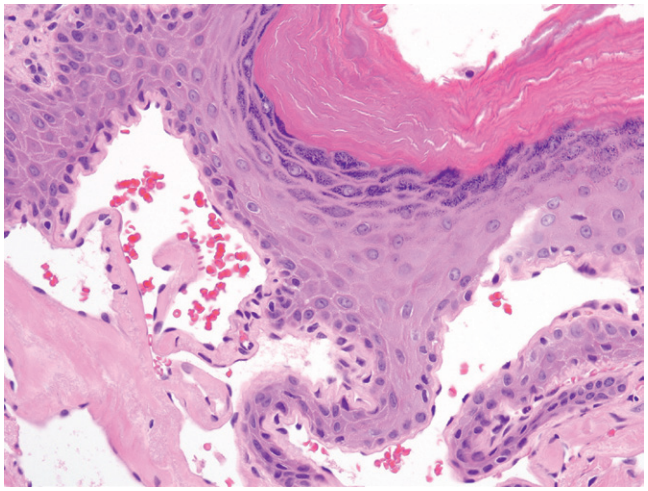


FIGURE 3

Angiokeratoma. Ectatic vascular spaces immediately adjacent to the overlying epidermis, which displays hypergranulosis and hyperkeratosis.

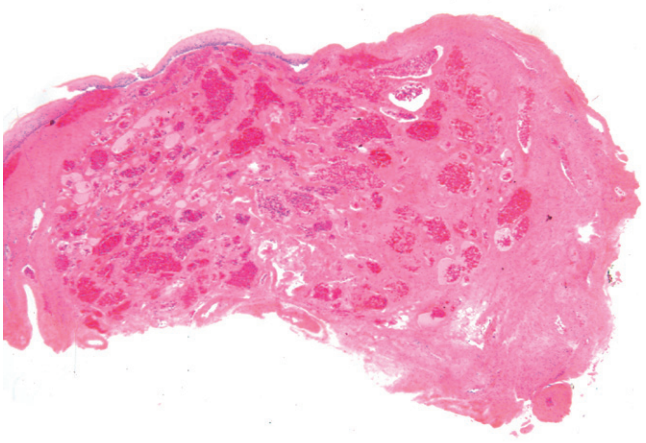


FIGURE 4

Cavernous hemangioma. At low magnification this is a discrete mass-forming lesion in the dermis.

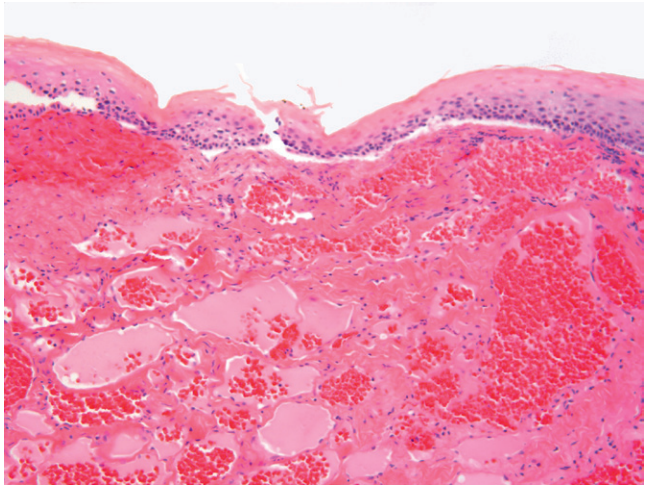


FIGURE 5

Cavernous hemangioma. In contrast to angiokeratoma there is a sharp separation between the epidermis and the lesion.

GRANULAR CELL TUMOR

Definition—A (usually) benign soft tissue tumor of the vulva of presumably neural crest lineage.

Clinical Features

Epidemiology

- Uncommon.
- Can occur at any age, with a mean age of presentation of 50 years.
- More common in African-American women.

Presentation

- Present as slow-growing asymptomatic nodules and often found incidentally.
- Vary from 1 to 12 cm in size.

Prognosis and Treatment

- Excision is usually curative.
- Local recurrences are uncommon even in incompletely excised tumors but may be higher in lesions with infiltrative borders.
- Rare malignant tumors reported.

Pathology

Histology

- Located in the subcutis.
- Polygonal cells with abundant eosinophilic granular cytoplasm.
- Centrally located variably hyperchromatic nuclei.
- Pushing or infiltrative borders.
- There can be a distinctive pseudoepitheliomatous hyperplasia of overlying squamous mucosa that can mimic squamous cell carcinoma (PITFALL).

Diagnostic Terminology

- Granular cell tumor (granular cell myoblastoma is no longer used for obvious reasons).

Immunopathology (Including Immunohistochemistry)

- S100 and NSE stains are usually positive; NKI-C3 (lysosomal) is also positive.

Main Differential Diagnosis

- Squamous cell carcinoma, if the pseudoepitheliomatous hyperplasia is prominent.
- Rhabdomyoma—tumor cells will have cross-striations and a more homogeneous eosinophilic versus granular cytoplasm.

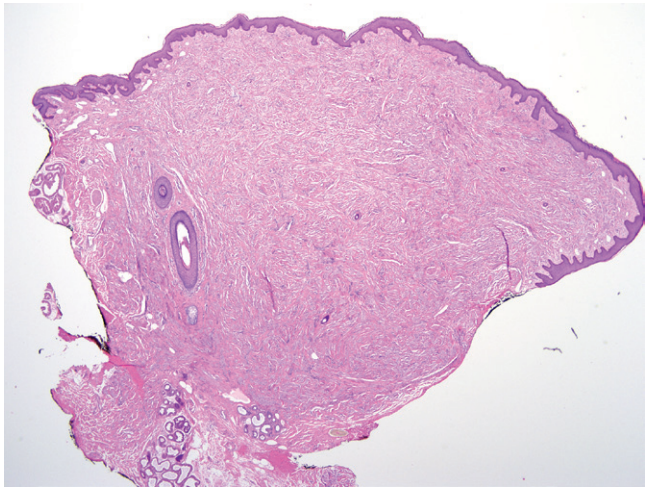


FIGURE 1

Granular cell tumor. At low power this tumor appears as a nondescript soft tissue mass.

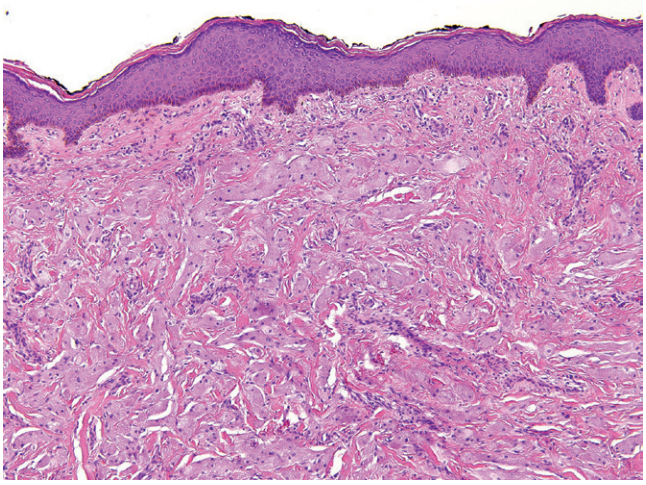


FIGURE 2

Granular cell tumor. At higher magnification the polyhedral cells can be appreciated amid the collagen bundles beneath the surface.

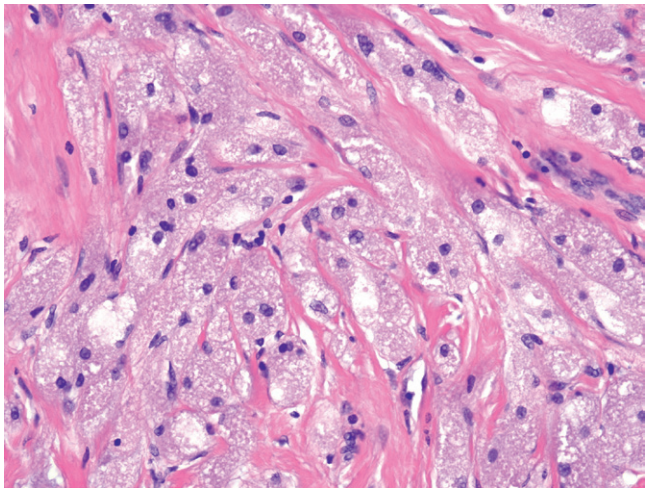


FIGURE 3

Granular cell tumor. At high magnification the prominent granular eosinophilic cytoplasm is evident.

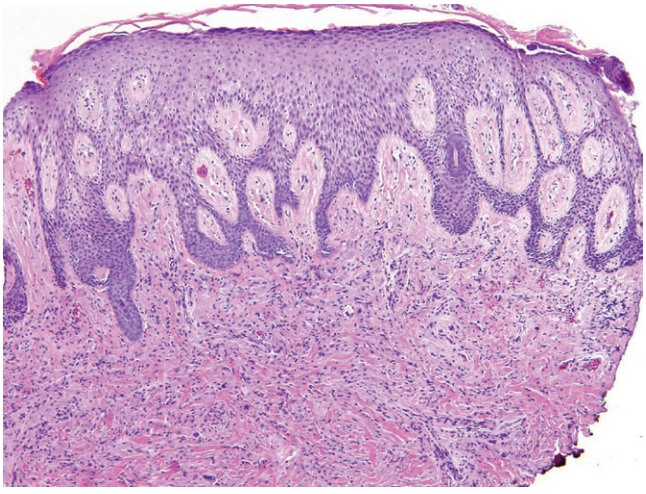


FIGURE 4

Pseudoepitheliomatous hyperplasia overlying a granular cell tumor.

PREPUBERTAL VULVAR FIBROMA

Definition—A rare, benign, spindle cell proliferation that occurs in the vulva of prepubertal women.

Clinical Features

Epidemiology

- Rare.
- Prepubertal women, age ranging between 4 and 12 years (median age is 8 years).

Presentation

- Gradual vulvar swelling, resulting in asymmetrical labial enlargement.
- Painless vulvar mass.
- Most commonly affects the labia majora.

Prognosis and Treatment

- This is a benign lesion; controversy exists regarding its classification as a true neoplasm.
- Conservative excision is appropriate treatment.
- If incompletely excised, there is a tendency for recurrence.

Pathology

Histology

- A hypocellular, ill-defined proliferation of bland spindle cells with ovoid nuclei.
- The cells are arranged in a patternless pattern and set within a variably edematous to myxoid to collagenous matrix.
- Small- to medium-sized vessels are scattered throughout the lesion, some with thick walls.
- The lesional cells characteristically infiltrate adjacent adipose tissue, nerve bundles, and adnexal structures.

Immunopathology (Including Immunohistochemistry)

- Positive for CD34.
- SMA, desmin, and S100 are negative.

Main Differential Diagnosis

- Deep aggressive angiomyxoma—these tumors are more deeply situated and have the characteristic myxoid stroma with thick-walled vessels.
- Cellular angiofibroma—well circumscribed, more cellular than prepubertal fibroma.
- Fibroepithelial stromal polyp—typically polypoid, usually a thick-walled central vessel.
- Superficial angiomyxoma—subcutaneous as opposed to submucosal; polypoid.

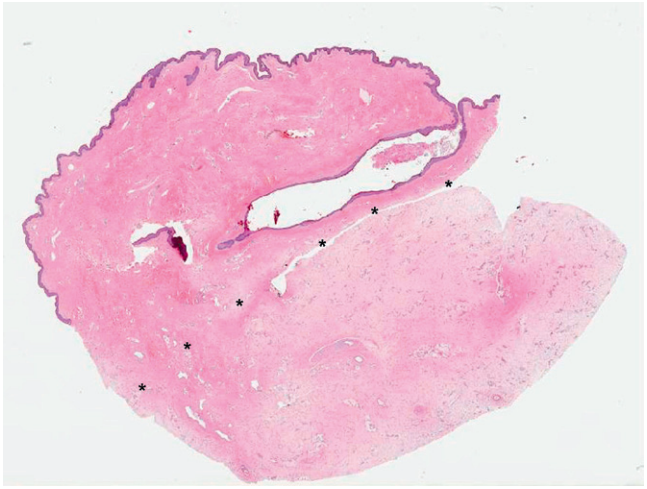


FIGURE 1

Prepubertal vulvar fibroma. This low-power image illustrates an ill-defined submucosal mass (below the *).

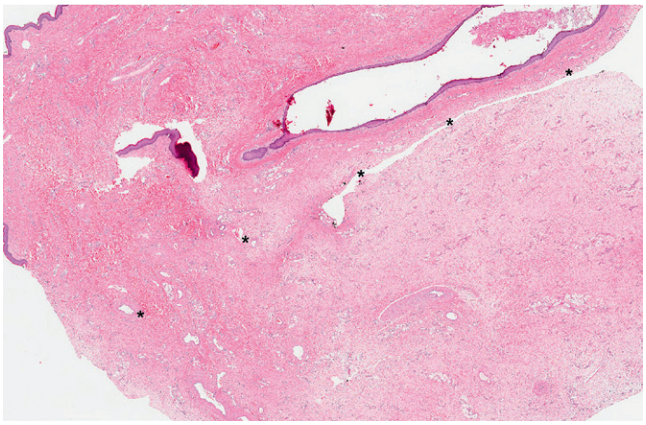


FIGURE 2

Prepubertal vulvar fibroma. At higher magnification the interface between the normal and abnormal stroma is demarcated (*).

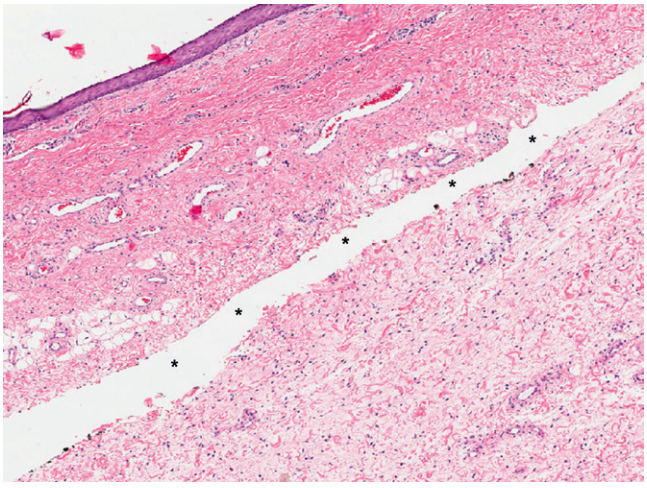


FIGURE 3

Prepubertal vulvar fibroma. At higher magnification the interface between the normal and abnormal stroma is demarcated (*).

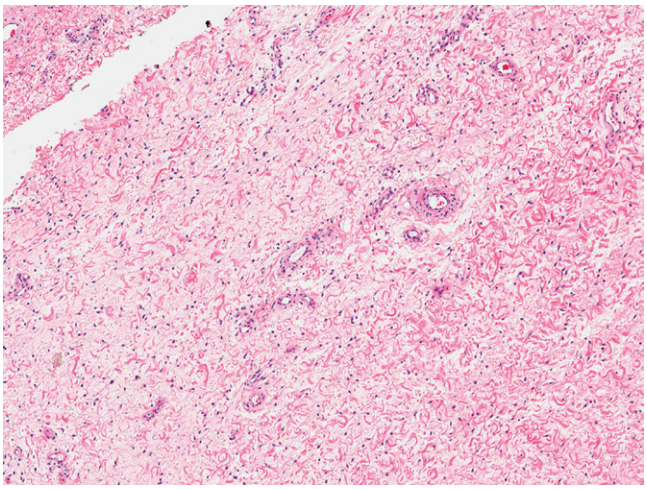


FIGURE 4

Prepubertal vulvar fibroma. Spindled cells with ovoid nuclei set in an edematous, collagenous stroma. Note the small blood vessels.

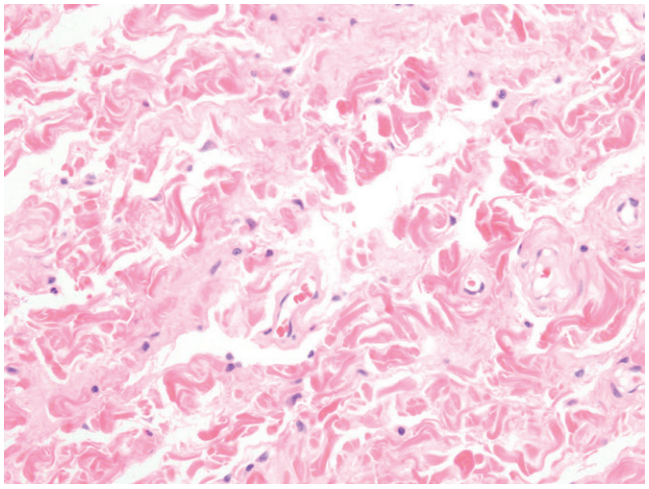


FIGURE 5

Prepubertal vulvar fibroma. Collagenous background with bland spindle cells. Delicate capillary-like vessels are present.

ANAL CONDYLOMA

Definition—A human papillomavirus (HPV)–related exophytic lesion of the perianal skin and anal canal.

Clinical Features

Epidemiology

- Associated with low-risk HPV infection (types 6 and 11).
- Increased incidence with immunosuppression, including human immunodeficiency virus (HIV).
- Other risk factors include anal intercourse, other sexually transmitted diseases, and multiple sexual partners.

Presentation

- Seen clinically as pink to gray warty excrescences, sometimes with filiform fronds.

Prognosis and Treatment

- Prognosis is variable; lesions may persist for some time.
- Highly associated with increased risk of subsequent high-grade squamous intraepithelial lesion diagnosis; clinical follow-up is required.
- Treatment options include excision, laser vaporization, and topical antiviral agents.

Pathology

Histology

- The condyloma trifecta includes acanthosis (thickening of the epidermis), papillomatosis (fronds), and koilocytosis (viral cytopathic effect). The latter may vary, however, in keratinized mucosa.
- Nuclear atypia is variable but must be confined to the upper layers of epidermis.
- Multiple lesions are frequently present.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- High-grade squamous intraepithelial lesion—atypia akin to other high-grade lesions in the vulva or vagina.
- Hemorrhoids—lack the verruciform acanthosis of condyloma.
- Reactive epithelia changes with cytoplasmic halos—minimal atypia present.
- Nonspecific acanthosis—minimal anisokaryosis and no koilocytosis.
- Fibroepithelial stromal polyp–like hemorrhoids—lack the acanthosis and papillomatosis of condyloma.

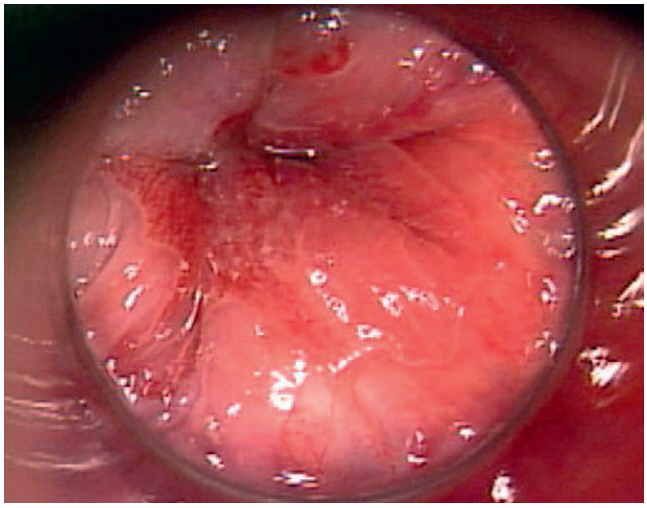


FIGURE 1

Colpophotograph of the anal squamocolumnar junction. *(Courtesy N. Jay and J.M. Berry, UCSF.)*

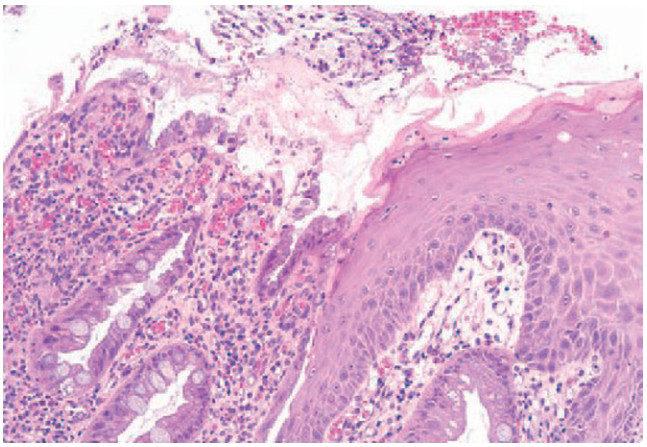


FIGURE 2

Photomicrograph of the squamocolumnar region.

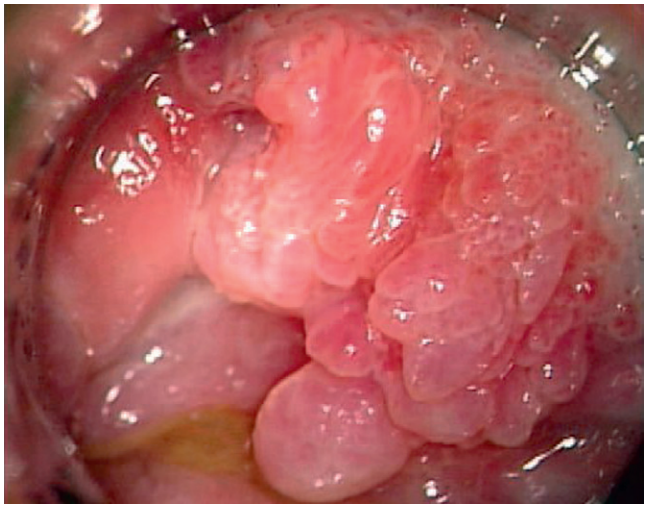


FIGURE 3

Colpophotograph of an exophytic anal condyloma. *(Courtesy N. Jay and J.M. Berry, UCSF.)*

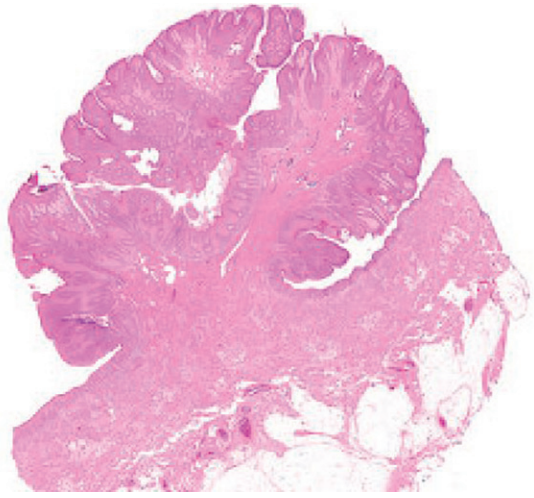


FIGURE 4

Low-power image of an exophytic anal condyloma.

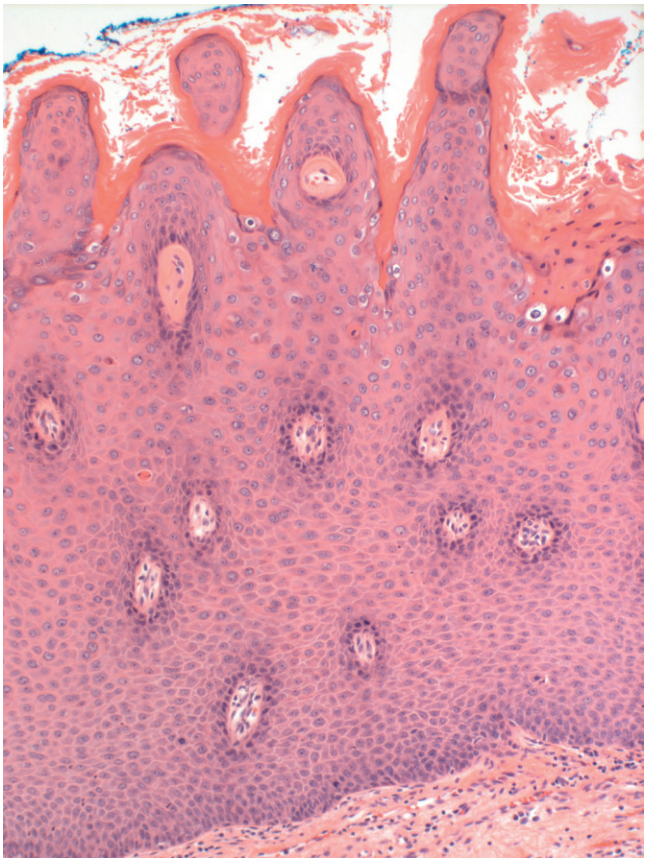


FIGURE 5

Anal condyloma. Acanthosis with small spirelike epithelial projections. Hyperkeratosis is noted throughout. Focal parakeratosis can be identified within the hyperkeratotic layer on the right side. Note the small zone of koilocytotic atypia.

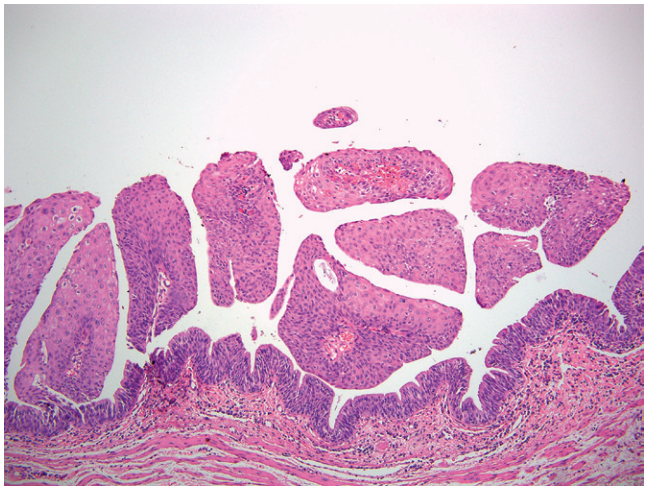


FIGURE 6

Anal condyloma. Papillary-like projections with koilocytic atypia are best seen in the leftmost spire. Note the lack of any cytopathic effect in other areas, a manifestation of lesions that arise in a transitional epithelium.

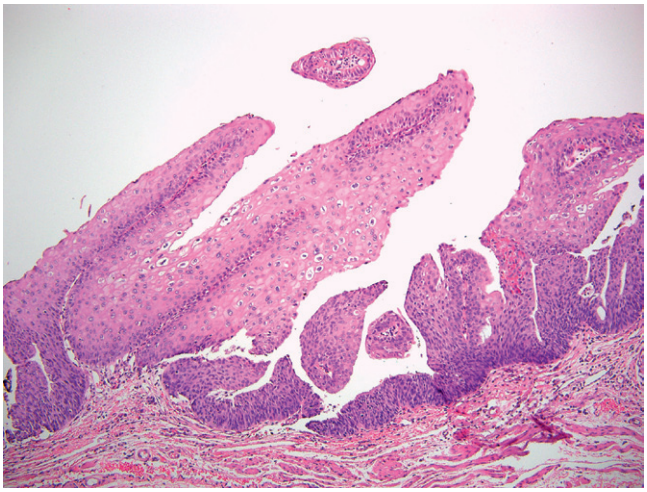


FIGURE 7

Anal condyloma. Fine papillary projections with conspicuous viral cytopathic effect, merging with transitional epithelium on the right. In both Figures 6 and 7 the small papillae with lack of cytopathic effect is similar to that seen with immature condylomas of the cervix arising in immature metaplastic epithelium and similar low-risk HPV infections in the urethra.

ANAL INTRAEPITHELIAL NEOPLASIA II AND III

Definition—A high-grade, human papillomavirus (HPV)–associated, in situ lesion of the squamous anal mucosa.

Clinical Features

Epidemiology

- Associated with oncogenic HPV types (16 and 18).
- Increased risk with HPV, human immunodeficiency virus (HIV), anal intercourse, and multiple sexual partners.

Presentation

- May be an incidental finding following an unrelated procedure (such as hemorrhoidectomy).
- Clinical appearance ranges from an inconspicuous smooth or granular flat lesion to a denuded and ulcerated patch.

Prognosis and Treatment

- Natural history is not well understood.
- Regression rates appear low.
- Treatment options include surgical excision (for large lesions), trichloroacetic acid (TCA), and cryotherapy.

Pathology

Histology

- Lesions are characterized by uniform, full-thickness atypia with loss of nuclear polarity.
- Dyskeratosis and frequent mitoses (including atypical forms) are present.
- Parakeratosis with atypical nuclei is often present.
- Lesions often involve skin appendages, especially hair follicles.

Immunopathology (Including Immunohistochemistry)

- Positive for p16.

Main Differential Diagnosis

- Inflamed or reactive epithelium—particularly in the anal transition zone where the native epithleium can appear immature or "transitional."

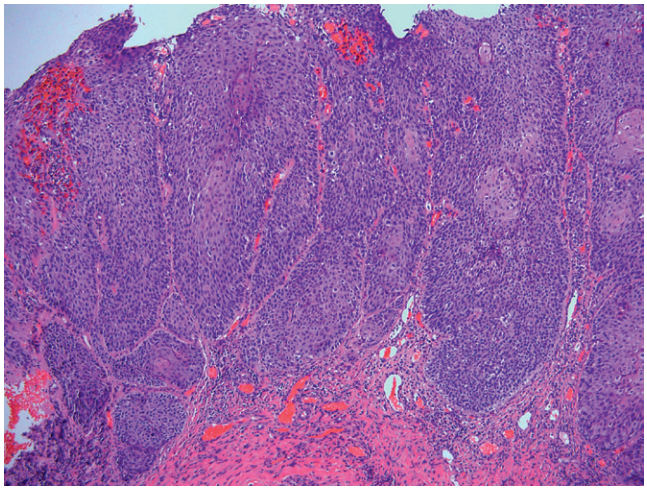


FIGURE 1

Anal intraepithelial neoplasia (AIN) II/III. Acanthotic squamous epithelium with full-thickness loss of maturation and marked cell crowding. Features analogous to those seen in high-grade dysplasia of the vulva, vagina, or cervix.

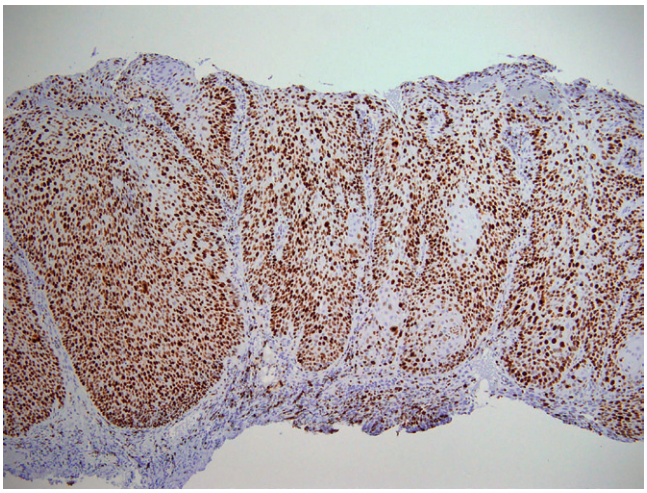


FIGURE 2

AIN II/III. Ki-67 immunostain showing a diffuse increase in labeling, with positive nuclei present in the uppermost epithelial layer.

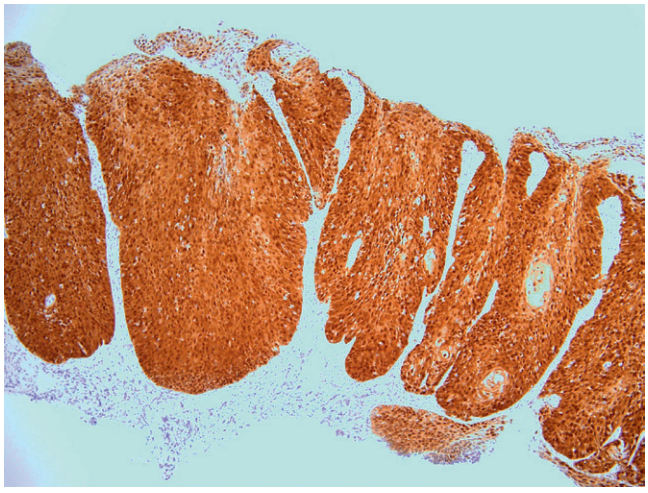


FIGURE 3

AIN II/III. Immunostaining for p16 showing strong, diffuse, nuclear and cytoplasmic positivity.

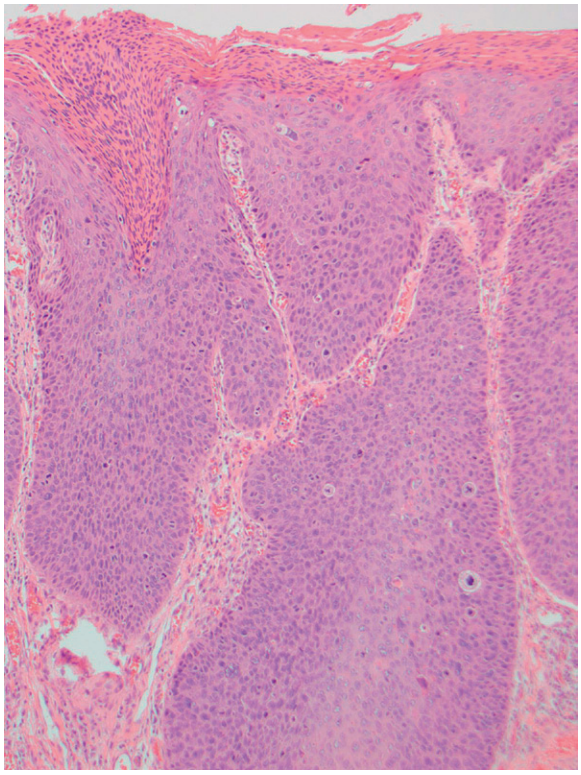


FIGURE 4

II/III. Full-thickness nuclear atypia with numerous apoptotic cells and striking parakeratosis with atypical nuclei.

ANAL CARCINOMA

Definition—Malignant tumors arising from the epithelium of the anal canal.

Clinical Features

Epidemiology

- Rare; incidence is estimated at 7 per million women and 9 per million men.
- Incidence is increasing at a rate of approximately 2% a year.
- Squamous cell carcinomas (SCC) account for 80% of cases; risk factors include human papillomavirus (HPV), human immunodeficiency virus (HIV), anal intercourse, and number of sexual partners.
- Adenocarcinomas are much less frequent and account for approximately 20% of tumors.

Presentation

- Often nonspecific and varies with tumor size.
- May present with pruritus, pain, changes in bowel habits, or sensation of a mass.

Prognosis and Treatment

- Overall 5-year survival ranges from 60% to 80% for SCC.
- First-line therapy for SCC is typically chemoradiation; radial resections are reserved for those patients who cannot tolerate other modalities or for salvage therapy.
- Prognosis for SCC varies with tumor stage (including lymph node status) and tumor grade.

Pathology

Histology

- Three major morphologic variants of anal SCC exist: large-cell keratinizing, large-cell nonkeratinizing, and basaloid.
- The large-cell variants are composed of irregularly shaped nests and cords of large cells with pale pink cytoplasm and vesicular nuclei.
- Keratin production may manifest as brightly eosinophilic whorls (pearls) or as single cells with intensely eosinophilic cytoplasm.
- The basaloid (cloacogenic or transitional) variant is characterized by nests of smaller cells with high nuclear-to-cytoplasmic ratios and central necrosis.
- The basaloid nests often exhibit peripheral palisading of nuclei and artifactual retraction from the surrounding stroma.
- An adjacent high-grade intraepithelial squamous lesion is often identified.
- Other rare variants exist, including verrucous carcinoma and anal duct carcinoma.
- Adenocarcinoma of the anal canal is divided into three groups: adenocarcinoma of the anal mucosa, anal gland carcinoma (rare), and adenocarcinoma within a fistula.
- Adenocarcinoma of the anal mucosa has the morphologic appearance of a typical colorectal carcinoma.

Immunopathology (Including Immunohistochemistry)

- SCC may be p16 positive.

Main Differential Diagnosis

- Pseudoepitheliomatous hyperplasia.
- Benign or giant condyloma.
- Basal cell carcinoma.

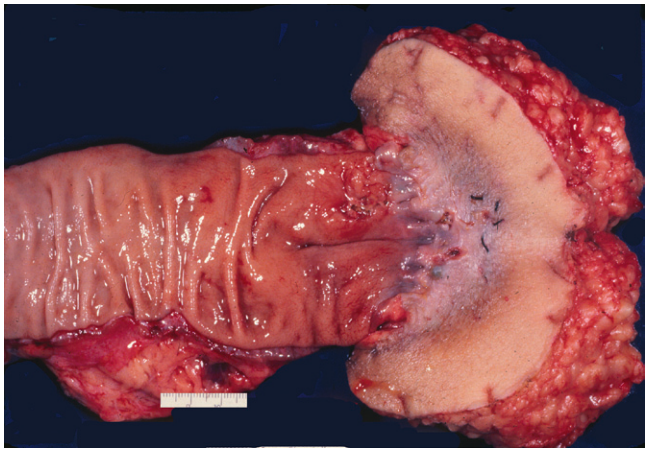


FIGURE 1

Anal carcinoma. A gross photograph showing a 2 cm area of ulceration at the squamocolumnar junction. *(Courtesy Dr. Laura Lamps.)*

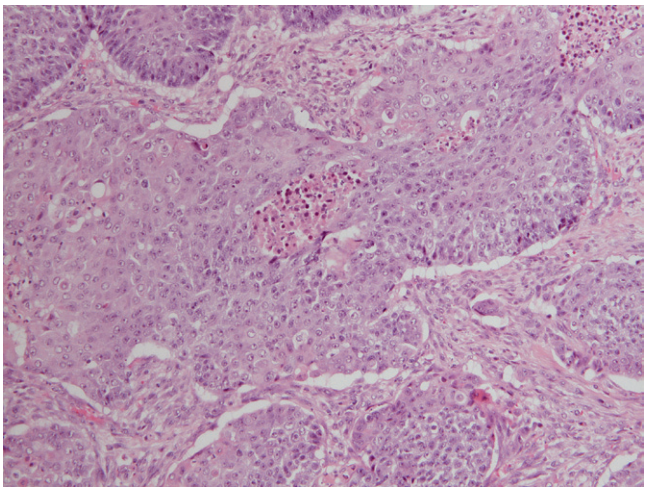


FIGURE 2

Anal carcinoma. Infiltrating nests of SCC with abundant eosinophilic cytoplasm and vesicular nuclei. *(Courtesy Dr. Laura Lamps.)*

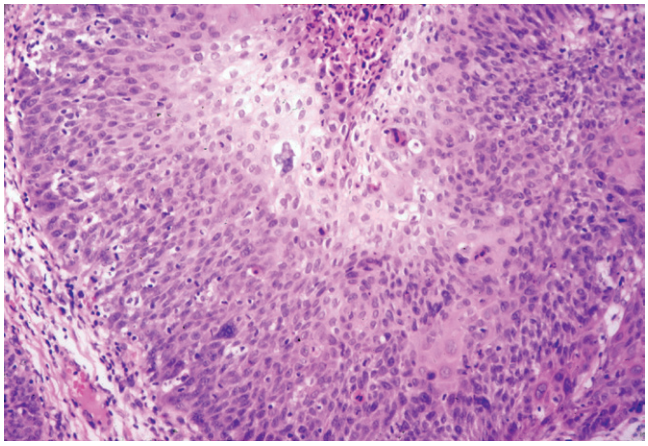


FIGURE 3

Anal carcinoma. SCC with focal dyskeratosis displayed by the occasional brightly eosinophilic cell. Focal, marked pleomorphism can be seen as well. *(Courtesy Dr. Laura Lamps.)*

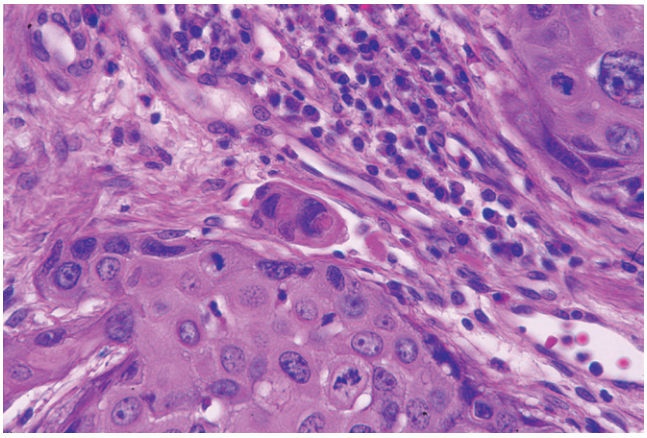


FIGURE 4

Anal carcinoma. A small cluster of dyskeratotic squamous cells within a vascular space. Note the marked increase in cell and nuclear size when compared with the adjacent lymphocytes. *(Courtesy Dr. Laura Lamps.)*

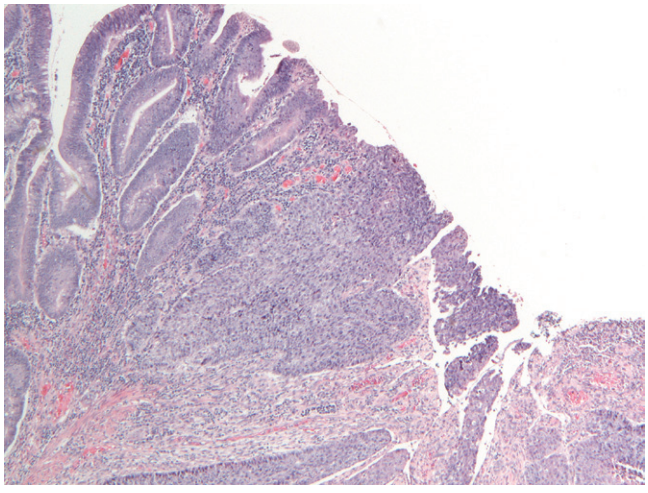


FIGURE 5

Anal carcinoma. Basaloid-type SCC arising adjacent to an area of adenomatous glandular dysplasia. *(Courtesy Dr. Laura Lamps.)*

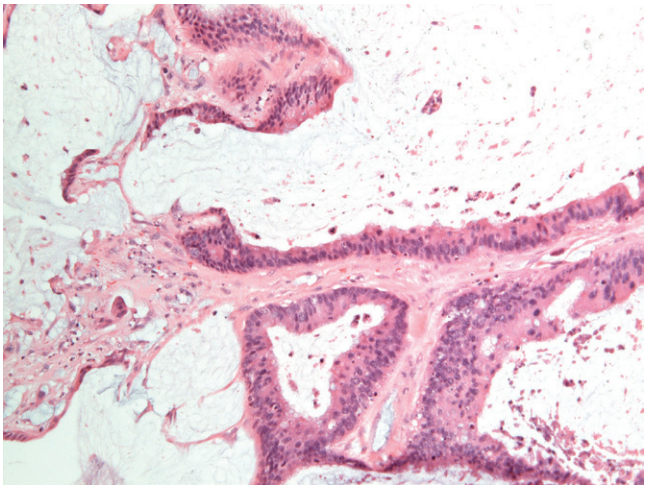


FIGURE 6

Anal carcinoma. Glandular "cloacogenic carcinoma" composed of glands that are identical to those seen in colonic adenocarcinoma. *(Courtesy Dr. Laura Lamps.)*

ANAL PAGET'S DISEASE

Definition—Infiltration of the perianal squamous epithelium by mucin-producing neoplastic cells associated with an anorectal neoplasm. Also called type 2 Paget's disease.

Clinical Features

Epidemiology

- Uncommon; represents only 1% to 2% of vulvar malignancies.
- The average age at presentation is 65 years; the majority of patients are over 60 years.

Presentation

- Perianal pruritus is the most common symptom.
- Ill-defined, erythematous plaques on the anus.
- Involved skin may exhibit eczematous changes or ulceration.
- Paget's disease may precede the diagnosis of invasion by months or years.

Prognosis and Treatment

- Wide local excision for noninvasive and either local excision or radical abdominoperitoneal resection for invasive carcinomas.
- Close follow-up is necessary; disease recurs in up to 50% of patients, even with negative margins.
- Ten-year median disease-specific survival for invasive carcinoma. For noninvasive lesions the survival is similar to age-matched controls.
- An associated internal malignancy (e.g., colorectal carcinoma) has been reported in up to 10% to 15% of cases.

Pathology

Histology

- Nests and single cells percolate through the epidermis, frequently extending into adnexal structures.
- The neoplastic cells are large, often with abundant pale blue cytoplasm, large vesicular nuclei, and small conspicuous nucleoli.
- Rarely Paget's cells may form glands within the epidermis.
- A basal keratinocyte is often present between the Paget's cells and the basement membrane.
- Stromal invasion by Paget's cells may be difficult to distinguish from adnexal involvement.

Immunopathology (Including Immunohistochemistry)

- Positive for CK20.
- Negative for CK5/6 (positive in squamous epithelium), S100, p63, CK7, and GCDFP.

Main Differential Diagnosis

- Vulvar or perineal Paget's disease: These are typically CK7 positive.
- Urothelial carcinoma (via direct extension): Typically more poorly differentiated in appearance. Will be both CK7 and CK20 positive.
- Pagetoid vulvar intraepithelial neoplasia: These are rare in the vulva and rarer in the perianal region. Will be p63 positive.
- Melanoma: Will be CK20 negative, Melan-A and MART1 positive.

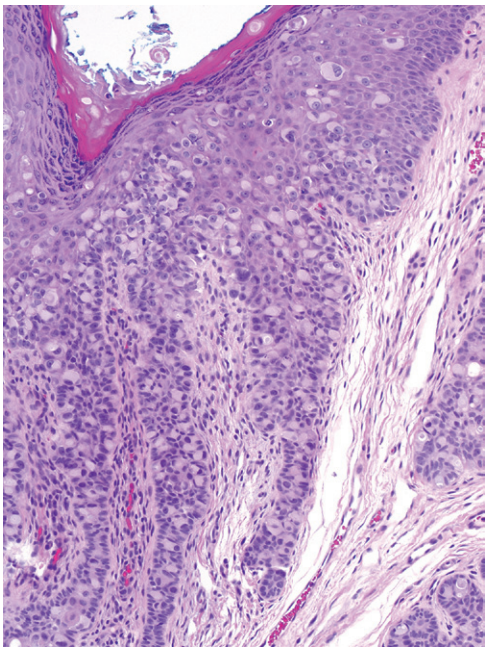


FIGURE 1

Anal Paget's disease. The entire thickness of the epithelium is permeated with neoplastic cells.

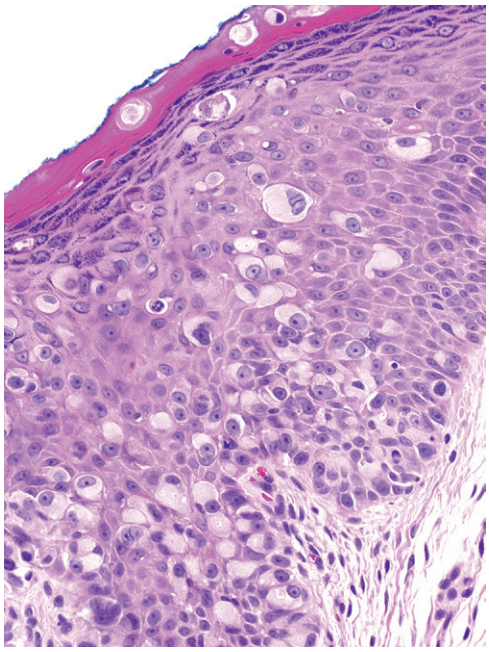


FIGURE 2

Anal Paget's disease. At higher magnification the characteristic Paget's cells with ample cytoplasm are throughout the epithelium.

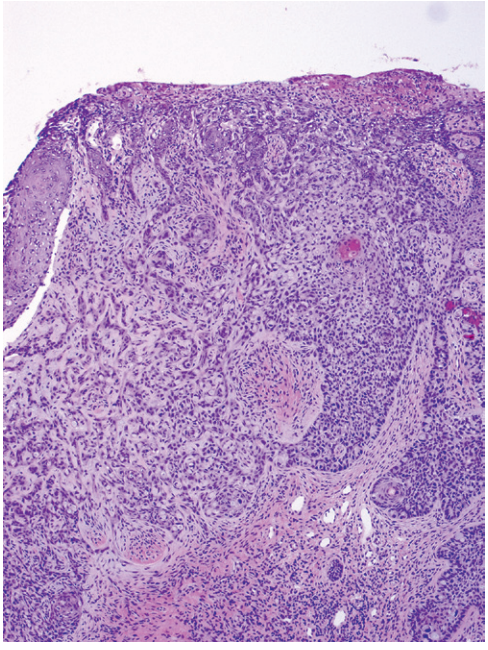


FIGURE 3

Anal Paget's disease. Invasive carcinoma is seen on the left.

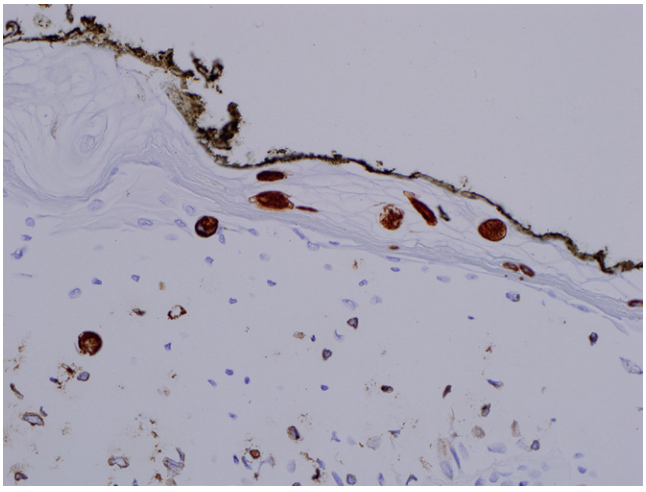


FIGURE 4

Anal Paget's disease. Several Paget's cells are positive for CK20.

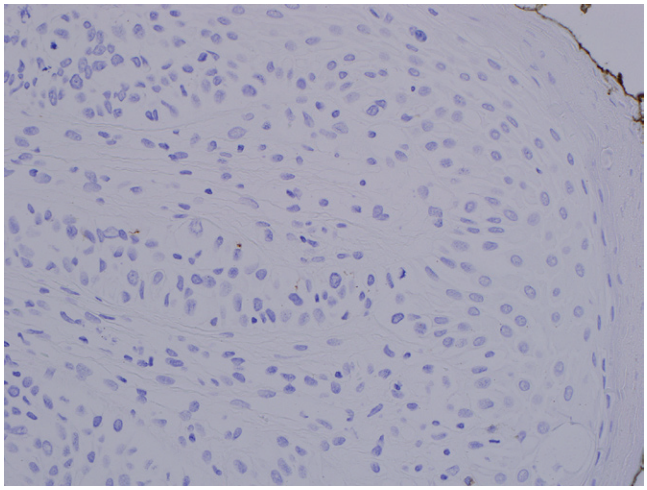


FIGURE 5

Anal Paget's disease. These are typically CK7 negative.

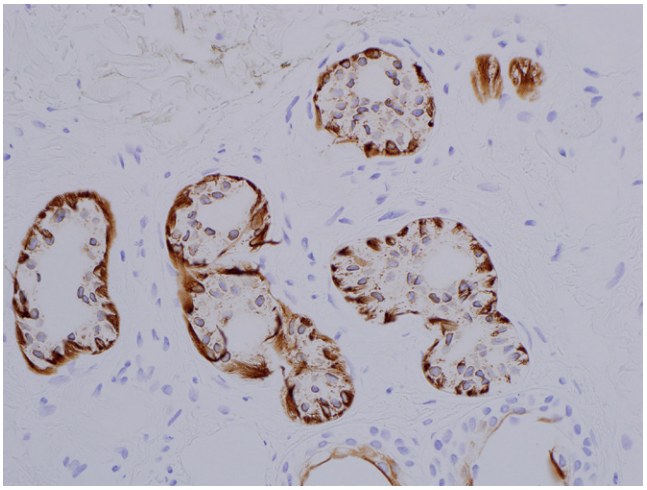


FIGURE 6

Perianal glands are CK7 positive and should not be confused with Paget's cells.

PROLAPSED FALLOPIAN TUBE

Definition—Protrusion of the fallopian tube into the vagina.

Clinical Features

Epidemiology

- Occasionally affects women after simple hysterectomy.

Presentation

- May present as a mass in the upper vagina following simple hysterectomy when the tubes are fixed near the vaginal apex. Cases have been reported in laparoscopic procedures where the adnexa are spared. Clinically may appear similar to granulation tissue or recurrent carcinoma (in clinically appropriate setting).

Prognosis and Treatment

- Excellent; excision is curative.

Pathology

Histology

- Typical tubal histology is present. Plica lined with variable amounts of secretory and ciliated cells is present. Marked acute and chronic inflammation with granulation tissue may be present as well as reactive atypia. In some cases the stroma undergoes an exuberant angiomyofibroblastic response that may mimic a stromal neoplasm. These lesions may be mistaken for adenocarcinoma if the tubal epithelium is not appreciated.

Immunopathology (Including Immunohistochemistry)

- PAX8 staining may be helpful if cilia are not present and there is a concern for a neoplasm that is not müllerian.

Main Differential Diagnosis

- Granulation tissue—This is another sequel to hysterectomy and can mimic prolapsed fallopian tube clinically.
- Recurrent adenocarcinoma (in clinically appropriate setting)—This is usually easily distinguished from prolapsed tube, but the combination of both a prolapsed tube and a prior history of endometrial carcinoma is a recipe for a misdiagnosis.

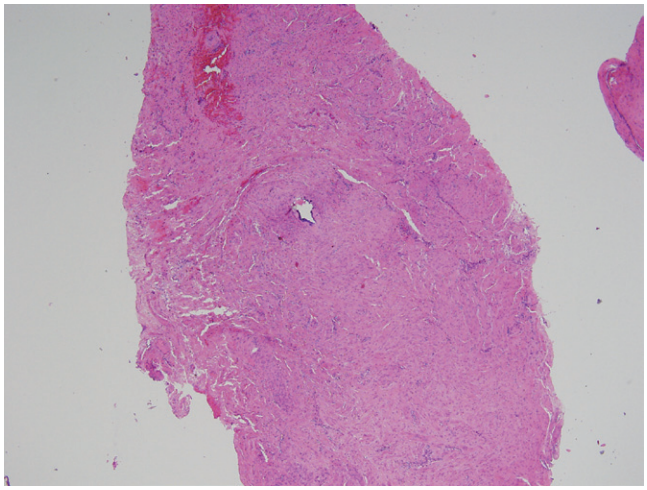


FIGURE 1

A segment of prolapsed tube with a small lumen and surrounding smooth muscle.

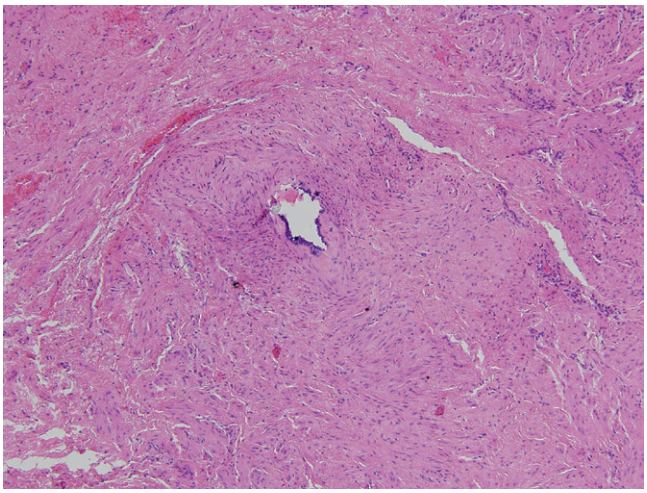


FIGURE 2

Higher magnification showing the lumen and tubal wall.

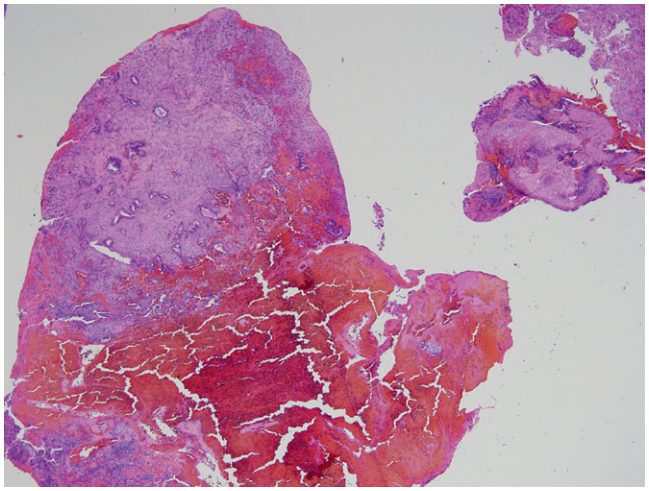


FIGURE 3

Prolapsed fallopian tube. A typical appearance of haphazardly arranged glandlike structures in a fibrotic and inflamed stroma.

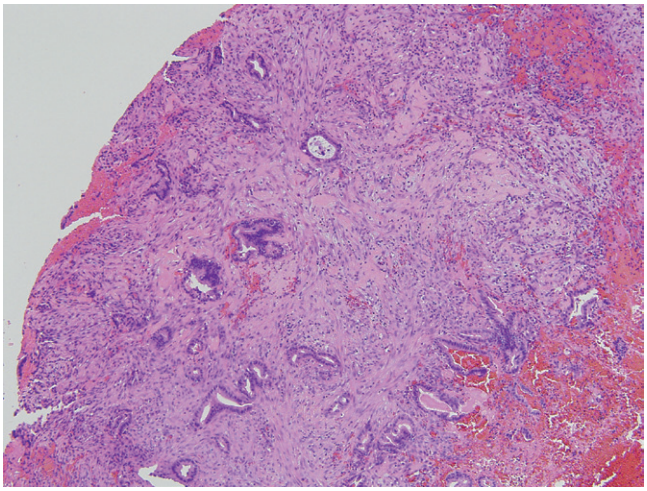


FIGURE 4

Higher magnification of Figure 3. Note the epithelium, being inflamed, may not display evidence of ciliated differentiation, which can make the exclusion of a neoplasm initially difficult.

GRANULATION TISSUE

Definition—A fibrovascular response to injury comprised of small vascular structures, loose stroma, and admixed inflammation.

Clinical Features

Epidemiology

- Affects all age groups; vaginal granulation tissue is commonly seen after surgery in the vaginal cuff.

Presentation

- Vaginal granulation tissue presents as a red papule in the upper vagina, adjacent to the sutured vaginal cuff.
- Grossly the lesion may be friable and bleed easily, mimicking recurrent carcinoma.
- Patients may present with vaginal bleeding.

Prognosis and Treatment

- Excellent; the lesions are self-limited.
- Simple excision may be considered for large painful lesions.

Pathology

Histology

- Marked inflammation, both acute and chronic, with admixed proliferating vessels and edematous stroma are present in variable proportions.
- The surface may display erosions.
- Reactive atypia may be prominent and mimic neoplastic change.
- As the lesions age, increasing amounts of fibrous tissue will be found.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Carcinoma—this can be a diagnostic problem if squames are trapped within the granulation tissue.

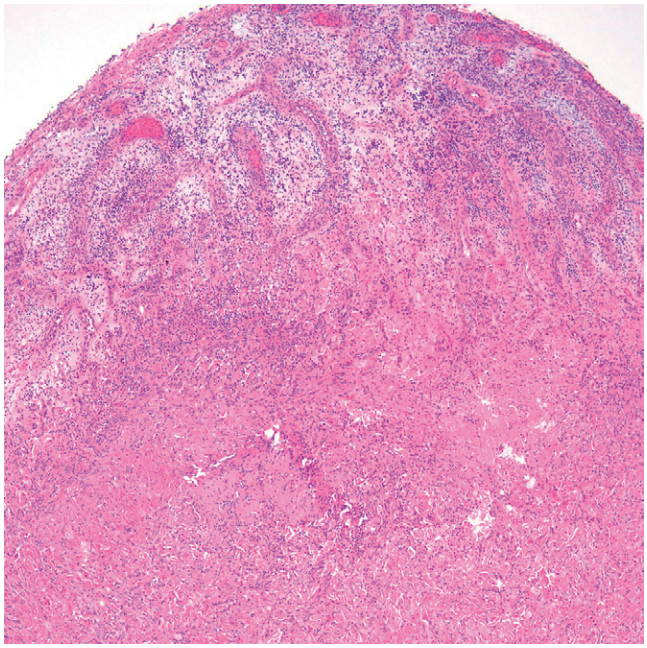


FIGURE 1

Granulation tissue. Stromal edema, inflammatory cells, and vascular ingrowth can be seen at low power. Note that the surface is denuded.

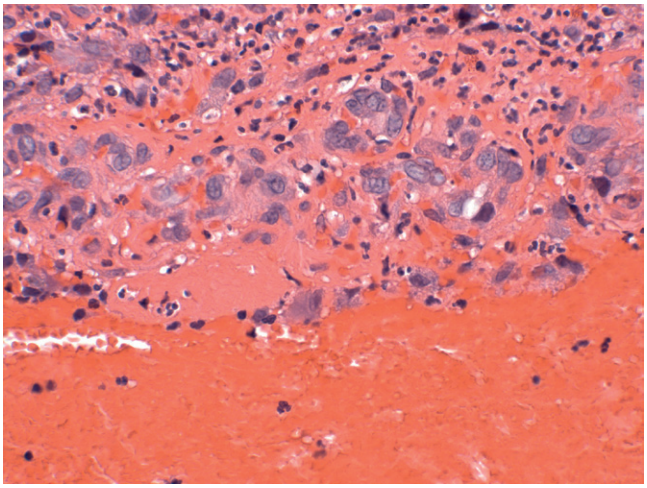


FIGURE 2

Granulation tissue. Admixed inflammatory cells and vascular endothelial cells. The vascular endothelial cells may display reactive atypia that can mimic malignancy.

VAGINAL ADENOSIS

Definition—Congenital glandular differentiation present within the vaginal mucosa.

Clinical Features

Epidemiology

- Prior to the use of diethylstilbestrol (DES) and in patients not exposed to DES the incidence of vaginal adenosis was rare. In patients who were exposed to DES the incidence of adenosis approaches one third.

Presentation

- Clinical examination will reveal the presence of red, granular vaginal mucosa. This can be seen in continuity with the cervix. The upper vagina is affected in the vast majority of cases.

Prognosis and Treatment

- There is a small but significant association with DES-associated adenosis and vaginal clear cell carcinoma, which can be seen in 1 in 1000 to 5000 exposed patients. Simple excision is curative.

Pathology

Histology

- The glands comprising adenosis may have differing morphologies including benign endocervical glands, which may be complicated by squamous, tubal, endometrial, and tubal-endometrial metaplasia. Large lesions may rarely contain papillary structures, microglandular change, Arias-Stella effect, and intestinal metaplasia. Varying degrees of glandular atypia may be present.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Endometriosis—this may be particularly difficult to distinguish from adenosis given that the latter often displays tubal-endometrial metaplasia. The presence of separate endocervical-like glands with reserve cells and/or metaplasia supports adenosis.
- Prolapsed fallopian tube—this is another entity that can display bland-appearing "glands" with features of endocervical epithelium. Reserve cells and squamous metaplasia will be absent.
- Mucous cyst of the vagina—this is technically "adenosis" and can undergo squamous metaplasia but is usually an isolated cyst.
- Adenocarcinoma—this can be a concern when there is atypia and criteria used to distinguish clear cell carcinoma or other neoplasms from Arias-Stella effect or reactive changes are applied.

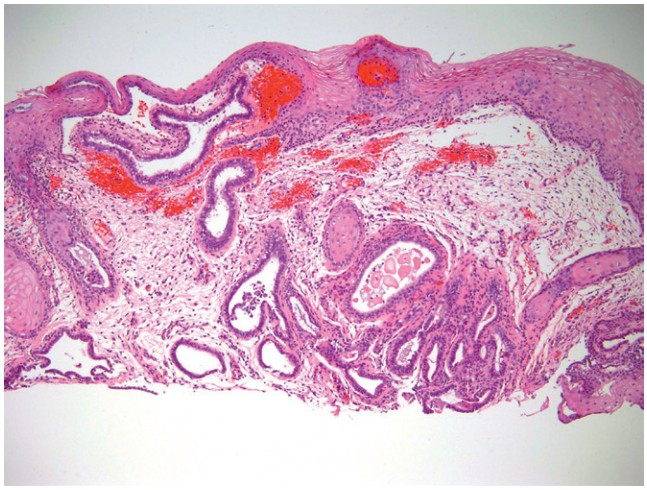


FIGURE 1

Vaginal adenosis. Here a range of columnar epithelial differentiation is seen, mostly tubal-endometrial, but with squamous metaplasia.

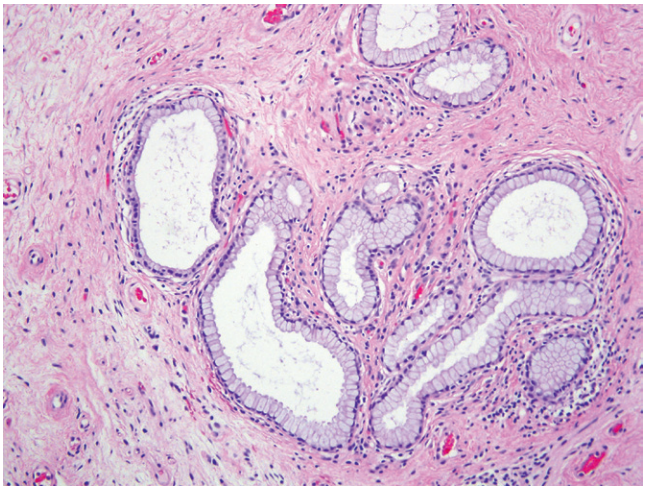


FIGURE 2

Vaginal adenosis. This epithelium is classic endocervical type.

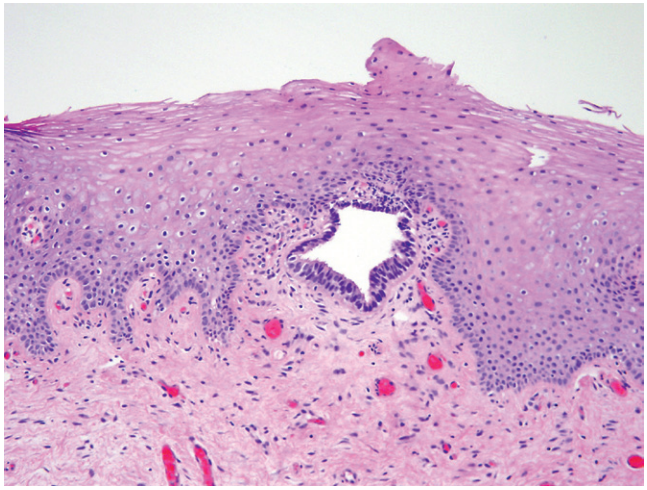


FIGURE 3

Vaginal adenosis. A single tubal-endometrial–type gland beneath squamous metaplasia is virtually identical to stroma-poor endometriosis.

POLYPOID ENDOMETRIOSIS

Definition—A mass-forming, proliferative focus of misplaced endometrial glands and stroma within the vagina.

Clinical Features

Epidemiology

- Uncommon; vaginal endometriosis accounts for less than 10% of all endometriosis, with the most common form being traditional endometriosis composed of glands and stroma (as opposed to the mass-forming "polypoid" variety).

Presentation

- Patients present with a mass in the vagina with or without vaginal bleeding.

Prognosis and Treatment

- Excellent; lesions may be cured by excision; however, these lesions do have a small risk of malignant transformation.

Pathology

Histology

- The vaginal mass is composed of variable amounts of endometrial glands and stroma. Rarely lesions may lack or have very rare endometrial glands (stromatosis).
- Hemosiderin deposition (old hemorrhage) may be present within the stroma.
- Because of the mass-forming nature of these lesions, a diagnosis of carcinoma or sarcoma may be entertained; however, endometriosis will lack the malignant stroma and irregular glands of malignant mimics.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Fibrous polyp—will lack the typical endometrial stroma.
- Adenosarcoma—this must always be excluded and will be by the absence of abnormal architecture and stromal condensation. However, rare cases of polypoid endometriosis have been followed by adenosarcoma.

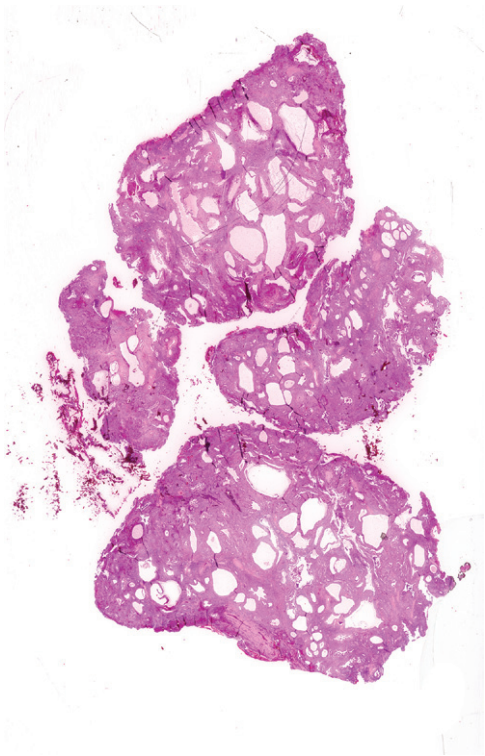


FIGURE 1

Polypoid endometriosis. Polypoid mass of glands and stroma.

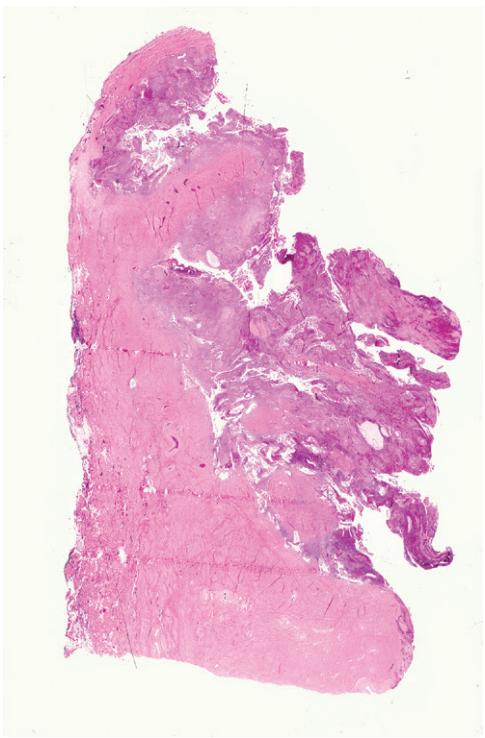


FIGURE 2

Polypoid endometriosis. A polypoid mass predominantly composed of stroma with rare interspersed glands.

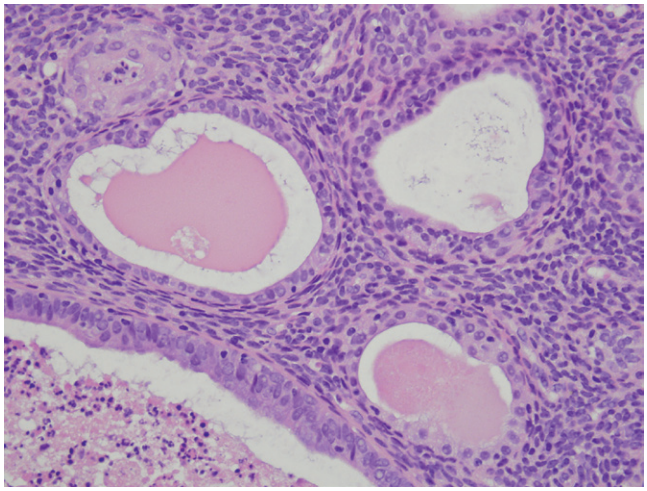


FIGURE 3

Polypoid endometriosis. Close inspection will reveal otherwise normal endometrial glands and stroma in varying amounts.

VAGINAL PAPILLOMATOSIS (RESIDUAL HYMENAL RING)

PITFALL

Definition—Villiform remnants of hymenal ring.

Clinical Features

Epidemiology

- Typically seen in young women of reproductive age.
- No symptoms.
- Not related to human papillomavirus (HPV).

Presentation

- In these patients speculum examination of vulvovaginal region leads to their discovery.

Prognosis and Treatment

- Vestibular papillomas do not require treatment.

Pathology

Histology

- Vestibular papillomatosis consists of multiple branching microvillus-like papillae (villiform) analogous to a villiform polyp.
- There is no koilocytosis or atypia.

Immunopathology (Including Immunohistochemistry)

- Not applicable. Will stain weak or negative for Ki-67 and p16.

Main Differential Diagnosis

- Condyloma—exhibits true papillomatosis and koilocytotic atypia.
- White sponge nevus—this is a rare familial lesion of the oral cavity that can be mildly verruciform and involve the vagina.
- Fibroepithelial stromal polyp—typically solitary or few in number, keratinized.

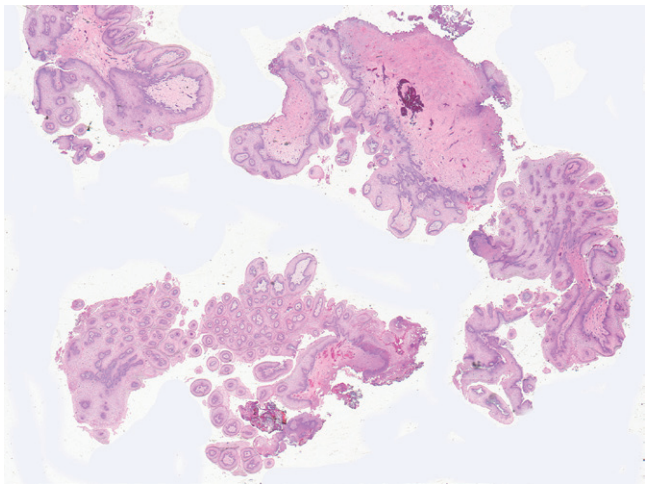


FIGURE 1

Vestibular papilloma. At scanning power multiple fragments of mucosa exhibit a microvillus architecture.

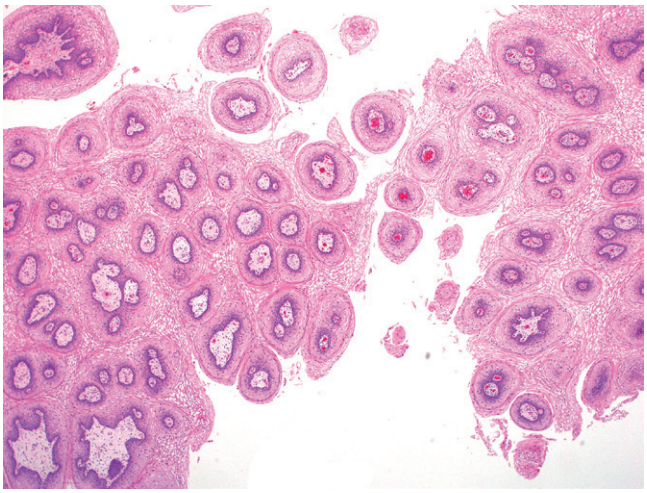


FIGURE 2

Vestibular papilloma. At higher magnification numerous coalescing stromal villi are seen.

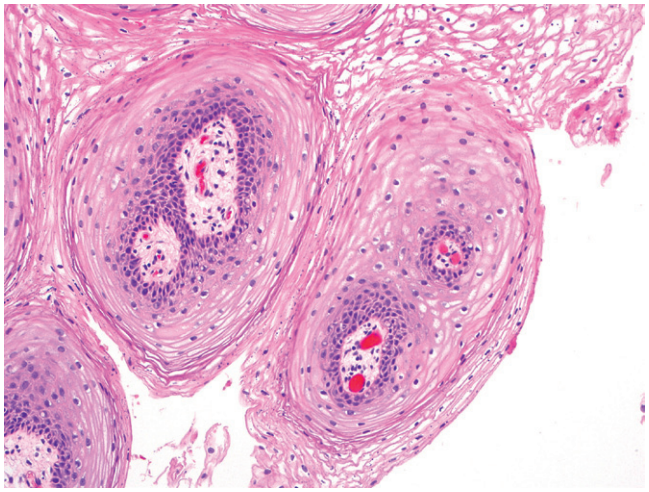


FIGURE 3

Vestibular papilloma. At high magnification there is no evidence of either atypia or coalescing verrucopapillary growth.

LOW-GRADE VAGINAL INTRAEPITHELIAL LESION (VAGINAL INTRAEPITHELIAL NEOPLASIA I AND CONDYLOMA)

Definition—Human papillomavirus (HPV)–related proliferation of the vaginal mucosa.

Clinical Features

Epidemiology

- Patients present at a slightly older age than those with cervical dysplasia, with the majority presenting around 40 years of age.
- Sixty-five percent of patients with vaginal intraepithelial lesion (VAIL) have concurrent or prior cervical dysplasia.
- HPV is responsible for the majority of lesions, and predisposing factors include previous cervical intraepithelial neoplasia (CIN), history of previous hysterectomy for dysplasia, history of local radiation therapy, and immunosuppression.

Presentation

- In patients at risk, speculum examination with the intent of discovery of vaginal lesions leads to their discovery in most cases.

Prognosis and Treatment

- The prognosis is excellent; however, the majority of low-grade lesions do not progress.
- Observation is a viable option for most patients.
- If therapy is indicated, topical treatment with fluorouracil (5-FU) or laser vaporization may be pursued.
- Excessive treatment can lead to increased morbidity including adhesions and dyspareunia.

Pathology

Histology

Low-grade vaginal intraepithelial lesion

- Similar to low-grade cervical lesions, these lesions demonstrate mild atypia in the basal layers with a mild increase in the nuclear density.
- The most conspicuous finding is koilocytotic atypia (including binucleate cells) within the middle to upper third of the epithelium.
- In contrast to condyloma, these flat lesions lack verrucopapillary architecture and may display less acanthosis and parakeratosis. Associated with a range of HPV types including high-risk HPVs.

Condyloma (exophytic low-grade VAIL)

- Exophytic lesions with similar nuclear changes to flat lesions described earlier.
- Condyloma is typically associated with infection by HPV 6 and 11.

VAIL not amenable to precise grading

- This category consists of lesions with features of both VAIN1 and VAIN2.
- The basal layer shows more extensive expansion with loss of maturation extending to the middle half of the epithelium.
- Koilocytotic atypia and binucleate cells may be present, although may be decreased in contrast to traditional low-grade lesions.

- Verrucopapillary architecture may or may not be prominent.

Immunopathology (Including Immunohistochemistry)

- Ki-67 (MIB1) immunostaining will highlight superficial keratinocyte nuclei that are actively undergoing DNA turnover in low-grade lesions/condyloma.

Main Differential Diagnosis

- Acantholytic change (prolapse associated).
- Fibrous polyp of the introitus.
- Reactive epithelial changes with pseudokoilocytosis.

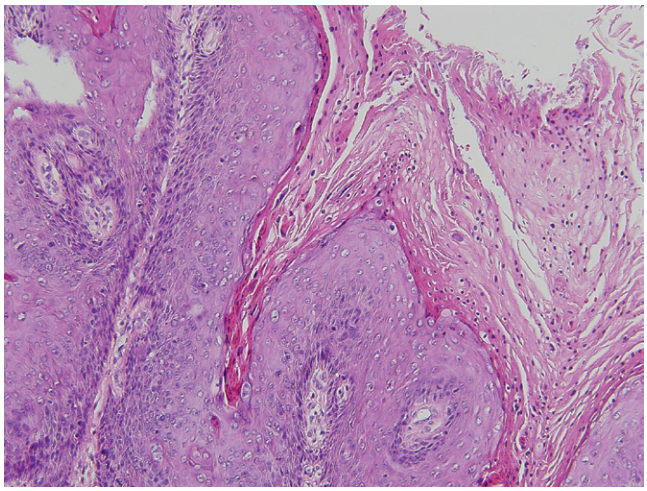


FIGURE 1

Vaginal low-grade squamous intraepithelial lesion. Spirelike hyperkeratosis with parakeratosis. Superficial maturation is present. Note the lack of conspicuous koilocytotic atypia.

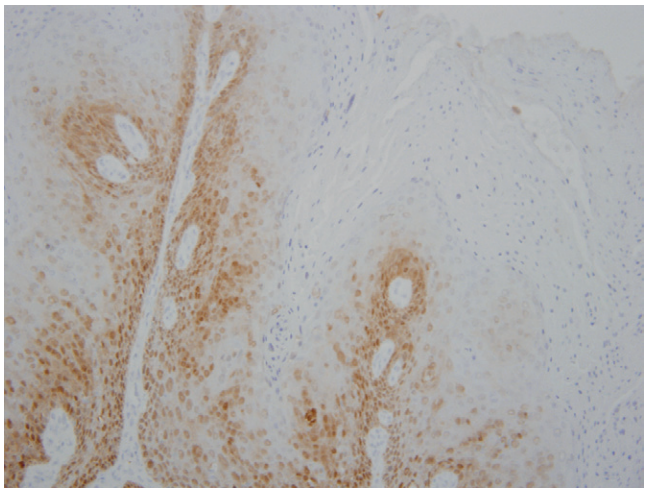


FIGURE 2

Vaginal low-grade squamous intraepithelial lesions/lesions difficult to grade. Immunohistochemical staining for p16 of the case in Figure 1. Note the patchy, basal positivity.

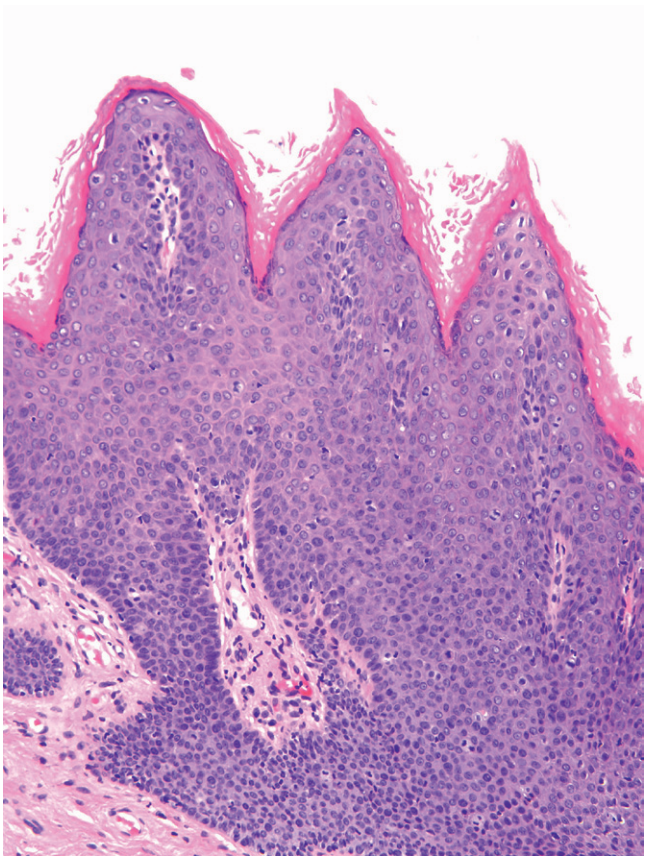


FIGURE 3

Vaginal low-grade squamous intraepithelial lesion difficult to grade. Tangential sectioning of a lesion bordering on a high-grade vaginal squamous intraepithelial lesion. Superficial maturation is present, although not to the extent as in Figures 1 and 2. These lesions are often associated with high-risk HPVs and may be p16 positive, but should be managed with an eye toward a conservative approach that minimizes morbidity.

HIGH-GRADE VAGINAL INTRAEPITHELIAL LESION (VAGINAL INTRAEPITHELIAL NEOPLASIA II-III)

Definition—Human papillomavirus (HPV)–related proliferation of the vaginal mucosa that leads to extensive, full-thickness loss of maturation of the vaginal epithelium.

Clinical Features

Epidemiology

- Patients present at a slightly older age than those with cervical dysplasia, with the majority presenting around 55 to 57 years of age for high-grade VAIN.
- The advanced age is thought to lead to an increased incidence of invasive disease in this population.
- Sixty-five percent of patients with vaginal intraepithelial lesion (VAIL) have concurrent or prior cervical neoplasia.
- HPV is responsible for the majority of lesions, and predisposing factors include previous cervical intraepithelial neoplasia (CIN), history of previous hysterectomy for dysplasia, history of local radiation therapy, and immunosuppression.

Presentation

- Similar to that of patients with low-grade VAIL.
- Speculum examination with the intent of discovery of vaginal lesions leads to their discovery in most cases.

Prognosis and Treatment

- The prognosis for patients with high-grade VAIL is more guarded than that for those with low-grade dysplasia.
- Around 5% of patients with high-grade VAIL will progress to invasive disease despite close follow-up.
- More aggressive therapy is indicated for high-grade lesions.
- Topical agents (fluorouracil [5-FU]), CO_2 laser therapy, or excision based on the distribution of the lesion may be used.
- Recurrence, ulceration, and scarring may occur.

Pathology

Histology

- Loss of maturation and atypia involving the full thickness of the vaginal epithelium are the hallmark of this lesion.
- Nuclear chromatin is frequently hyperchromatic and coarse.
- Increased mitotic activity with mitoses extending into the upper half of the epithelium is typically present.
- High-grade lesions with papillary architecture (papillary squamous cell carcinoma in situ) have been associated with a risk of concomitant invasion. These lesions are identified by their prominent papillae with fibrovascular cores, full-thickness dysplasia, and lack of stromal invasion.

Immunopathology (Including Immunohistochemistry)

- Ki-67 (MIB1) immunostaining will diffusely highlight superficial keratinocyte nuclei that are actively undergoing DNA turnover.
- Immunostaining with p16 is typically strong and diffusely positive.
- HPV nucleic acid testing is an option, although not usually required.

Main Differential Diagnosis

- Atrophy—more uniform population, low MIB-1 index, p16 negative.
- Radiation effect—p16 negative.
- Reactive changes—p16 negative, but MIB-1 index may be elevated.

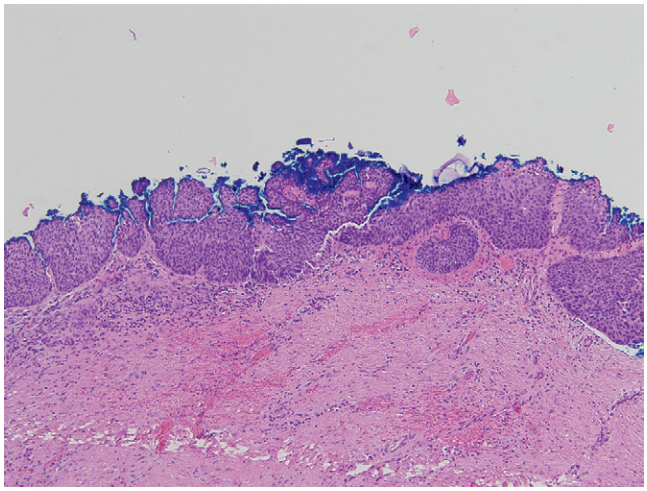


FIGURE 1
High-grade VAIL. Full-thickness loss of maturation evident at low power.

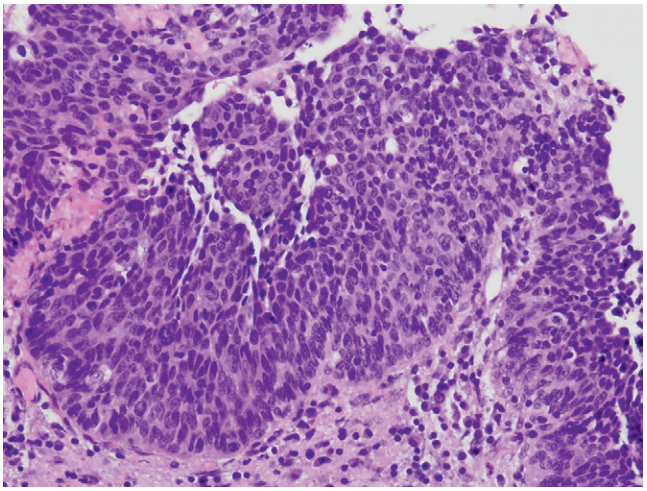


FIGURE 3
High-grade VAIL. Loss of nuclear and cellular maturation extending to the surface of the epithelium.

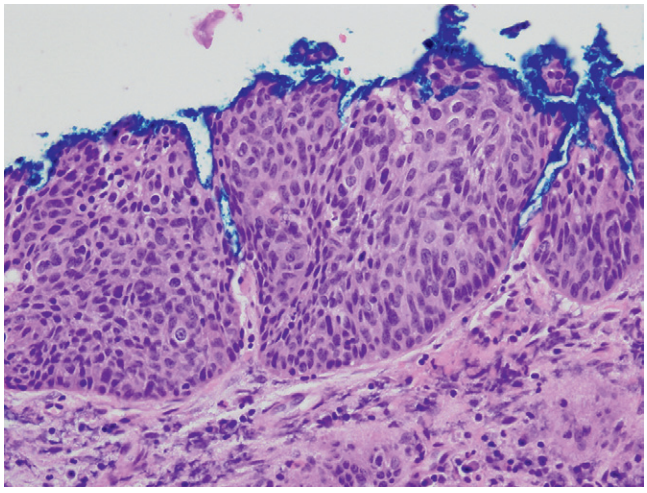


FIGURE 2
High-grade VAIL. Loss of nuclear and cellular maturation extending to the surface of the epithelium.

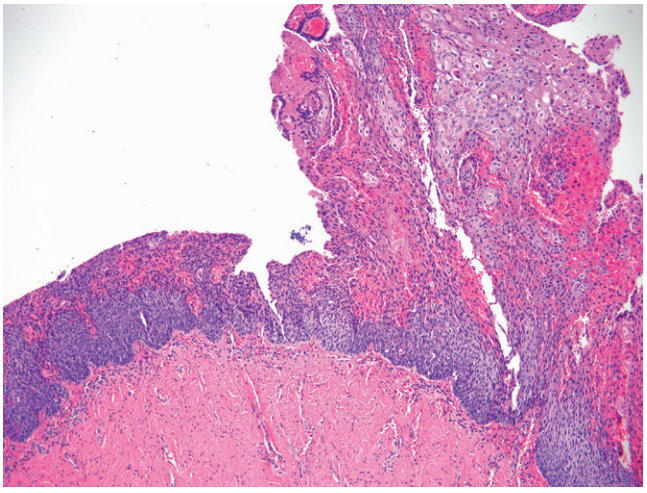


FIGURE 4
High-grade VAIL. Traditional high-grade VAIL merging with a papillary squamous cell carcinoma in situ. Note the lack of stromal invasion.

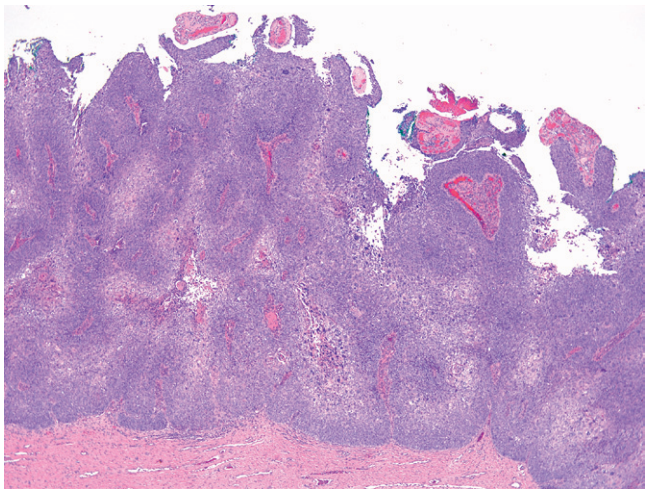


FIGURE 5

High-grade VAIL. Papillary squamous cell carcinoma in situ with numerous fibrovascular cores lined by neoplastic cells. No stromal invasion is present.

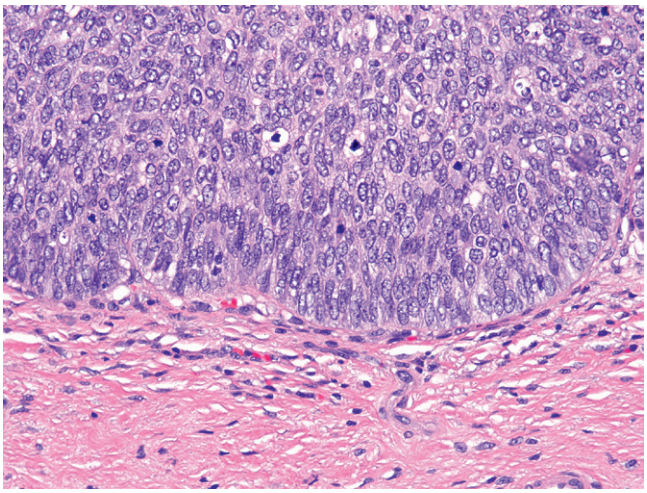


FIGURE 6

High-grade VAIL. The base of a papillary squamous cell carcinoma in situ. Marked nuclear crowding and increased mitotic figures can be seen. No stromal invasion is present.

HIGH-GRADE VAGINAL INTRAEPITHELIAL NEOPLASIA III

Definition—Human papillomavirus (HPV)–related proliferation of the vaginal mucosa that leads to extensive, full-thickness loss of maturation of the vaginal epithelium.

Clinical Features

Epidemiology

- Patients present at a slightly older age than those with cervical dysplasia, with the majority presenting around 55 to 57 years of age for high-grade dysplasia.
- The advanced age is thought to lead to an increased incidence of invasive disease in this population.
- Sixty-five percent of patients with vaginal intraepithelial lesion (VAIL) have concurrent or prior cervical high-grade squamous intraepithelial lesion (HSIL).
- HPV is responsible for the majority of lesions, and predisposing factors include previous cervical intraepithelial neoplasia (CIN), history of previous hysterectomy for dysplasia, history of local radiation therapy, and immunosuppression.

Presentation

- Similar to that of patients with low-grade vaginal dysplasia.
- Speculum examination with the intent of discovery of vaginal lesions leads to their discovery in most cases.

Prognosis and Treatment

- The prognosis for patients with high-grade dysplasia is more guarded than that of low-grade dysplasia.
- Around 5% of patients with high-grade dysplasia will progress to invasive disease despite close follow-up.
- More aggressive therapy is indicated for high-grade lesions.
- Topical agents (fluorouracil [5-FU]), CO_2 laser therapy, or excision based on the distribution of the lesion may be used.
- Recurrence, ulceration, and scarring may occur.

Pathology

Histology

- Loss of maturation and atypia involving the full thickness of the vaginal epithelium are the hallmark of this lesion.
- Nuclear chromatin is frequently hyperchromatic and coarse.
- Increased mitotic activity with mitoses extending into the upper half of the epithelium is typically present.
- High-grade lesions with papillary architecture (papillary squamous cell carcinoma in situ) have been associated with a risk of concomitant invasion. These lesions are identified by their prominent papillae with fibrovascular cores, full-thickness dysplasia, and lack of stromal invasion.

Immunopathology (Including Immunohistochemistry)

- Ki-67 (MIB1) immunostaining will diffusely highlight superficial keratinocyte nuclei that are actively undergoing DNA turnover.
- Immunostaining with p16 is typically strong and diffusely positive.
- HPV nucleic acid testing is an option, although not usually required.

Main Differential Diagnosis

- Atrophy—distinguished by a uniform population of immature keratinocytes with bland chromatin; however, some cases show atypia. MIB1 and p16 stains are helpful in occasional cases.
- Radiation effect—this is typically characterized by nuclear enlargement, opaque chromatin, and preservation of a low nuclear-to-cytoplasmic (N/C) ratio. As in atrophy, special stains will exclude HSIL.

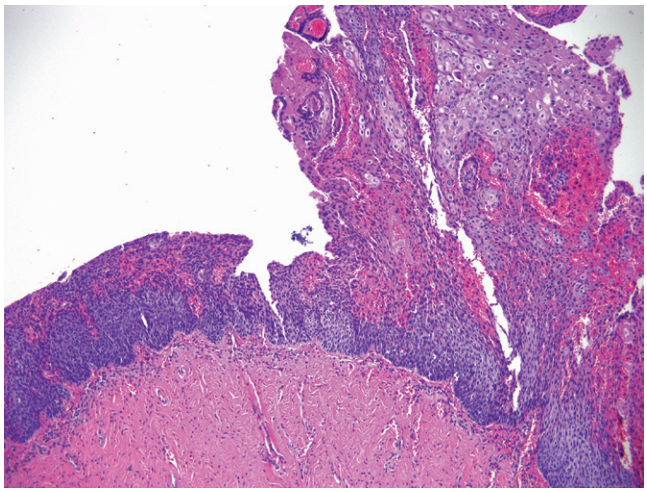


FIGURE 1

High-grade VAIL. At low power the lesion can show variable thickness ranging from flat to focally exophytic.

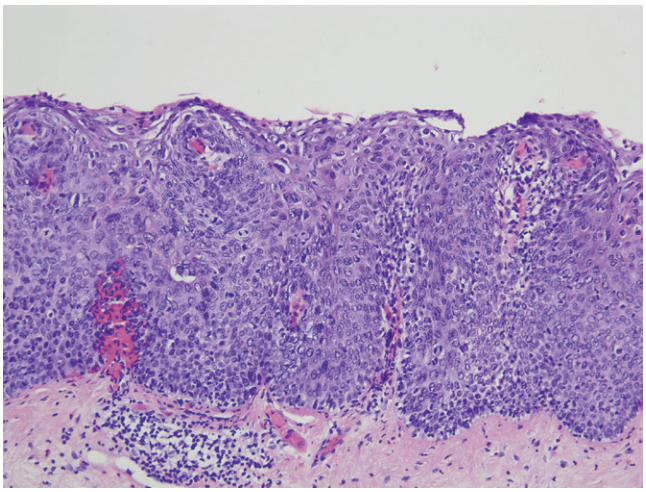


FIGURE 3

High-grade VAIL. A highly cellular epithelium with high N/C ratio and slight surface maturation.

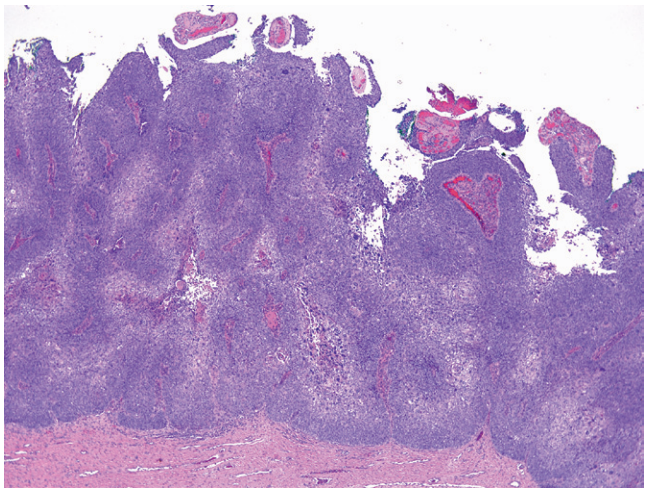


FIGURE 2

High-grade VAIL. At low power the lesion can show variable thickness ranging from flat to focally exophytic.

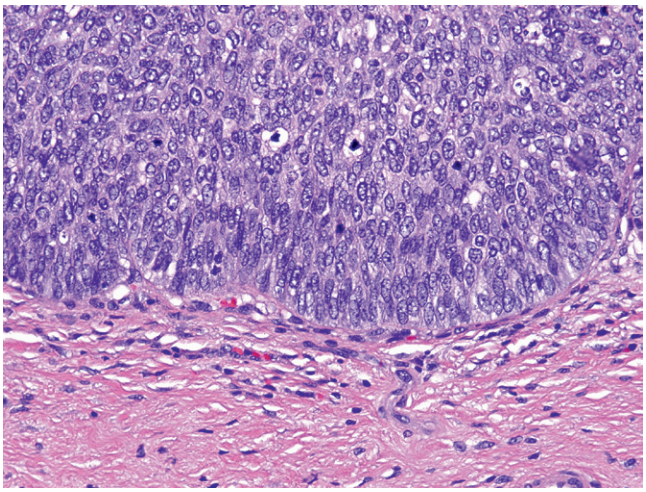


FIGURE 4

High-grade VAIL. Note high nuclear density and numerous mitotic figures.

RADIATION-INDUCED ATROPHY

Definition—Iatrogenically induced atrophic changes seen in the vaginal mucosa following radiation therapy.

Clinical Features

Epidemiology

- Common occurrence following radiation therapy.

Presentation

- Patients experience pain and vaginal itching and dryness, similar to that seen in atrophic vaginitis.
- Colposcopic examination reveals thinned, friable vaginal mucosa with loss of the rugae. Lack of glycogenization leads to poor uptake of Lugol's solution.
- Irregular vessels may be visible, mimicking intraepithelial neoplasia.

Prognosis and Treatment

- Radiation-induced atrophic changes tend to be chronic with significant morbidity.

Pathology

Histology

- Marked reactive changes including cytoplasmic vacuolization, cytomegaly and nucleomegaly, and multinucleation may be present.
- Keys to recognizing these changes as reactive include preservation of the nuclear-to-cytoplasmic ratio and homogeneous, sometimes smudgy nuclear chromatin.
- Vascular changes consisting of fibrosis and thrombosis are occasionally seen.

Immunopathology (Including Immunohistochemistry)

- Noncontributory. p53 immunostaining can be increased following therapy.

Main Differential Diagnosis

- Atrophic vaginitis.
- Reactive changes secondary to other irritating stimuli.

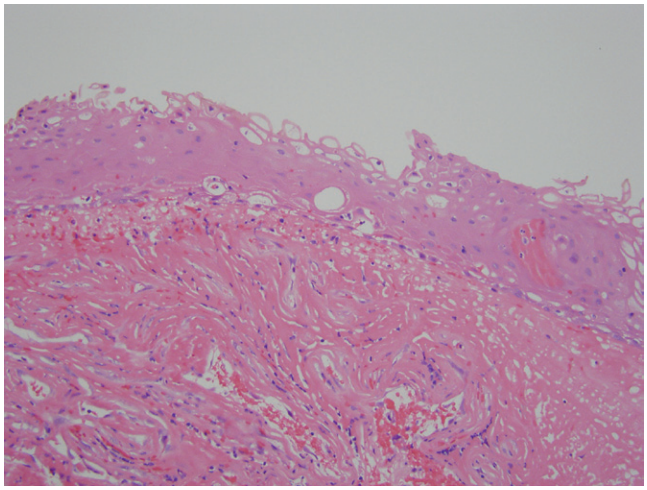


FIGURE 1

Radiation-induced vaginal atrophy. Thinned mucosa with loss of glycogen.

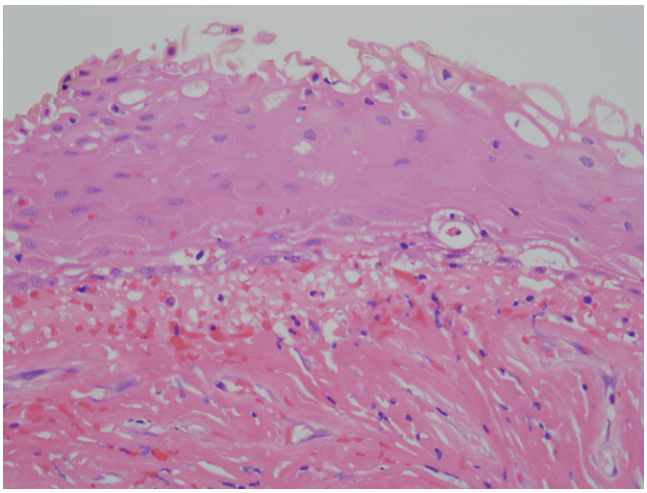


FIGURE 2

Radiation-induced vaginal atrophy. Occasional cytoplasmic vacuoles can be seen.

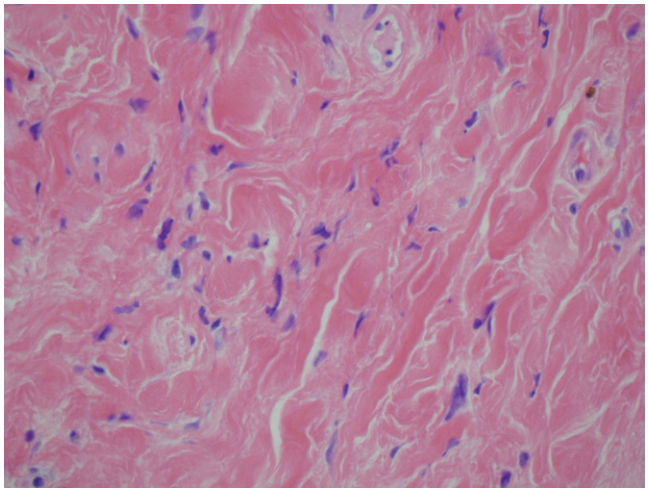


FIGURE 3

Radiation-induced vaginal atrophy. Underlying vaginal stroma with fibrosis and irregular, atypical stromal cells.

PAPILLARY SQUAMOUS CARCINOMA

Definition—A malignant neoplasm of the vagina comprised of squamous epithelial cells with prominent papillary architecture.

Clinical Features

Epidemiology

- Associated with high-risk human papillomavirus (HPV) infection and may follow preexisting cervical intraepithelial or invasive neoplasia.
- Usually older women, in the sixth to ninth decades.

Presentation

- Patients typically present with abnormal bleeding, especially following intercourse.
- Patients may also present with pain or a clinically identifiable mass lesion.
- Presents clinically as an exophytic mass near the apex of the vagina.

Prognosis and Treatment

- Many lesions are superficial and can be treated by local excision.
- Radical therapy may be required for deeply invasive lesions.
- Brachytherapy in cases that cannot be resected.
- Generally a favorable outcome, particularly for localized lesions.

Pathology

Histology

- Papillary/exophytic architecture.
- Polarized neoplastic epithelium overlying stromal cores, ranging from squamous (similar to high-grade squamous intraepithelial lesions [HSIL]) to a transitional appearance.
- Invasion may be particularly difficult to confirm if underlying stroma at the base of the tumor is not appreciated. For this reason, a diagnosis of "papillary HSIL with complex architecture" might also be made in some smaller samples, with the proviso that invasion must be excluded.

Immunopathology (Including Immunohistochemistry)

- Positive for CK7 and p63.
- Diffusely positive for p16ink4.
- Negative for CK20.

Main Differential Diagnosis

- Verrucopapillary HSIL—overlaps with this entity, but extensive frankly exophytic lesions are usually classified as carcinomas irrespective of whether invasion can be demonstrated, albeit with a caveat that depth of invasion cannot be determined.
- Occasional primitive basaloid carcinomas—these are typically not papillary.
- Transitional cell carcinoma of urothelial origin—will be CK20 positive.
- Metastatic uterine or extrauterine papillary (serous) carcinoma—might mimic a squamotransitional lesion if poorly differentiated and will be p16ink4 positive, but also p53 positive.

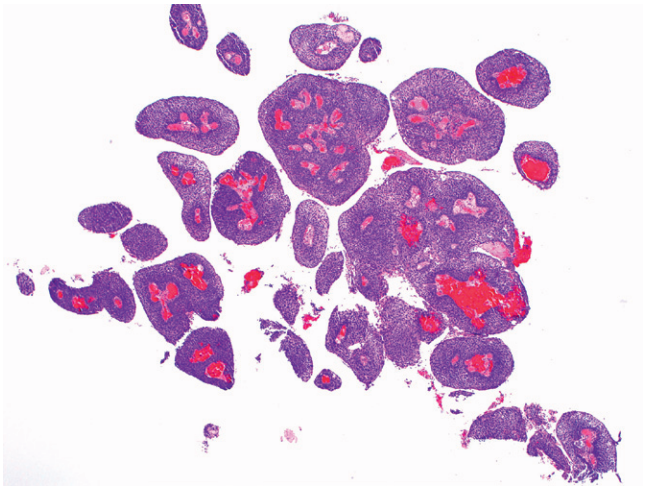


FIGURE 1

Papillary squamotransitional cell carcinoma (STCC) of the vagina. A typical biopsy showing free-floating papillae lined by neoplastic squamous epithelium.

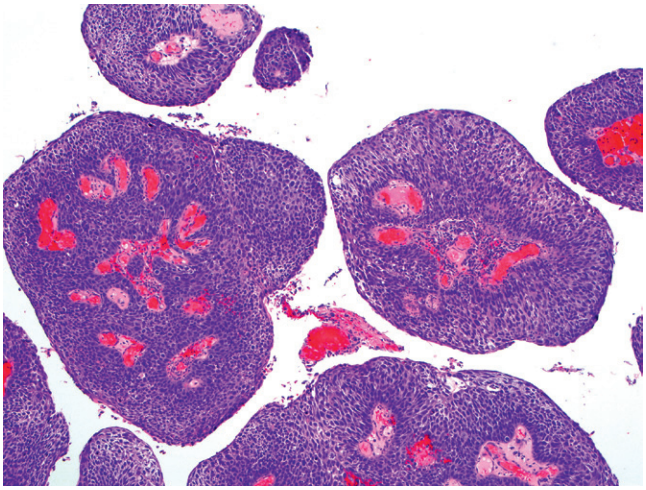


FIGURE 2

STCC. At higher magnification the papillae of STCC exhibit the typical lining, composed of a polarized high-grade neoplastic squamous epithelium. "Transitional" features may be seen, but the immunophenotype is typically squamous.

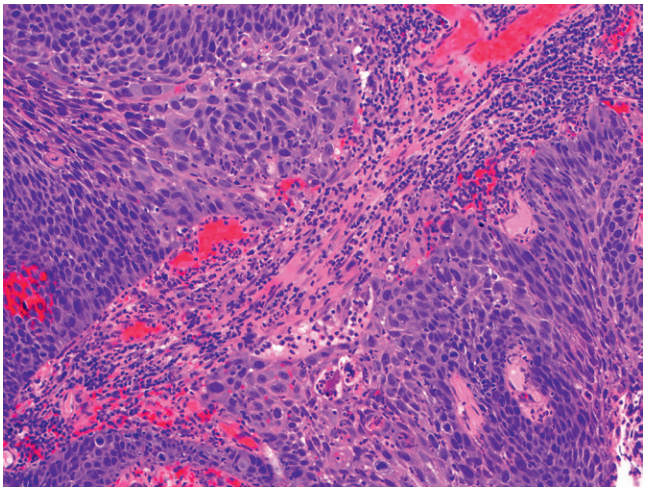


FIGURE 3

An occasional papilla may reveal stroma with features suggesting early invasion, including cytoplasmic maturation and loss of polarity at the lesional-stromal interface. However, ascertaining the true extent of the lesion will invariably require excision of the lesion with margins, if clinically possible.

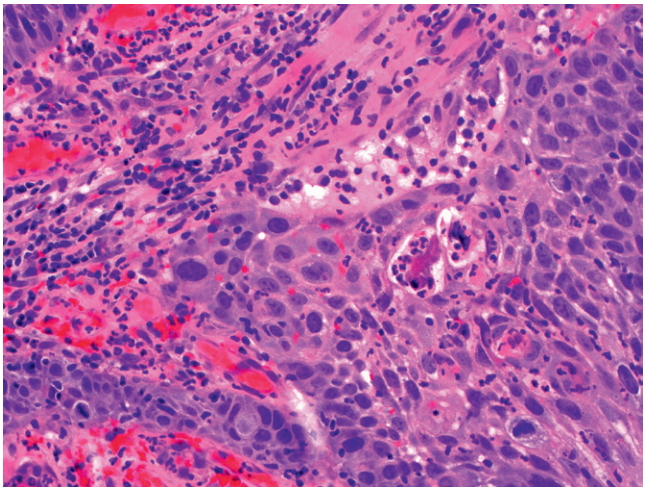


FIGURE 4

Higher magnification of a focus suggesting stromal invasion.

CLEAR-CELL ADENOCARCINOMA

Definition—An uncommon primary adenocarcinoma of the vagina, associated with in utero exposure to synthetic estrogen.

Clinical Features

Epidemiology

- Rare, except in women who were exposed to diethylstilbestrol (DES) in utero.
- The risk in DES-exposed women is estimated to be between 1 : 1000 and 1 : 5000 individuals.
- The peak age at diagnosis for DES-exposed women is 20, and it is rarely seen in women over 40.
- In non–DES-exposed women, the age at presentation is usually in the seventh or eighth decade of life; however, the age distribution seems to be bimodal, with a smaller group presenting around the time of menarche.

Presentation

- Vaginal bleeding or discharge.
- Often a visible vaginal (or cervical) mass or ulceration is present, usually centered on the anterior wall in the upper one third of the vagina.

Prognosis and Treatment

- Prognosis is closely tied to stage; most patients present with early (stage I or II) disease.

Pathology

Histology

- Clear-cell adenocarcinoma of the vagina has the microscopic appearance of clear-cell adenocarcinomas found elsewhere in the genital tract of women.
- These tumors are characterized by polyhedral cells with optically clear (to eosinophilic) cytoplasm and strikingly atypical pleomorphic nuclei.
- The cells may be arranged in solid sheets, or forming tubules, cysts, or papillary structures with hyaline stromal changes.
- When seen lining spaces, the cells are typically present as a single layer and often have a "hobnail" appearance.

Immunopathology (Including Immunohistochemistry)

- Noncontributory in most primary cases.
- PAX8, HINF1-β, and Napsin-A staining might be helpful in confirming an origin in a primary clear-cell carcinoma of the genital tract.

Main Differential Diagnosis

- Endometrioid adenocarcinoma with secretory differentiation—nuclear atypia, hobnail patterns, and hyaline stromal changes are helpful. Squamous metaplasia argues against this diagnosis.
- Arias-Stella effect—this will typically be found within adenosis or endocervix and not as a separate lesion.

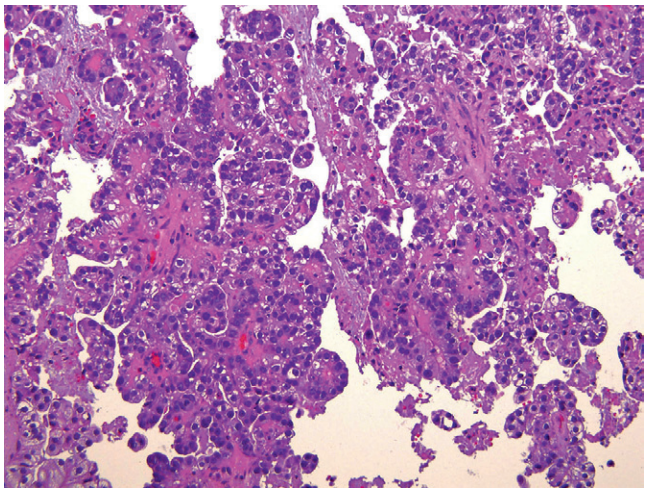


FIGURE 1

Vaginal clear-cell carcinoma. Cells are eosinophilic and only focally clear. Note the hyaline change to the stroma.

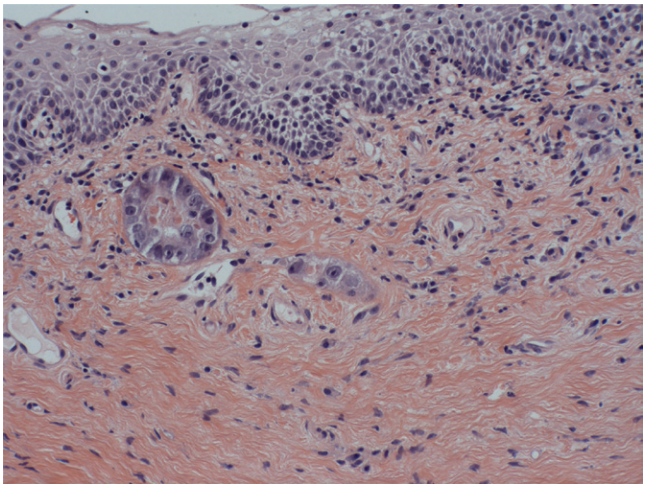


FIGURE 2

Metastatic clear-cell carcinoma of the vagina. Markedly atypical cells are present, several of which are in a lymphatic space *(center)*.

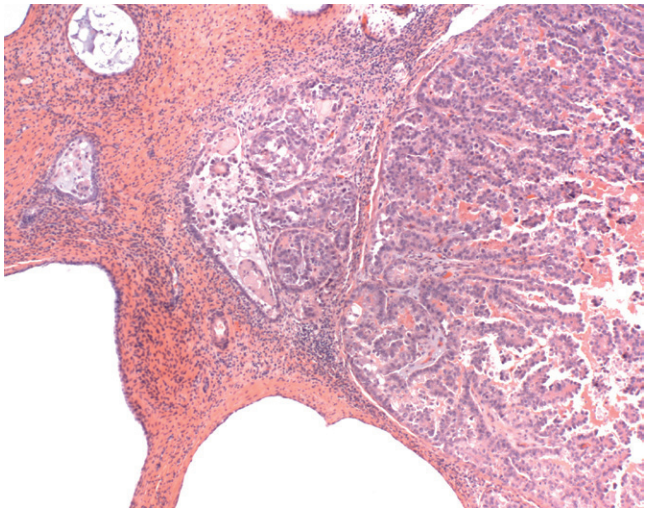


FIGURE 3

Metastatic clear-cell carcinoma of the vagina. The tumor in Figure 2 is derived from this clear cell carcinoma of the endometrium with a prominent papillary architecture and hobnail cells.

METASTATIC ADENOCARCINOMA

Definition—Epithelial malignancies that metastasize to the vagina.

Clinical Features

Epidemiology

- Patients with a primary carcinoma of another site.
- The vast majority are of endometrial origin.
- Over 90% of adenocarcinomas identified in the vagina are metastatic.

Presentation

- Vaginal mass, nodularity, or epithelial irregularity.
- Vaginal bleeding.

Prognosis and Treatment

- Varies with the specific primary tumor.

Pathology

Histology

- Endometrioid endometrial adenocarcinoma.
- Uterine or pelvic serous carcinoma.
- Carcinosarcoma.
- Renal cell carcinoma.
- Urothelial carcinoma.
- Breast carcinoma.
- Colorectal adenocarcinoma.

Immunopathology (Including Immunohistochemistry)

- Varies with the suspected primary tumor.

Main Differential Diagnosis

- Adenocarcinoma arising in endometriosis.
- Clear cell adenocarcinoma of the vagina.

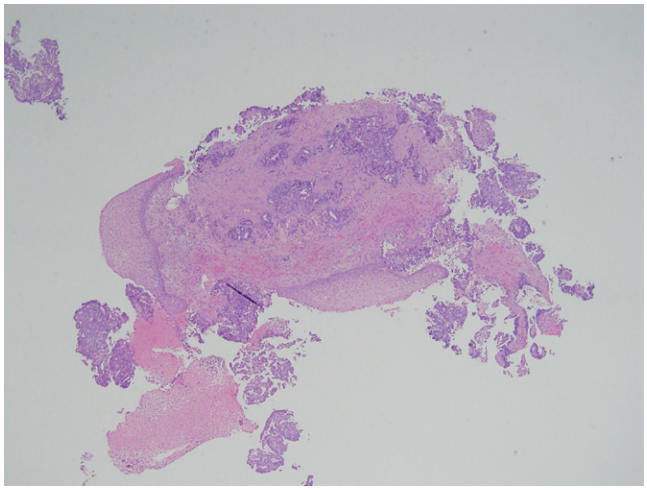


FIGURE 1

Carcinoma metastatic to the vagina. Metastatic endometrioid endometrial adenocarcinoma. Note the extensive stromal involvement and normal overlying epithelium.

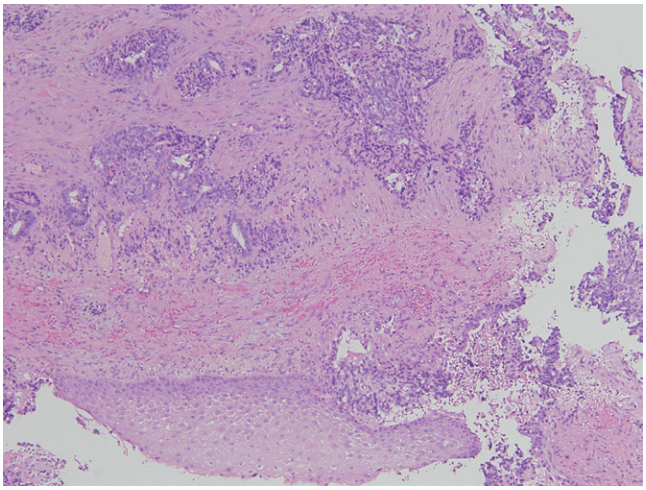


FIGURE 2

Carcinoma metastatic to the vagina. Metastatic endometrioid endometrial adenocarcinoma with squamous morular metaplasia.

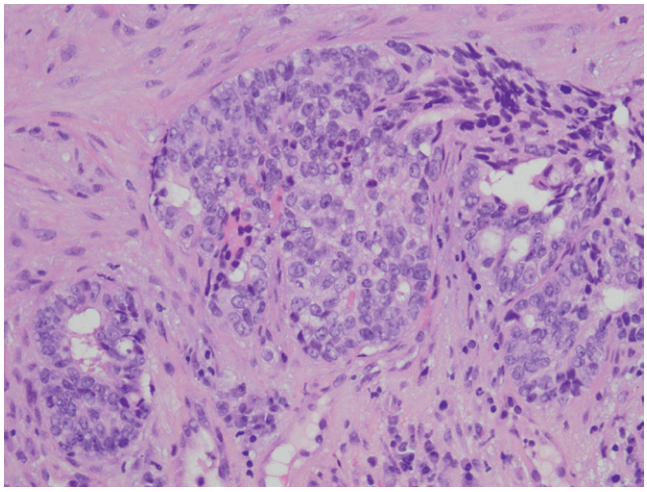


FIGURE 3

Carcinoma metastatic to the vagina. Metastatic endometrioid endometrial adenocarcinoma.

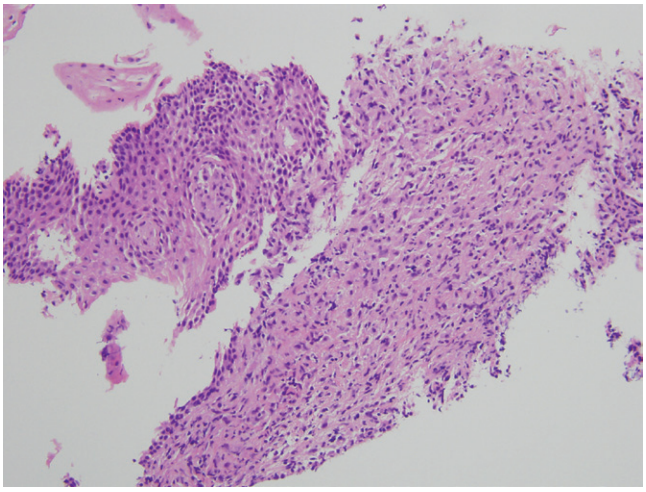


FIGURE 4

Carcinoma metastatic to the vagina. Metastatic breast carcinoma. Note the single file lines of cells.

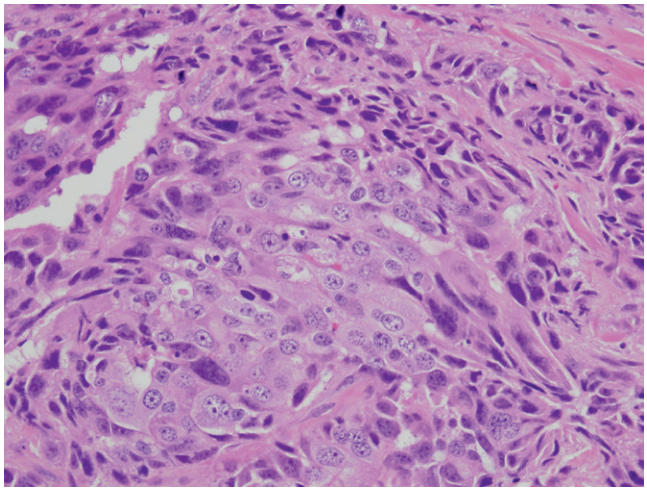


FIGURE 5

Carcinoma metastatic to the vagina. Metastatic serous carcinoma displaying prominent nuclear pleomorphism.

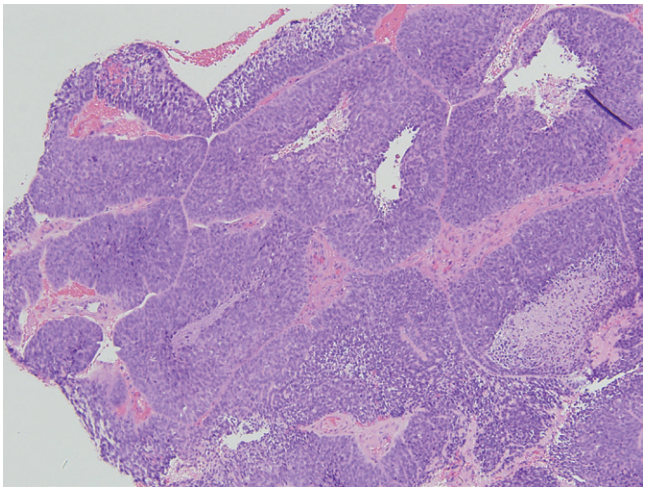


FIGURE 6

Carcinoma metastatic to the vagina. Metastatic rectal carcinoma.

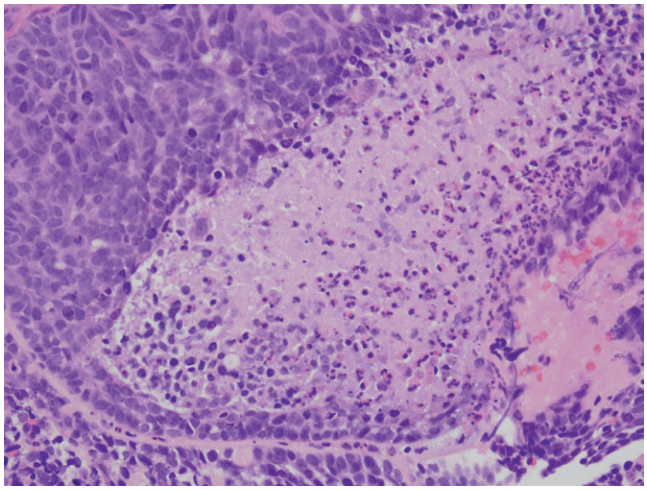


FIGURE 7

Carcinoma metastatic to the vagina. Metastatic rectal carcinoma with necrosis.

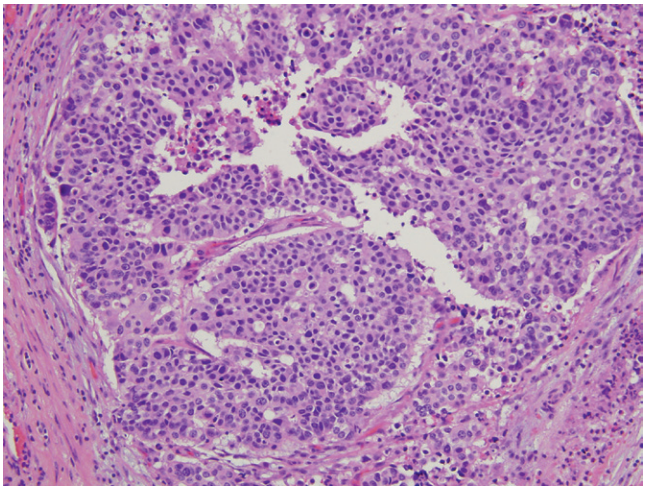


FIGURE 8

Carcinoma metastatic to the vagina. Metastatic transitional cell carcinoma.

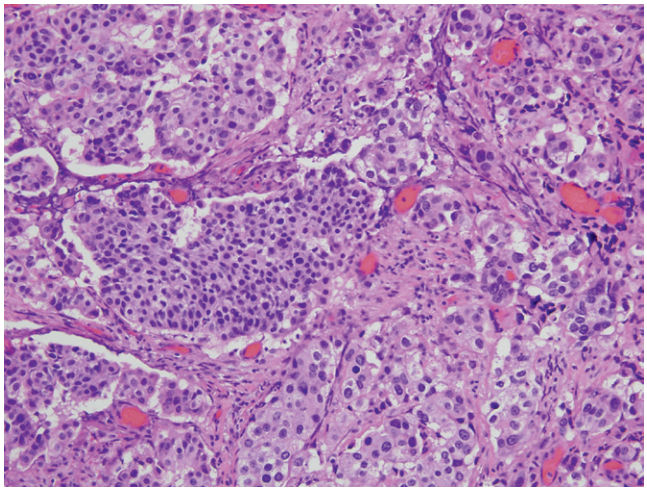


FIGURE 9

Carcinoma metastatic to the vagina. Metastatic transitional cell carcinoma. Note the focal nuclear streaming near the center of the image.

MELANOMA

PITFALL

Definition—A very aggressive malignant tumor of dermal melanocytes arising in the vagina.

Clinical Features

Epidemiology

- Uncommon but not rare.
- Typically seen in postmenopausal women.
- May be more common in patients with a BRCA2 mutation.

Presentation

- Vaginal bleeding or discharge.
- A palpable mass may or may not be present.
- The most common location is the lower one third of the vagina.

Prognosis and Treatment

- Poor; these tumors are more aggressive than cutaneous or vulvar melanomas.
- Deep invasion and extensive superficial spread of the tumor are particularly problematic.
- Five-year survival ranges from 5% to 20% depending on the study.
- Radical surgery and adjuvant chemoradiation are the standard treatments, but these tumors have a poor response rate and some studies have shown that wide local excision has a similar survival rate.

Pathology

Histology

- The epidermal component is composed of single cells and nests of monotonous, severely atypical melanocytes with irregular chromatin and prominent nucleoli.
- Effacement of the epithelial-stromal junction is common, resulting in a "moth-eaten" appearance.
- The stromal component is most often composed of epithelioid cells with a similar histology to those present in the overlying epidermis and without "maturation."
- Melanoma is known for its variable morphology, and the spectrum is broad; cases range from the epithelioid tumors described earlier to a malignant spindle cell proliferation that can be confused with a sarcomatoid squamous cell carcinoma or a mesenchymal neoplasm (PITFALL).
- Melanin pigment is variably present.

Immunopathology (Including Immunohistochemistry)

- S100 positive.
- MART1, HMB45, and Melan-A are generally positive but may be lost in poorly differentiated tumors.

Main Differential Diagnosis

- Squamous cell carcinoma.
- Poorly differentiated carcinomas.
- Sarcomas.

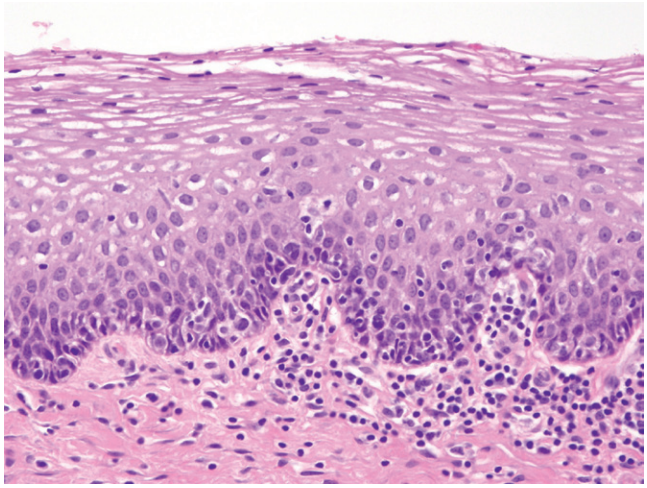


FIGURE 1

Vaginal melanoma. Vaginal epithelium with numerous atypical melanocytes is seen in the basal layer.

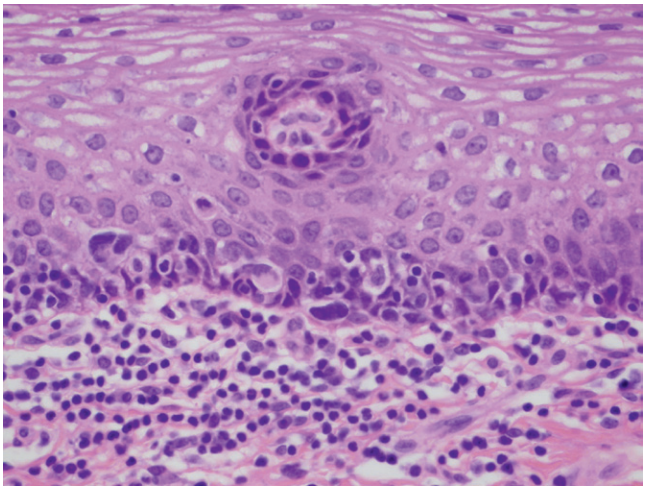


FIGURE 2

Vaginal melanoma. Marked melanocytic atypia.

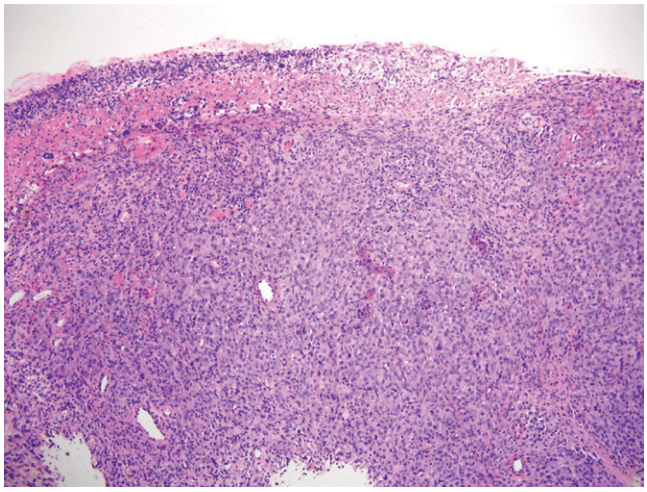


FIGURE 3

Vaginal melanoma. An ill-defined mass of atypical cells is present. Note the superficial ulceration.

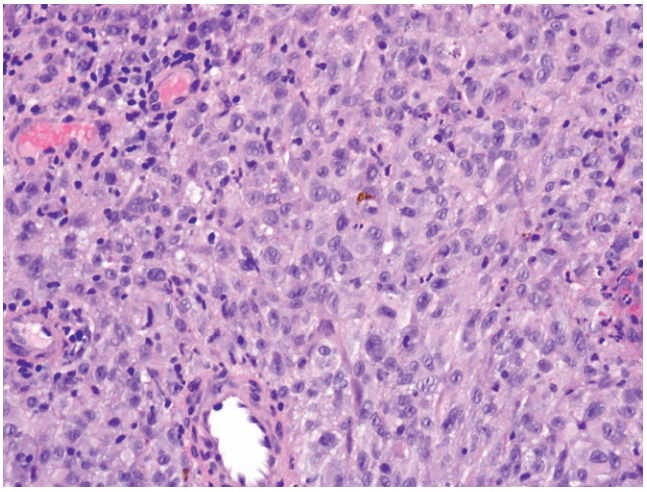


FIGURE 4

Vaginal melanoma. High-power examination of Figure 3 demonstrates marked nuclear atypia, prominent nucleoli, and rare pigment.

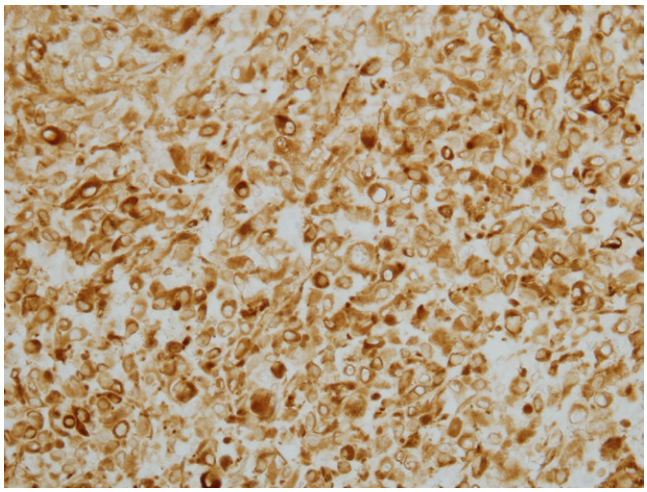


FIGURE 5

Vaginal melanoma. Positive immunohistochemical staining for Melan-A.

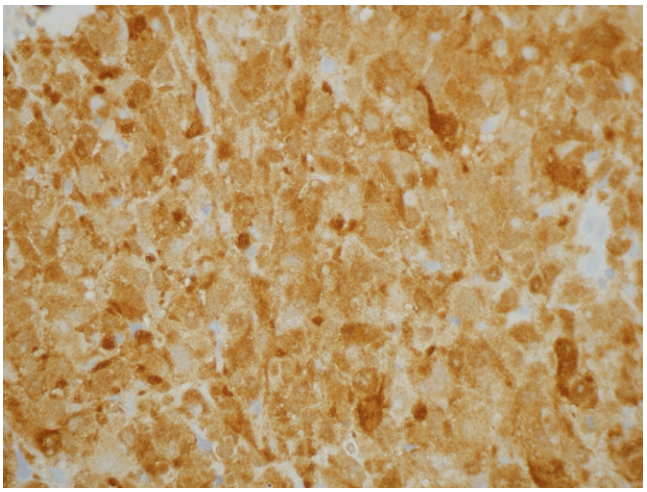


FIGURE 6

Vaginal melanoma. Positive immunohistochemical staining for S100.

SPINDLE CELL EPITHELIOMA

PITFALL

Definition—A benign vaginal tumor composed of keratin-positive stromal cells.

Clinical Features

Epidemiology

- Uncommon.
- Seen in a wide age range (20 to 80 years), with a mean age of 40 years.

Presentation

- Submucosal vaginal mass, often located near the hymenal ring.
- Often discovered incidentally during routine gynecologic examination.

Prognosis and Treatment

- Excellent; this is a benign tumor.
- Recurrence has been reported, so complete surgical excision is advised.

Pathology

Histology

- A well-circumscribed, but unencapsulated, proliferation of spindled cells ranging from 1 to 9 cm in size.
- The predominant cell type is a bland spindle cell with round-to-oval nuclei and scant amounts of eosinophilic-to-pale cytoplasm.
- The spindled cells are variably arranged as nests or sheets, often with focally corded or reticular architecture.
- Mitoses are infrequent.
- Minor epithelial elements are occasionally identified; they can consist of glandular or squamous epithelium or squamous morula.
- If present, the glandular epithelium is typically cuboidal to low columnar with periodic acid–Schiff (PAS)–positive, diastase-sensitive luminal secretions.

Immunopathology (Including Immunohistochemistry)

- Stroma-like cells are positive for AE1/AE3, and sometimes for CK7 or CK20.
- Stroma-like cells are positive for CD10; SMA, desmin, and caldesmon are variably positive.
- Both the stromal and epithelial components are frequently positive for ER and PR.
- S100 is negative in both components.

Main Differential Diagnosis

- Smooth muscle neoplasms—contrasting epithelial and spindled cell differentiation helps to distinguish spindle cell epithelioma.

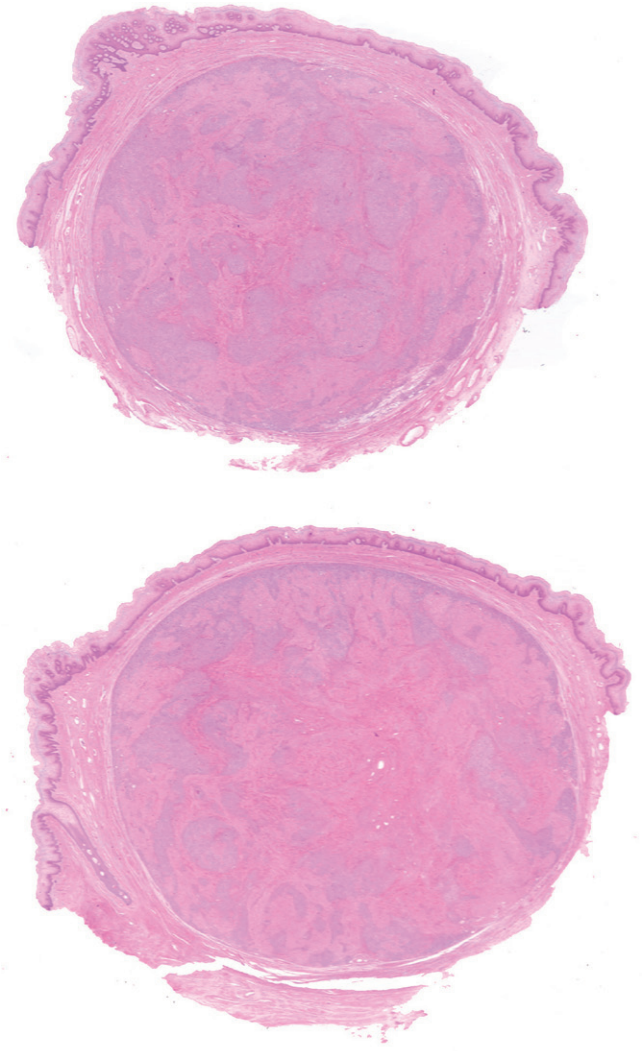


FIGURE 1

Spindle cell epithelioma. Two low-power images of well-circumscribed mass underlying the vaginal epithelium.

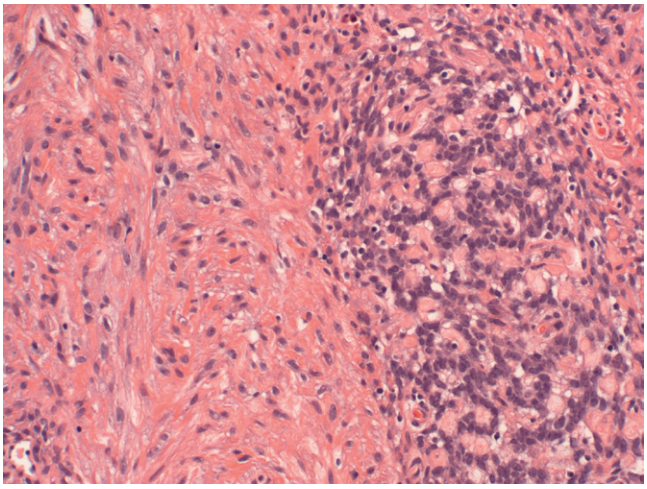


FIGURE 2

Spindle cell epithelioma. Bland spindle cells admixed with nodules of glandular structures composed of low cuboidal epithelium.

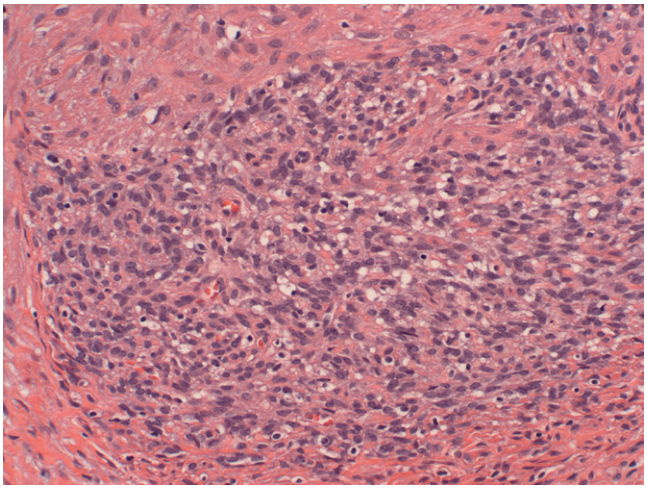


FIGURE 3

Spindle cell epithelioma. Bland spindle cells forming a fascicle, note the lack of atypia and mitotic activity.

EMBRYONAL RHABDOMYOSARCOMA

Definition—A malignancy of skeletal muscle presenting as a polypoid vaginal mass in young girls.

Clinical Features

Epidemiology

- Uncommon.
- Usually seen in females under the age of 5 years.

Presentation

- A bulky, polypoid vaginal mass that can resemble a cluster of grapes (botryoid).
- Vaginal bleeding may be the presenting symptom.

Prognosis and Treatment

- Prognosis is good in contrast to other subtypes of rhabdomyosarcoma.
- Surgical excision with chemotherapy and radiation is the standard of care.

Pathology

Histology

- The low-power architecture is composed of exophytic, polypoid papillary structures.
- The subepithelial condensation of cells (the so-called cambium layer) is characteristic.
- Rhabdomyoblasts, which compose the cambium layer, are characterized by a high nuclear-to-cytoplasmic ratio and prominent brightly eosinophilic (rhabdoid) cytoplasmic inclusions.
- Cytoplasmic striations can be identified in a subset of cells with elongated cytoplasm (strap cells).
- The deceptively bland stromal core of the polypoid projections is composed of a loose fibromyxoid tissue, often containing inflammatory cells.

Immunopathology (Including Immunohistochemistry)

- Skeletal muscle markers are positive (Myf-4 and MyoD1).

Main Differential Diagnosis

- Fibroepithelial stromal polyp—lacks the rhabdoid cells or cambium layer.
- Adenosarcoma—spindled cells admixed with glands.

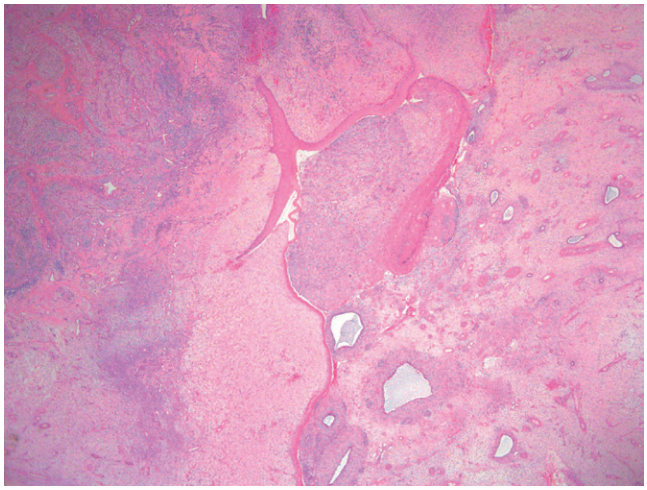


FIGURE 1

Embryonal rhabdomyosarcoma. Polypoid projections of tumor can be seen underlying the vaginal squamous epithelium. Subepithelial condensation of the cells (cambium layer) is apparent at low power.

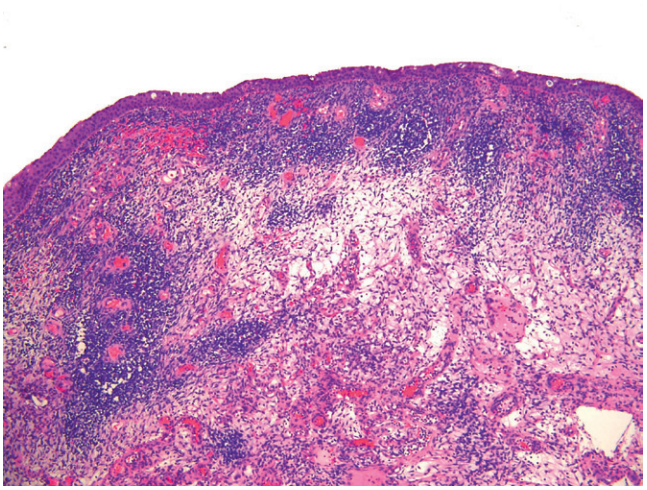


FIGURE 2

Embryonal rhabdomyosarcoma. Vaginal epithelium with a distinctive cambium layer.

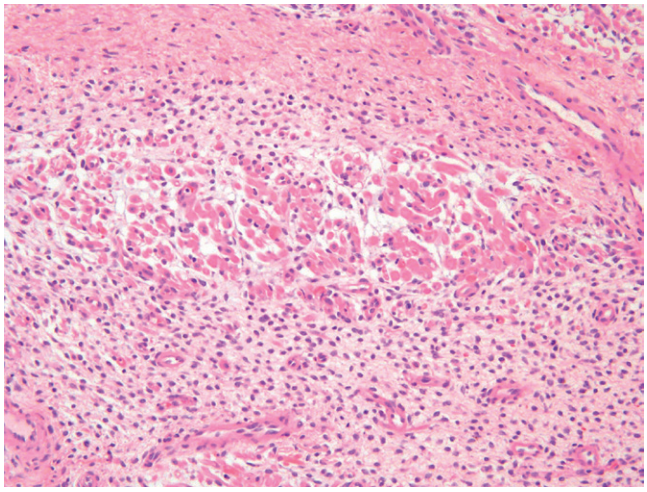


FIGURE 3

Embryonal rhabdomyosarcoma. Rhabdomyoblasts with abundant, brightly eosinophilic cytoplasm.

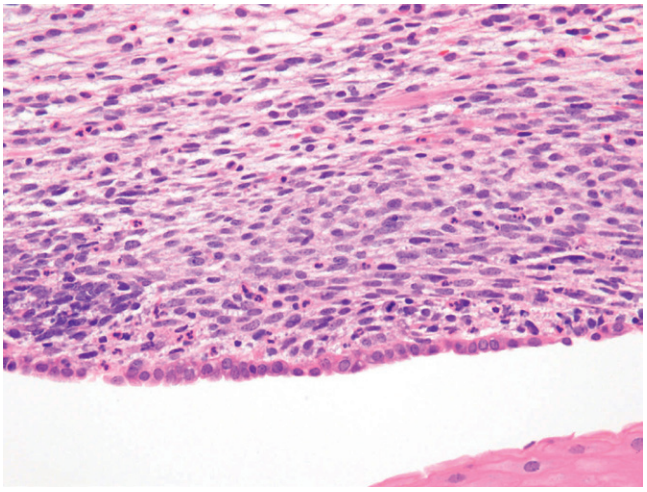


FIGURE 4

Embryonal rhabdomyosarcoma. A cambium layer with only rare rhabdomyoblasts, best seen in the upper half of the photo.

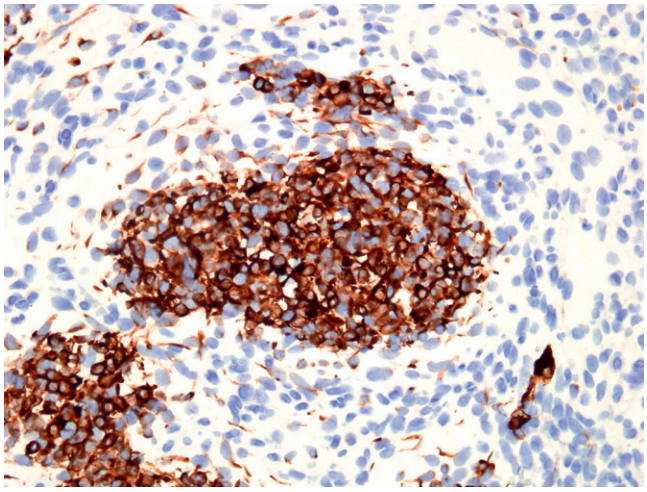


FIGURE 5

Embryonal rhabdomyosarcoma. Positive immunohistochemical staining for desmin.

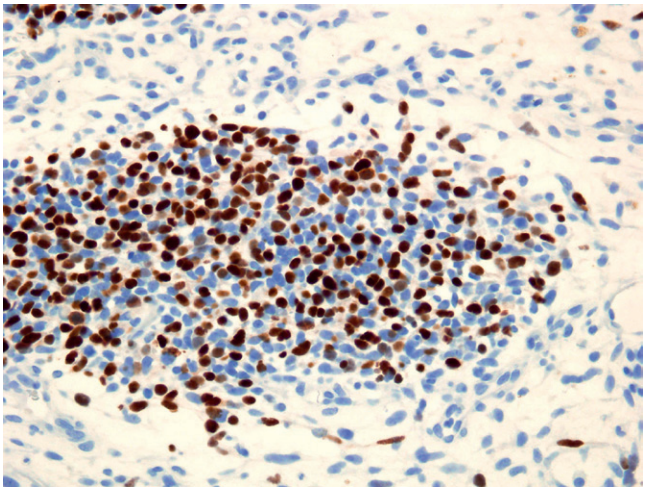


FIGURE 6

Embryonal rhabdomyosarcoma. Positive immunohistochemical staining for myogenin.

SECTION 2

Cervix

EXOPHYTIC LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

Definition and Terminology

- An exophytic cervical condyloma represents an infection of the mature ectocervical or metaplastic cervical transformation zone epithelium by human papillomavirus (HPV) type 6 or 11 (low–cancer-risk subtypes).
- The most appropriate term is low-grade squamous intraepithelial lesion (LSIL).

Clinical Features

Epidemiology

- Reproductive-age, sexually active women.

Presentation

- Papanicolaou smear typically classified as atypical squamous cells of undetermined significance (ASCUS) or LSIL.
- Colposcopic abnormality, typically an exophytic lesion on the cervix.

Prognosis and Treatment

- Clinicians can opt to treat exophytic condyloma patients in one of two ways: cryoablation or follow-up.
- Conservative management is the rule, with attention to periodic follow-up. Large lesions may require ablation.
- Patients infected with HPV 6 or 11 are not directly at risk for cancer, but having HPV places them at risk of infection with the other strains that predispose to cancer.

Pathology

Histology

- Exophytic LSILs are characterized by a mature squamous epithelium with verruciform architecture, acanthosis (epidermal hyperplasia or thickening), and parakeratosis (retention of nuclei at the epithelial surface).
- A mildly increased nuclear density is present in the surface epithelium.
  - An increased nuclear-to-cytoplasmic ratio is seen.
  - Koilocytotic atypia with perinuclear halos, irregular nuclear membranes, and enlarged single or binucleate forms is seen in the upper epithelial layers.
  - Only mild atypia is present in the lower epithelial layers.

Immunohistochemistry

- Ki-67 expression is mild to moderate, with staining in the upper epithelial layers particularly in areas of viral cytopathic effect.
- p16ink4 expression is negative or patchy, the latter being the most prominent in maturing cell cytoplasm with variable nuclear staining. This is the classic pattern seen in low-risk HPV types and is very helpful in distinguishing this entity from papillary high-grade squamous intraepithelial lesions (HSILs) or papillary squamous carcinomas.

Differential Diagnosis and Pitfalls

- The most common pitfall is reactive epithelial changes.
- Rarely, well-differentiated squamous carcinomas will manifest with koilocytosis.
- Exophytic condylomas may coexist with HSILs, but the two entities are caused by two distinct HPV types. Always exclude HSIL and ensure that the cytologic diagnosis matches the histology. An HSIL will manifest with strong p16 staining unlike condyloma. If HSIL is suspected on cytology, further sampling is indicated.

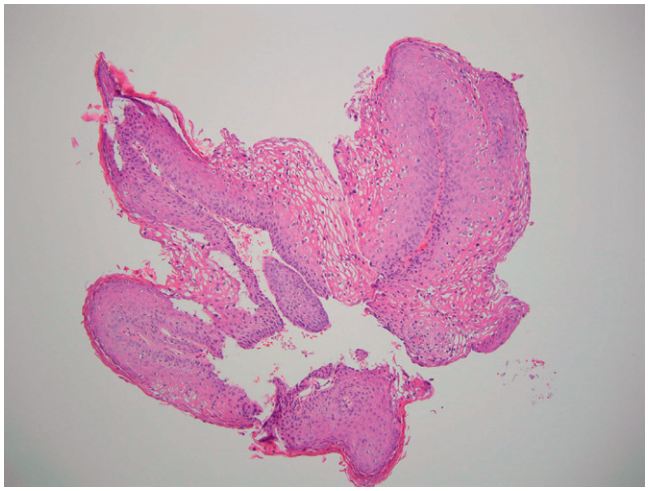


FIGURE 1

Exophytic LSIL. At low power the characteristic verruciform architecture and acanthosis are apparent. A suggestion of koilocytic forms is visible at this power.

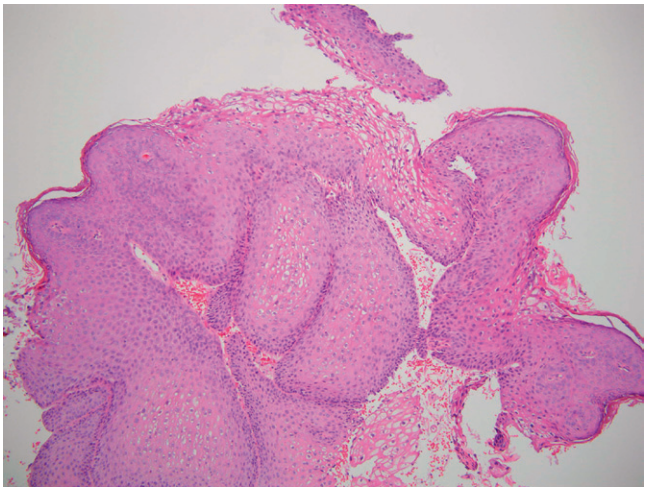


FIGURE 2

Exophytic LSIL. An example with prominent acanthosis. Mildly increased nuclear density toward the surface of the epithelium can already be appreciated at this power.

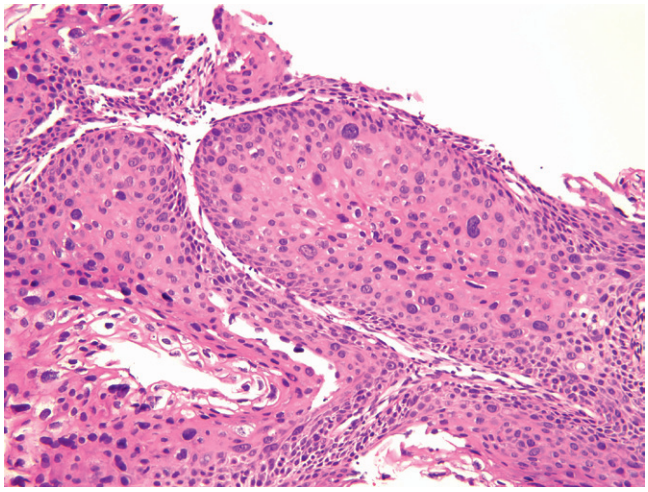


FIGURE 3

Exophytic LSIL. At higher power, scattered atypical cells with enlarged, irregular nuclei are present. Mild nuclear atypia is seen in the basal layers of the epithelium. There is an increased density of nuclei at the epithelial surface.

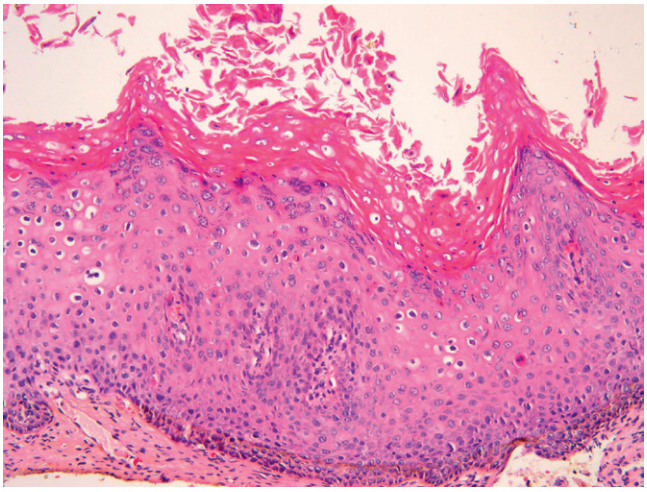


FIGURE 4

Exophytic LSIL. This example has prominent hyperkeratosis in addition to the parakeratosis. Abundant koilocytic forms are present. There is only focal mild nuclear atypia in the basal layers of the epithelium.

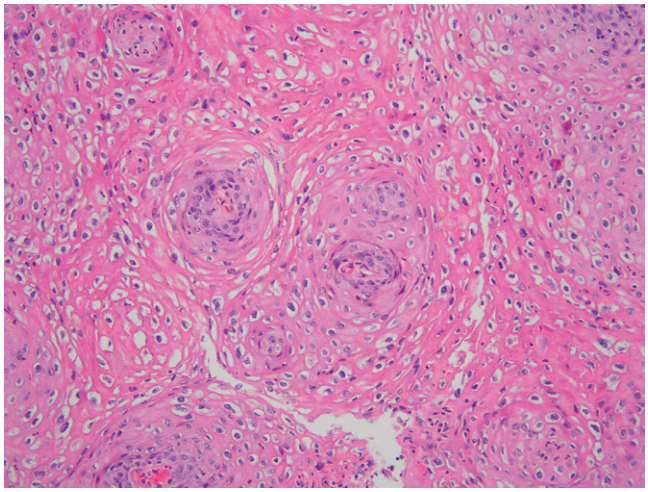


FIGURE 5

Exophytic LSIL. Koilocytes with prominent perinuclear halos and irregular nuclear membranes are present.

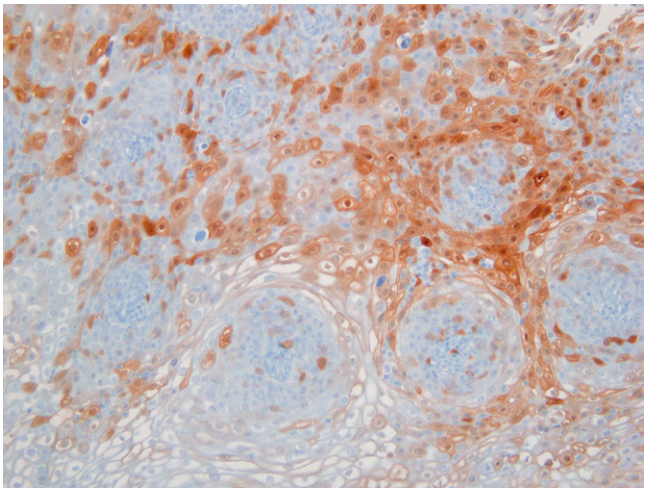


FIGURE 6

Exophytic LSIL. p16 immunostain corresponding to the hematoxylin and eosin (H&E) seen in Figure 5. A typical p16 staining pattern for low-risk HPV infections. There is patchy positivity, especially in the more superficial layers of the epithelium. Rare nuclear positivity is noted, and cytoplasmic positivity is more apparent.

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION (FLAT CONDYLOMA/CERVICAL INTRAEPITHELIAL NEOPLASIA I)

Definition—An infection of the mature ectocervical and/or metaplastic cervical transformation zone epithelium by human papillomavirus (HPV).

Clinical Features

Epidemiology

- Most commonly seen in sexually active, reproductive-age women.
- Can be diagnosed in any age group.
- Flat low-grade squamous intraepithelial lesions (LSILs) can be caused by either low- or high-risk HPV subtypes. Approximately one-half of ectocervical/metaplastic (squamocolumnar [SC] junction–negative) lesions contain high-risk HPVs in contrast to nearly all SC junction–positive lesions.

Presentation

- Typically identified on screening Pap smears with a diagnosis of atypical squamous cells of undetermined significance (ASCUS) or LSIL.
- Colposcopic examination may display a sessile cervical lesion or may only appear as a white area following the application of acetic acid (acetowhite epithelium).

Prognosis and Treatment

- These are low-grade lesions, and as such have a good prognosis. SC junction–negative lesions have been shown to rarely be followed by a diagnosis of high-grade squamous intraepithelial lesion (HSIL). Lesions in the SC junction may have a higher HSIL outcome, but this appears to be minimized if the diagnosis of LSIL is agreed on by multiple observers.
- Treatment may consist of either follow-up alone or cryoablation.
- A 1-year follow-up is usual in most patients as the vast majority of these lesions will regress on their own.
- A persistent biopsy diagnosis of LSIL may require consideration of treatment rather than follow-up alone.

Pathology

Histology

The biopsy appearance of a flat LSIL varies depending on where the lesion is located, and these appearances will be described separately.

- *LSIL in mature squamous epithelium:*
  - The most notable features are preserved epithelial maturation and nuclear polarity with a subtle expansion of the basal third of the epithelium, combined with conspicuous atypia in the superficial layers.
  - This superficial cell atypia may consist of binucleated or multinucleated cells, nuclear hyperchromasia, and/or nuclear enlargement, often with irregular nuclear membranes.
  - The nuclear-to-cytoplasmic ratio is, in general, preserved in these lesions.
  - The cells in the lower portions of the epithelium are bland, uniform, and have minimal or no nuclear atypia.
- *LSIL in immature squamous epithelium (transition zone, squamous metaplasia):*
  - This appearance is more common for lesions in the SC junction. In these areas the degree of maturation is less apparent than in mature squamous epithelium,

but it is still present, and there is only minimal nuclear overlapping.
    - The upper epithelial layers are notable for increased nuclear density, and less prominent koilocytic changes may be seen in mature squamous epithelium.
    - The nuclei are very uniform, but mitotic activity is minimal to low, and the nuclei are not hyperchromatic.
- *LSIL in cytologic preparations (Pap test):*
    - Intermediate and superficial cells with nuclear enlargement at least 2.5× to 3× larger than normal intermediate cells, nuclear hyperchromasia, and slightly irregular nuclear borders.
    - Binucleate koilocytes with enlarged hyperchromatic nuclei and sharply defined cytoplasmic halos may be present, but are not required.
    - Binucleation alone is not sufficient for a diagnosis of LSIL.
    - The amount of cytoplasm in low-grade lesions is abundant, and an increase in the nuclear-to-cytoplasmic ratio should not be appreciated.

Immunopathology (Including Immunohistochemistry)

- Ki-67 expression is mild to moderate, with some staining in the upper epithelial layers.
- p16 expression is variable, but will be linear and continuous (i.e., positive) in up to 70% of cases, particularly if in the SC junction. In our experience the p16 immunostain does not have a significant impact on outcome (i.e., HSIL risk) if the lesion is indisputably an LSIL by histologic examination.
- It is critical to note that p16 staining is not a reliable marker to distinguish a low-grade lesion from a high-grade lesion without taking into consideration the histologic features.

Main Differential Diagnosis

- Reactive epithelial changes (may contain surface atypia or cytoplasmic halos).
- High-grade squamous intraepithelial lesions with focal surface maturation.
    - Well-differentiated squamous cell carcinoma (superficial biopsy).

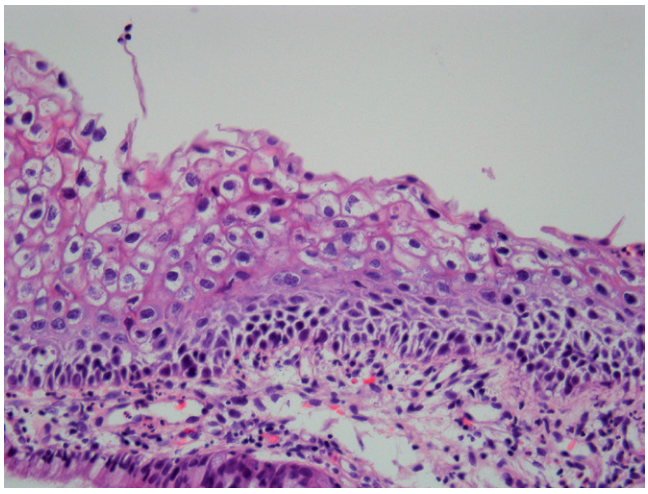


FIGURE 1

Classic example of an LSIL in mature metaplastic squamous epithelium. There is abrupt maturation with some increased density of nuclei toward the surface with clear if not striking nuclear atypia. The surface cells are hyperchromatic, with irregular nuclear membranes. The basal layers are bland and lack atypia.

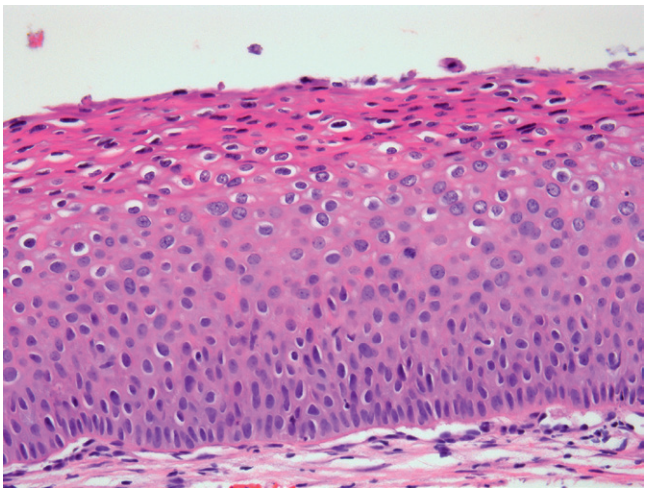


FIGURE 2

This variant of metaplastic LSIL has an expanded zone of parabasal cells with uniform differentiation and preserved polarity. Note the absence of any conspicuous nuclear enlargement in the lower epithelium. Both nuclear contour and chromasia in this region are rather uniform.

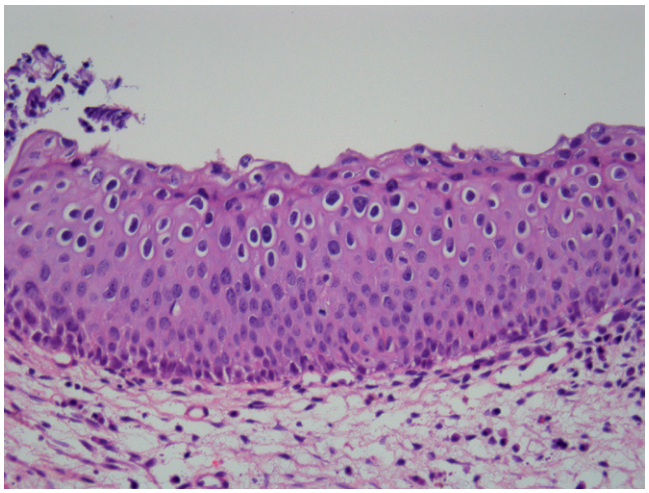


FIGURE 3

An LSIL from the region of the SC junction. This is similar to Figures 1 and 2, with some expansion of the less mature cells, but without appreciable atypia.

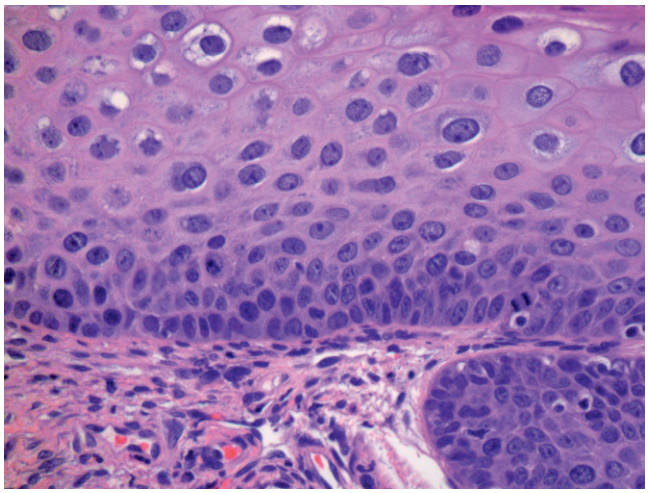


FIGURE 4

A closer view of basal and parabasal cells in an LSIL. Note this compartment, which is responsible for cell replenishment, does not display the more conspicuous nuclear chromatin and size differences characteristic of cervical intraepithelial neoplasia 2 (CIN2) (HSIL).

HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (CERVICAL INTRAEPITHELIAL NEOPLASIA II AND III)

Definition and Terminology

- A precancerous lesion arising at the cervical squamocolumnar (SC) junction that displays near full-thickness atypia and variable maturation of the neoplastic epithelium.
- Should be associated *always* with high-risk human papillomaviruses (HPVs) and with HPV16 in 40% to 60% of cases depending on the cytologic presentation.

Clinical Features

Epidemiology

- Reproductive-age, sexually active women.

Presentation

- Papanicolaou smear typically classified as low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or atypical squamous cells of undetermined significance (ASCUS).
- Colposcopic abnormality, typically acetowhite epithelium at the SC junction.

Prognosis and Treatment

- From 40% to 60% of CIN2 have been described to resolve spontaneously in up to 3 years in young women. Resolution of cervical intraepithelial neoplasia III (CIN3) is much less.
- Small risk of concurrent carcinoma (less than 1%) in women under age 25.
- Long-term risk of progression to carcinoma estimated at 5% for CIN2 and 12% for CIN3. Estimates based on untreated women followed for long periods of time are higher.
- Typically treated by cone biopsy or loop electrosurgical excision procedure (LEEP). Cryotherapy used previously and still appropriate if the entire lesion can be visualized (CIN2). Recurrence rates depend on whether excision margins are free of disease; usually less than 10%.
- In young women (under age 25) with CIN2 there is the option of follow-up with a repeat exam in 6 months in hopes the lesion will regress, permitting the patient to preserve cervical anatomy and lower the risk of future pregnancy complications that could occur following a cone biopsy. However, this is contingent on full visualization of the lesion, absence of any areas suspicious for invasion, and cervical cytology that is concordant. Continued follow-up is always needed to ensure resolution.

Pathology

Histology

- High nuclear density throughout the epithelium with nuclear overlap.
- Relatively more conspicuous atypia in the lower epithelial layers distinguishes CIN2 from CIN1 (LSIL).
- Variations in both nuclear size and staining and contour and chromasia.
  - An increased nuclear-to-cytoplasmic ratio in lower epithelial layers.
  - Surface maturation, with koilocytosis, can be seen in CIN2, but the cells usually display greater degrees of nuclear enlargement and atypia.
  - Atypical parakeratosis.

Immunohistochemistry

- Diffuse linear p16ink4 staining. If the diagnosis of CIN2 is made with certainty, a p16ink4 can be used to *confirm the presence of an HPV-associated lesion*. *Reliance on the p16ink4 stain solely to make the diagnosis of CIN2 is not recommended by these authors.*
- High Ki-67 nuclear staining index (>50%), in all layers.
- Strong krt7 and arg2 staining is typical of these lesions arising in the SC junction.
- Superficial biopsy of a carcinoma.
- LSIL, tangentially sectioned.
- LSILs associated with low-risk HPVs will show weak or patchy p16 staining.
- LSILs associated with high-risk HPVs on the ectocervix often manifest with weak or negative krt7 and arg2 staining.
- LSILs arising in the SC junction have a high frequency of association with high-risk HPVs and are strongly p16 positive. *They can only be distinguished from CIN2 by histology given the common HPV types and p16 staining pattern.*

Differential Diagnosis and Pitfalls

- Reactive epithelial changes—the most common pitfall (prominent nucleoli, negative or patchy p16 staining).

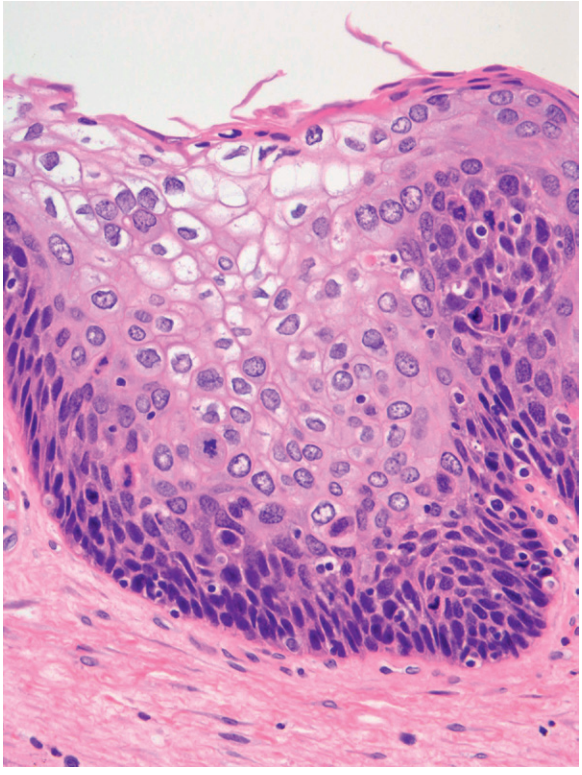


FIGURE 1
HSIL (CIN2). Conspicuous maturation but prominent parabasal atypia.

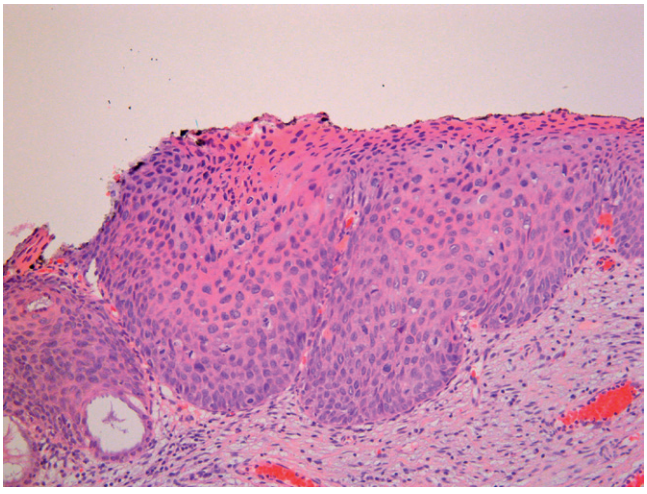


FIGURE 2
HSIL (CIN2), keratinizing.

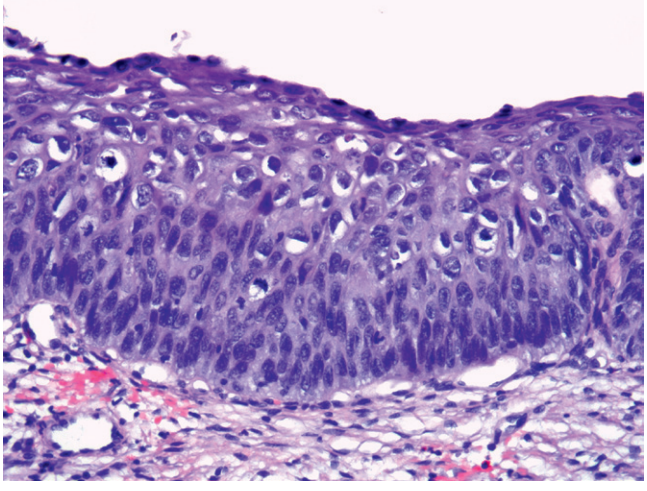


FIGURE 3
HSIL (CIN2) with slight maturation

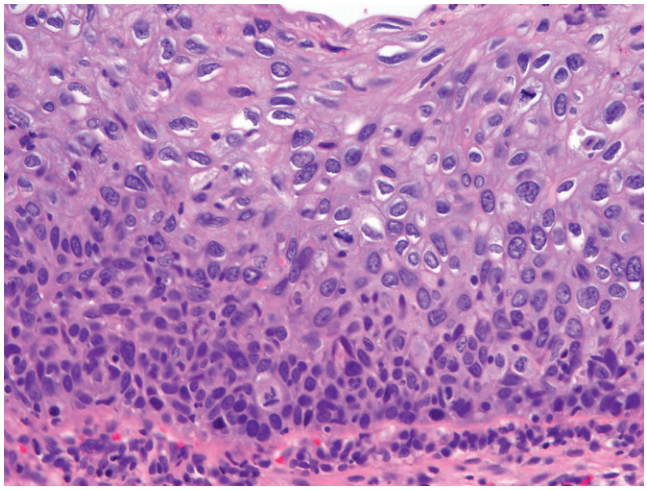


FIGURE 4
HSIL (CIN2) with koilocytosis. Note the parabasal atypia.

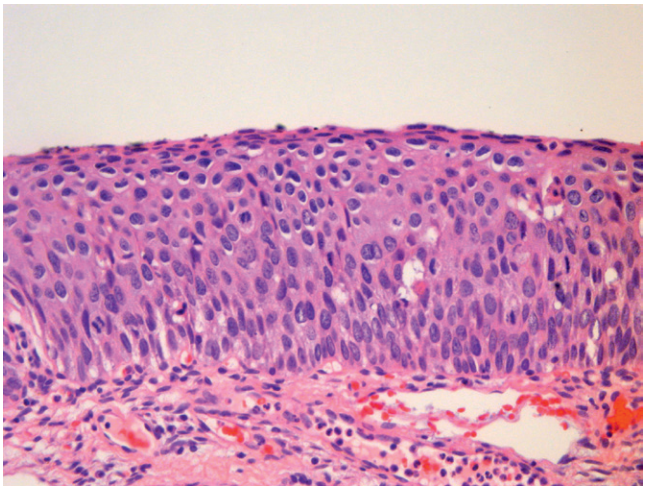


FIGURE 5
HSIL (CIN2). A less abrupt transition from immature to mature in this CIN2.

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION (GIANT CONDYLOMA)

PITFALL

Definition—A variant of condyloma that presents as a grossly enlarged mass and appears to replace or cover the cervix and/or distal vagina.

Clinical Features

Epidemiology

- Sexually active, reproductive-age women.
- Uncommon.

Presentation

- A Pap smear diagnosis of atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL), or occasionally high-grade squamous intraepithelial lesions (HSIL).
- A conspicuous verruciform or fungating mass detected on digital and speculum exam in the distal vagina/ectocervix.

Prognosis and Treatment

- Conservative removal, cryotherapy, and/or laser ablation.

Pathology

Histology

- Giant condyloma is characterized by mildly atypical immature metaplastic epithelium with papillary architecture.
- The papillae are thin and slender (filiform), not verrucous and blunt like the papillae seen in condyloma acuminata.
- A mild increase in nuclear density can be appreciated, as can a mildly increased nuclear-to-cytoplasmic ratio.
- The nuclei are well spaced and do not overlap each other.
- The cell borders can be prominent.
- Koilocytic changes are minimal or absent in these lesions.
- Overlying columnar cell layers may be preserved.

Immunohistochemistry

- Ki-67 expression is mild to moderate, and staining in the upper epithelial layers is low due to lack of viral cytopathic effect.
- p16ink4 expression is negative or patchy, the latter being most prominent in maturing cell cytoplasm with variable nuclear staining. This is the classic pattern seen in low-risk human papillomavirus (HPV) types and is very helpful in distinguishing this entity from most HSILs or papillary squamous carcinomas.

Differential Diagnosis and Pitfalls

- The major pitfall is misclassifying this entity as a verrucous carcinoma. The latter can be excluded if any of the following are found, including cytopathic effect and extension into crypt epithelium. It is very important to exclude a large condyloma and use a diagnosis of verrucous carcinoma in any well-differentiated exophytic lesion of the cervix in a young woman.
- Papillary carcinoma is easily distinguished by more poorly differentiated epithelium and strong diffuse p16 immunostaining.

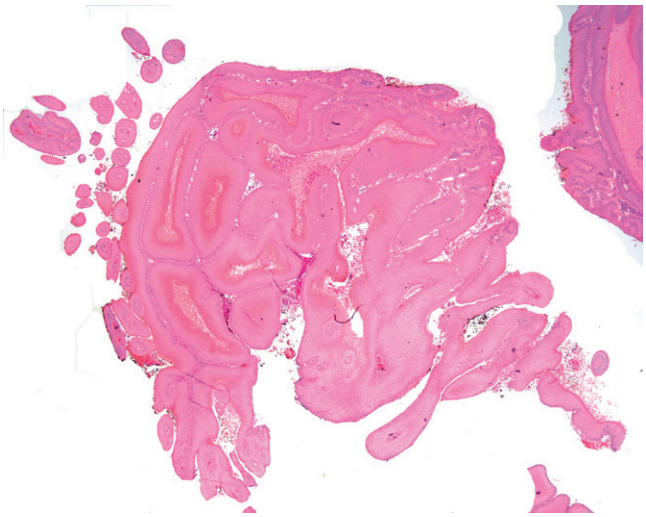


FIGURE 1

LSIL (giant condyloma). Low-power image of a large cervical condyloma. Note the relatively slender, filiform papillae.

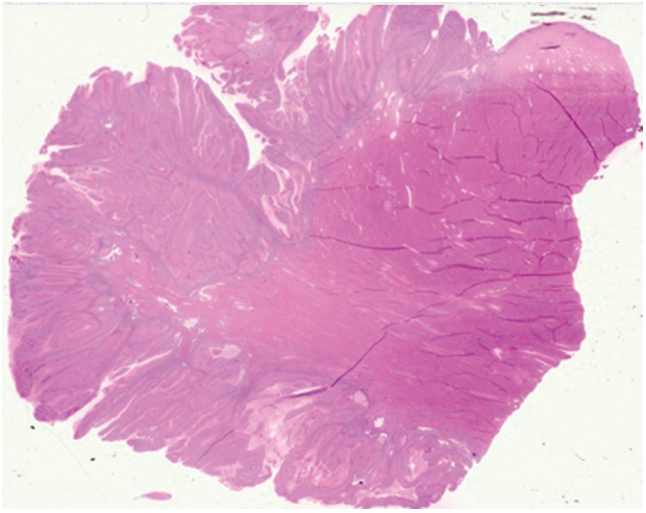


FIGURE 2

LSIL (giant condyloma). This lesion has a broader base.

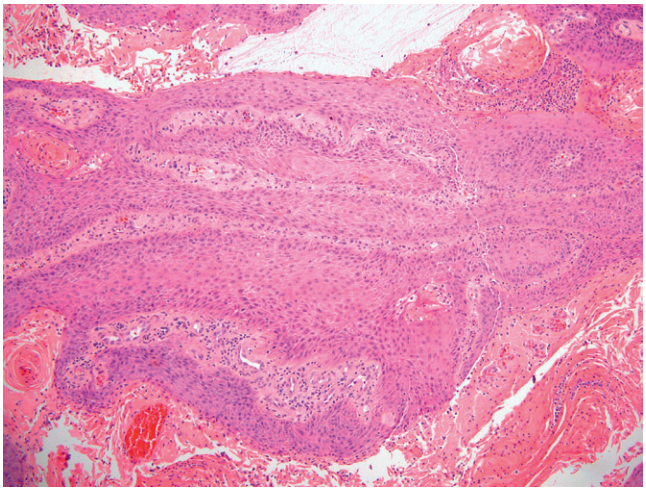


FIGURE 3

LSIL (giant condyloma). Extension into crypts supports the diagnosis of an intraepithelial lesion versus verrucous carcinoma.

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION (IMMATURE CONDYLOMA)

Definition—Immature condyloma represents an infection of the immature metaplastic cervical transformation zone epithelium by human papillomavirus (HPV) type 6 or 11. Also variably called squamous papilloma or papillary immature metaplasia; the most appropriate term is low-grade squamous intraepithelial lesion (LSIL) (immature condyloma).

Clinical Features

Epidemiology

- Reproductive-age, sexually active women.

Presentation

- Papanicolaou smears are typically classified as atypical squamous cells of undetermined significance (ASCUS), as LSIL, or occasionally as high-grade squamous intraepithelial lesions (HSIL).
- The colposcopic abnormality typically presents as an exophytic or discrete cerebriform lesion on the cervix corresponding to the papillary metaplastic epithelium.

Prognosis and Treatment

- Clinicians can opt to treat immature condyloma patients in two ways: cryoablation or follow-up.
- Conservative management should only be done for patients with favorable biopsy, Papanicolaou smear, and colposcopy results who can ensure close follow-up.
- Patients infected with HPV 6 or 11 are not directly at risk for cancer, but having HPV places them at risk of infection with the other strains that predispose to cancer.

Pathology

Histology

- The histologic features of immature exophytic LSIL represent a spectrum of changes.
- At low power these lesions exhibit prominent papillary growth composed of small, filiform papillae.
- Notably there is minimal to no epithelial maturation toward the surface of the papillae.
- The cells are uniform and bland, with only mildly increased nuclear-to-cytoplasmic ratios, and minimal nuclear crowding.
- Nuclear atypia, if present, is mild.
- Koilocytes are not present, and often the overlying columnar epithelial cells are preserved.

Immunohistochemistry

- Ki-67 expression is low to moderate, with sparing of the upper epithelial layers.
- p16 staining is negative or patchy.

Differential Diagnosis and Pitfalls

- Condyloma acuminatum—this is an acceptable diagnosis but might not be suspected in the absence of cytopathic effect.
- Papillary carcinoma in situ—if the mitotic rate is high or there is any appreciable nuclear overlap or loss of the monotonous uniform nuclei with nucleoli, consider this diagnosis. A strong diffuse p16 stain and a high MIB1 index will characterize this lesion versus immature condyloma.
- Papillary carcinoma—it must be excluded if the diagnosis of papillary carcinoma in situ is made.

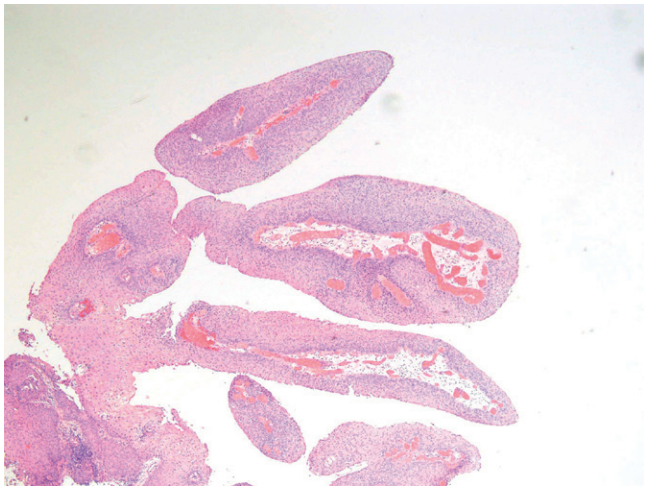


FIGURE 1

Immature condyloma (LSIL). Note the papillary architecture at low-power magnification.

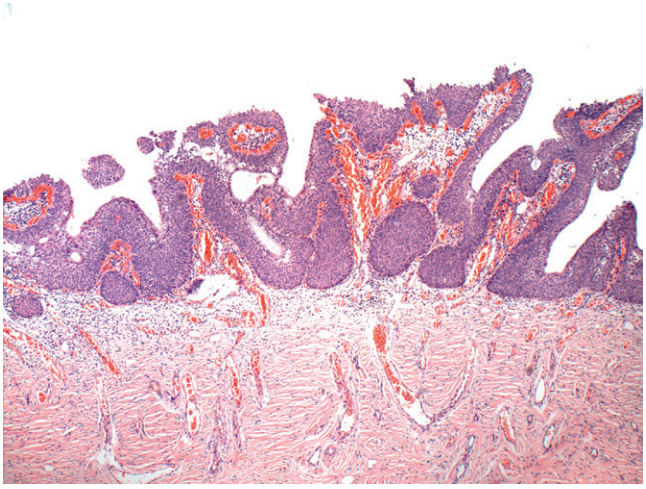


FIGURE 2

Immature condyloma. Note the papillary architecture at low-power magnification.

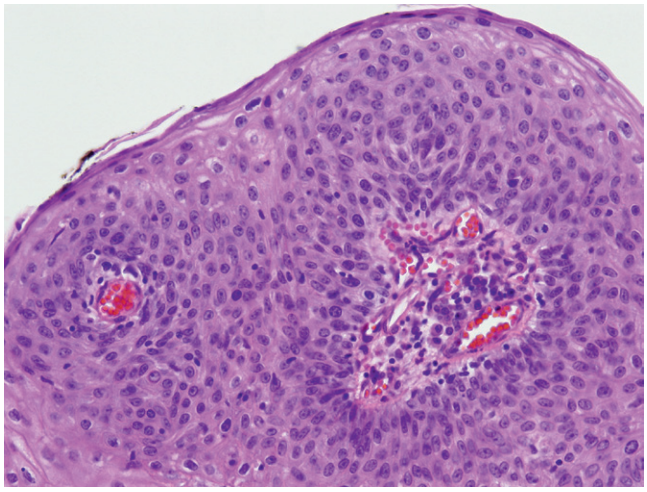


FIGURE 3

Immature condyloma. Immature condyloma at high magnification. Note the relatively high nuclear density; however, the cell population, while immature, is uniform, with regular nuclear spacing. There is a low mitotic index.

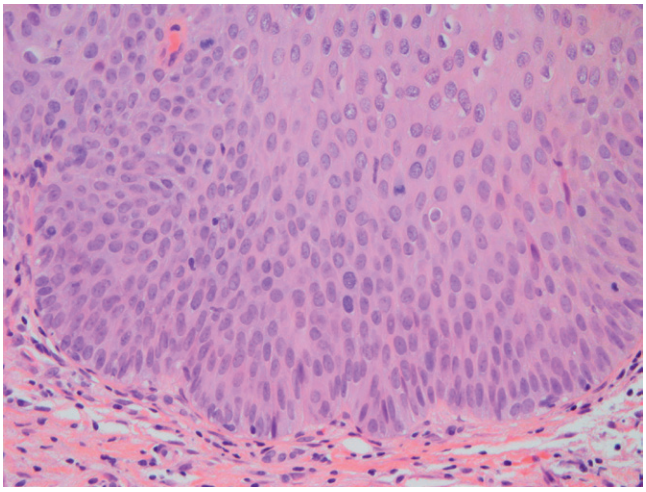


FIGURE 4

Immature condyloma. At higher power, again note the bland, uniform, slightly crowded nuclei. There is minimal nuclear atypia and overlapping.

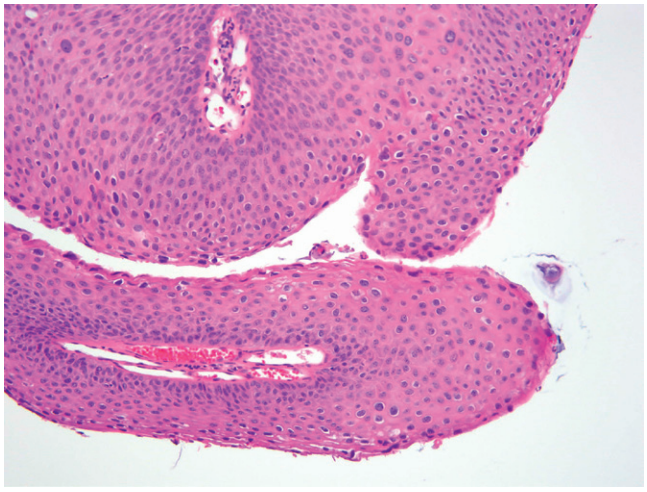


FIGURE 5

Immature condyloma. Note the lack of significant koilocytic change.

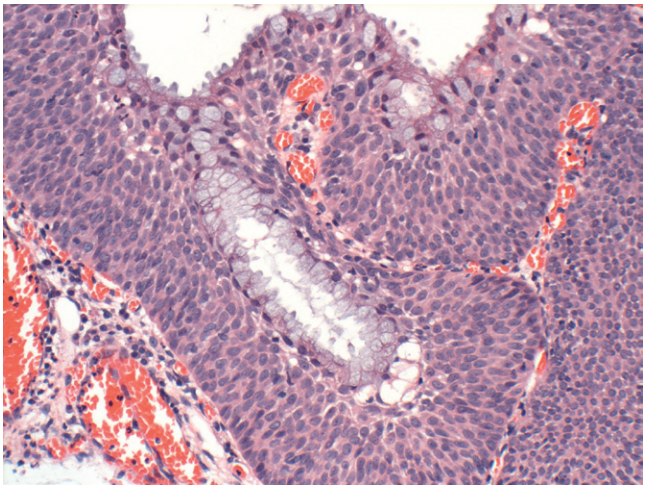


FIGURE 6

Immature condyloma. Immature metaplastic cells undermining columnar epithelium. Note the high cell density in contrast to normal metaplastic epithelium.

MIXED-PATTERN SQUAMOUS INTRAEPITHELIAL LESION (LOW- AND HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS)

Definition—The presence of two different human papillomavirus (HPV)–type specific lesions in the same specimen.

Clinical Features

Epidemiology

- Reproductive-age, sexually active women, in the vulva or anal region may be associated with immunosuppression but not specific for this condition.

Presentation

- Papanicolaou smear typically classified as atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL).
- Colposcopic or gross abnormality, typical for squamous intraepithelial lesion (SIL).

Prognosis and Treatment

- Management is directed toward the more severe lesion.
- Treatment of any underlying predisposing factors.

Pathology

Histology

Three scenarios in which both LSIL and HSIL are encountered are as follows:

- Coexisting condyloma or LSIL of the vulva or anus and HSIL (vulvar intraepithelial neoplasia II/III) or anal intraepithelial neoplasia (AIN II/III).
- Coexisting LSIL of the cervix and either HSIL or adenocarcinoma in situ.
- Coexisting immature condyloma (LSIL) and HSIL.
- The two lesions will either be juxtaposed or in separate biopsy specimens.

Immunohistochemistry

- Ki-67 and p16ink4 expression will often define two different processes. HPV testing is not usually employed but will reveal two different HPV types.

Differential Diagnosis

- A spectrum of atypia is often present in SIL, such that a small focus of LSIL might be seen in continuity with HSIL. In our experience these are usually a manifestation of a single HPV infection and contrast with the presence of two distinctly different lesions (often separated or in separate biopsies) that typify a double infection.

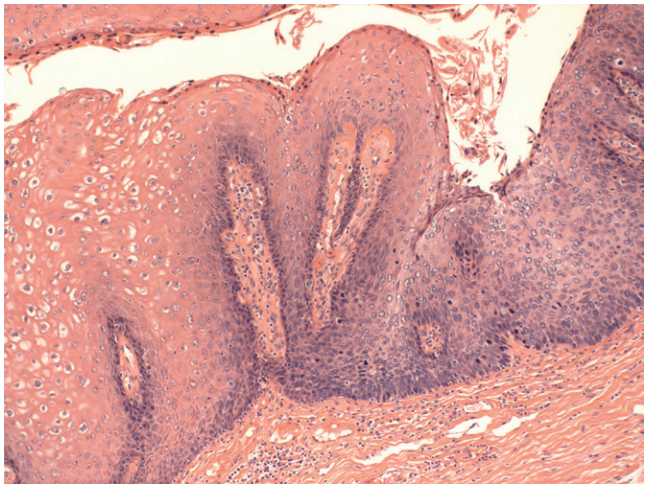


FIGURE 1

Mixed pattern SIL(s). This condyloma of the anal canal *(left)* merges abruptly with a higher-grade lesion (AIN 2 and 3) *(right)*.

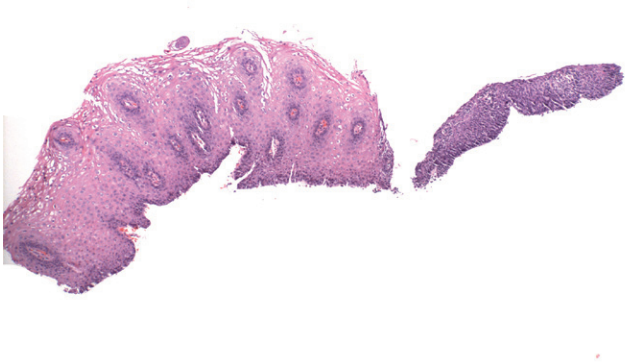


FIGURE 2

Mixed pattern SIL(s). This cervical biopsy contains both HSIL *(right)* and LSIL (condyloma, *left*).

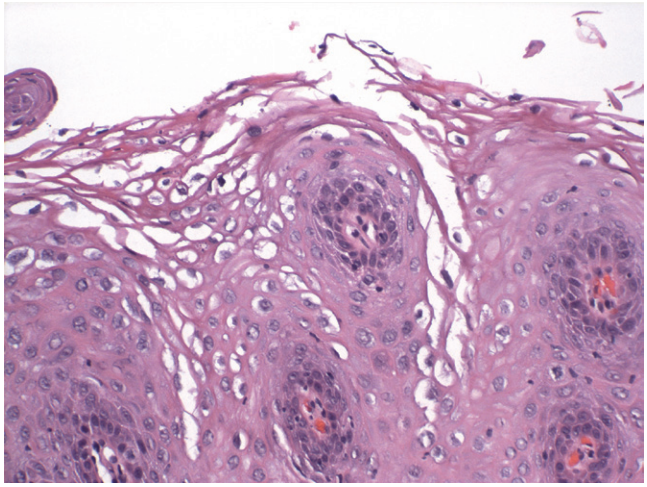


FIGURE 3

Higher magnification of the condyloma in Figure 2.

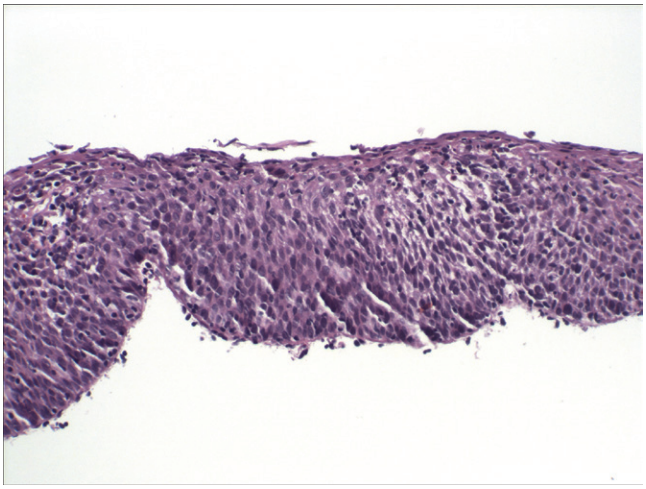


FIGURE 4

Higher magnification of the HSIL in Figure 2.

ATROPHY INCLUDING SQUAMOUS INTRAEPITHELIAL LESION IN ATROPHY

Definition—Any one of the spectrum of alterations within the cervical epithelium of postmenopausal women, including squamous intraepithelial lesions (SILs).

Clinical Features

Epidemiology

- Occurs predominantly in postmenopausal women.
- Also can be seen in any low-estrogen state (postpartum, breast-feeding).

Presentation

- Typically detected on routine Pap smear analysis.
- Misinterpretation of atrophy for neoplasia can lead to colposcopy and biopsy.
- In some instances, atypia may be striking and mimic squamous cell carcinoma.

Prognosis and Treatment

- Excellent prognosis; this is a benign condition.
- The management of atypical atrophy often involves a trial of vaginal estrogen cream. This will usually resolve the atrophy and normalize the vaginal cytology.

Pathology

Histology

- **Atrophy**
  - Histologic features of atrophy include hyperchromasia and elongated nuclei with occasional grooves (transitional metaplasia).
  - Chromatin is usually finely distributed.
  - Mitotic activity is not typically present, but occasional mitoses may be found if there are inflammation and repair.
  - The nuclei are uniform throughout the epithelial compartment.
- **"Mature" Atrophy**
  - The surface shows some features of maturation including a decrease in nuclear size relative to the amount of cytoplasm.
  - Variable amounts of glycogenated epithelium are present, resulting in pseudokoilocytosis.
  - The basal layer is typically distinct and not thickened.
- **Atypical Atrophy**
  - Occasional cases have enlarged, atypical nuclei with or without partial maturation.
  - These cases are distinguished from SIL by the lack of appreciable mitotic activity, the presence of conspicuous intercellular bridging, and widely spaced nuclei.

Immunopathology (Including Immunohistochemistry)

- The Ki-67 labeling index is not increased.
- In some cases, patchy cytoplasmic p16 positivity is noted.

Main Differential Diagnosis

- High-grade SILs (cervical intraepithelial neoplasia [CIN] III).

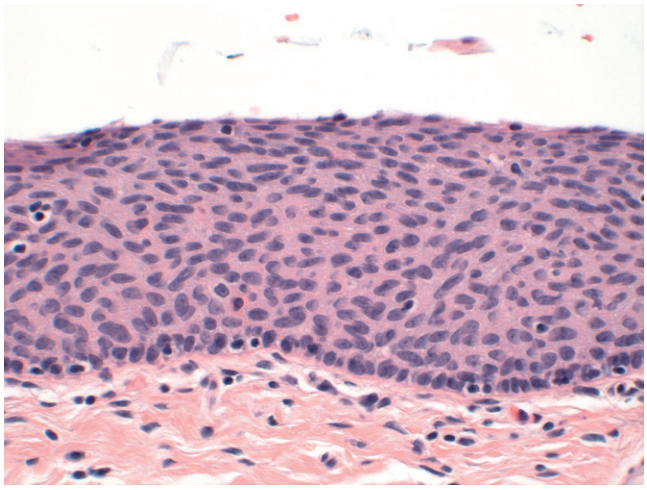


FIGURE 1

Cervical atrophy. This typical example of atrophy shows uniform, somewhat hyperchromatic, nuclei evenly distributed throughout the thickness of the sample. The nuclei are elongated, with occasional grooves. Maturation toward the surface is not present. Mitoses are not identified.

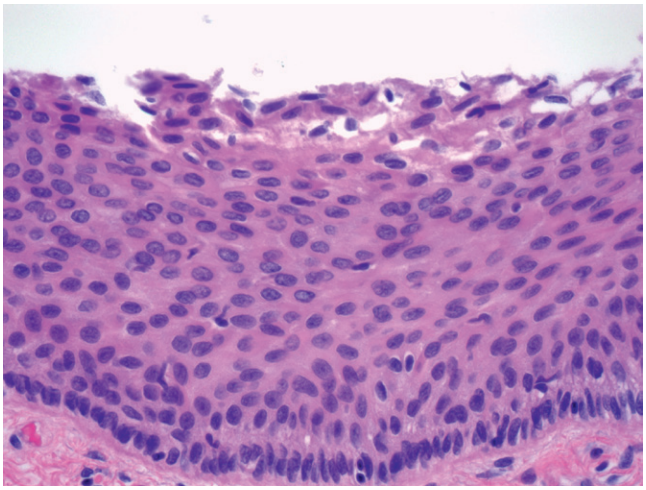


FIGURE 2

Cervical atrophy. A classical example of cervical atrophy. The basal nuclei are small, and the cells above that layer are uniformly hyperchromatic with elongated grooved nuclei. Nuclear atypia in the superficial layers is not present. Mitotic figures are not seen.

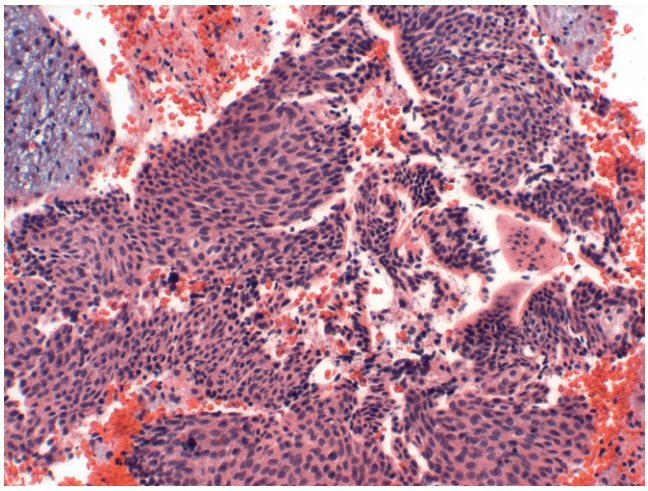


FIGURE 3

Cervical atrophy. In this curettage specimen, many fragments of atrophic cervical epithelium are present. The cells are uniform, hyperchromatic, elongated, and bland. Mitoses are not seen.

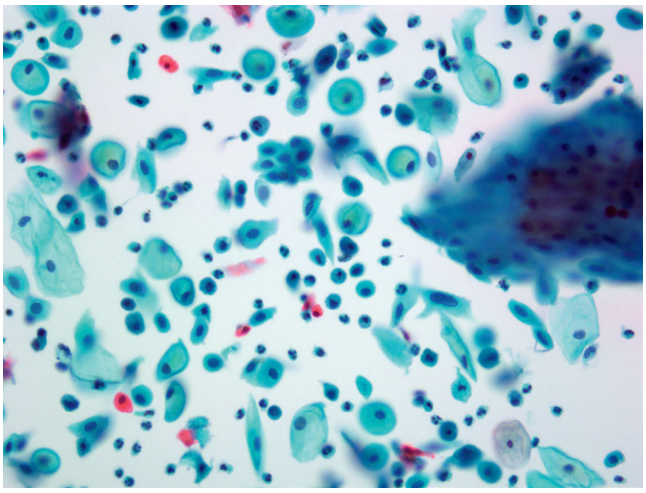


FIGURE 4

Benign atrophy in a cervical cytologic preparation. The variable nuclear size and dyskeratosis might mislead the cytopathologist. When uncertain, the pathologist should recommend a trial of intravaginal estrogen followed by a repeat cytology.

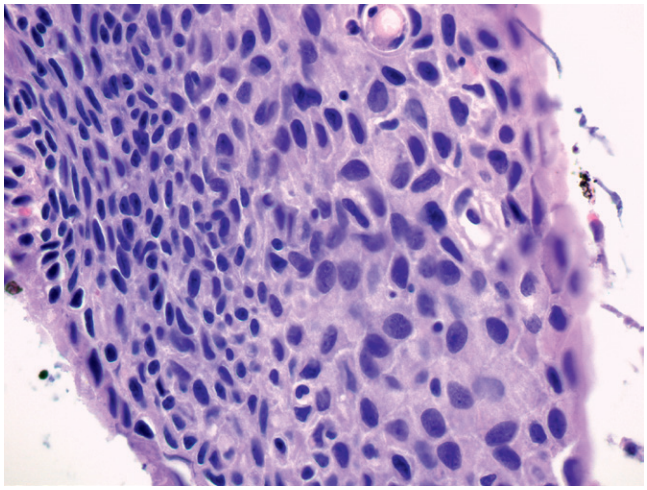


FIGURE 5

Cervical atrophy. A detached fragment of atypical atrophy. The nuclei are hyperchromatic, and some are enlarged and atypical. Features favoring a diagnosis of atrophy include the prominent intracellular bridges and the complete lack of mitotic activity.

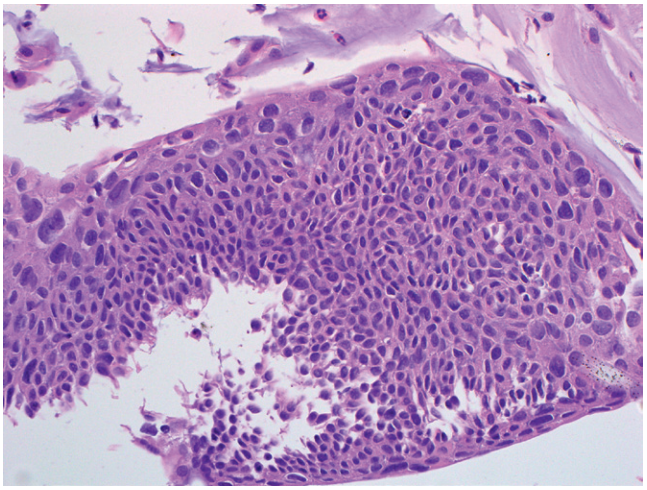


FIGURE 6

SIL occurring in atrophic changes. Note the focal discrete nuclear atypia. This biopsy specimen was strongly positive for p16.

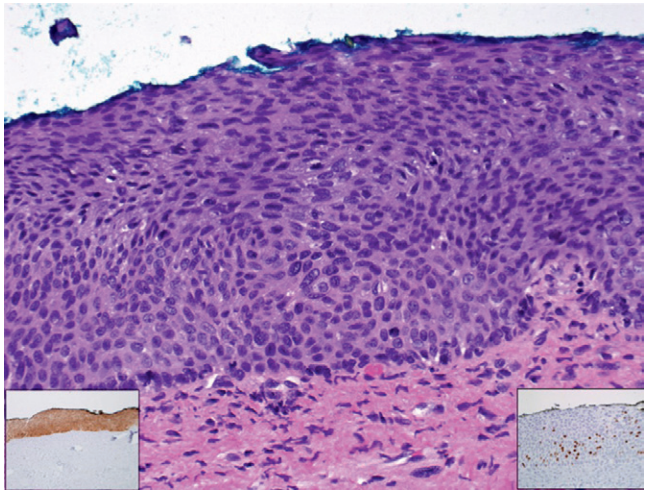


FIGURE 7

A rather subtle SIL associated with atrophy and not amenable to precise grading. p16 *(left inset)* and MIB1 staining *(right inset)* are increased.

MINOR p16-POSITIVE METAPLASTIC ATYPIAS

Definition—Immature metaplastic or reserve cell proliferations with mild atypia and strong p16 immunostaining.

Clinical Features

Epidemiology

- Reproductive-age women.
- Inconsistent human papillomavirus (HPV) association.
- Typically present with atypical squamous cells of undetermined significance (ASCUS) cervical smear.

Presentation

- Variable, some acetowhite epithelium on colposcopy.

Prognosis and Treatment

- Limited follow-up at present to determine the risk of high-grade squamous intraepithelial lesion (HSIL) outcome.
- No data supporting this as a significant cancer precursor but some are likely an early form of SIL and more followup is needed.
- Managed by follow-up with reevaluation of the cervix.

Cytopathology

- Commonly ASCUS.

Histology

- Immature metaplastic phenotype or basal proliferation with columnar differentiation.
- Uniform epithelial stratification with some cytoplasmic differentiation.
- Low level of anisokaryosis.
- Slightly higher nuclear density in all epithelial layers with some reduction near the surface.

Immunopathology (Including Immunohistochemistry)

- p16ink4—diffusely positive.
- MIB1—less than 50% of the cells and typically confined to basal layers.
- Positive for squamocolumnar junction markers (CK7).

Main Differential Diagnosis

- Reactive or immature metaplasia—this entity will usually demonstrate more pronounced drop in cell density near the surface relative to immature low-grade squamous intraepithelial lesion (LSIL) with cytoplasmic maturation.
- Immature metaplastic squamous intraepithelial lesion (SIL)—higher nuclear density and nuclear-to-cytoplasmic (N/C) ratio, lack of uniform nuclear spacing, less distinct cytoplasmic borders, some syncytial groupings of surface nuclei, and "microheterogeneity" in nuclear size. Increase in MIB1 index in addition to being strongly p16 positive.
- This entity will pose some difficulty in management under the current guidelines for managing SIL in the laboratory. Some pathologists might interpret this process as reactive or low grade in nature, and manage with follow-up. However, if the pathologist is concerned about HSIL, the use of a p16 immunostain (which will be positive) might prompt treatment with cone biopsy or loop electrosurgical excision procedure (LEEP). In younger women, depending on the setting, management with a repeat exam in 6 months or LEEP might be performed.

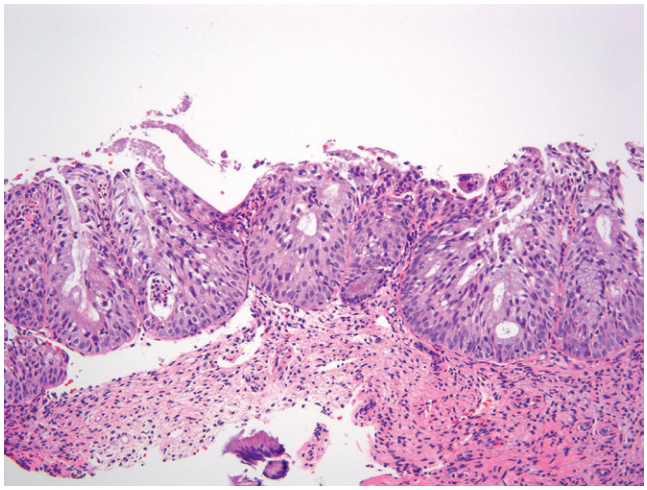


FIGURE 1

Mildly atypical immature metaplasia with columnar differentiation. Note the low nuclear density overall and the presence of mucin in the upper epithelial layers.

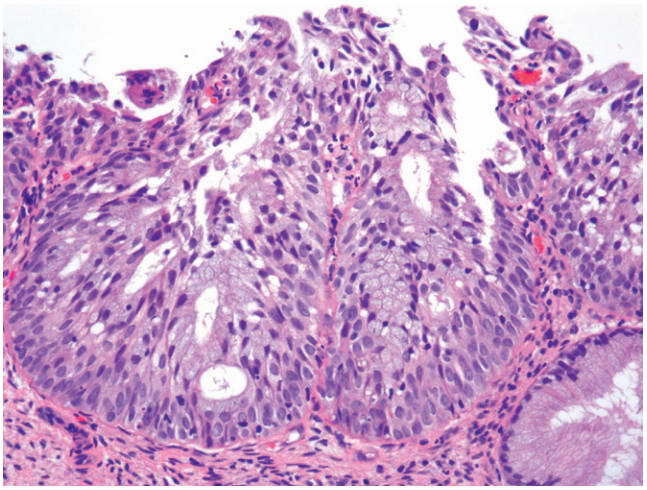


FIGURE 2

Higher magnification of Figure 1. Note the lack of appreciable atypia.

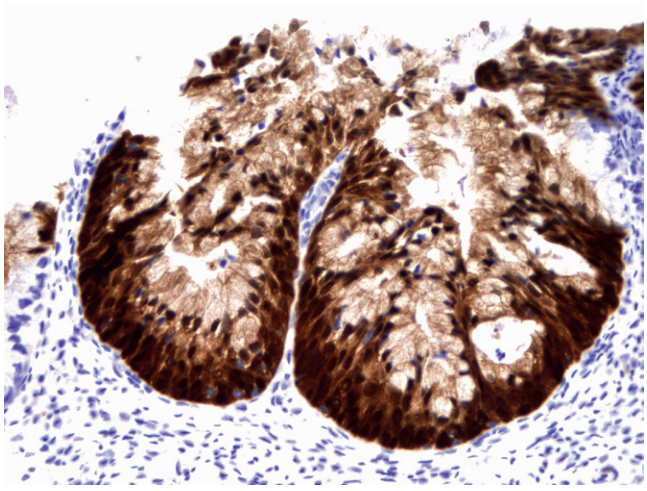


FIGURE 3

The p16 immunostain is intense, likely due to the immaturity of the epithelium.

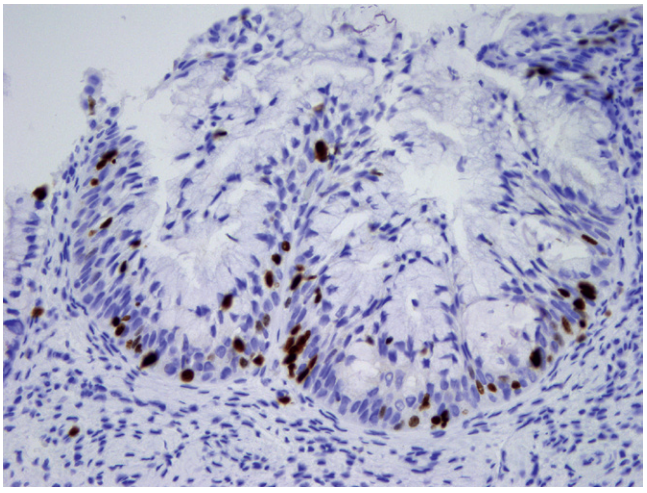


FIGURE 4

The MIB1 index is low despite the high p16 staining index.

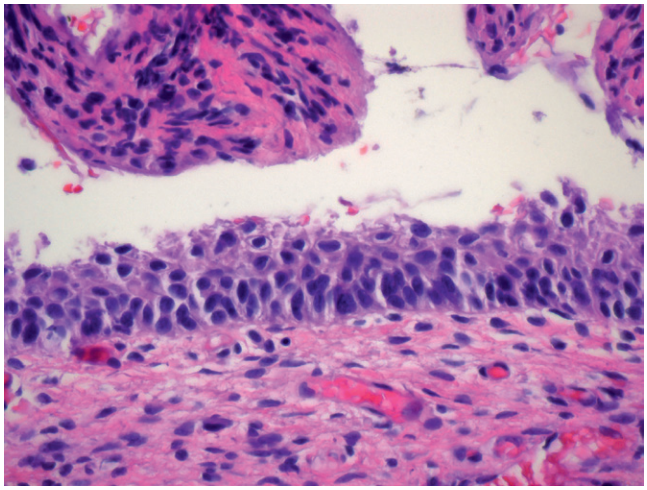


FIGURE 5

Mildly atypical immature metaplasia. The population is uniform with surface differentiation.

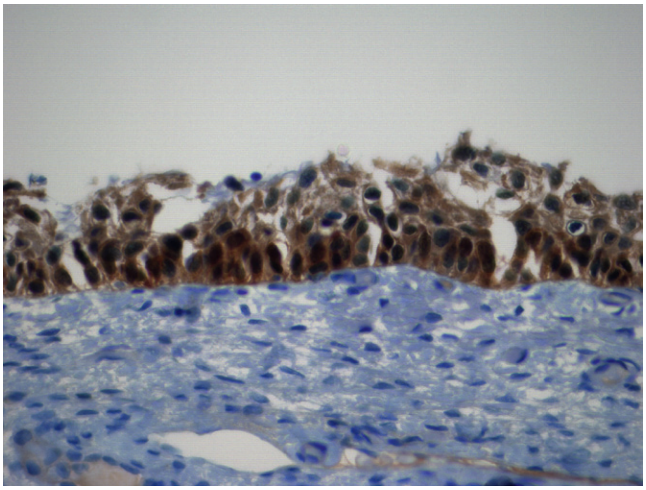


FIGURE 6

The p16, as in the prior case, is strongly positive.

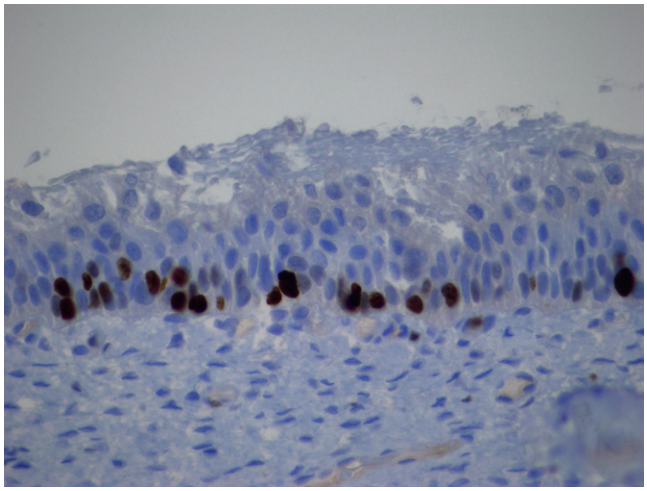


FIGURE 7

The MIB1 index is very low. This speaks against a diagnosis of HSIL and is of note given that some recent studies have not detected HPV in these lesions. Nevertheless, the possibility that these may be very early SILs in metaplastic epithelium must be considered.

SQUAMOUS INTRAEPITHELIAL LESION, NOT AMENABLE TO PRECISE GRADING (QSIL)

Definition—A squamous intraepithelial lesion not amenable to precise grading (QSIL) that demonstrates features seen in both low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL).

Clinical Features

Epidemiology

- Typically encountered in reproductive-age women with atypical squamous cells of undetermined significance (ASCUS) or squamous intraepithelial lesion (SIL) on cervical cytology.

Presentation

- The vast majority of lesions are first identified by routine screening with Pap smears.
- The pathologist is usually faced with two scenarios:
  1. The level of atypia is intermediate between cervical intraepithelial neoplasias 1 (CIN1) and 2 (CIN2).
  2. The lesion is immature (metaplastic), and there is a disparity between the degree of immaturity and level of cytologic atypia. This includes some cases that arise in microglandular change.

Prognosis and Treatment

- These lesions usually generate some disagreement in terms of grade, with some observers classifying them as LSIL and others opting for HSIL.
- In general, if there is agreement that the lesion does not fulfill the criteria for HSIL, the odds of HSIL on follow-up are low. If there is agreement on CIN2, the frequency of spontaneous resolution within 6 months is still approximately 40% and may be higher in young women under age 25.
- The fundamental question that should be asked by the pathologist when he or she examines the biopsy specimen is whether the patient should be managed by observation with a repeat exam or an ablative or excisional procedure. Given the high rate or resolution of many SILs including CIN2, management options thus include either cryotherapy/loop electrosurgical excision procedure (LEEP) taking into account the cytologic and colposcopic findings or follow-up exam in approximately 6 months.

Pathology

Histology

- Lesions with intermediate levels of atypia may exhibit:
  Increased parabasal cellularity
  Increased mitotic activity
  Abnormal mitotic figures
- Lesions with a disparity between level of atypia and degree of maturity exhibit:
  A metaplastic phenotype
  Persistently high nuclear density in the upper epithelial layers
  Uniform nuclear spacing
  Mild to moderate increase in the nuclear chromatin
  Absence of marked nuclear pleomorphism or coarse chromatin
- SIL associated with microglandular change:
  Lesions associated with microglandular change can be identified by their lobular architecture at low power that resembles squamous metaplasia.
  The cells are often immature and display cytoplasmic maturation with minimal crowding of the nuclei.
  The nuclei themselves are typically enlarged with occasional multinucleation.
  These lesions are frequently associated with high-risk HPV and may be diagnosed as mentioned earlier; however, the clinical impression (colposcopic) and cytologic findings should be considered.

Immunopathology (Including Immunohistochemistry)

- These lesions are typically strongly p16 positive.
- Staining for squamocolumnar (SC) junction markers (CK7) will usually be strong.

Main Differential Diagnosis

- HSIL (CIN2 and CIN3)—This lesion will generate a higher level of agreement for HSIL due to greater nuclear overlap, irregularity in nuclear morphology, and more complex chromatin patterns, including abnormal mitoses.
- Atrophy or immature metaplasia with reactive changes. Both will be p16 negative. Reactive changes might display nuclear enlargement, but the chromatin is usually open with nucleoli.

Diagnostic terminology: *Squamous intraepithelial lesion, not amenable to precise grading* (*CIN1 and CIN2*), with the proviso that management options include ablation/excision and observation with a repeat exam in approximately 6 months, or as clinically appropriate.

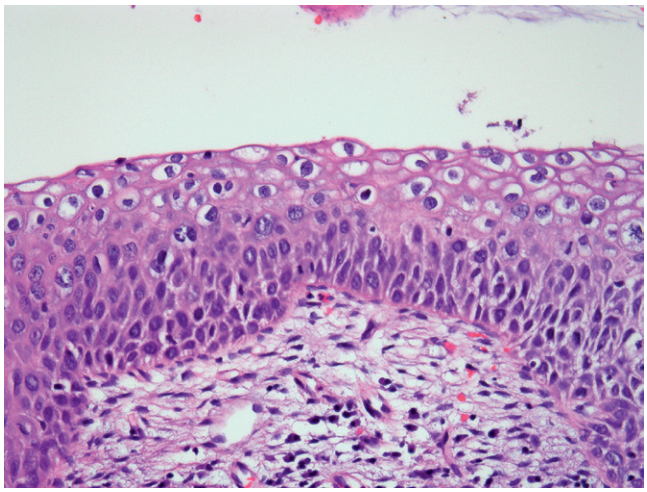


FIGURE 1

"QSIL" (SIL, not amenable to precise grading). There is increased nuclear chromasia and crowding in the lower third of the epithelium. This would often be classified as LSIL or QSIL, depending on the pathologist.

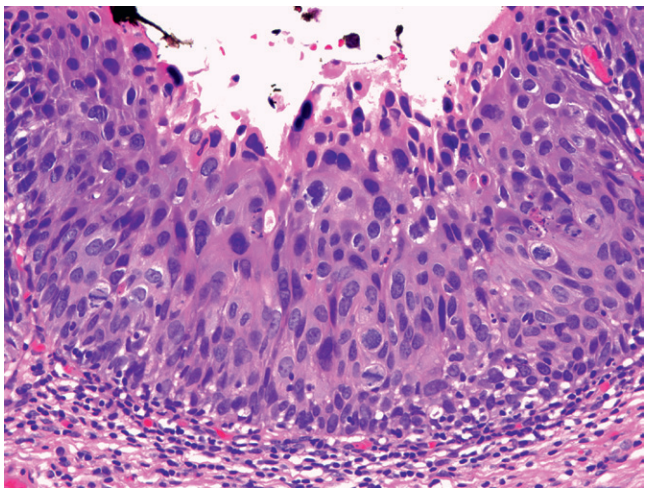


FIGURE 2

SIL, not amenable to precise grading (or QSIL). The cell growth appears somewhat disorganized with mitotic activity, but note the low nuclear-to-cytoplasmic (N/C) ratio, numerous multinucleated cells, and rather bland chromatin.

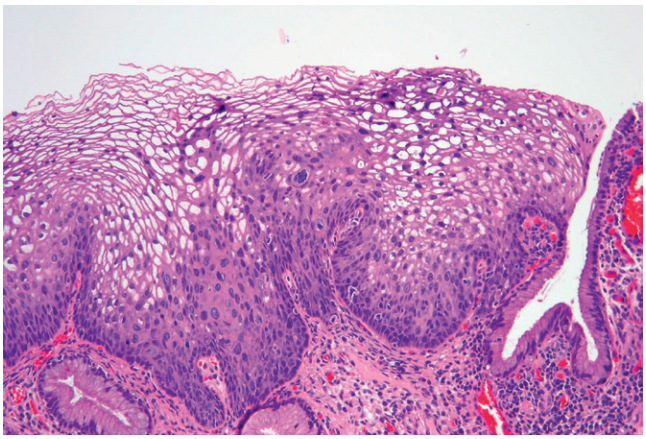


FIGURE 3

SIL, not amenable to precise grading (or QSIL). The overall architecture is that of an LSIL, but there is some increased parabasal atypia and a prominent abnormal mitosis in the center.

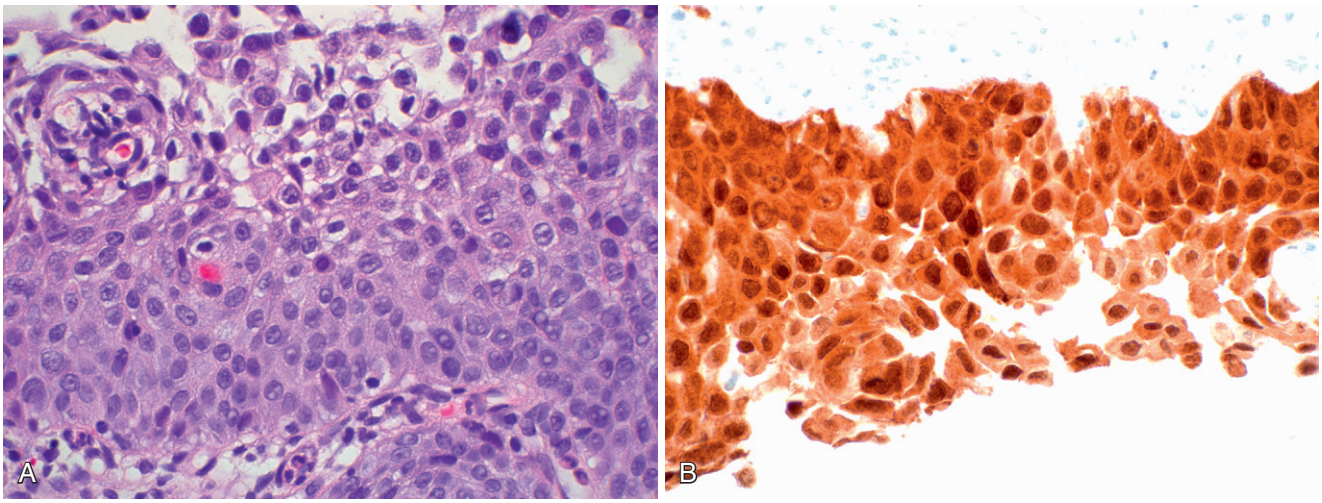


FIGURE 4

SIL, not amenable to precise grading (or QSIL). (**A**) Note the rather high nuclear density with rounded nuclei in the superficial layers of this metaplastic epithelium, yet the nuclei are uniform and do not overlap. (**B**) The lesion stains strongly for p16.

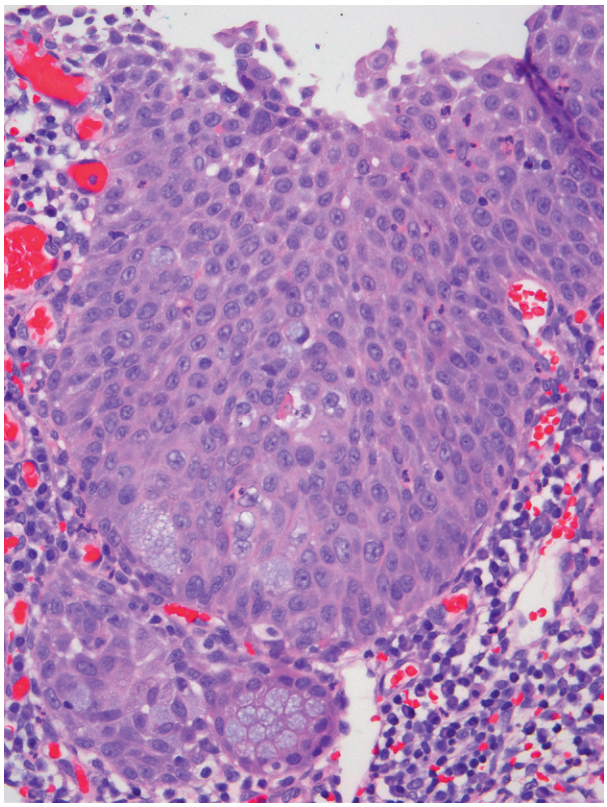


FIGURE 5

SIL, not amenable to precise grading (or QSIL). This is similar to the lesion in Figure 4, displaying a high nuclear density from base to surface. Both this and the prior lesion might be interpreted as reactive metaplasia by some given the lack of marked atypia. Others might prefer to classify them as "SIL in metaplasia, favor LSIL." Irrespective of the choice of words in the diagnosis, these lesions do not fit into the current concept of LSIL and HSIL as illustrated in most texts. Both are probably best managed by a repeat exam in approximately 6 months if more worrisome features are not seen on colposcopic exam.

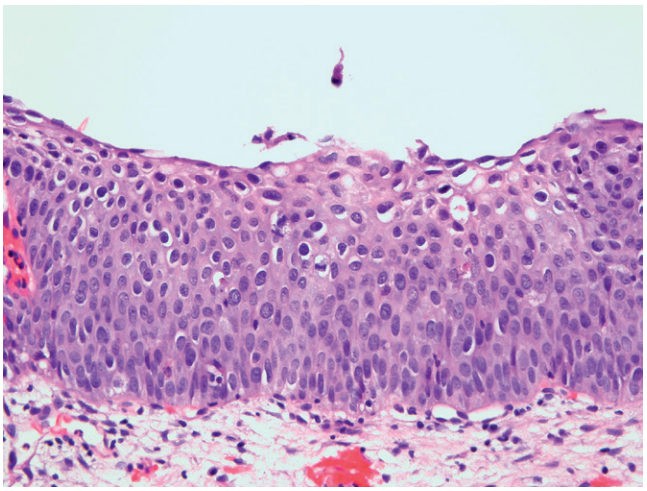


FIGURE 6

SIL, not amenable to precise grading (or QSIL). Another SC junction SIL that was variably classified as CIN1 and CIN2 by multiple observers. Note there is some nuclear overlap in the lower third of the epithelium, but there seems to be an orderly transition to differentiation without the more striking abnormalities in chromatin that typify HSIL.

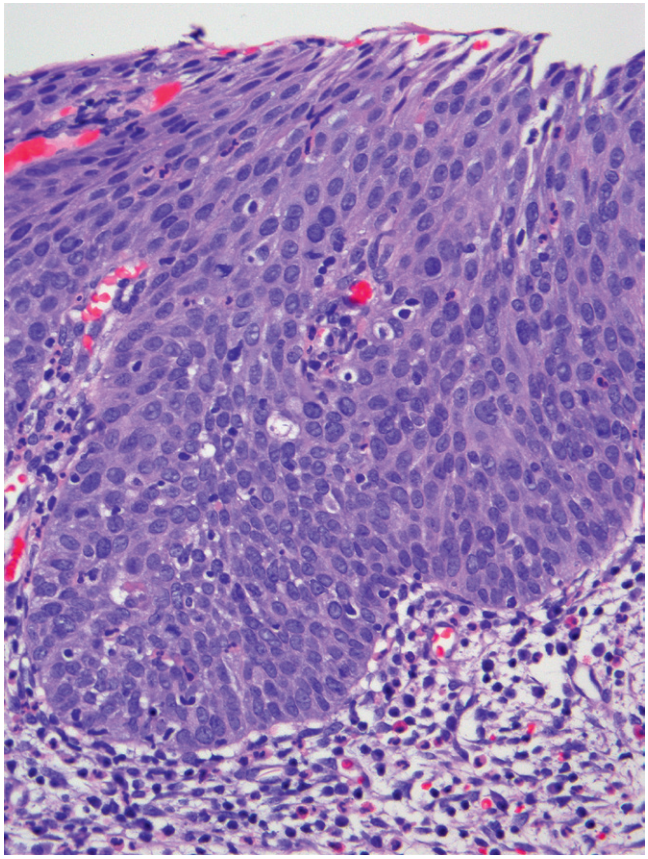


FIGURE 7

QSIL or HSIL? This metaplastic proliferation shows in addition a greater degree of nuclear overlap and hyperchromasia. Nucleoli are less conspicuous. In this case the pathologist will most likely render a diagnosis of HSIL.

SUPERFICIALLY INVASIVE SQUAMOUS CELL CARCINOMA

Definition—Early invasive squamous cell carcinoma (SCC) measuring no more than 3 mm in depth in the biopsy or conization specimen.

Clinical Features

Epidemiology

- Associated with high-risk human papillomavirus (HPV) infection and preexisting cervical intraepithelial neoplasia.
- Will be found in approximately 1 : 200 cone biopsies of high-grade squamous intraepithelial lesion (HSIL).
- Can be found at any age; median age around 35 to 40 years.

Presentation

- Patients are often asymptomatic and are being evaluated for an abnormal cervical cytology.
- The cytologic findings may be atypical squamous cells of undetermined significance (ASCUS), HSIL, or malignant cells.
- Some patients typically present with abnormal bleeding, especially following intercourse.

Prognosis and Treatment

- Small lesions have an excellent outcome with conservative management (cold knife cone), provided that the lesion is less than 7 mm in length and there is no capillary lymphatic space invasion, with 5-year survival of 99% for stage IA1 lesions.
- Hysterectomy is the treatment of choice for those not desiring to preserve fertility.
- If lymphovascular invasion or deep stromal invasion (beyond 3 mm) is discovered, radical hysterectomy or trachelectomy (or large conization) will usually be performed as clinically appropriate.
- Risk of lymph node metastases increases from a few percent for lesions under 3 mm to over 5% for invasion over 3 mm.

Histology

Several well-defined criteria must be applied to accurately diagnose stromal invasion:

- A desmoplastic stromal response.
- Blurring of the epithelial-stromal interface with loss of polarity of the cells at the epithelial-stromal border.
- Irregular or jagged stromal-epithelial interfaces.
- "Pseudocrypt" involvement with variable amounts of retraction artifact and occasional areas of central necrosis.
- Complex or reduplicated layers of epithelium with no intervening stroma.
- Abnormal keratinization of deep epithelial cells.
- Epithelial budding into the stroma, and single cells or clusters of small cells below the epithelial-stromal interface (early stromal invasion).
- A desmoplastic response can often be seen surrounding the aforementioned features.

In all cases of superficially invasive SCC a depth of invasion, horizontal extent, and the number of foci of invasion should be reported.

In cases of early superficial invasion the presence or absence of capillary-lymphatic space invasion should always be noted. If tumor is in spaces but the pathologist is unsure that they signify vascular invasion, it should be noted.

In biopsies the diagnosis of superficially invasive carcinoma should be made with caution and only if there is sufficient tissue to recognize the lesion as superficial. If the entire biopsy contains tumor, it should be stated as such and the dimensions of the biopsy given.

Preferred diagnostic term: Superficially invasive SCC (*well, moderately, poorly*) differentiated, measuring (specify) _____mm in length by (specify) _____mm in depth. Lymphovascular space involvement is present/absent. Margins are free of invasive carcinoma (closest margin is (specify) _____mm).

Immunopathology (Including Immunohistochemistry)

- Generally noncontributory excepting stains to verify capillary endothelium. Superficial carcinoma of the cervix is almost universally positive for pan-cytokeratins, CK7, and p63 immunostains, but these are rarely needed.

Main Differential Diagnosis

- Tangentially sectioned epithelium.
- Displaced epithelium due to previous procedures.
- Marked inflammation in cervical intraepithelial neoplasia (CIN) with blurring of the epithelial-stromal interface.
- Gland (crypt) involvement (can be tangentially sectioned).
- Prominent endothelial cells.

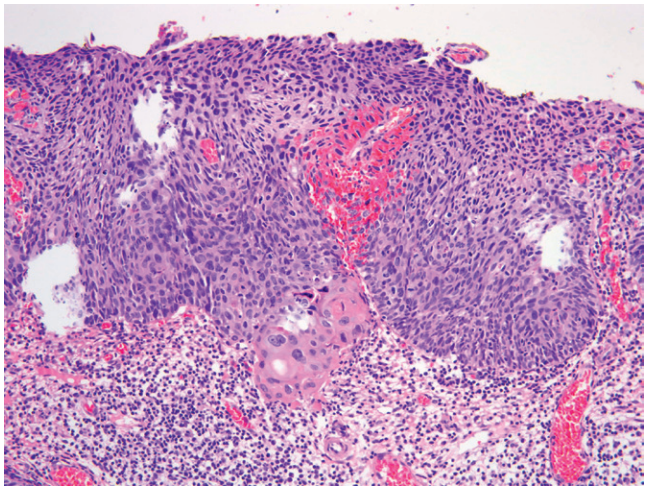


FIGURE 1

Early budding invasion. An invasive tongue *(center)* demonstrates loss of polarity and cytoplasmic differentiation.

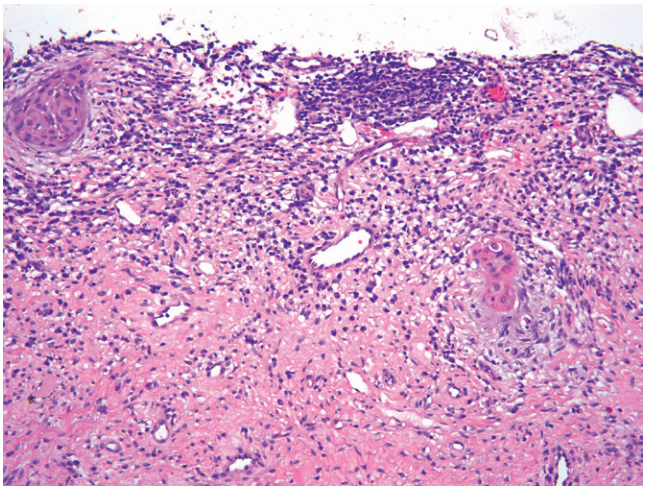


FIGURE 3

Subtle superficial invasion. The surface is eroded. Note the small nests of invasive carcinoma with stromal reaction.

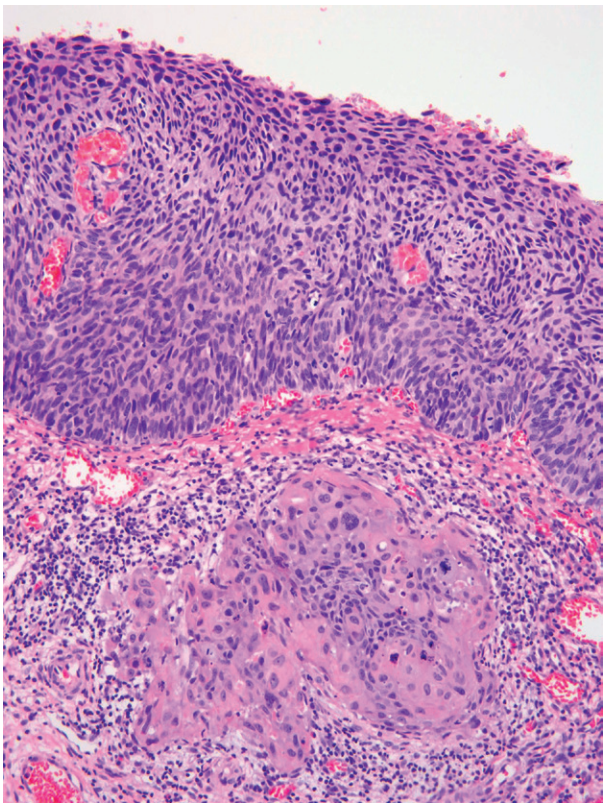


FIGURE 2

The same case as Figure 1 with superficial invasion.

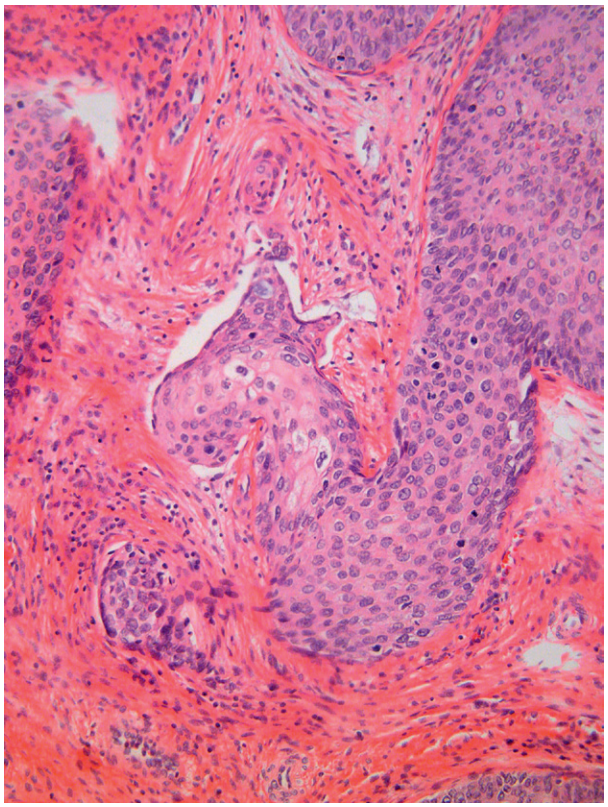


FIGURE 4

Another invasive tongue of epithelium. The complexity of this protruding neoplastic epithelium is inconsistent with crypt involvement.

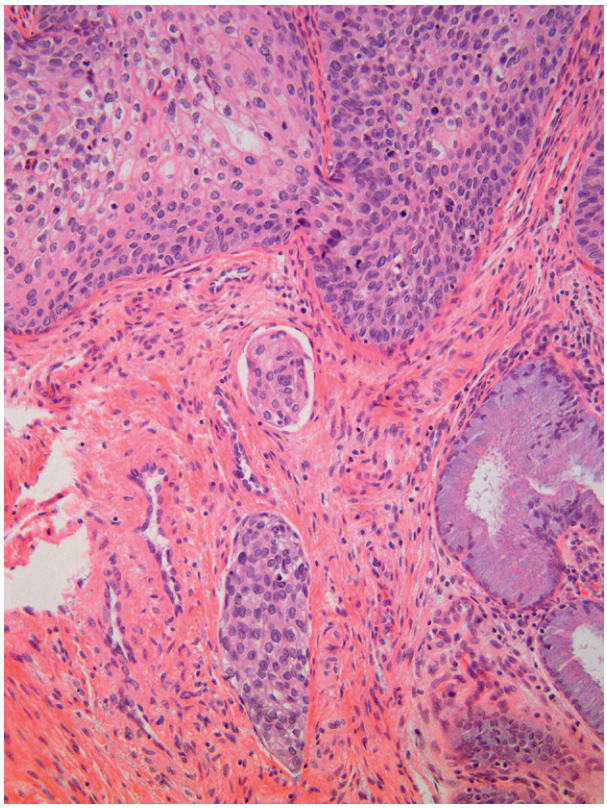


FIGURE 5

Lymphovascular invasion with rounded tumor nests in small sharply defined spaces devoid of stromal reaction.

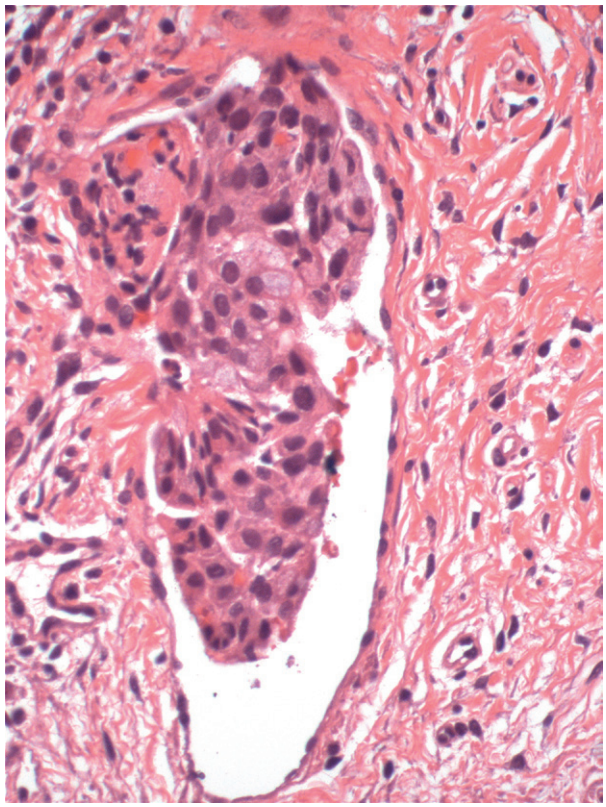


FIGURE 6

Pseudovascular invasion with detached fragments in a space. This can occur with injection of anesthetic or during specimen processing.

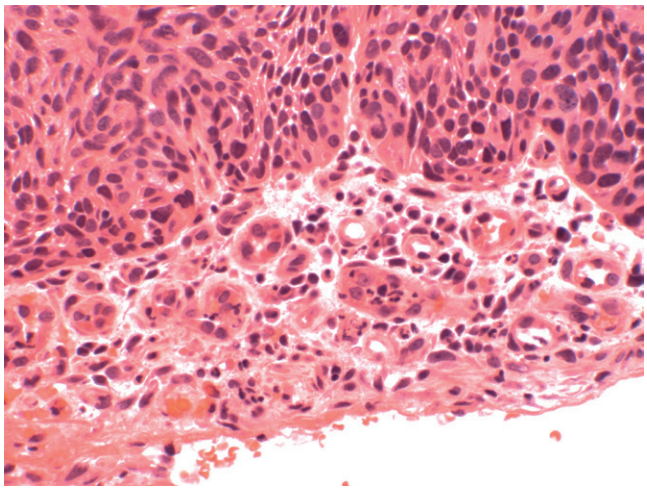


FIGURE 7

Pseudoinvasion in the form of prominent subepithelial capillaries with endothelial hyperplasia.

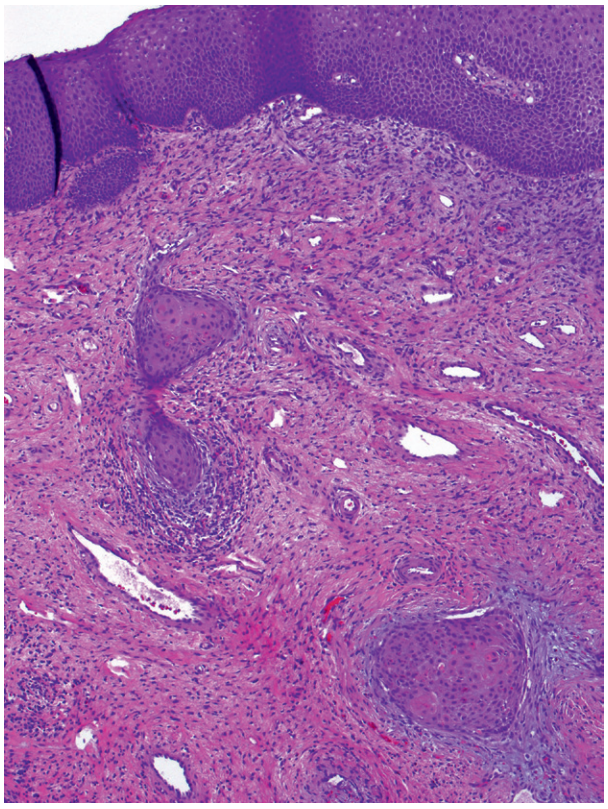


FIGURE 8

Pseudoinvasion created by prior biopsy that buried the epithelium in the superficial stroma.

CONVENTIONAL SQUAMOUS CELL CARCINOMA

Definition—A malignant neoplasm of the cervix comprised of squamous epithelial cells. Variants include large-cell keratinizing, large-cell nonkeratinizing, and small-cell nonkeratinizing squamous cell carcinoma (SCC), as well as papillary SCC.

Clinical Features

Epidemiology

- Associated with high-risk human papillomavirus (HPV) infection and preexisting cervical intraepithelial neoplasia.
- The progression rate from a high-grade squamous intraepithelial lesion to invasive squamous cell carcinoma in a patient undergoing close follow-up is less than 1%.
- The majority of patients that present with SCC are those who have not undergone regular screening with Pap smears.
- Historically the incidence is dropping, and a larger percentage are presenting at lower stage. In 2010, 11,800 women developed cervical cancer in the United States and 3,900 died of the disease.

Presentation

- Patients typically present with abnormal bleeding, especially following intercourse.
- Patients may also present with pain or a clinically identifiable mass lesion.

Prognosis and Treatment

- Small lesions have an excellent outcome with conservative management (cold knife cone\trachelectomy), with 5-year survival between 97% and 99% for stage IA lesions.
- Radical hysterectomy is the treatment of choice in patients not desiring to preserve fertility. Patients with high risk factors reported on their final pathology will receive adjuvant chemotherapy and/or radiation therapy.
- If lymphovascular invasion or deep stromal invasion is present, lymph node dissection may be undertaken.
- Patients with stage IIB and above tumors are treated with concurrent chemotherapy and radiation therapy.
- Five-year survival rates rapidly decrease to 80% (stage IB), 65% (stage II), 33% to 39% (stage III), and 9% to 17% for stage IV disease.
- Outcome is not dictated by lesion grade or subtype within this spectrum of common variants.

Pathology

Histology

Large-cell keratinizing (well-differentiated) SCC

- Uncommon, characterized by mild to moderate nuclear atypia and prominent keratinization.

Large-cell nonkeratinizing (moderately or poorly differentiated) SCC

- Most common variant, with moderate to marked atypia, presenting sheets of squamous cells with focal keratinization. Mucin droplets often present.

Small-cell nonkeratinizing (poorly differentiated) SCC

- Sharply demarcated nests of basal-type carcinoma cells with minimal keratinization.
- Some differentiation with features of large-cell nonkeratinizing carcinoma may be seen.

Papillary squamotransitional carcinoma

- This variant overlaps with papillary forms of high-grade squamous intraepithelial lesion (HSIL) and usually presents on biopsy with irregular fragments of papillary or frondlike neoplasia without associated stroma and

with complex reduplication of epithelial layers without intervening stroma. The diagnosis of invasion may not be possible without further sampling.

Cytologic features of SCC

- Several features have been identified in cytologic preparations associated with invasive disease:
  - Tumor diathesis composed of cellular, necroinflammatory debris (may be absent on liquid-based preparations).
  - Large, abnormally keratinized cells, frequently with "ink black" nuclei.
  - Large groups of hyperchromatic cells that may resemble endometrial or endocervical cells.
  - Enlarged, atypically shaped squamous cells that are frequently keratinized.

Immunopathology (Including Immunohistochemistry)

- SCC of the cervix is almost universally positive for pan-cytokeratins, CK7, and p63 immunostains.

Main Differential Diagnosis

- Tangentially sectioned HSIL, displaced epithelium due to previous procedures and marked inflammation in cervical intraepithelial neoplasia (CIN) with blurring of the epithelial-stromal interface, and gland (crypt) involvement are more relevant to the differential diagnosis of early invasion.
- Poorly differentiated adenocarcinoma or adenosquamous carcinoma—these are the most common mimics and best separated by p63 immunostains.
- Sarcomatoid (spindled) SCC and lymphoepithelial-like SCC are discussed elsewhere.
- Melanoma—rare in the cervix (versus vagina) but must always be considered with undifferentiated large-cell tumors. The presence of melanin pigment and immunostains for CK7 and HMB45 will aid in making this distinction.
- Basaloid carcinoma of the cervix—rare variant with unique pattern of basaloid cell growth with no appreciable squamous differentiation.
- Adenoid basal carcinoma of the cervix—a rare variant with not only squamous but also basal and adenoid differentiation. This mixture of patterns will distinguish it from a conventional cervical SCC.
- Neuroendocrine carcinomas of the cervix—distinguished by the absence or near absence of squamous differentiation (some tumors can be admixed with SCC or adenocarcinoma), discohesive growth, minimal inflammatory response, and positivity with neuroendocrine markers.
- Cervical involvement by, or sampling of, poorly differentiated endometrial carcinoma—these are typically heterogeneous for p16ink4 staining, vimentin positive, and HPV negative.

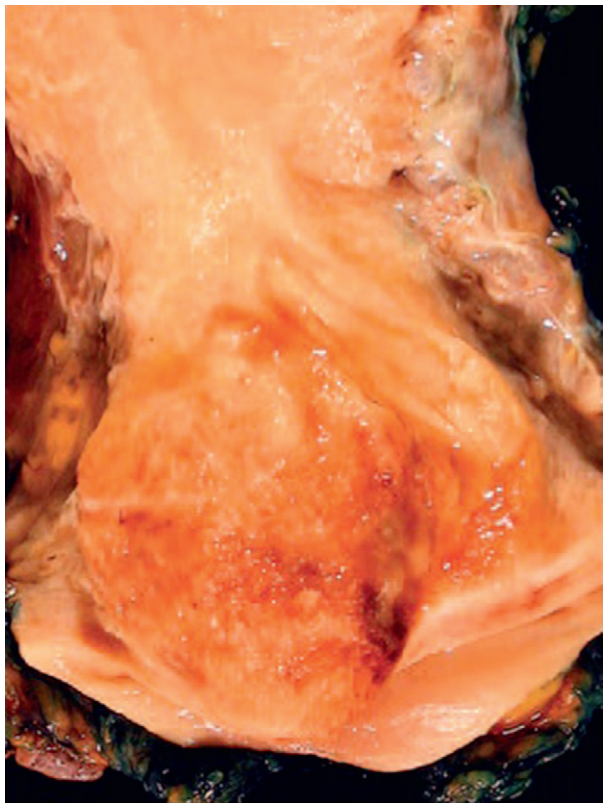


FIGURE 1

A small carcinoma forms a disc-shaped erosion at the squamocolumnar junction *(at left)*.

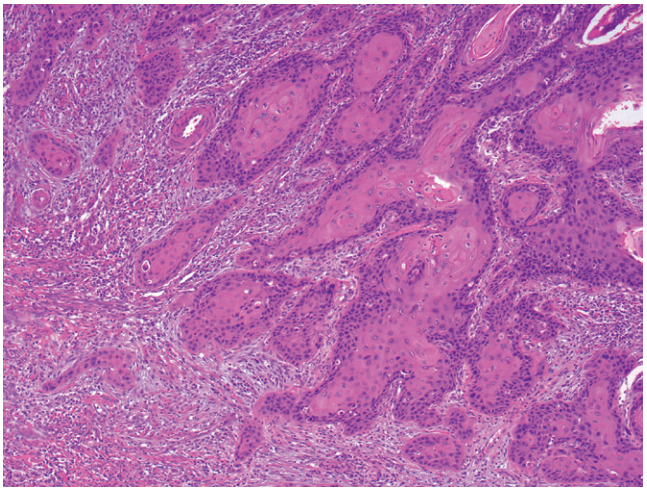


FIGURE 2

Large-cell keratinizing or well-differentiated cervical SCC. Note the prominent keratinization and mild atypia. This is a rare variant in the cervix as opposed to the vulva.

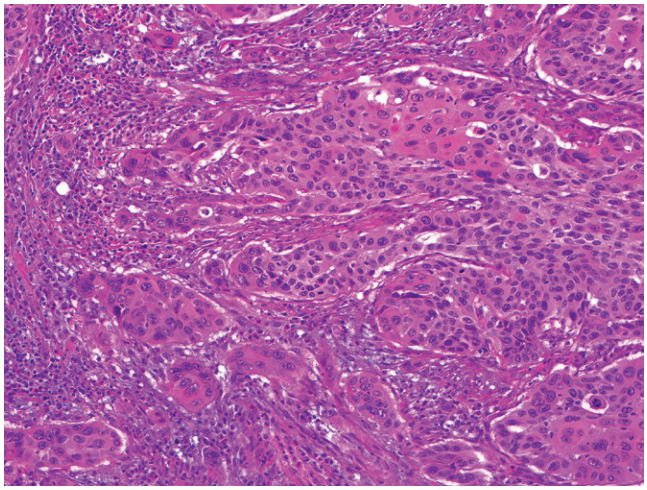


FIGURE 3

Large-cell nonkeratinizing or moderately differentiated SCC. This is by far the most common variant of cervical SCC. Keratinization is not conspicuous but can be present. Cells tend to be large and grow in sheets.

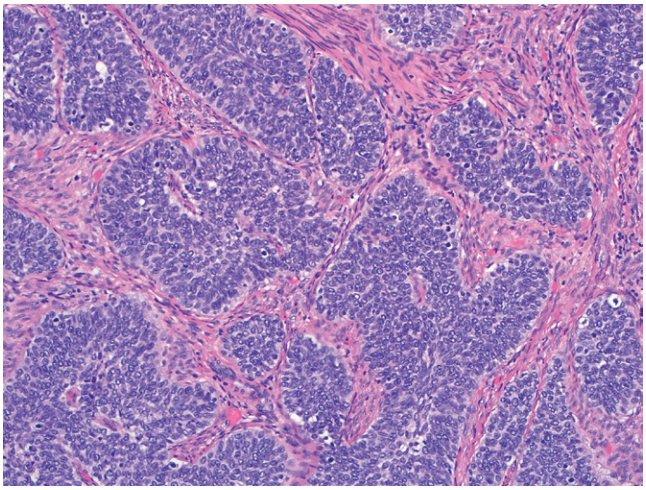


FIGURE 4

Small-cell nonkeratinizing or poorly differentiated SCC. Like the well-differentiated variant, this is relatively uncommon. Note the uniform sheetlike growth and preserved tumor cell cohesion.

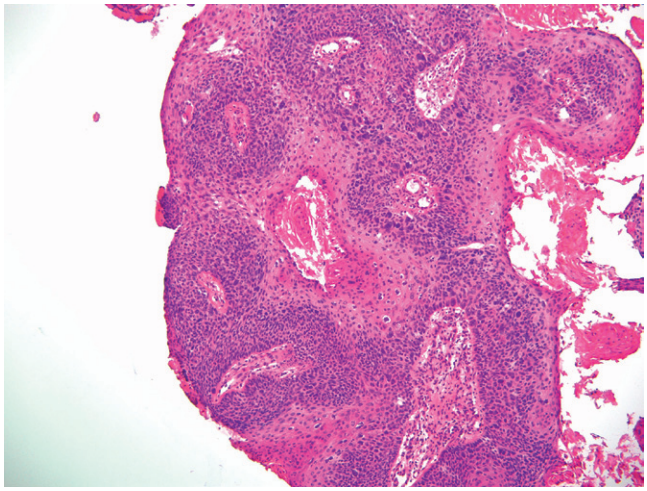


FIGURE 5

Papillary squamotransitional SCC. A typical presentation in curettings consists of poorly formed squamous neoplasia arranged in confluent papillae.

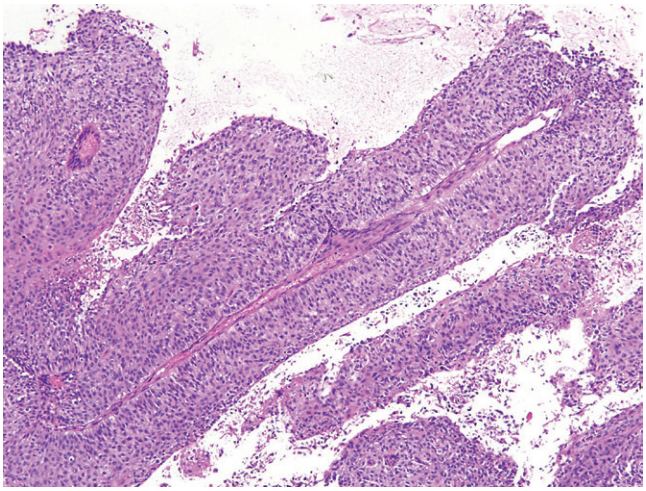


FIGURE 6

Papillary squamotransitional SCC. A particularly "transitional" appearance. Note that invasion cannot be assessed in this field.

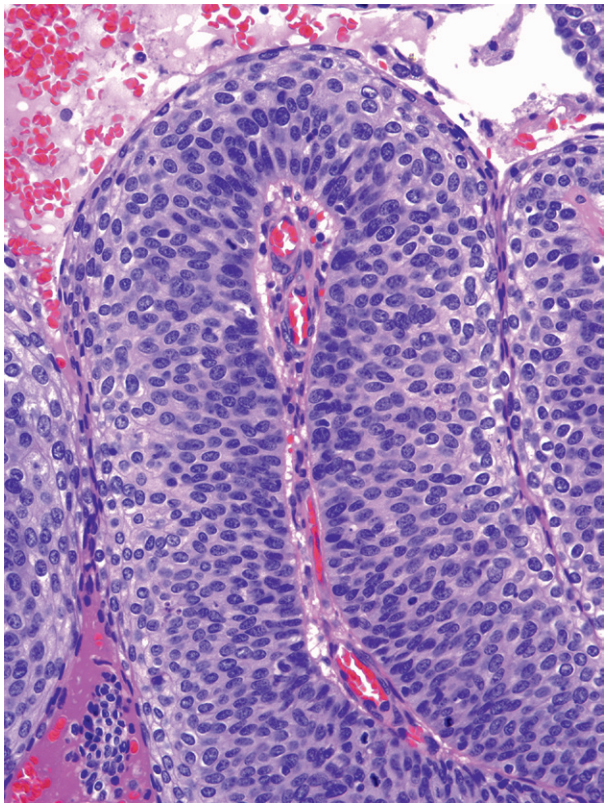


FIGURE 7

Papillary squamotransitional SCC. The lining cells show preserved polarity and cannot be distinguished from HSIL. The latter is excluded by confirming stromal invasion.

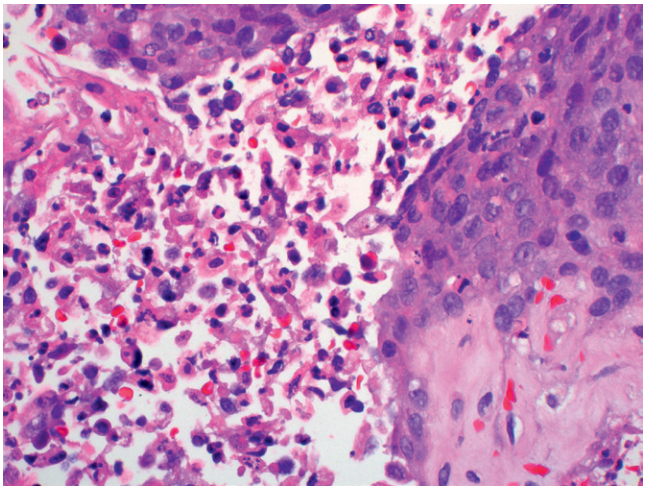


FIGURE 8

Exfoliated keratinized tumor cells from cervical SCC.

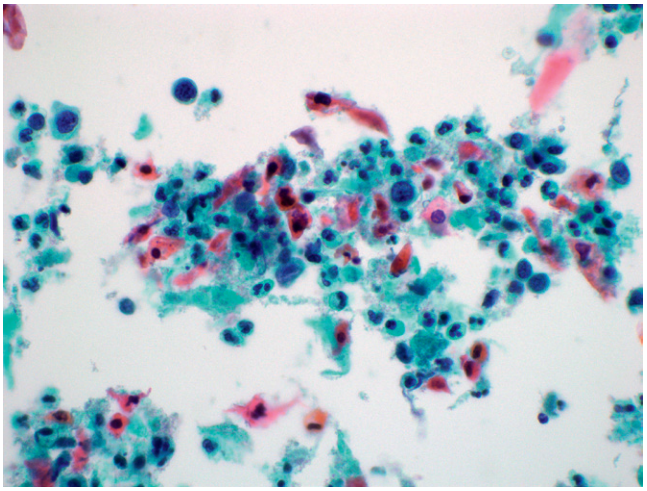


FIGURE 9

Pap smear showing cells identical to those in Figure 8 (same case).

PSEUDOCRYPT INVOLVEMENT BY SQUAMOUS CELL CARCINOMA

Definition—A specific pattern of invasive carcinoma that either mimics crypt involvement or combines crypt involvement with invasion, thus mimicking noninvasive carcinoma.

Clinical Features

Epidemiology

- The same as conventional invasive squamous carcinoma.

Presentation

- Typically encountered on examination of a cone biopsy for high-grade squamous intraepithelial lesion (HSIL).
- Patients may also present with a clinically identifiable mass lesion.

Prognosis and Treatment

- Similar to conventional carcinoma, and depends on lesion size, depth of invasion, and status of regional lymph nodes.

Pathology

Histology

- Tumor arranged in large discrete nests closely resembling crypt involvement.
- Cryptlike growths display irregular outlines and vary in caliber.
- Intense inflammatory response in adjacent stroma.
- Subtle irregularity in the epithelial-stromal interface with loss of polarity and/or budding invasion.
- Necrotic keratin debris in the centers of the pseudocrypts.
- Variable desmoplastic response in the adjacent stroma.

Immunopathology (Including Immunohistochemistry)

- Keratin immunostains might highlight the irregularity in the interface.

Main Differential Diagnosis

- Crypt involvement by HSIL. The presence of normal columnar epithelium is helpful but not necessary. Preserved epithelial polarity, minimal interface inflammation.
- Adenoid basal carcinoma of the cervix. The squamous component of this tumor can closely mimic crypt involvement and when seen alone the pathologist must both exclude crypt involvement and recognize the possibility that the tumor is an adenoid basal carcinoma, which has minimal risk of metastases.

Reporting Terminology

Typically classified as invasive squamous cell carcinoma. If the only invasion appears to be coming from a crypt, the pathologist should report two measurements: the distance of the invasive nest from the crypt and the distance of the invasion from the highest epithelial stromal interface.

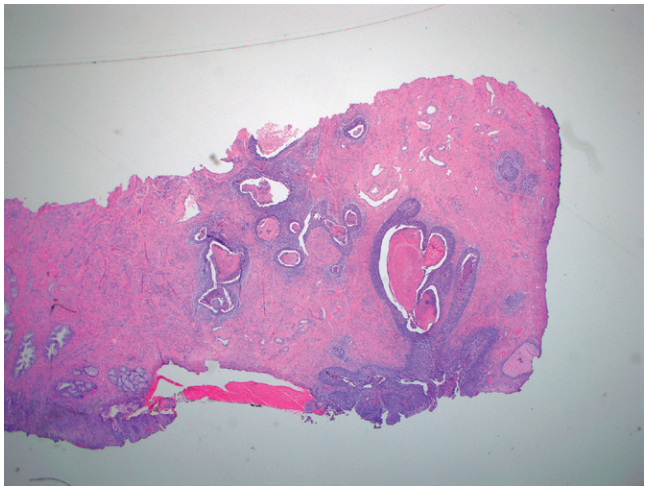


FIGURE 1

Pseudocrypt pattern of invasive squamous carcinoma. Note the irregular distribution of pseudocrypts with deep involvement.

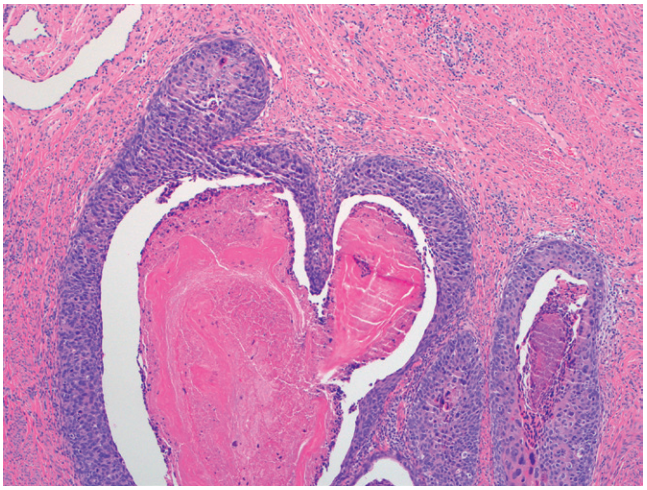


FIGURE 2

Pseudocrypt pattern of invasive squamous carcinoma. The irregular pattern on the left is characteristic of invasive carcinoma.

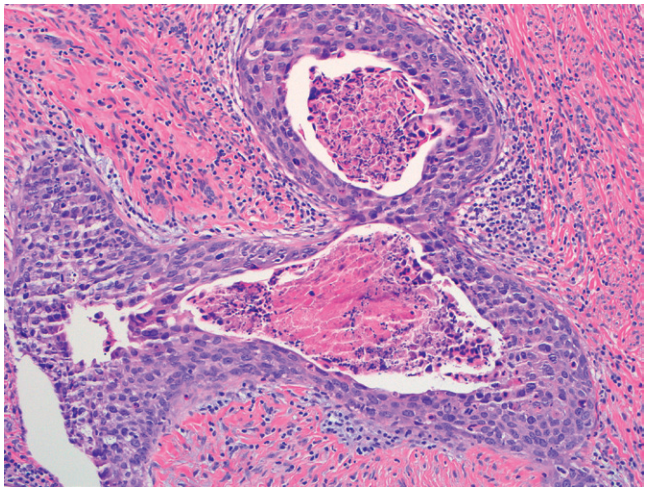


FIGURE 3

Pseudocrypt pattern of invasive squamous carcinoma. The "crypts" exhibit an anastomosing pattern not typical of normal crypt involvement.

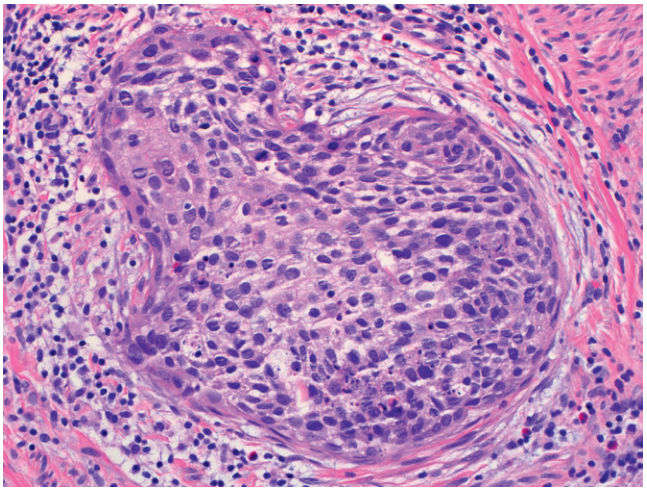
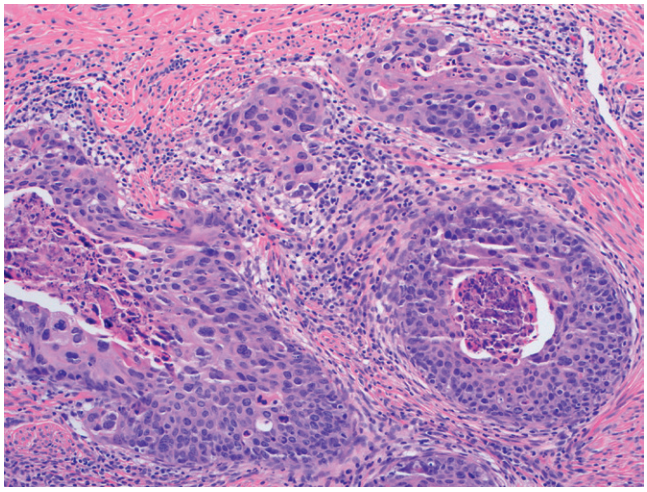


FIGURE 4

Pseudocrypt pattern of invasive squamous carcinoma. Note the desmoplastic response.



FIGURES 5

Pseudocrypt pattern of invasive squamous carcinoma. Here the irregular epithelial stromal interface and loss of polarity are obvious.

LYMPHOEPITHELIAL-LIKE SQUAMOUS CARCINOMA

Definition—A poorly differentiated nonkeratinizing squamous carcinoma with prominent lymphocytic infiltrates.

Clinical Features

Epidemiology

- A malignant cervical neoplasm.
- Most prevalent in the fourth to sixth decades of life.
- Human papillomavirus (HPV) testing of a few cases has been negative; thus its relationship to HPV is unclear.
- Unrelated to Epstein-Barr virus infection.

Presentation

- Patients may present with abnormal bloody or blood-tinged cervical discharge.
- Patients may be asymptomatic or present with signs and symptoms of lower genital tract or abdominal spread of tumor.
- Detected on Pap smear screening.

Prognosis and Treatment

- Treated as any cervical cancer, according to stage.
- Prognosis may be better than the typical squamous carcinoma, but there are too few cases in the literature to confirm this.

Pathology

Histology

- A hallmark of this tumor is ill-defined nests of epithelioid cells within a prominent inflammatory stroma.
- The infiltrate is predominantly lymphocytes with plasma cells and eosinophils.
- Morphologically resembles the nasopharyngeal tumor by the same name.

Immunopathology (Including Immunohistochemistry)

- LCA stains will discriminate the lymphoid from epithelial cells.
- Epithelial cells are strongly p63 and p16ink4 positive.

Main Differential Diagnosis

- Severe inflammatory changes or lymphoma in the cervix—p63 or keratin stains will highlight the epithelial cells.

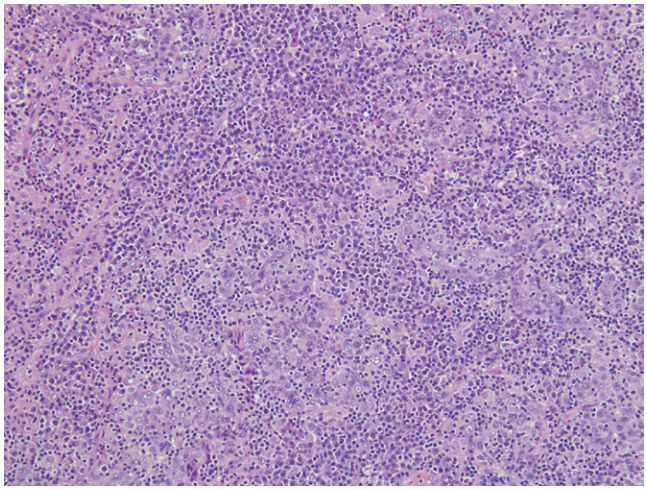


FIGURE 1

Lymphoepithelial-like cervical squamous carcinoma. At low power the ill-defined epithelial nests blend with the background lymphoplasmacytic infiltrate.

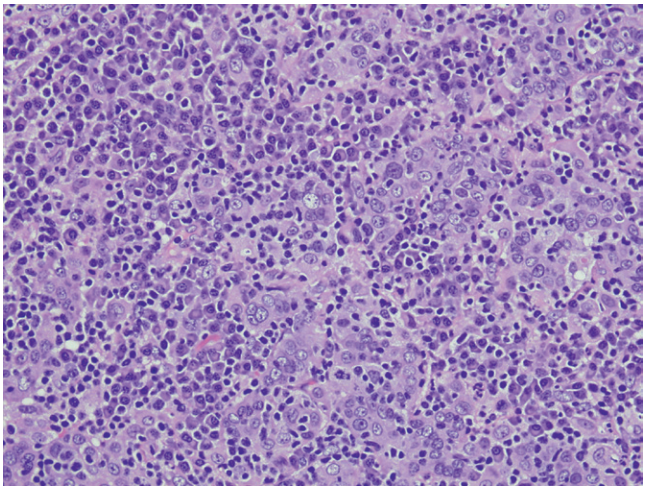


FIGURE 2

At higher magnification the epithelial cells are more easily distinguished.

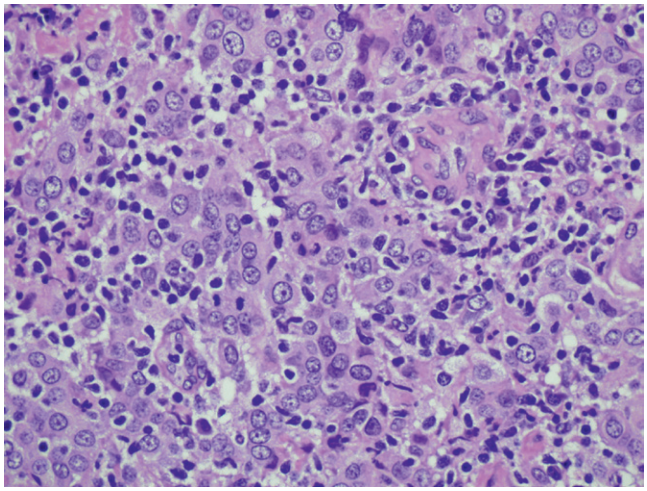


FIGURE 3

This field contains predominantly epithelial cells.

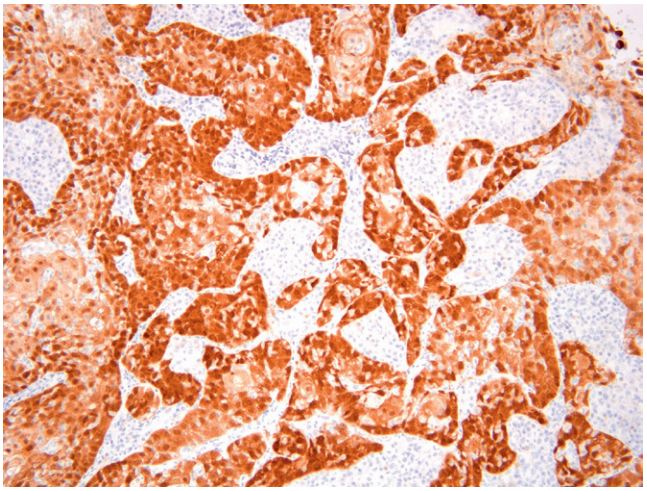


FIGURE 4

p16ink4 immunostaining is diffuse and strong in the epithelial tumor cells.

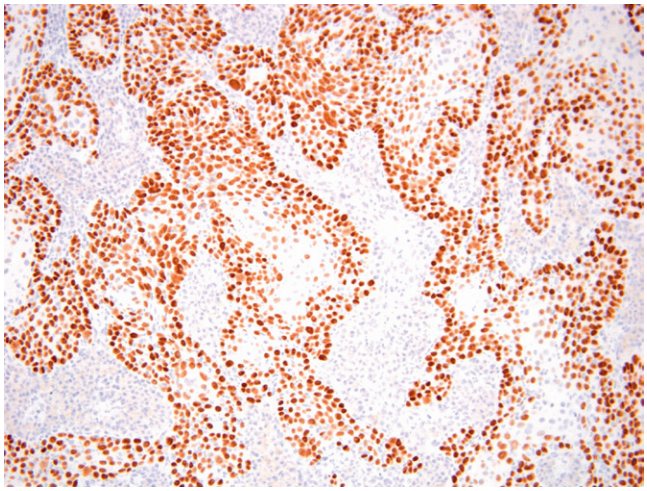


FIGURE 5

The tumor cells are strongly p63 positive, characteristic of a squamous carcinoma.

SUPERFICIAL (EARLY) ADENOCARCINOMA IN SITU

Definition—A subtle pattern of endocervical adenocarcinoma in situ (AIS) which is frequently mistaken for reactive epithelial change.

Clinical Features

Epidemiology

- Young women; mean age at diagnosis is early 20s.
- Human papillomavirus (HPV) associated.

Presentation

- Abnormal Pap.
- Incidental, diagnosed during workup for a squamous intraepithelial lesion (SIL).

Prognosis and Treatment

- Same as for conventional AIS.

Pathology

Histology

- At low power these lesions are present as discrete foci only in the superficial epithelium, making them easy to overlook.
- At high power they are characterized by nuclear hyperchromasia and stratification; mitotic activity and apoptosis are not as prominent as in conventional patterns of AIS.
- These discrete lesions lack the ciliated surface cells typical of benign endocervical epithelium.

Immunopathology (Including Immunohistochemistry)

- Positive for p16 (diffuse) and Ki-67 (diffuse).

Main Differential Diagnosis

- Reactive epithelial changes or tubal metaplasia. Either can appear discrete. The former can exhibit a high proliferative index but is p16 negative. Problematic cases of tubal metaplasia will stain heterogeneous with p16.

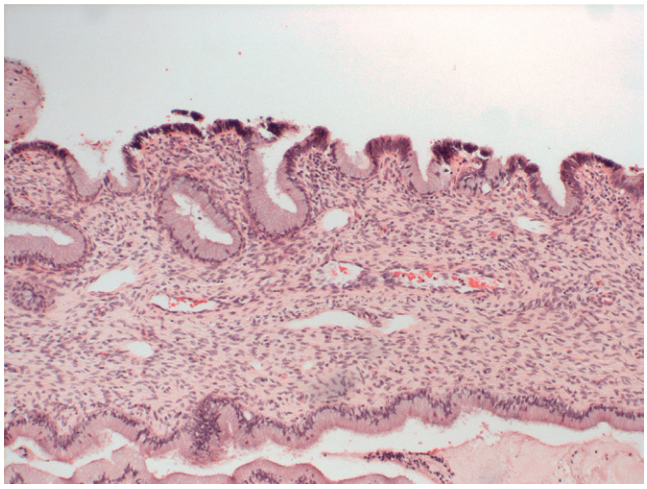


FIGURE 1

Superficial cervical AIS. At low power, foci of hyperchromatic glandular epithelial cells are present at the surface of the biopsy specimen. The cells deeper in the glands appear unremarkable.

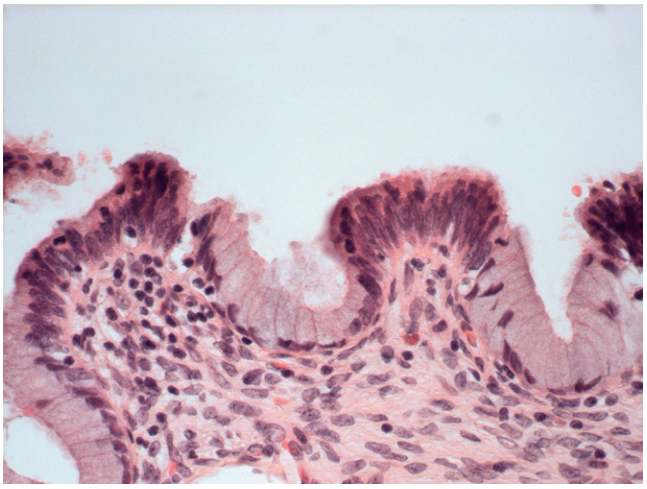


FIGURE 2

Superficial cervical AIS. Higher power of the lesion seen in Figure 1. The cells are stratified, are hyperchromatic, and lack the usual component of mucin. Apical mitoses are also present, although they are not prominent in this image.

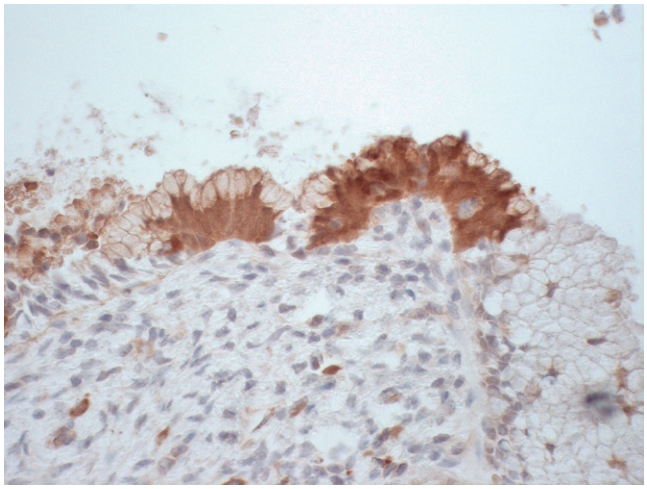


FIGURE 3

Superficial cervical AIS. p16 stain for the area seen in Figure 2. The hyperchromatic stratified cells are strongly and diffusely positive for p16. The bland-appearing epithelial cells are negative.

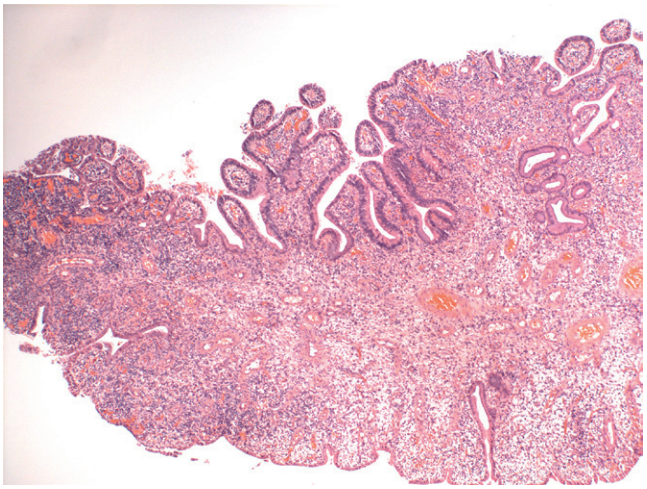


FIGURE 4

Superficial cervical AIS. In this endocervical polyp the AIS cells line the surface of the polyp on the superior half of the image. This can easily be mistaken for reactive change. The hyperchromatic-appearing cells are stratified, and apical mitoses can be identified.

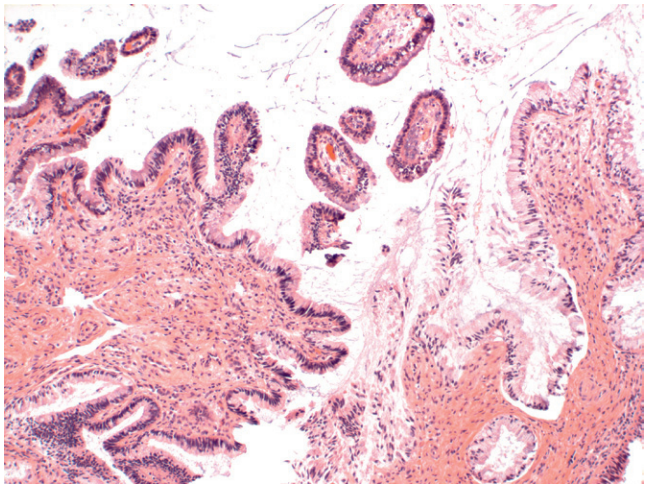


FIGURE 5

Superficial cervical AIS. AIS is seen on the left, in contrast to the normal endocervical cells on the right. Without the contrast, the cells on the left can easily be confused with a reactive process.

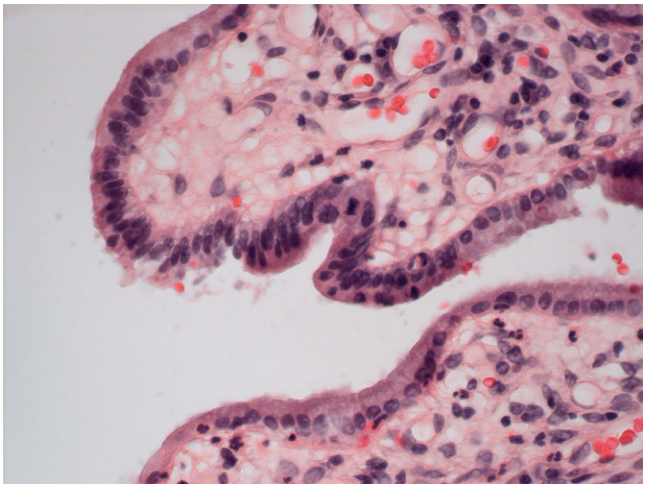


FIGURE 6

Superficial cervical AIS. In this subtle example the AIS cells are at the center and center-left. There is subtle nuclear stratification. A p16 stain was strongly positive in this area.

CONVENTIONAL ADENOCARCINOMA IN SITU

Definition—Precursor lesion to invasive endocervical adenocarcinoma.

Clinical Features

Epidemiology

- Average age at diagnosis is 38 years.
- Human papillomavirus (HPV) related (>90%), especially types 16 and 18 in roughly equal proportion.
- About half of cases have a concurrent squamous intraepithelial lesion (SIL).
- Positive association with oral contraceptive use, although a potential mechanism is unclear.

Presentation

- Abnormal Pap smear (atypical glandular cells of undetermined significance [AGUS]), although Pap smears have an overall low sensitivity for glandular lesions.
- Abnormal examination at the time of colposcopy in 75% of cases.
- Often diagnosed concurrently with an in situ squamous lesion at the time of colposcopy for a cytologic diagnosis of SIL.

Prognosis and Treatment

- Cervical cone biopsy (usually cold knife cone) is the standard treatment.
- Up to 45% of patients with negative margins at the time of cone biopsy have residual or recurrent disease at subsequent hysterectomy.
- Other studies have reported that 13% of patients with negative margins at the time of cone biopsy go on to develop recurrent adenocarcinoma in situ (AIS), and rarely, invasive adenocarcinoma.
- Rare variants are associated with endometrial, tubal, or ovarian involvement. These tend to be extensive lesions that may spread by direct extension to other locations in the reproductive tract. However, they seem to have a good prognosis.

Pathology

Histology

- At low power, AIS is usually near the squamocolumnar junction but can be found more deeply situated in the endocervix.
- The diagnostic criteria include the presence of epithelial cell crowding (nuclear stratification, tufting), moderate hyperchromasia, and mitotic figures.
- Other features that may aid in diagnosis include apoptotic bodies, which are found in the basal epithelium in 70% of cases, and architectural changes such as cribriforming, or papillae.
- Luminal eosinophilia with suspended mitoses is also a feature, albeit somewhat nonspecific.
- Architectural abnormalities may be florid, but this feature alone does not warrant a diagnosis of invasive adenocarcinoma, even in the presence of surrounding inflammation.
- Histologic variants (often present with conventional AIS) include:

  Endometrioid AIS, which is characterized by marked nuclear stratification and minimal amounts of cytoplasm, and therefore bears a resemblance to endometrial epithelium.

  Unusual variants, including intestinal or gastric (pyloric) AIS and stratified AIS, are discussed in other chapters.

  Tubal AIS is exceedingly rare; diagnostic features of AIS must be unequivocal as the vast majority of ciliated lesions in the cervix are benign.

- If seen on a cytologic preparation, AIS presents as clusters of hyperchromatic cells with the following features suggestive of glandular differentiation: (1) columnar cells with basally oriented nuclei and pale cytoplasm, (2) cellular feathering or radial projection of the nuclei around the periphery of the cellular clusters, and (3) glandlike structures or rosettes.

Immunopathology (Including Immunohistochemistry)

- Positive for p16 (diffuse) and Ki-67 (usually exceeding 50% of neoplastic cell nuclei).

Main Differential Diagnosis

- Reactive epithelial changes (tubal metaplasia, Arias-Stella reaction, cervicitis)—these may have a high proliferative index but will exhibit patchy p16 immunostaining.
- Early invasive endocervical adenocarcinoma. Florid variants of AIS may be difficult to distinguish from invasion but have an excellent prognosis.

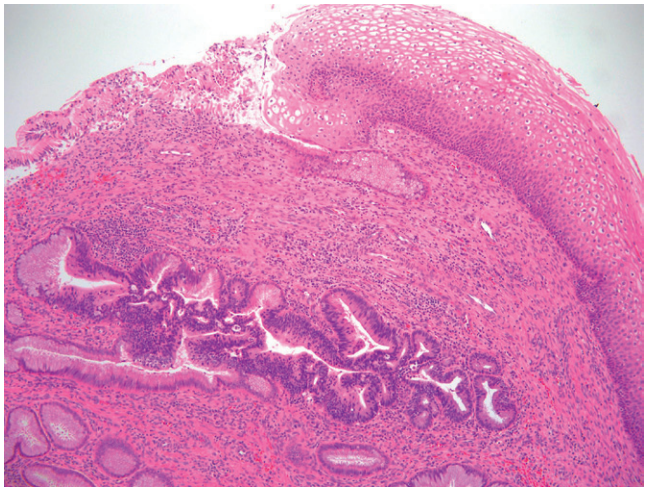


FIGURE 1

Conventional AIS. Low-power examination shows a hyperchromatic population of glandular cells in the transition zone of the cervix. Squamous epithelium is to the right and benign glandular epithelium to the left.

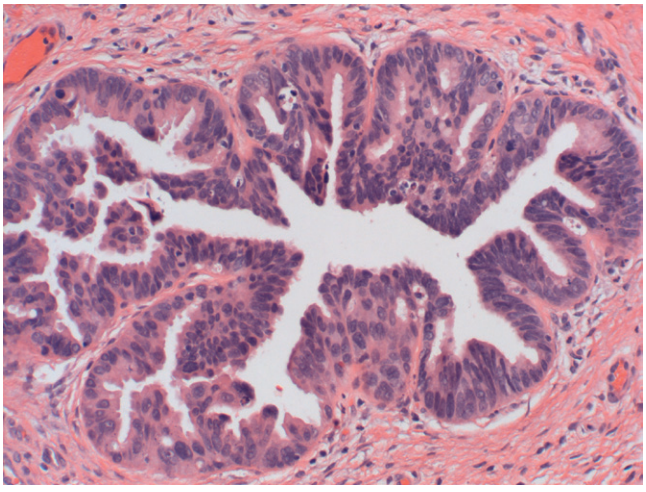


FIGURE 3

Conventional AIS. In addition to nuclear stratification and "tufting," the cells in this example of AIS show a prominent papillary and micropapillary growth pattern.

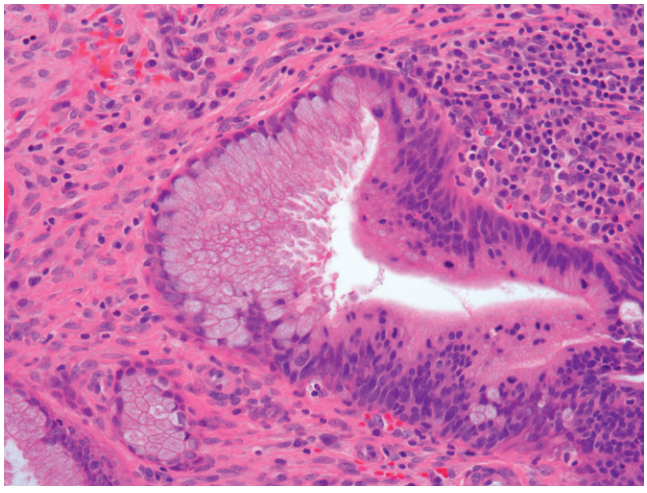


FIGURE 2

Conventional AIS. High-power examination reveals pseudostratified glandular epithelial cells with apical mitoses. These changes are seen in contrast to the background benign endocervical epithelium on the left, which has basally positioned nuclei with abundant mucinous cytoplasm.

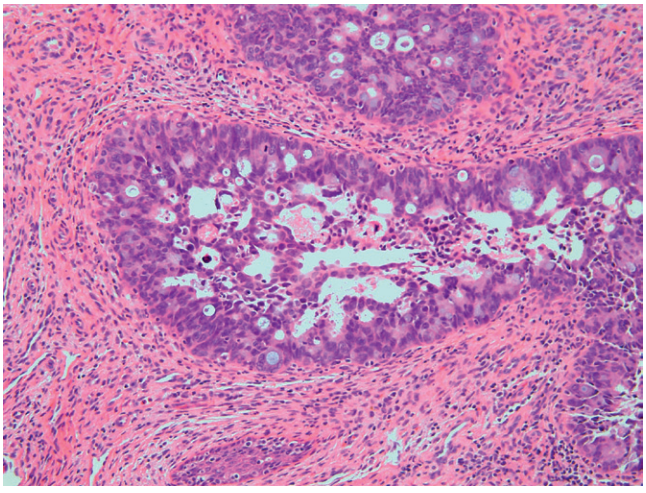


FIGURE 4

Conventional AIS. In this example the nuclear stratification is somewhat obscured by the microacinar growth pattern of the cells.

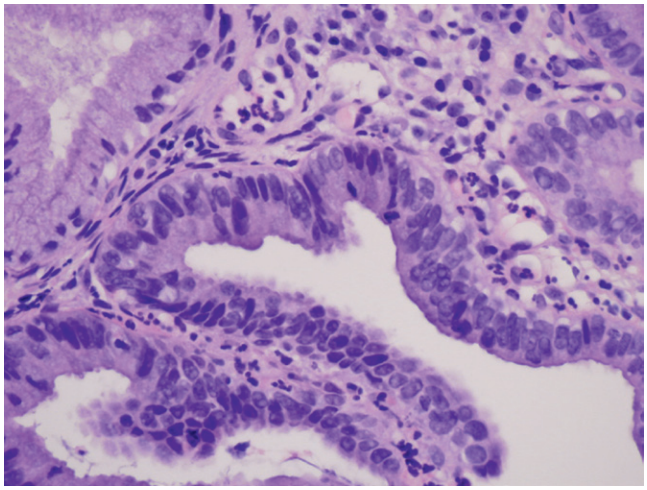


FIGURE 5

Conventional AIS. There is subtle nuclear stratification and rare apical mitoses in this example, but the changes contrast to normal epithelium in the upper left.

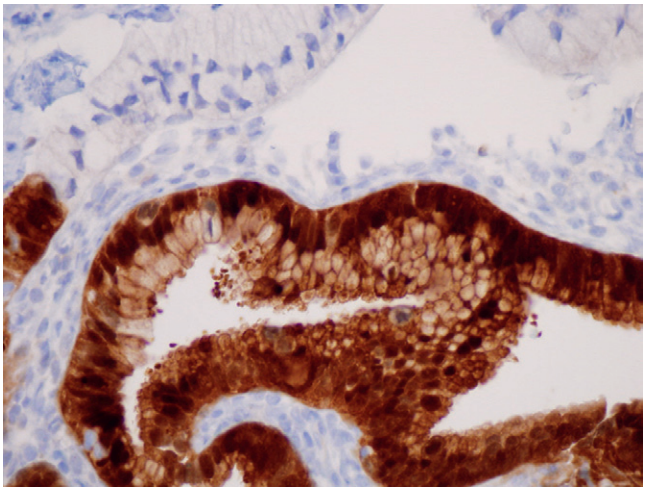


FIGURE 6

Conventional AIS. The corresponding p16 immunohistochemical stain for the biopsy seen in Figure 5. The atypical appearing endocervical cells are diffusely positive (nuclear and cytoplasmic) for p16. The background normal epithelium is entirely negative.

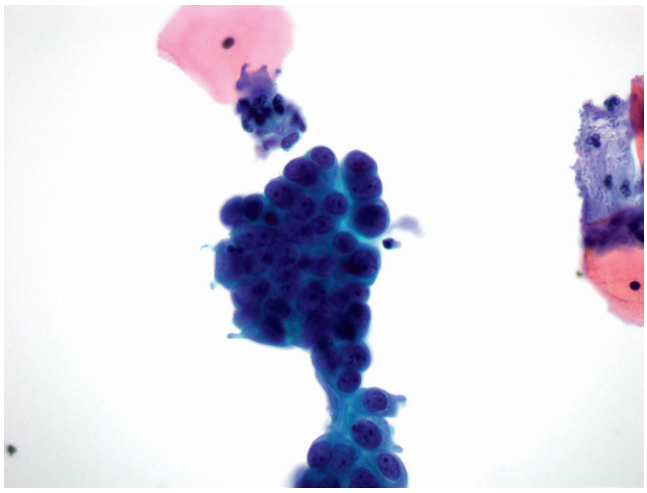


FIGURE 7

AIS on a Pap smear. A hyperchromatic cluster of atypical glandular cells is present.

STRATIFIED ADENOCARCINOMA IN SITU

Definition—A stratified mucin-producing intraepithelial lesion with prominent columnar cell differentiation (also called stratified adenocarcinoma in situ [AIS]).

Clinical Features

Epidemiology

- Young women, most ranging in age from 20 to 40 years.
- High-risk human papillomavirus (HPV) associated.

Presentation

- Abnormal Pap, atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells of undetermined significance (AGUS), AIS, and high-grade squamous intraepithelial lesion (HSIL).
- Diagnosed during workup for a squamous intraepithelial lesion (SIL).

Prognosis and Treatment

- Same as for conventional AIS.
- Some of these lesions are associated with invasion. The latter might occur more frequently in these precursors relative to conventional HSIL.

Pathology

Histology

- These are high-grade intraepithelial lesions with prominent columnar differentiation. They are emblematic of the bridge between squamous and columnar differentiation and are sometimes classified as adenosquamous carcinomas in situ.
- Some may have basal cells with prominent squamous features blending with superficial columnar cell differentiation with mucin-containing vacuoles in the middle or superficial epithelial layers (i.e., HSIL with columnar differentiation).
- Many do not contain conspicuous basal squamous cells and are composed entirely of cells with mucin vacuoles, the latter in a honeycomb arrangement throughout the epithelium. These are aptly termed stratified adenocarcinomas in situ.

Immunopathology (Including Immunohistochemistry)

- Positive for p16 (diffuse) and Ki-67 (diffuse); mucin stains are positive in at least the mid to upper layers. Importantly, all layers, including mucin positive cells, are p16 positive.

Main Differential Diagnosis

- Low-grade squamous intraepithelial lesion (LSIL) or mild metaplastic atypia with columnar differentiation—the nuclear density is lower and the lesion more closely resembles a benign metaplasia with mucin vacuoles. Low proliferative index, but a diffusely positive p16 staining distribution.
- Metaplastic HSIL—these lesions can have a slight columnar appearance since they may occupy crypts and undermine normal columnar cells.

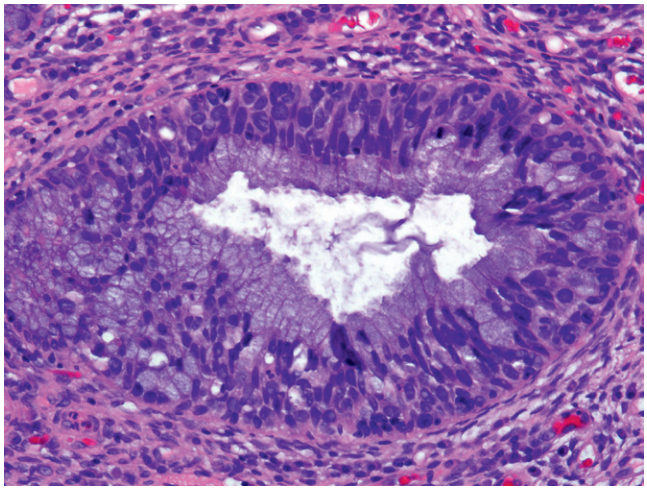


FIGURE 1

HSIL with superficial columnar differentiation. This lesion undergoes a transition from a basal squamous phenotype to columnar differentiation on the surface.

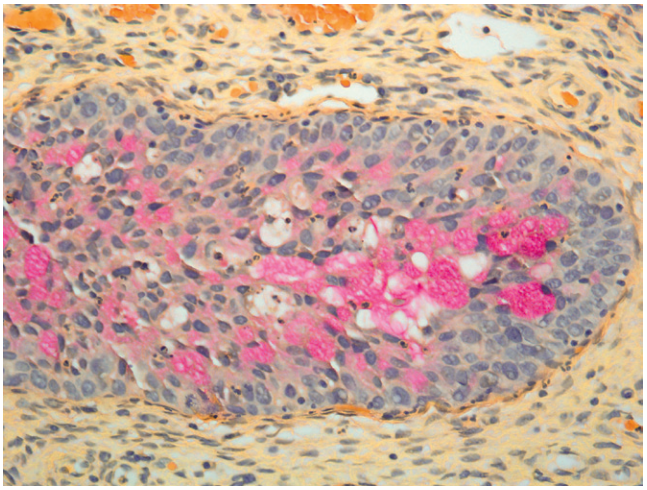


FIGURE 2

The case in Figure 1 displays superficial mucin positivity only.

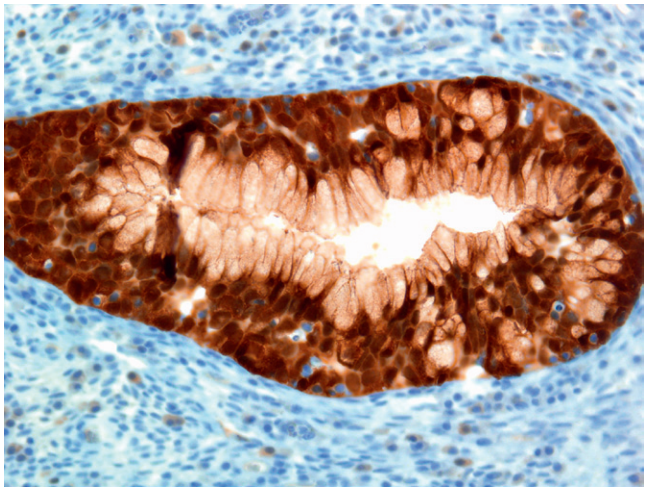


FIGURE 3

The case in Figure 1 contains diffuse p16 staining, in keeping with the fact that the entire process, including the columnar differentiation, is neoplastic.

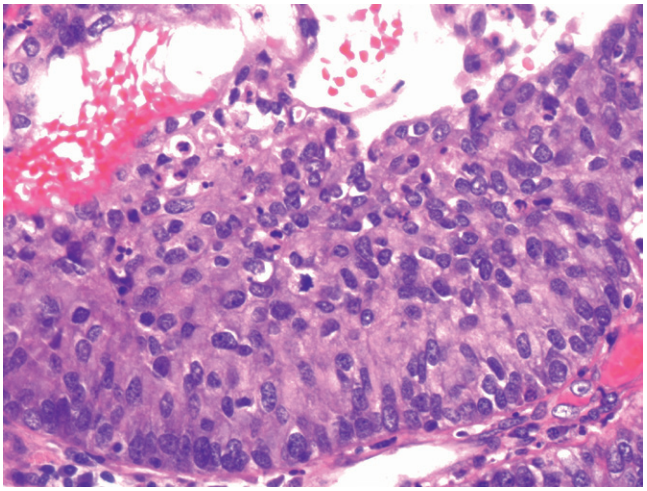


FIGURE 4

Stratified adenocarcinoma in situ. Note the vacuoles extend to the basal cells. There is no evidence of squamous differentiation.

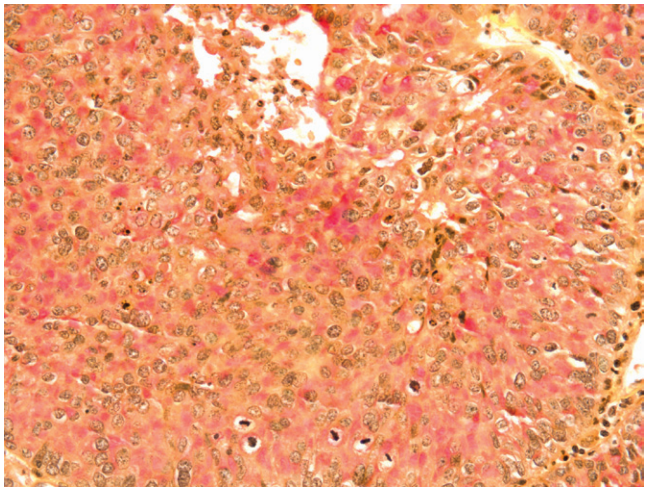


FIGURE 5

The biopsy specimen from the case in Figure 4 is diffusely positive for mucin, signifying scant if any squamous differentiation.

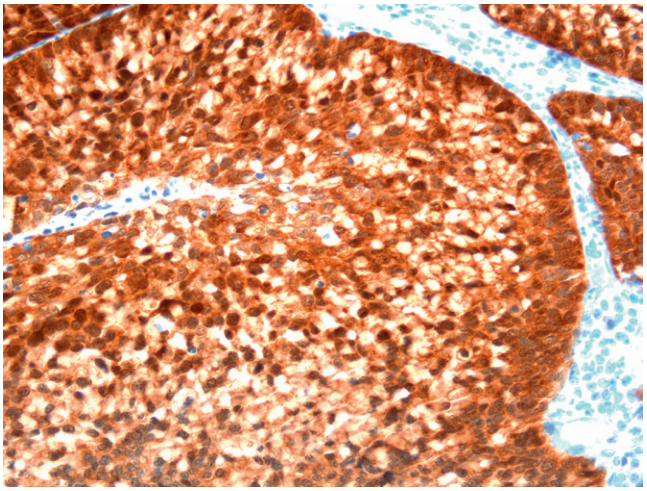


FIGURE 6

Like the prior case (Figures 1-3), the p16 staining is diffuse, underscoring the neoplastic character of the columnar differentiation.

INTESTINAL VARIANT OF ADENOCARCINOMA IN SITU

Brooke E. Howitt, MD

Definition—A distinct subset of adenocarcinoma in situ (AIS) with intestinal differentiation.

Clinical Features

Epidemiology

- Average age at diagnosis is 45 years (about 10 years older than conventional AIS).
- Human papillomavirus (HPV) detected in approximately 66%.

Presentation

- Detected by an abnormal cervical cytology.

Prognosis and Treatment

- Standard therapy is cone biopsy or loop electrosurgical excision procedure (LEEP) if preservation of fertility is desired.
- Hysterectomy is recommended if not, due to the potential risk of multifocal disease or risk of recurrence despite negative margins.

Pathology

Histology

- The lesion histology is punctuated by features of conventional AIS, such as hyperchromasia, apoptosis, and increased mitotic activity.
- Prominent cytoplasmic vacuoles are typical of goblet cell intestinal differentiation.

Immunopathology (Including Immunohistochemistry)

- p16—will stain a proportion of these lesions strongly, but may be weak or unremarkable.
- Ki-67—staining index is usually over 50% in conventional AIS but may be less conspicuous in the intestinal variant.
- HPV testing—may be negative in up to one third of cases.

Main Differential Diagnosis

- Goblet cell differentiation, even in the absence of atypia, should prompt a search for ACIS.
- Gastric differentiation should also be distinguished, and is associated with lobular hyperplasias and rarely minimal deviation adenocarcinomas.

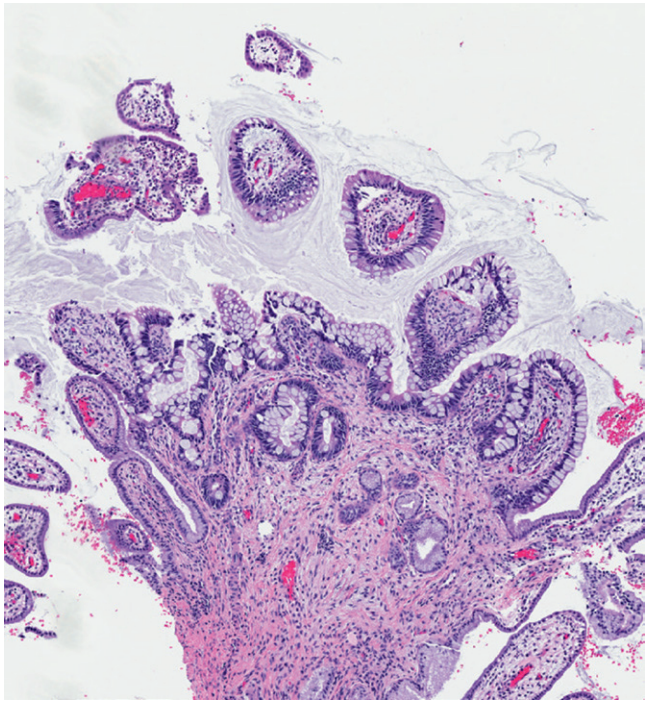


FIGURE 1

Intestinal AIS of the cervix. Note the normal mucosa at the far right and left. The center of the image is punctuated by hyperchromatic columnar epithelium with prominent vacuoles.

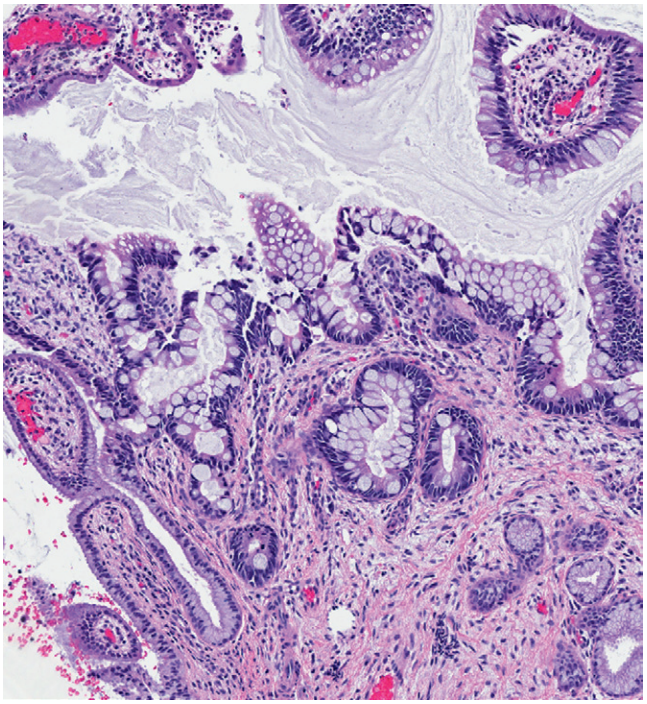


FIGURE 2

Intestinal AIS. Note the sharp transition from normal to neoplastic epithelium.

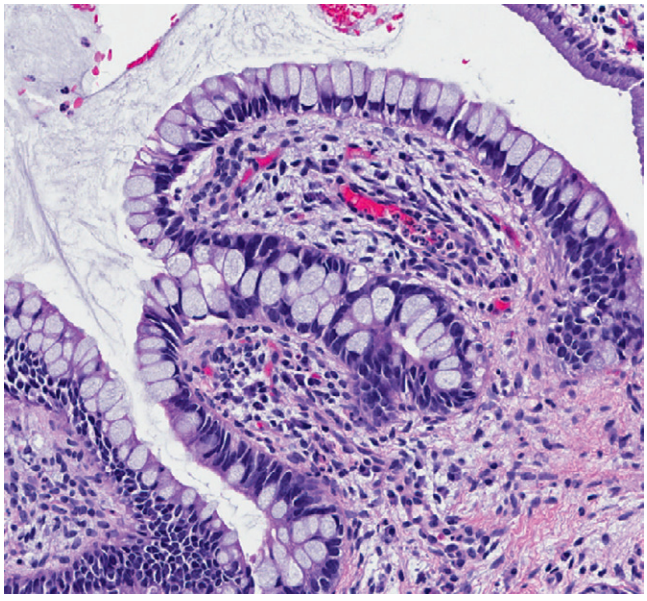


FIGURE 3

Intestinal AIS. At high magnification this field demonstrates uninterrupted goblet cells.

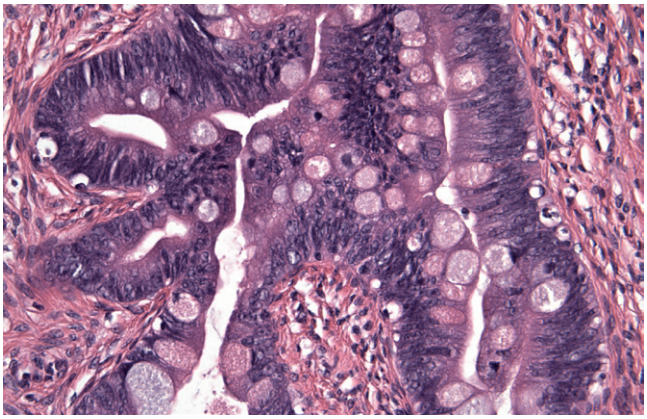


FIGURE 4

Intestinal AIS. Numerous apoptotic bodies are seen near the base of the epithelium. Mitoses are not conspicuous and are not a critical parameter for the diagnosis.

CERVICAL ENDOMETRIOSIS

Definition—Ectopic endometrial glands and stroma (endometriosis) or endometrial stroma in isolation (stromatosis).

Clinical Features

Epidemiology

- Endometriosis is common.
- Seen across all ages and demographic groups.
- Often follows punch or cone biopsy presumably because endometrial tissue colonizes the exposed stroma.

Presentation

- In reproductive-age women, fluctuations in hormone levels lead to symptoms such as pain or abnormal bleeding.
- Many patients are asymptomatic.
- Pap smears may detect glandular cells.
- Pigmented lesion on the cervix.

Prognosis and Treatment

- The prognosis is favorable, and generally, no treatment is needed.
- Severe cases of endometriosis may require surgery or hormonal therapy.
- Rare cases of endometrioid carcinoma arising in endometriosis have been known to occur.

Pathology

Histology

- Well-developed examples are similar to endometriosis at other sites and have both endometrial glands and stroma, often with evidence of old bleeding in the form of hemosiderin deposition.
- The endometrial stromal component may be attenuated or blend imperceptibly with cervical stroma.
- Occasional cases may consist solely of endometrial glands closely apposed to cervical stroma.
- In cases with little to no stroma, care must be taken to distinguish the glands from those seen in endocervical adenocarcinoma in situ (AIS), as both display stratified nuclei and mitotic activity.
- Endometriotic glands are uniformly spaced and have less nuclear hyperchromasia and pleomorphism than their AIS counterparts.
- The presence of old hemorrhage is helpful in cases of endometriosis.
- Following cone biopsy, squamous overgrowth may occur.

Immunopathology (Including Immunohistochemistry)

- CD10 can stain endometrial stroma.
- Reticulin stains endometrial stroma in a pericellular fashion.
- Endometrial stroma is red on a trichrome stain, whereas cervical stroma is blue (due to the higher levels of collagen in the cervical stroma).
- Endometrioid glands stain positive for ER and heterogeneous for p16.

Main Differential Diagnosis

- Cervical adenocarcinoma, endometrioid type—intense p16 staining.
- Cervical AIS—this can be excluded if the pathologist is reasonably familiar with endometrioid gland histology. AISs have hyperchromatic glands, mucin production, suspended mitoses, and often a rather dense eosinophilic apical cytoplasm. Atypia alone is less helpful, since tubal metaplasia often exhibits a pleomorphic appearance due to the mixture of ciliated and nonciliated cells. p16 staining will also be intense.
- Metastatic low-grade endometrial endometrioid adenocarcinoma—two mimics including superficially situated "drop metastases" and mesonephric-like metastases from endometrial adenocarcinomas can pose a diagnostic problem (discussed elsewhere). However, neither matches the morphology of normal endometrial glands, which typify endometriosis, even in the absence of stroma.

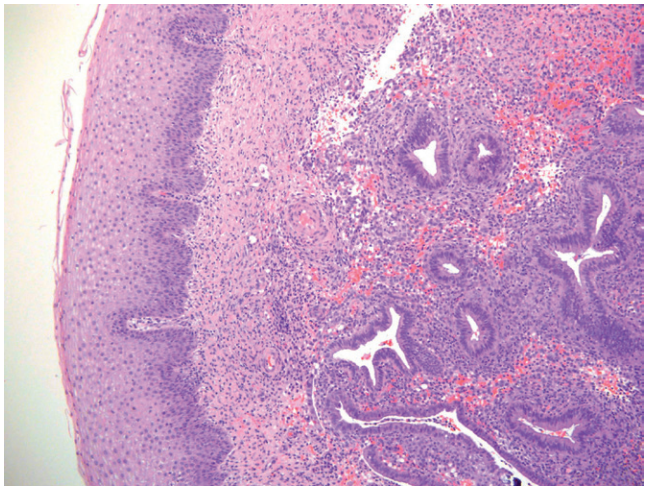


FIGURE 1

Cervical endometriosis. Low power reveals the presence of endometrioid glands and stroma centered in the cervical stroma, deep to the ectocervical squamous epithelium. The background cervical stroma is pink, with small spindled cells. The endometrioid stroma is darker, with larger spindled to ovoid nuclei. There is some evidence of recent hemorrhage, which is likely just procedural.

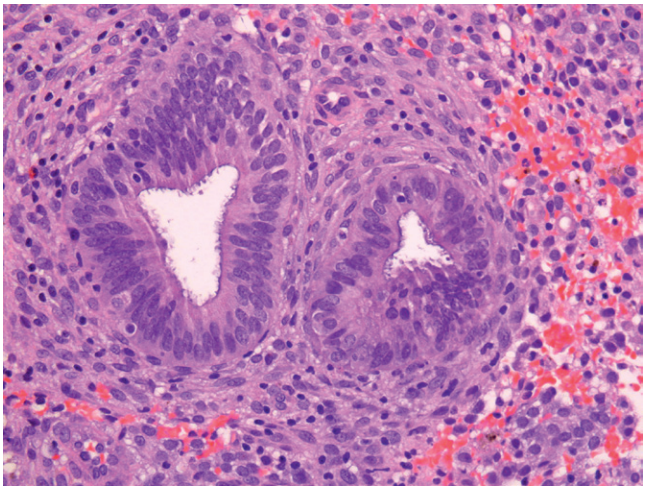


FIGURE 2

Cervical endometriosis. Higher-power examination reveals glands with typical endometrioid histology with large elongated stratified nuclei. The endometrioid stroma is loose, with large plump nuclei and scattered mononuclear lymphocytes. Mitoses in the epithelium and stroma are often identified. Rare clusters of pigment consistent with hemosiderin are present in this example.

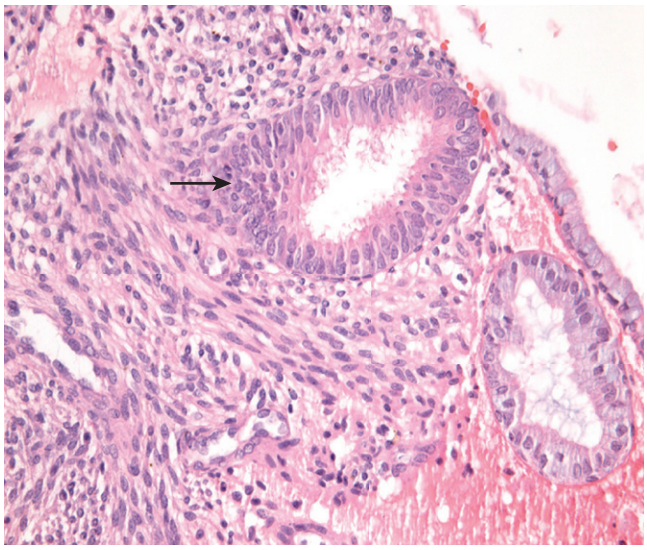


FIGURE 3

A focus of stroma-poor endometriosis (or tubal-endometrioid metaplasia). A mitotic figure is present *(arrow)*.

PREGNANCY-RELATED CHANGES IN THE CERVIX

Definition—Hormonally driven benign morphologic alteration of the endocervical epithelium, most commonly associated with pregnancy or the recent postpartum state.

Clinical Features

Epidemiology

- Endocervical Arias-Stella effect may be seen in up to 50% of extensively examined gravid cervices.
- Occasionally a rare, focal finding in nonpregnant women.

Presentation

- Incidental finding at the time of cervical sampling.

Prognosis and Treatment

- Excellent; no treatment is required.

Pathology

Histology

- Cells with Arias-Stella effect exhibit marked cytomegaly and protrude into lumina in a striking tufted or hobnail pattern.
- The cytoplasm is abundant, is eosinophilic to clear, and occasionally has extensive basal vacuole formation.
- Eosinophilic inclusions may be noted.
- Nuclear changes are variable and include atypia with smudged, vacuolated, or clear nuclei.
- Mitotic figures are very rare.
- The extent of these changes is variable and may involve all the glands within a given specimen, a single gland, or a portion of one gland.
- A generally unreported consequence of pregnancy is basal vacuoles seen as discrete round vacuoles at the epithelial-stromal interface. This is not of clinical importance but is distinctly pregnancy related.

Immunopathology (Including Immunohistochemistry)

- Ki-67 labeling index is low.
- p16 and p53 stains may be positive but are usually patchy.

Main Differential Diagnosis

- Clear-cell adenocarcinoma—this usually presents as an expansile lesion and a slightly higher N/C ratio.
- Endocervical adenocarcinoma in situ (both conventional and intestinal types)—these typically exhibit more complex architecture and are readily distinguished by the strong p16 immunostaining.
- Intramucosal metastases from an endometrial or upper genital tract high-grade serous carcinoma—this can occur but typically the nuclear-to-cytoplasmic (N/C) ratio is higher, and the cells are strongly p53 positive.
- Radiation effect—this can also cause nuclear atypia with an Arias-Stella effect–like appearance. The cells will usually exhibit degenerative changes with smudged or ground-glass chromatin and a lower N/C ratio.

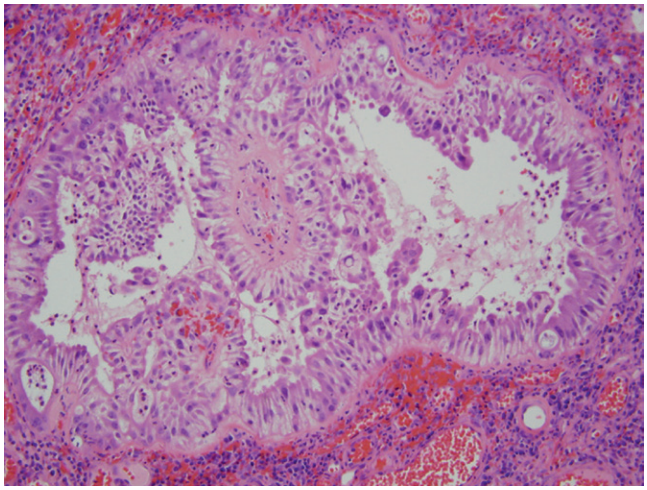


FIGURE 1

Hypersecretory changes in the cervical columnar epithelium in pregnancy. This is not technically Arias-Stella effect but is an accentuation of secretory activity with basal vacuoles, also a feature of pregnancy.

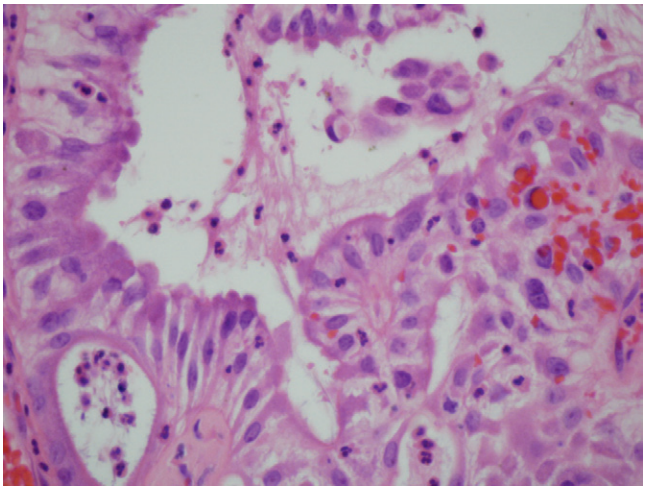


FIGURE 2

Hypersecretory changes in the cervical columnar epithelium in pregnancy. At higher magnification these vacuoles span the entire length of the cell.

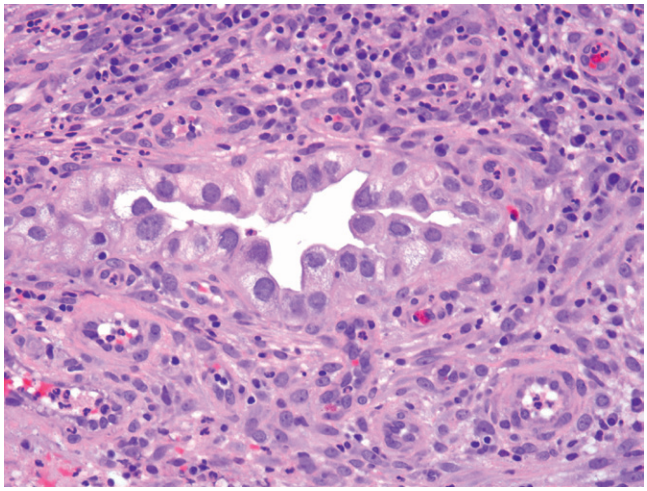


FIGURE 3

Cervical Arias-Stella effect. This crypt shows the characteristic single layer of epithelial cells with nuclear enlargement and cytoplasmic vacuoles.

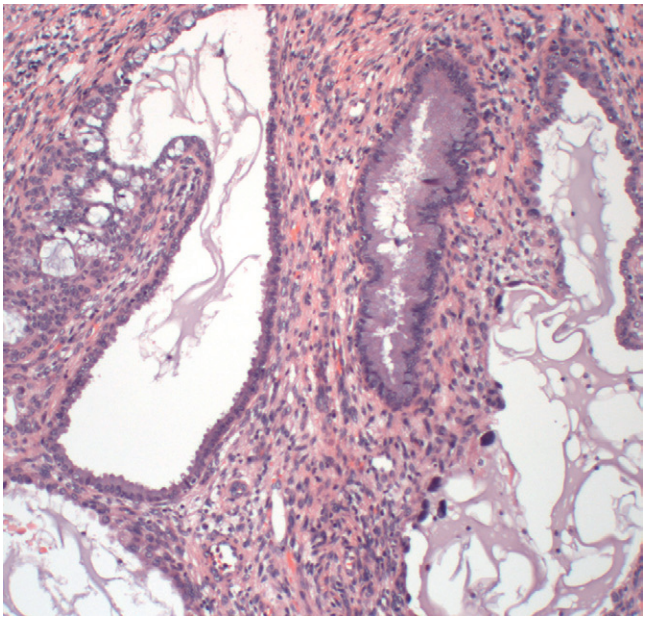


FIGURE 4

Arias-Stella effect in a cervical polyp. Note the hyperchromatic nuclei lining the crypt at the lower right of the image.

REACTIVE ATYPIAS IN THE ENDOCERVIX

Definition—A multinucleated endocervical cell atypia commonly associated with chronic inflammation.

Clinical Features

Epidemiology

- Relatively common, occasionally pronounced.
- Typically reproductive age, but can occur at any age.

Presentation

- Incidental finding.

Prognosis and Treatment

- Not pathologic.

Pathology

Histology

- Typically, multinucleated endocervical cells with ground-glass or amphophilic cytoplasm.
- Some cases are not multinucleated and will simply display hyperchromatic nuclei with variable enlargement.
- Homogeneous chromatin.
- Usually intermittent, but can be focally prominent.

Immunopathology (Including Immunohistochemistry)

- Noncontributory except if excluding viral inclusions.

Main Differential Diagnosis

- Viral inclusions—denser and characteristic of cytomegalovirus (CMV) or herpes simplex virus (HSV). Usually not as polynucleated.
- Adenocarcinoma in situ—these are usually not polynucleated but rarely can be in which case the other features of adenocarcinoma in situ will be appreciated.
- Arias-Stella effect—usually not polynucleated and exhibits a denser hyperchromatic nucleus.

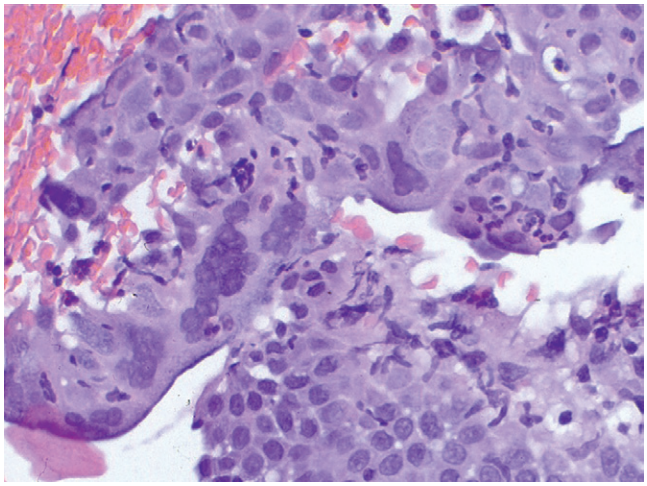


FIGURE 1

Classic reactive endocervical cell atypia with multinucleation and amphophilic cytoplasm.

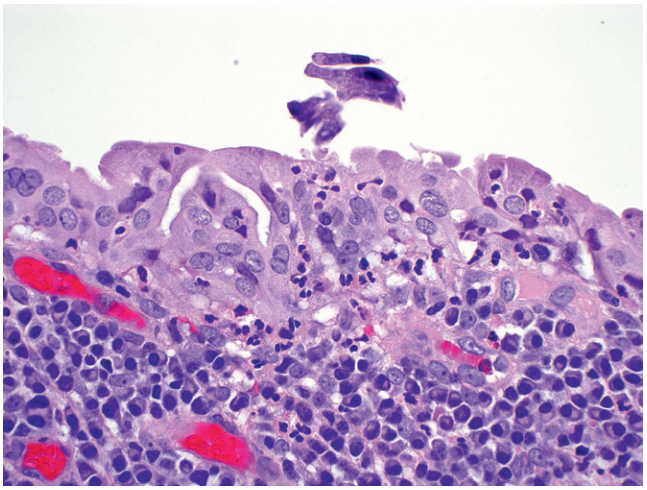


FIGURE 2

Another example of endocervical cell atypia overlying granulation tissue. Note the similarity to Figure 1, although there is less multinucleation.

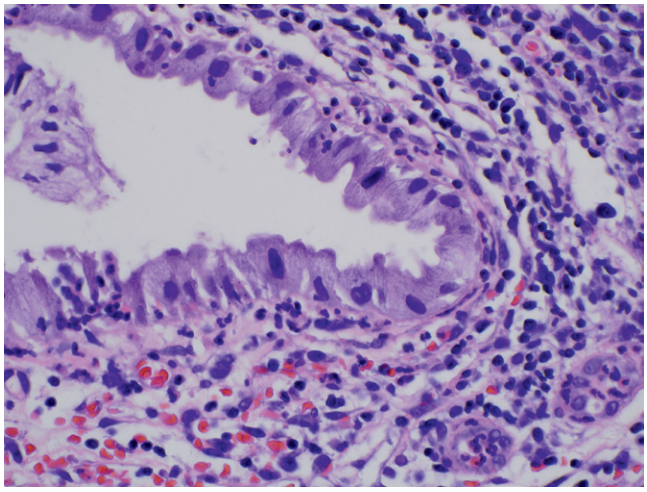


FIGURE 3

Focal reactive atypia in endocervical crypts manifesting as nuclear hyperchromasia only.

RADIATION ATYPIAS

Definition—Changes seen in the cervical-vaginal epithelium following radiation therapy.

Clinical Features

Epidemiology

- A common finding in tissue samples following radiation therapy to the genital area.

Presentation

- Often seen in conjunction with radiation-induced atrophy of the vaginal canal epithelium.
- Presenting symptoms include vaginal itching, dryness, and pain, which often lead to colposcopic examination.

Prognosis and Treatment

- Radiation effect of the cervix/vagina tends to be chronic, and significant morbidity can be attributed to both vaginal and cervical involvement.

Pathology

Histology

- Ectocervical/vaginal, endocervical, stromal, and endothelial cells can be affected.
- Cytomegaly with nuclear enlargement, irregular nuclear membranes, and hyperchromasia are most commonly seen; however, the nuclear chromatin is indistinct and has a smooth "smudgy" consistency, which is different from the coarse chromatin seen in dysplastic cells.
- Despite the marked atypia, there is a noticeable lack of mitotic activity and nuclear crowding.
- Abundant cytoplasm is present, resulting in a low nuclear-to-cytoplasmic (N/C) ratio despite the frequently impressive nuclear enlargement.
- Preservation of nuclear spacing should be present.
- Degenerative changes, such as cytoplasmic vacuoles, may or may not be prominent.
- Associated radiation necrosis of the underlying stroma may be present.

Immunopathology (Including Immunohistochemistry)

- Ki-67 is negative in radiation changes.
- p16 is negative in radiation changes.
- p53 might be positive, which can cause some diagnostic confusion.

Main Differential Diagnosis

- Adenocarcinoma in situ—should exhibit increased proliferative activity, higher nuclear density, mitotic figures, and so forth.
- Arias-Stella effect—similar, but can be distinguished by history.
- Clear-cell carcinoma—usually greater hyperchromasia and higher N/C ratio.
- Squamous intraepithelial neoplasia—usually will demonstrate a higher nuclear density and increased N/C ratio.
- Recurrent squamous carcinoma or adenocarcinoma—nuclear features more pronounced, with enlargement, hyperchromasia, and prominent nucleoli.

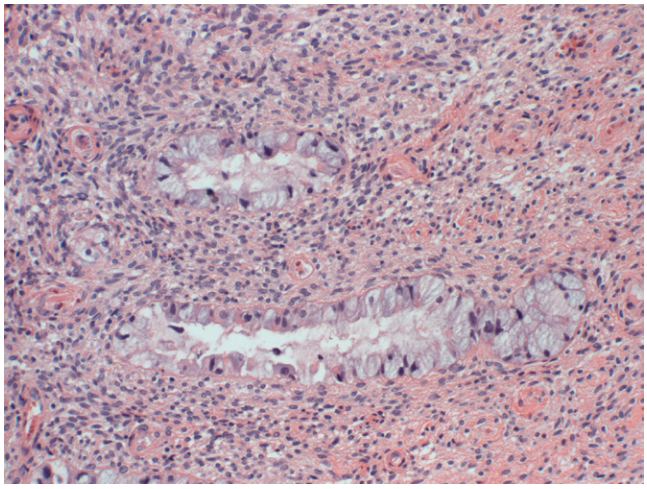


FIGURE 1

Radiation atypia. At medium power, scattered epithelial cells appear enlarged, hyperchromatic, and stand out from the background epithelium.

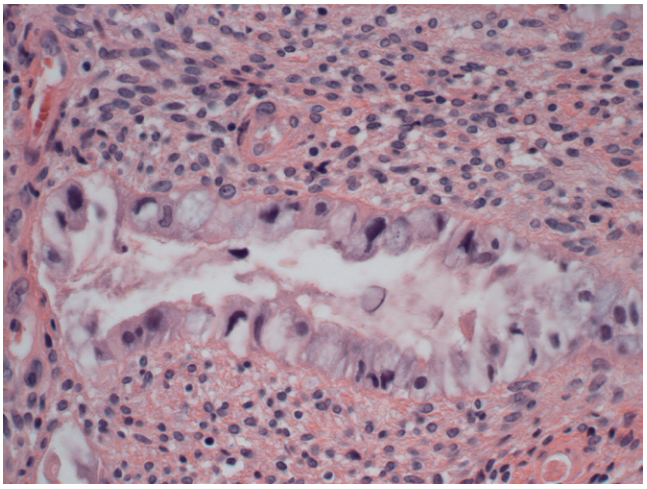


FIGURE 2

Radiation atypia. At higher power the hyperchromatic cells have normal N/C ratios and smooth, "smudgy" chromatin. Mitotic activity is not present.

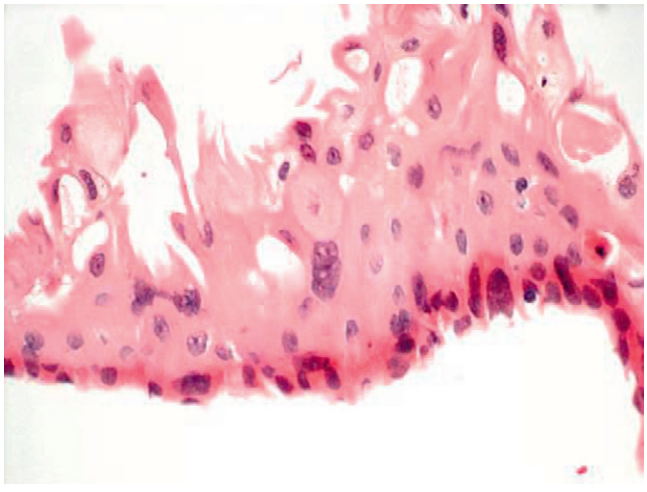


FIGURE 3

Radiation atypia. This vaginal squamous epithelium demonstrates the characteristic nuclear enlargement, low N/C ratio, and absence of coarse chromatin. Note also some cells are degenerated (apoptotic, center). *(Kindelberger DW, Crum CP: Diagnostic Gynecologic and Obstetric Pathology, Philadelphia, 2011, Saunders, Figure 11-6.)*

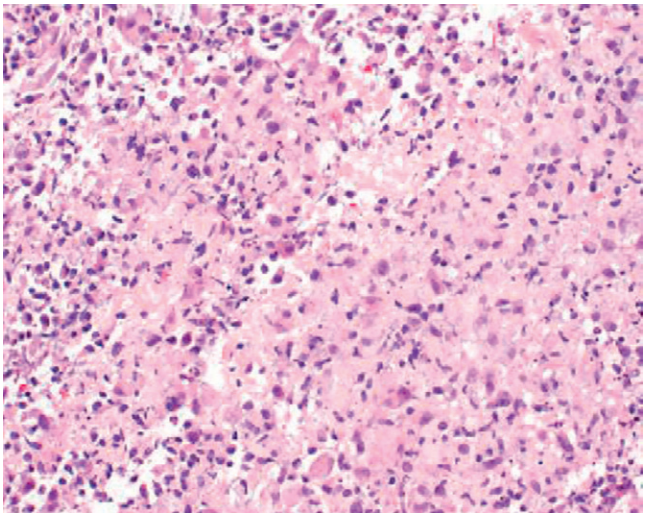


FIGURE 4

Radiation necrosis of the underlying stroma. *(Kindelberger DW, Crum CP: Diagnostic Gynecologic and Obstetric Pathology, Philadelphia, 2011, Saunders, Figure 11-7.)*

VILLOGLANDULAR ADENOCARCINOMA OF THE CERVIX

Definition—A well-differentiated adenocarcinoma with a major exophytic and villoglandular component.

Clinical Features

Epidemiology

- Wide age range (third to seventh decades) with a mean age of 38 years.
- Human papillomavirus (HPV) associated.

Presentation

- Most common symptom is abnormal vaginal bleeding (75%).
- Occasionally diagnosed on abnormal cervical cytology.
- Two thirds present in the International Federation of Gynecology and Obstetrics (FIGO) stage IB.

Prognosis and Treatment

- Standard treatment as for any cervical epithelial malignancy.
- Lymph node metastases occur in less than 10% of patients.
- Overall good prognosis although it is stage dependent.
- Disease-free 5-year survival of 75%.
- Should not be viewed as a distinct entity in terms of behavior inasmuch as some tumors may be quite invasive.

Pathology

Histology

- A distinctive feature of this tumor is a uniform branching, papillary, and interconnecting stromal network lined by a moderately atypical epithelium reminiscent of endometrial lining.
- Growth is predominantly exophytic and endophytic. Further sampling will be needed in some cases to ascertain the extent of invasion.
- Invasion may be pushing or infiltrative and may not be readily evaluable in a small superficial biopsy.

Immunopathology (Including Immunohistochemistry)

- May be helpful in cases where the origin of the tumor is uncertain including small biopsies.
- Strong p16 immunopositivity.

Main Differential Diagnosis

- Florid endocervical adenocarcinoma in situ—adenocarcinoma in situ can be exuberant, involving papillae or microglandular change. These variants usually do not display the prominent dense supporting stroma.

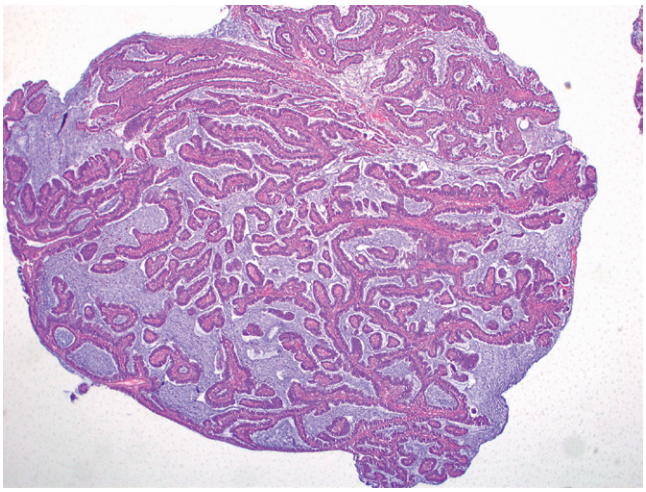


FIGURE 1

Villoglandular adenocarcinoma of the cervix. A typical superficial biopsy displays only the exophytic portion.

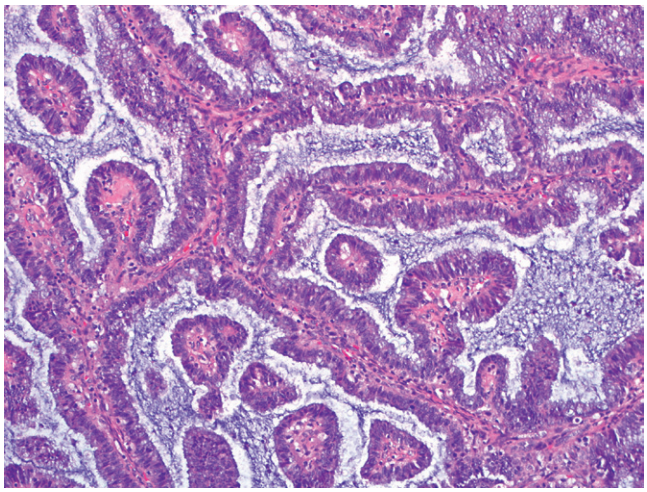


FIGURE 2

Higher magnification displays the regular network of stromal support.

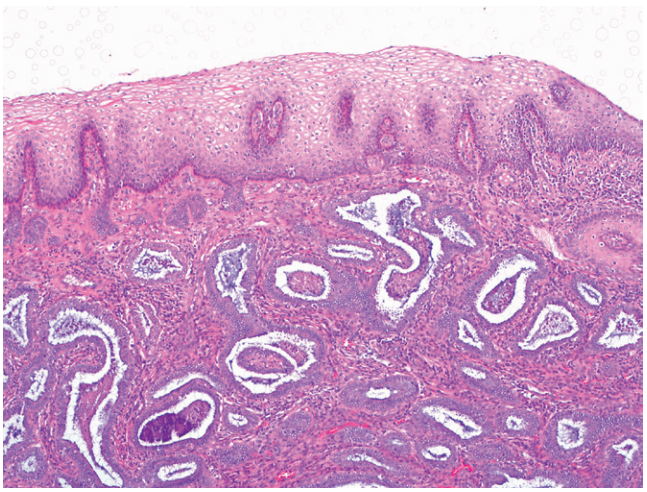


FIGURE 3

A blunt invasion of the underlying stroma is characteristic of many of these villoglandular carcinomas.

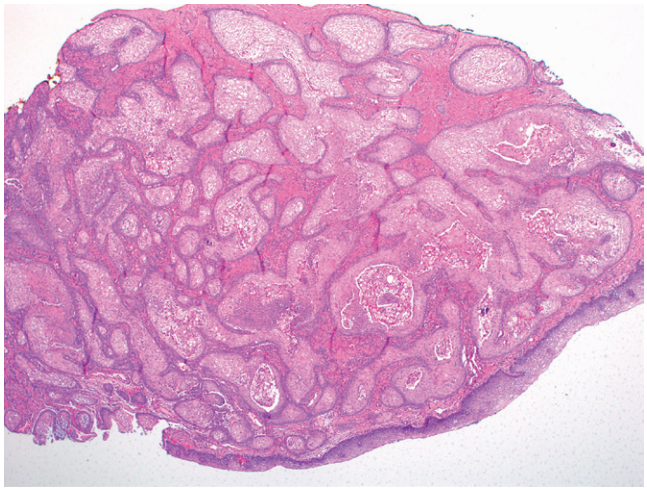


FIGURE 4

Rarely a nested pattern of squamous metaplasia will be seen. This is consistent with replacement of some of the neoplastic glandular epithelium by squamous metaplasia, a rare event in an untreated cervix.

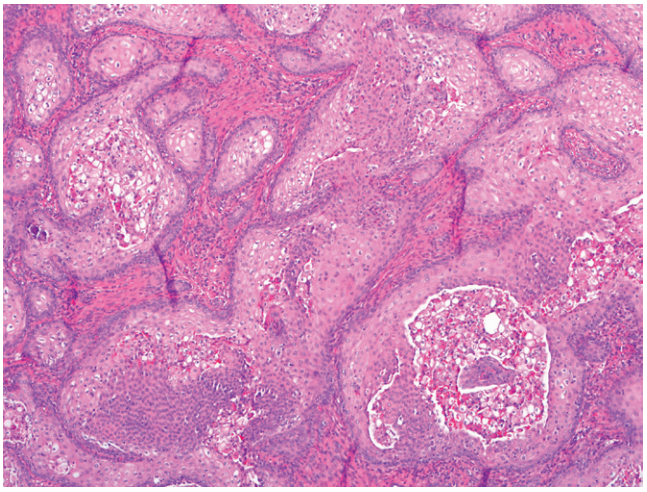


FIGURE 5

At higher magnification note how the squamous epithelium has populated the tracts previously occupied by the glandular lesion.

SUPERFICIALLY INVASIVE ENDOCERVICAL ADENOCARCINOMA

Definition—Early-stage invasive endocervical adenocarcinoma.

Clinical Features

Epidemiology

- Average age at diagnosis is early 40s.
- Human papillomavirus (HPV) associated.

Presentation

- Lack of a clinically visible lesion is a component of the definition of early invasive carcinoma.

Prognosis and Treatment

- Largely depends on the patient's desire for future childbearing, treatment ranging from cone biopsy alone to radical hysterectomy with pelvic lymph node dissection (most common). No consensus for appropriate treatment exists.
- Stage IA1 (cervical stromal invasion <3 mm) has a 1.5% risk of pelvic lymph node metastases.
- Stage IA2 (cervical stromal invasion 3 to 5 mm) has a slightly higher risk of lymph node spread.
- The presence or absence of lymphovascular space involvement is not included in the staging criteria. However, it will influence management in most institutions.

Pathology

Histology

- For a diagnosis of early invasive endocervical adenocarcinoma, the microscopic area of invasion does not exceed 7 mm in the greatest linear dimension and does not exceed 5 mm of cervical stromal invasion (see preceding section).
- The diagnosis is not reliable when there is any question of where in situ disease stops and invasion begins. For this reason, large expansile lesions resembling adenocarcinoma in situ (AIS) are not likely to be resolved. It is best achieved with infiltrative disease with a distinct transition from in situ to invasion.
- Exophytic growth must be evaluated separately.
- A diagnosis of early invasive adenocarcinoma should not be made on small biopsy specimens; the possibility may be suggested but a conclusive diagnosis must be reserved for larger samples, such as cervical cone biopsy.

Immunopathology (Including Immunohistochemistry)

- Not helpful for distinguishing early invasive disease from an in situ lesion; however, p16 may be helpful in determining the extent of neoplastic epithelium.

Main Differential Diagnosis

- Endocervical adenocarcinoma in situ involving microglandular change.

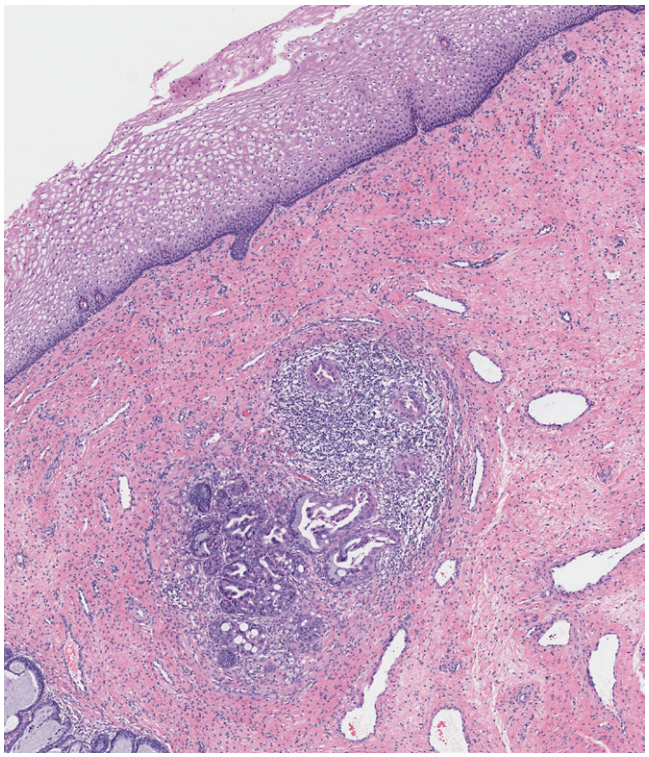


FIGURE 1

Early endocervical adenocarcinoma. An irregular nest of poorly oriented glands and inflammatory cells lies just beneath the normal mucosa.

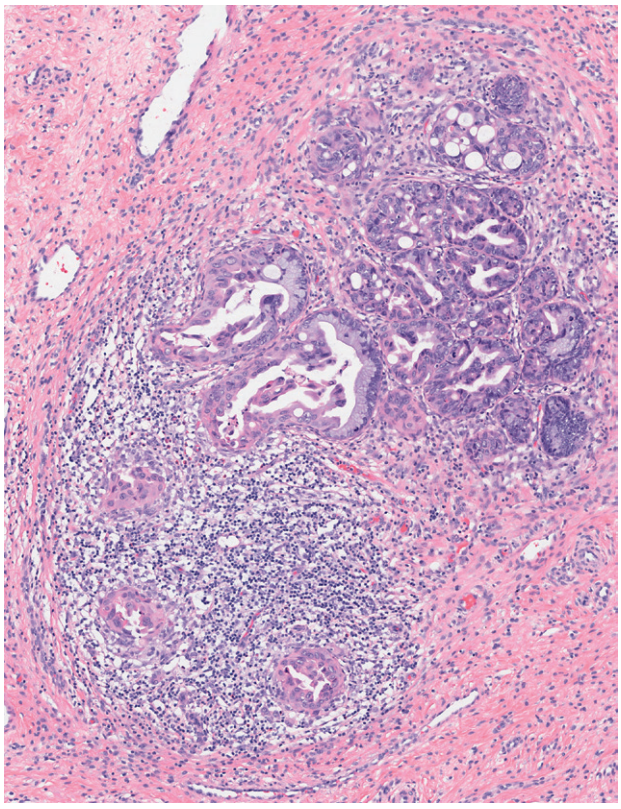


FIGURE 2

Early endocervical adenocarcinoma. Higher magnification of the focus in Figure 1.

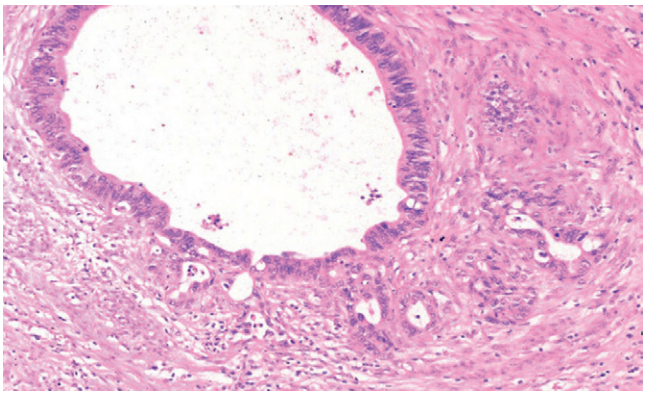


FIGURE 3

Early endocervical adenocarcinoma. Small poorly formed buds of neoplastic epithelium radiate from an involved crypt.

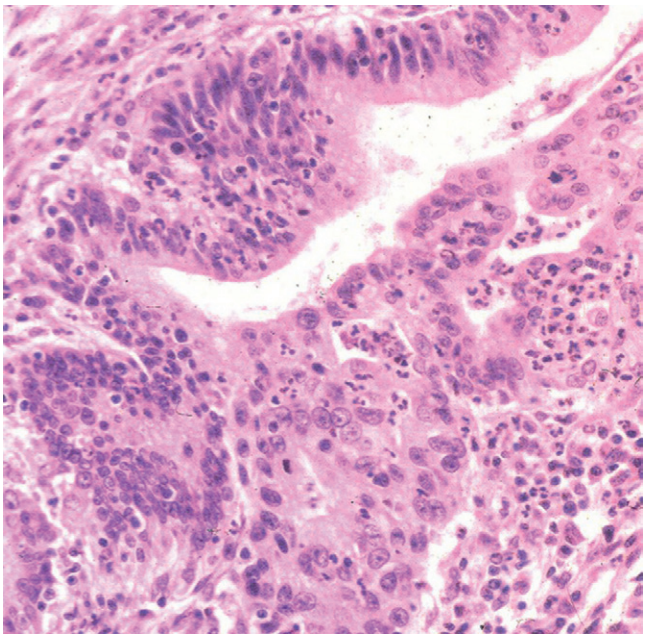


FIGURE 4

Early endocervical adenocarcinoma. In this field a small, solid, unoriented cell outgrowth is present at the bottom of a crypt.

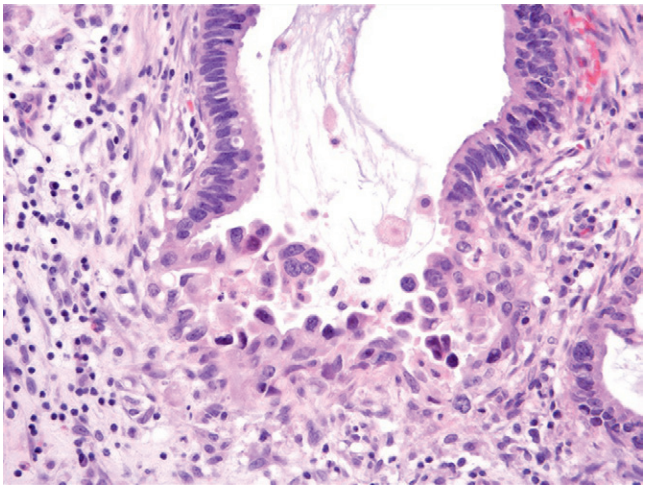


FIGURE 5

Early endocervical adenocarcinoma. In this focus the base of the crypt has dissolved, with complete loss of epithelial polarity.

EXTENSIVE ADENOCARCINOMA IN SITU VS INVASION

Definition—A florid pattern of endocervical adenocarcinoma in situ (AIS) that mimics invasive adenocarcinoma.

Clinical Features

Epidemiology

- The same as for conventional AIS.

Presentation

- The same as for conventional AIS.

Prognosis and Treatment

- The same as for conventional AIS, depending on the level of suspicion for invasive cancer.
- Because of the difficulty of separating this entity from early invasive adenocarcinoma, occasional cases will be associated with endometrial or even ovarian involvement. Cases requiring multiple cone biopsies should raise a "red flag" for this risk.

Pathology

Histology

- At low power these lesions are extensive and involve the native endocervical glands and even endocervical polyps.
- The epithelial architecture may be simple or complex (cribriforming, papillary).
- AIS may extensively involve endocervical glands circumferentially and extend into the high endocervix, but this alone is not sufficient for a diagnosis of invasion.
- At low power a smooth, lobulated appearance is seen around the glands, and at high power the eosinophilic basement membrane is present.
- Acute or chronic inflammation may be present surrounding the involved glands.
- In general, AIS replaces native endocervical epithelium and may expand the gland tracts, but does not extend more deeply into the cervical stroma than do adjacent normal endocervical glands.
- The depth of extension into the surrounding stroma compared with normal glands may be difficult to assess in the presence of a very diffuse process.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.
- As in other examples of AIS, p16 will be diffusely positive, but this finding does not help differentiate the lesion from invasive adenocarcinoma.

Main Differential Diagnosis

- Early invasive endocervical adenocarcinoma—this lesion also may have an expansile growth pattern, but the conformation of the glands is more irregular (un-cryptlike) and some stromal response is usually present.

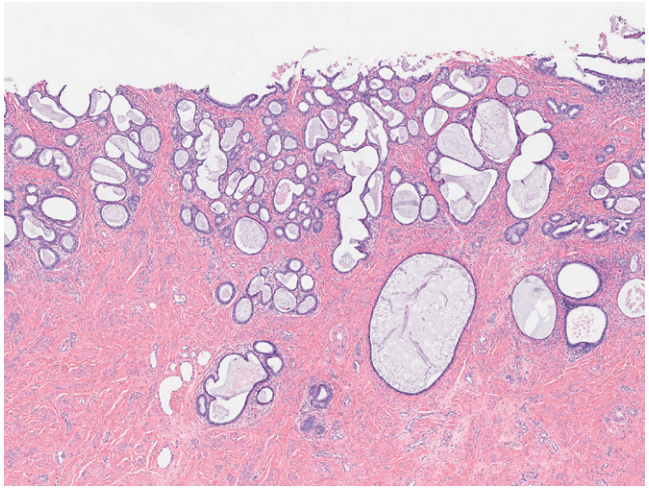


FIGURE 1

Extensive AIS. This field is not particularly difficult. Despite the relatively deep glands, the architecture is uniform.

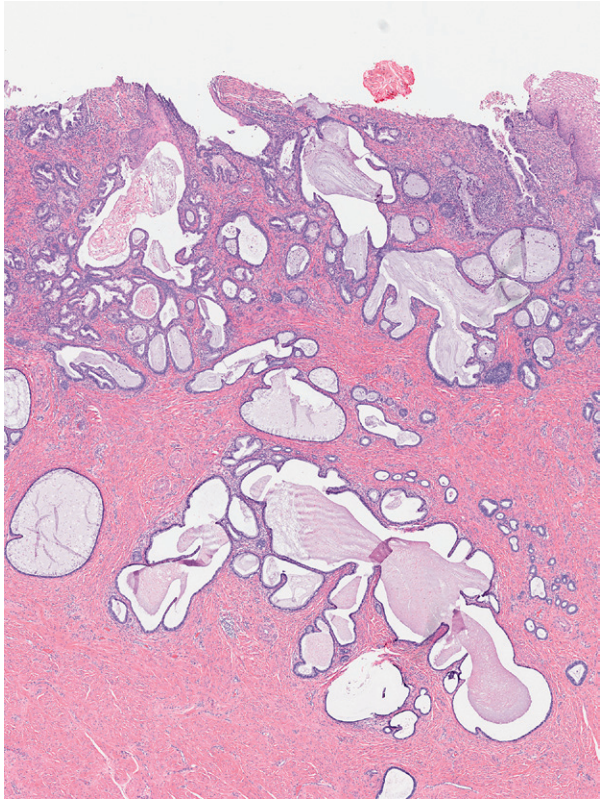


FIGURE 2

Extensive AIS. These glands (crypts) extend much more deeply into the cervical stroma. Note the lobular contour.

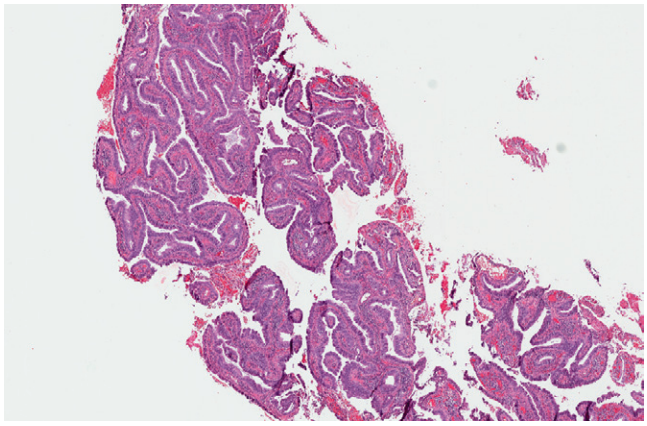


FIGURE 3

Extensive AIS in curettings. The glands interdigitate with nondesmoplastic stroma. This could be either an exophytic component of AIS or part of a villoglandular adenocarcinoma. Importantly the diagnosis of invasive adenocarcinoma should not be made based on this pattern in the curetting alone. If uncertain, the pathologist should recommend a cone biopsy.

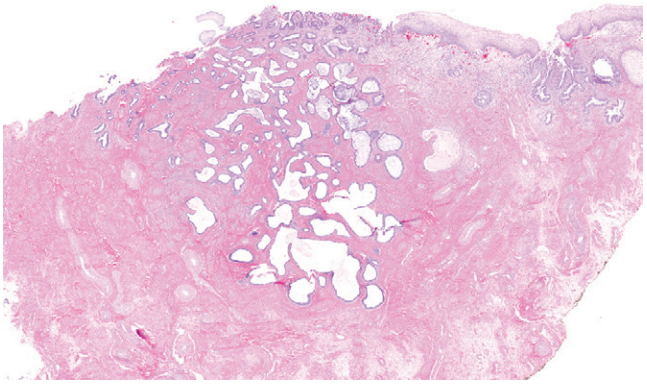


FIGURE 4

A particularly deep AIS with lobular contour. The distinction from invasive carcinoma becomes particularly difficult. Nonetheless, in the absence of stromal response the risk of lymph node metastases is considered extremely low.

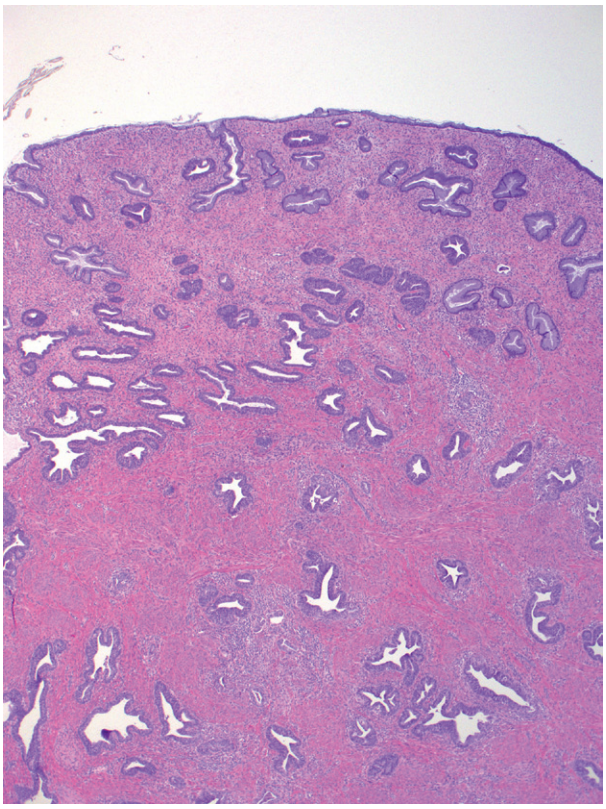


FIGURE 5

Invasive well-differentiated adenocarcinoma. Note the more widely distributed single neoplastic glands and the absence of a more lobulated contour as seen in Figures 1, 2, and 4.

INFILTRATIVE ENDOCERVICAL ADENOCARCINOMA

Definition—Invasive adenocarcinoma originating in the endocervix.

Clinical Features

Epidemiology

- Average age at diagnosis is early 40s.
- Human papillomavirus (HPV) associated.
- A positive association with oral contraceptive use has been noted, but the mechanism is not understood.
- Not associated with tobacco use.

Presentation

- Abnormal Pap smear, although this is an unusual presentation.
- Vaginal bleeding or a sensation of pelvic pressure and/or pain.
- Rarely abnormal pelvic exam with a visible cervical mass or a "barrel" cervix.

Prognosis and Treatment

- Treatment typically includes hysterectomy and pelvic lymph node dissection for early-stage tumors, with adjuvant chemotherapy and/or radiation therapy if there are high-risk factors on the final pathology. Patients with stage IIB or above tumors are treated with concurrent chemotherapy and radiation therapy, often followed by extra fascial hysterectomy.
- Traditionally thought to have worse prognosis than squamous cell carcinoma of the cervix, but outcomes are similar when adjusted for tumor size. However, patients with an adenocarcinoma with nodal metastases definitely have a worse prognosis.
- Ovarian metastases occur in 5% of patients.
- A wide variety of histologic variants have been described, but their presence does not affect prognosis. Carcinomas with a serous pattern of cytology and growth must be viewed carefully as they could signify "drop metastases" from a uterine or upper genital tract carcinoma.

Pathology

Histology

- Invasive endocervical adenocarcinomas are those with invasive foci greater than 7 mm in the greatest linear dimension, and/or invasion more than 5 mm into the cervical stroma.
- If the invasion is less than this, the lesion is termed "early endocervical adenocarcinoma."
- Usual endocervical adenocarcinoma is often associated with residual adenocarcinoma in situ (AIS) and resembles benign endocervical glands.
- The tumor cells are usually columnar and can be mucinous, eosinophilic, or a combination of both; a number of histologic variants exist and are described separately.
- The low-power architecture and pattern of invasion are variable.
- Infiltrative invasion is characterized by individual cells and irregularly shaped glands permeating through the cervical stroma.
- Expansile invasion is notable for its large, smooth-contoured nests of cells resembling AIS. These nests extend more deeply into the cervical stroma than do normal background glands.
- Exophytic invasion is characterized by tumor growth into the endocervical canal; the bulk of tumor is present as polypoid mass.
- On cytologic examination variable numbers of hyperchromatic cellular groups can be identified. The groups may show architectural disarray and loss of the normal honeycomb pattern seen in normal endocervical cells.
- The presence of large groups and papillary clusters in a cytologic preparation suggests an invasive process over AIS.
- When compared with cells representing AIS, invasive cells are frequently larger. The cytoplasm may display vacuoles and be pale to eosinophilic. Mitoses may be

identified, and the nuclear chromatin may be vesicular to coarse and darkly stained.

Immunopathology (Including Immunohistochemistry)

- Positive for Keratin 7 and p16 (in most cases).

Main Differential Diagnosis

- Early invasive endocervical adenocarcinoma.
- Florid benign microglandular change.

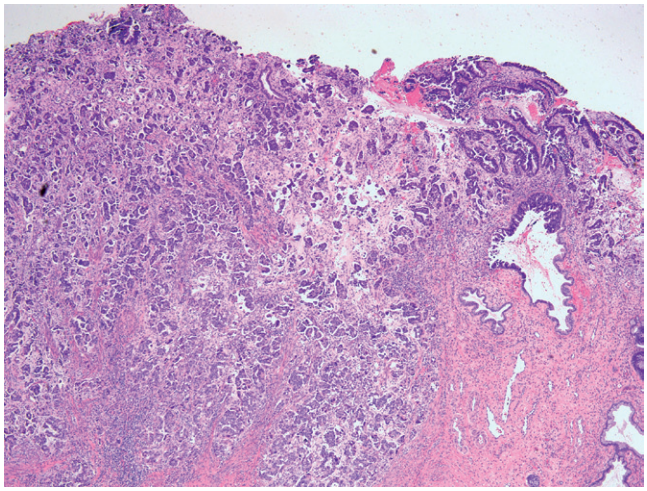


FIGURE 1

Endocervical adenocarcinoma. At low power the endocervix is partially effaced by a malignant appearing proliferation of cells. Residual AIS is noted on the right side of the image, suggesting that this represents an invasive endocervical adenocarcinoma (even at low power).

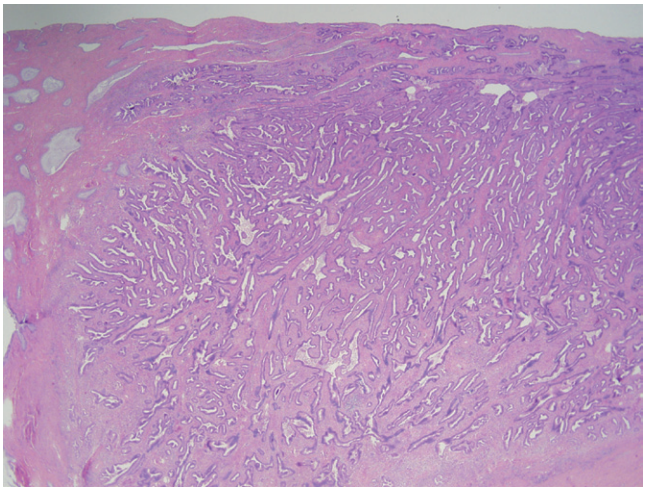


FIGURE 3

Endocervical adenocarcinoma. At low power an expansile proliferation of hyperchromatic glands is present in the endocervix. The overall growth pattern could be consistent with expansile invasion, but areas of stromal reaction and desmoplasia toward the edges suggest that classical infiltrative invasion is also present.

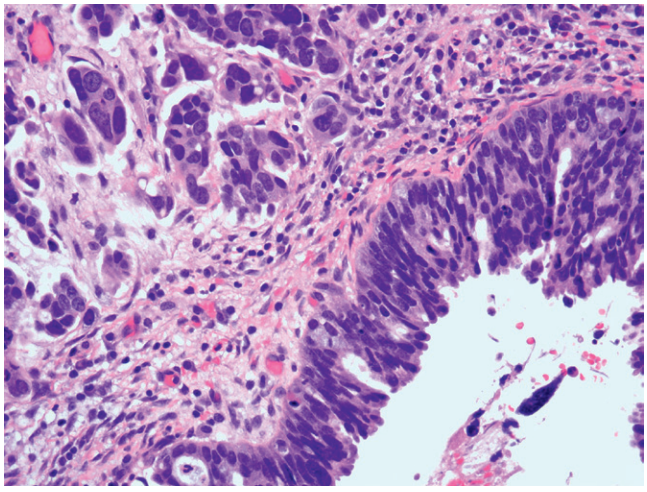


FIGURE 2

Endocervical adenocarcinoma. At high power the invasive adenocarcinoma on the left is sharply contrasted with AIS on the right. The cells of invasive carcinoma are noticeably larger, atypical, and pleomorphic.

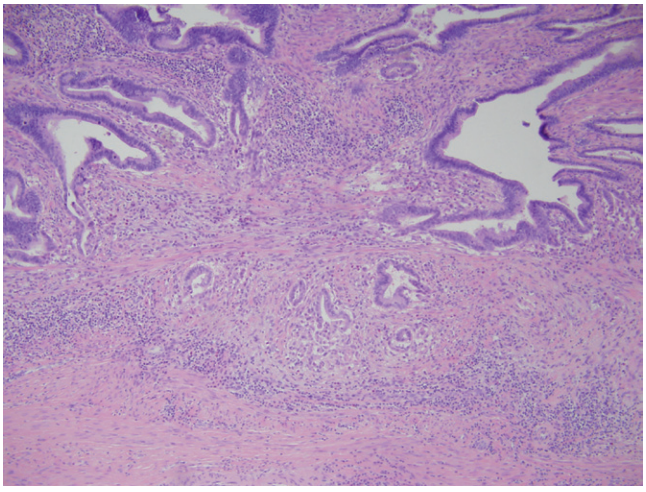


FIGURE 4

Endocervical adenocarcinoma. At low power, hyperchromatic glands involved by AIS are present in the top portion of the image. Small, irregularly shaped infiltrative invasive glands are present in the lower center, accompanied by inflammation and a stromal response.

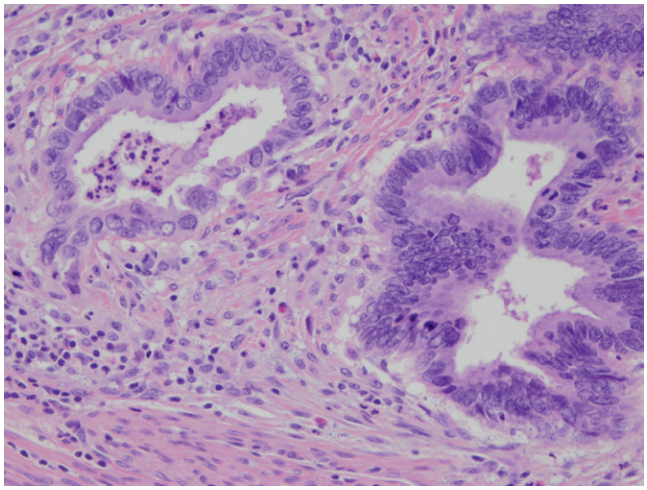


FIGURE 5

Endocervical adenocarcinoma. An invasive gland of endocervical adenocarcinoma is on the left, compared with AIS on the right side of the image. The invasive gland has more brightly eosinophilic cytoplasm and no longer has stratified nuclei. Inflammation and stromal changes suggestive of a desmoplastic response are present.

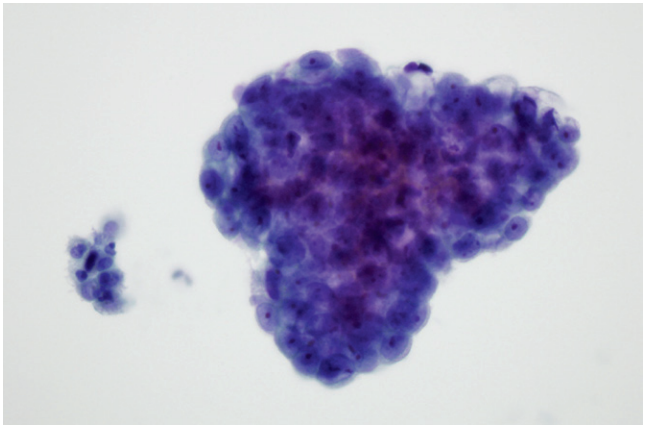


FIGURE 6

Endocervical adenocarcinoma in a Pap smear. A large cluster of hyperchromatic cells with enlarged nuclei and prominent nucleoli. A cluster of benign cells is seen on the left.

CLEAR-CELL CARCINOMA OF THE CERVIX

Definition—A unique, typically HPV-negative adenocarcinoma that has been associated with prenatal diethylstilbestrol exposure.

Clinical Features

Epidemiology

- Rare.
- Historically linked to diethylstilbestrol (DES) exposure in utero.
- Sporadic occurrences now much more frequent than DES-related cases.
- Wide age range, with a mean age of 45 to 50 years, but case reports include occurrences in children and adolescents.

Presentation

- Abnormal Pap smear.
- Cervical abnormality on physical exam, often described as a "fullness" of the cervix.
- Vaginal bleeding due to cervical ulceration.

Prognosis and Treatment

- Standard treatment includes total abdominal hysterectomy and pelvic lymph node dissection.
- Adjuvant chemotherapy and/or radiation therapy for patients with high-risk features.
- Studies regarding prognosis are conflicting; some report equivalent outcomes with conventional cervical adenocarcinoma, whereas others report a much more aggressive disease course.

Pathology

Histology

- Cervical clear-cell carcinoma has a similar histologic appearance to clear-cell carcinomas found elsewhere in the gynecologic tract.
- The low-power appearance is characterized by a predominantly endophytic growth pattern involving the deep cervical stroma.
- Tumor cells may be arranged in glands, papillae, solid sheets, or a tubulocystic pattern; often more than one pattern can be identified.
- At higher power, lining cells protrude into the lumina and spaces in a characteristic "hobnail" fashion.
- Pink hyaline stromal cores are characteristic when a papillary growth pattern is present.
- Tumor cells classically have a clear, glycogen-rich cytoplasm, but not infrequently the cytoplasm may appear more eosinophilic.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Benign microglandular hyperplasia, particularly solid forms, can mimic a clear-cell carcinoma. The presence of reserve cells is often helpful, but the key is to carefully scrutinize the level of atypia and the architecture. Above all, a diagnosis of clear-cell carcinoma in a discrete microacinar proliferation in the cervix in a young woman should be made with great caution.
- Other tumors can present with clear cytoplasm, including metastatic renal cell carcinoma, yolk sac tumors, and clear-cell adenosquamous carcinoma. However, the classic tubulocystic and papillary architecture of clear-cell carcinoma combined with the presentation should exclude these other entities.

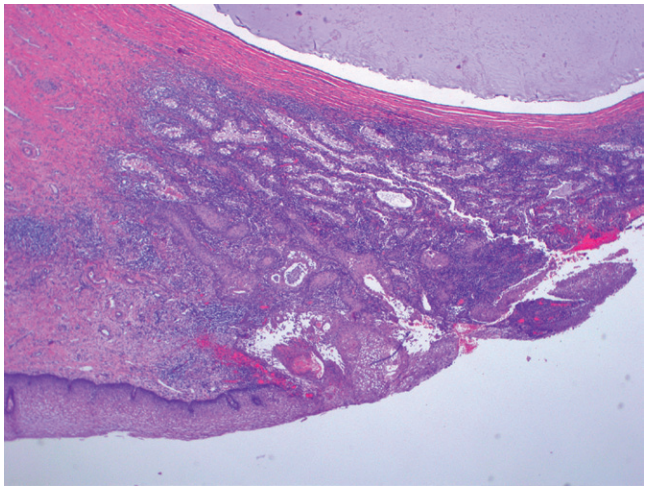


FIGURE 1

Cervical clear-cell carcinoma. This lesion is near the squamocolumnar junction.

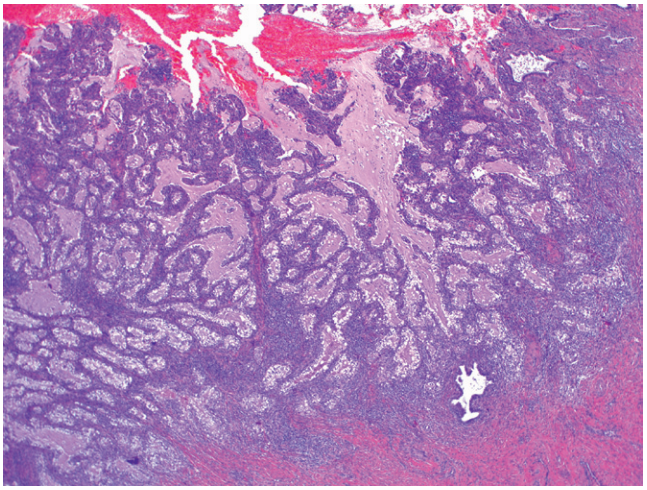


FIGURE 2

Cervical clear-cell carcinoma. An expansile, mostly exophytic lesion.

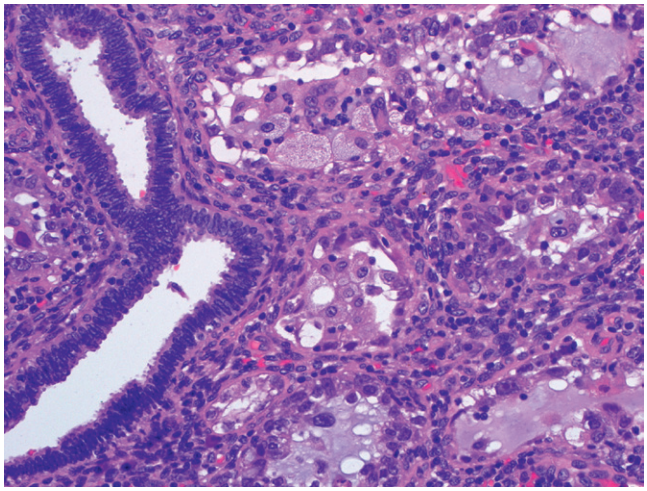


FIGURE 3

Cervical clear-cell carcinoma. Note the juxtaposition of the neoplastic epithelium and a focus of tubuloendometrial metaplasia.

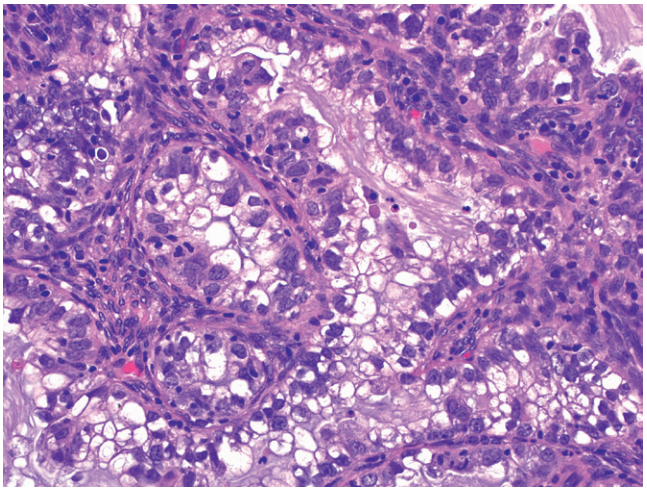


FIGURE 4

Clear-cell carcinoma. Tubulocystic glands are lined by cuboidal cells with enlarged nuclei and focally prominent nucleoli.

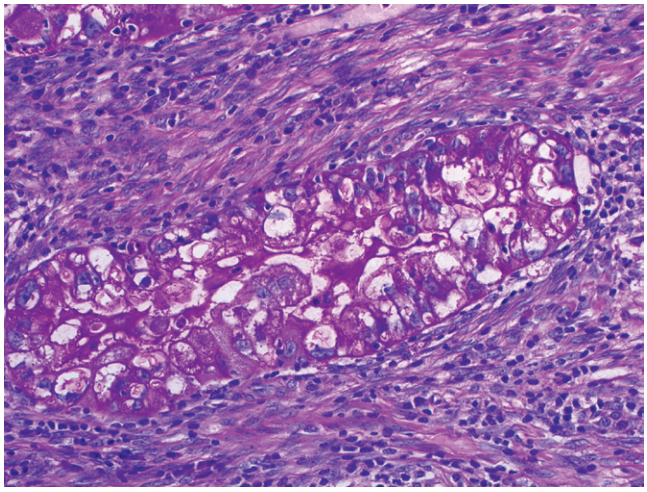


FIGURE 5

Clear-cell carcinoma. There is abundant periodic acid–Schiff (PAS)–positive, diastase-sensitive material (glycogen).

ATYPICAL LOBULAR ENDOCERVICAL GLANDULAR HYPERPLASIA AND INVASIVE (MINIMAL DEVIATION) ADENOCARCINOMA OF THE CERVIX WITH GASTRIC DIFFERENTIATION

Definition—A deceptively bland-appearing mucinous adenocarcinoma of the cervix. Atypical lobular endocervical glandular hyperplasia (ALGH) is considered a potential precursor to minimal deviation adenocarcinoma (MDA).

Clinical Features

Epidemiology

- Uncommon.
- *Not* associated with human papillomavirus (HPV).
- Reproductive-age women; mean age at diagnosis is 42 years.
- Associated with Peutz-Jeghers syndrome (10% to 15% of cases).

Presentation

- Vaginal bleeding and/or discharge.
- Firm, indurated cervix (barrel cervix).
- Some cases are associated with ovarian mucinous carcinomas (both primary and metastatic).

Prognosis and Treatment

- Possibly because of false-negative biopsies, this entity is often diagnosed at high stage.
- Worse prognosis than usual-type adenocarcinoma, with a reported overall survival rate of less than 30% based on the literature.
- Treatment includes resection, chemotherapy, and radiation.

Pathology

Histology

Minimal deviation adenocarcinoma

- The low-power histology is characterized by irregularly shaped endocervical glands invading deeply into the cervical stroma.
- Glands typically extend into the outer third of the cervical wall and can be seen adjacent to large vessels.
- A loss of the overall lobular architecture of the cervical glands is notable.
- At least some invasive glands are associated with a desmoplastic stromal response.
- Nuclear atypia should be found at least focally, although in some cases this can be remarkably subtle.
- Produces neutral mucins and gastric mucous cell phenotype (HIK 1083+).
- In small biopsies look for association with large vessels, variation in gland size and shape, particularly small

glands that appear deeply situated. This tumor can be missed in limited samples (PITFALL).

Atypical lobular endocervical glandular hyperplasia

- Often associated with MDA.
- Nuclear enlargement, irregular nuclear contour, nucleoli, mitoses, apoptosis, epithelial infolding with papillary projections.

Immunopathology (Including Immunohistochemistry)

- Generally noncontributory, but PAX2 may be negative.
- Positive for gastric markers HIK1083 and MUC6.

Main Differential Diagnosis

- Benign endocervical hyperplasia—both laminar and lobular hyperplasias may exhibit deep or irregular glands, but the lining of both is usually uniform and the variation from gland to gland is much less than that seen in minimal deviation adenocarcinomas.
- Endocervical adenomyoma.
- Usual mucinous endocervical adenocarcinoma.

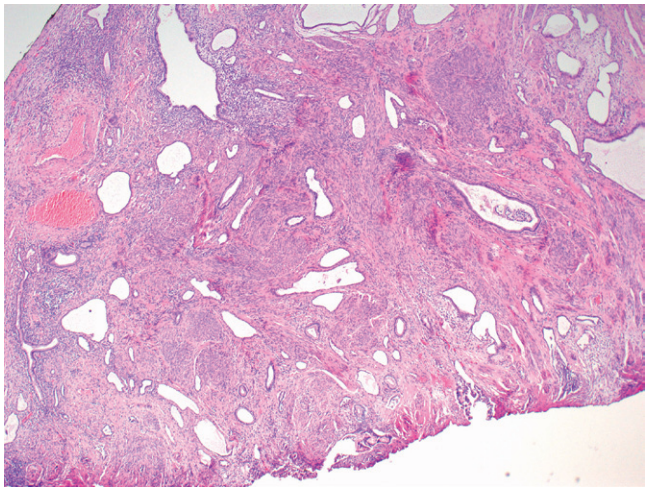


FIGURE 1

Minimal deviation adenocarcinoma. Low-power image of cervix showing a proliferation of bland-appearing but somewhat irregularly shaped glands extending deep into the cervical stroma. A desmoplastic stromal response is not seen here. There is a loss of the normal lobular configuration of endocervical glands, with some single, elongated glands present.

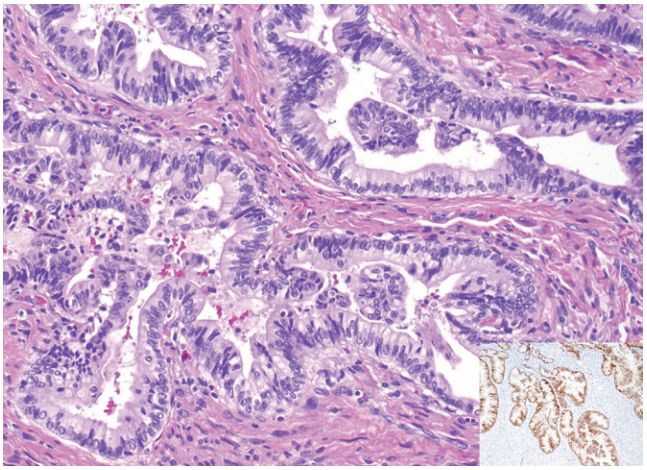


FIGURE 3

ALGH. Note the epithelial infolding with some atypia. Strong MUC6 staining *(inset)* is present.

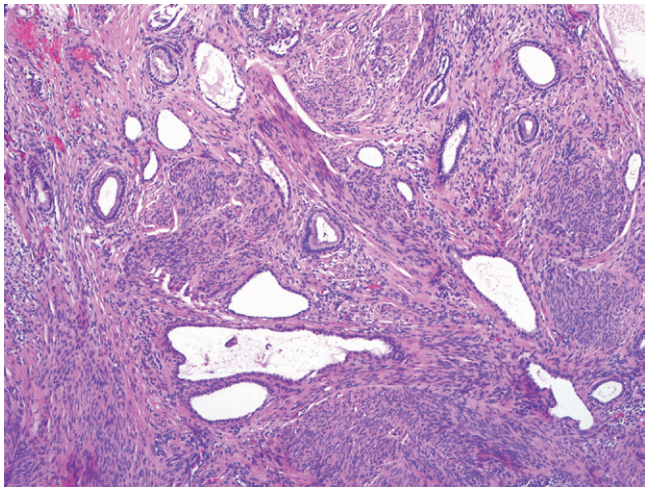


FIGURE 2

At higher magnification an irregular arrangement of otherwise bland-appearing glands can be seen.

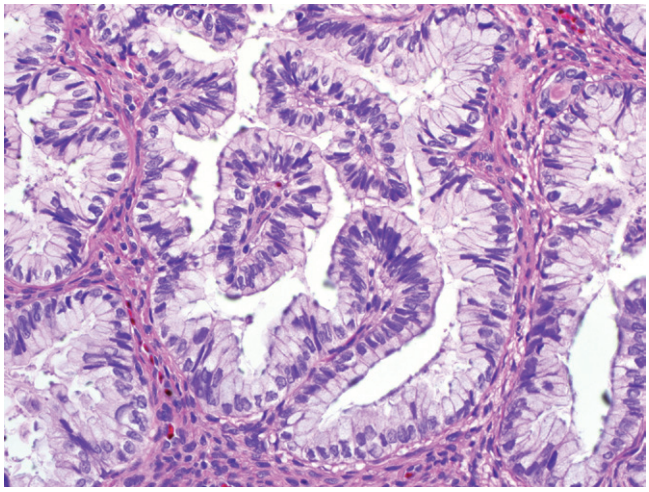


FIGURE 4

Another focus of LEGH with some mild nuclear hyperchromasia.

"SEROUS" CARCINOMA OF THE CERVIX

Definition—A carcinoma resembling an upper genital tract serous carcinoma but originating in the cervix and usually human papillomavirus (HPV) related.

Clinical Features

Epidemiology

- Rare.
- There is a distinctly bimodal age distribution; most patients are under age 45, but there is a second smaller peak after age 65.
- As a rule of thumb, for cases in older women a metastasis from the endometrium, tube, or ovary should be excluded.

Presentation

- Abnormal vaginal bleeding or discharge.
- Abnormal Pap smear.
- Physical exam is highly variable; most cases reveal an exophytic polypoid mass, although often no abnormality is identified.

Prognosis and Treatment

- Primary cervical cancers treated as any adenocarcinoma.
- Cases in older women should be worked up to exclude a metastasis.
- In general, treatment includes radical hysterectomy with pelvic lymphadenectomy and/or chemotherapy and radiation therapy.
- Early (stage I) tumors have a prognosis similar to that of usual endocervical adenocarcinoma.
- Later stage (II or III) tumors tend to be rapidly fatal and have a very low 5-year survival rate.

Pathology

Histology

- Histologic features in cervical serous carcinoma are similar to serous carcinomas of the endometrium and pelvis.
- At low power the tumor has a complex papillary and branching architecture, with characteristic cracks and crevices (a fjordlike appearance); a solid growth pattern may be apparent in deeper areas.
- At high power, complex epithelial budding with nuclear stratification is seen.
- The individual cells are markedly atypical and have high nuclear-to-cytoplasmic ratios, prominent nucleoli, and frequent mitotic figures.
- This histologic pattern (serous adenocarcinoma) may also be associated with areas of more typical, well-differentiated adenocarcinoma, which solidifies the cervical origin but does not affect prognosis.

Immunopathology (Including Immunohistochemistry)

- Primary carcinomas are usually p53 negative (heterogenous staining as opposed to very strong or completely absent staining), but not all are. Strong p16 staining will be seen in both primary and metastatic serous carcinomas.
- Usually positive in situ hybridization for HPV.

Diagnostic terminology: Poorly differentiated adenocarcinoma with a caveat if a metastatic serous carcinoma is suspected. In a young woman an unqualified diagnosis of

"serous carcinoma" in the cervix should not be made as it might confuse the clinician. If the term is introduced, it should be emphasized that this is a variant of cervical adenocarcinoma and should be treated as such.

Main Differential Diagnosis

- Metastatic uterine or pelvic serous carcinoma.

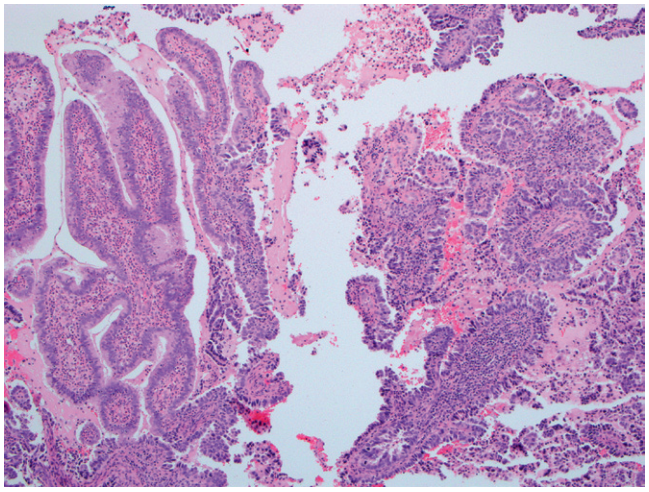


FIGURE 1

Cervical adenocarcinoma with serous histology. Lower-power image showing a villoglandular carcinoma on the left merging with a serous component on the right.

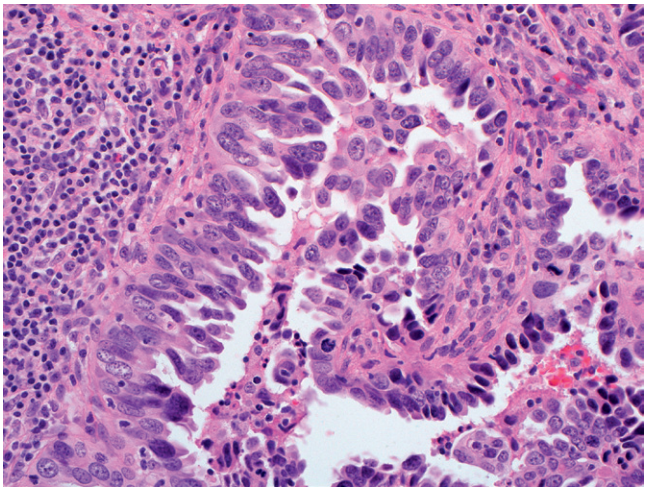


FIGURE 3

Cervical adenocarcinoma with serous histology. The serous component.

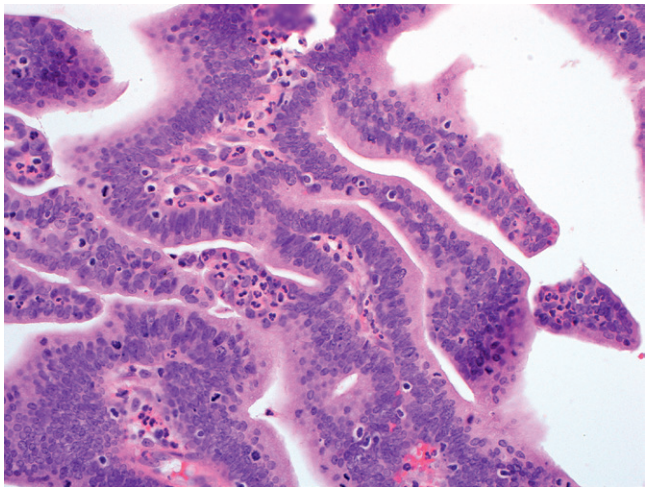


FIGURE 2

Cervical adenocarcinoma with serous histology. The conventional villoglandular component.

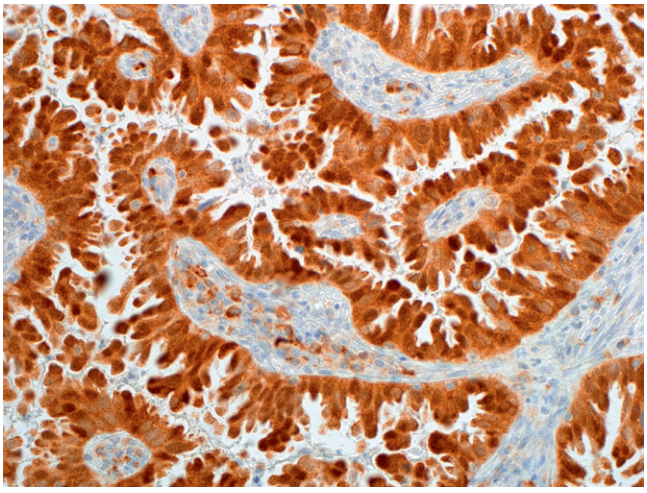


FIGURE 4

Strong p16 staining in the tumor.

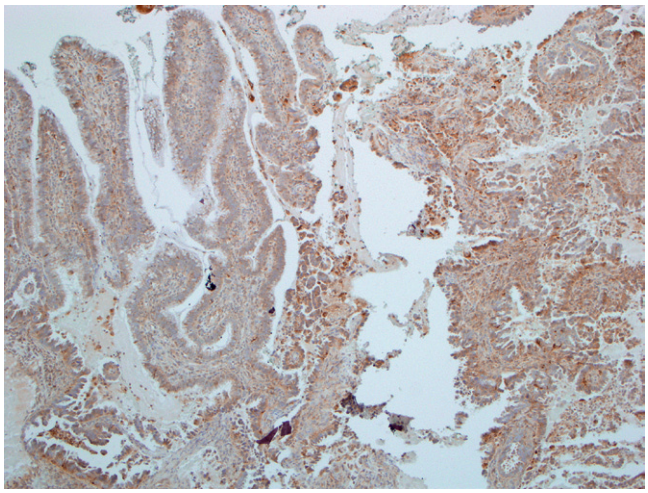


FIGURE 5

p53 staining is weak or heterogenous. However, some of these primary tumors may contain p53 mutations.

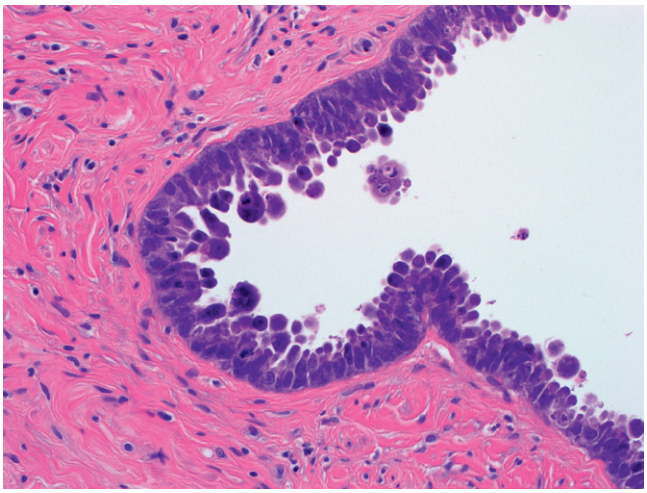


FIGURE 6

Metastatic serous carcinoma to the cervix in an older woman. The tumor occupies crypts and may not invade stroma.

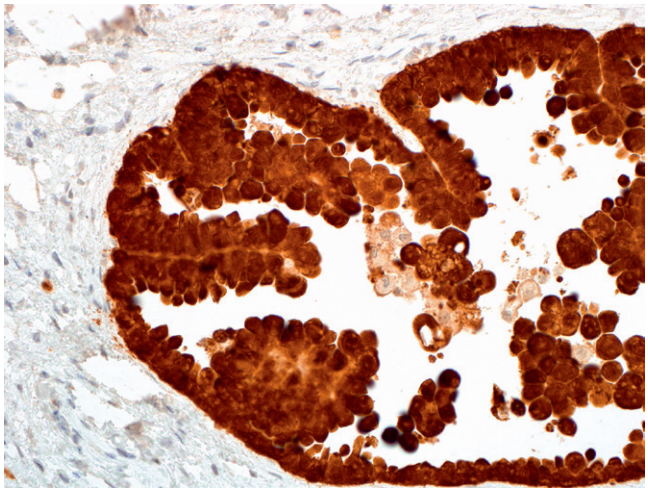


FIGURE 7

Strong p16 staining in a metastatic serous carcinoma to the cervix. This stain will not discriminate primary from metastatic.

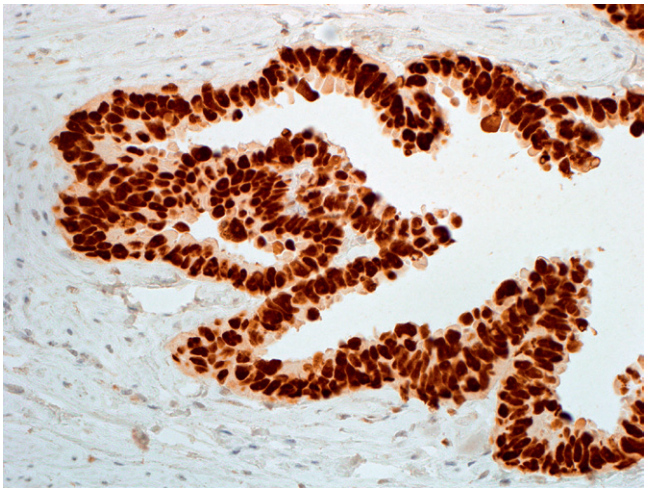


FIGURE 8

Strong p53 staining in a metastatic serous carcinoma to the cervix. Older age and strong p53 staining support a metastatic tumor from the endometrium or upper genital tract.

SIGNET-RING CELL CARCINOMA OF THE CERVIX

Definition—A *rare* variant of invasive adenocarcinoma originating in the endocervix.

Clinical Features

Epidemiology

- Limited to case reports.
- Wide age range, but most present in the fourth or fifth decade.
- Human papillomavirus (HPV) associated.
- May be found with other adenocarcinomas such as usual type of adenocarcinoma or neuroendocrine carcinoma (rare cases).

Presentation

- Vaginal bleeding is the most common presenting symptom.
- Occasional cases present with an abnormal Papanicolaou smear.
- Polypoid cervical mass in some.

Prognosis and Treatment

- Treatment typically includes hysterectomy and pelvic lymph node dissection.
- Advanced stage tumors are treated with concurrent chemotherapy and radiation therapy.
- Outcome is similar to other adenocarcinomas and stage dependent.
- Ovarian metastases reported in case reports.

Pathology

Histology

- Typically these tumors will have components that closely resemble the usual types of cervical adenocarcinoma.
- Signet-ring cell differentiation will be present in clusters of typical cells with eccentric nuclei.
- Strong mucicarmine positivity in the signet-ring cells.

Immunopathology (Including Immunohistochemistry)

- Strong Keratin 7 and p16 positivity.
- Variable CDX2 and CEA.
- Negative or weak GCDFP and CK20.

Main Differential Diagnosis

- Metastatic breast carcinoma—a conventional endocervical adenocarcinoma will not be seen. GCDFP may help, but history is important if there is no accompanying endocervical carcinoma.
- Florid benign microglandular change—this could conceivably be confused with a signet-ring cell carcinoma.
- Metastatic gastric carcinoma—this could be impossible to separate on histology alone and would require attention to coexisting conventional adenocarcinoma, and stains for p16.

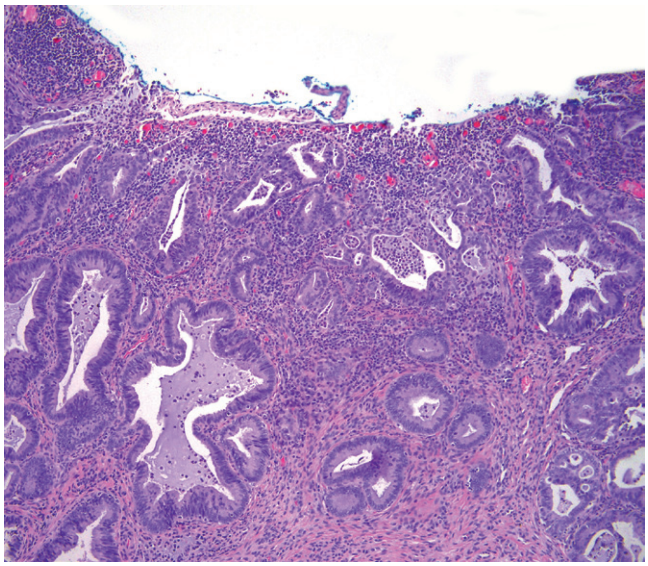


FIGURE 1

Signet-ring cell cervical carcinoma. At low power the dominant pattern is that of a conventional adenocarcinoma of the cervix.

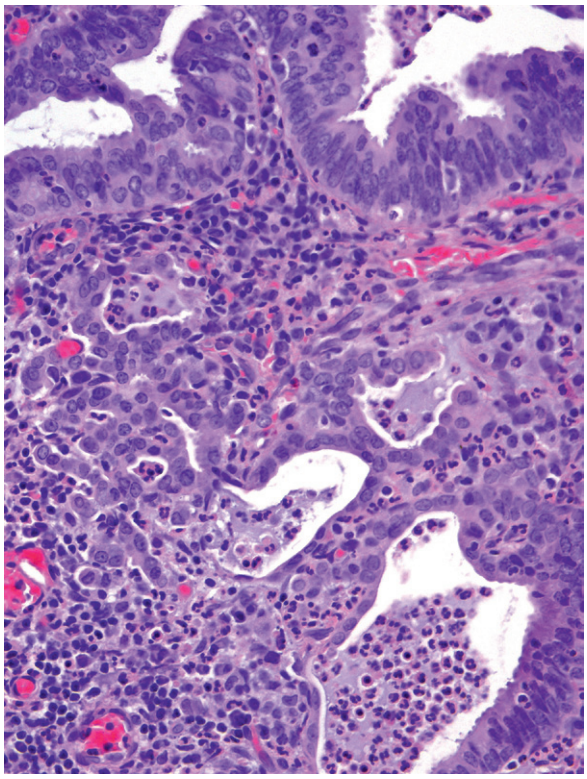


FIGURE 2

Signet-ring cell cervical carcinoma. In this field the glandular pattern *(above)* blends with disaggregated neoplastic epithelium below from which the signet-ring cell pattern will emerge *(below)*.

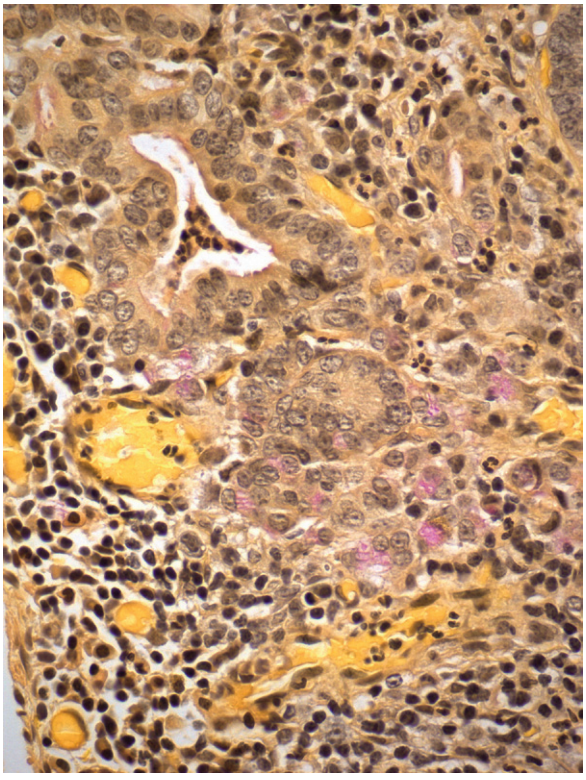


FIGURE 3

Signet-ring cell cervical carcinoma. Mucicarmine staining of the field in Figure 2 reveals positive mucin staining in a few cells in the lower field.

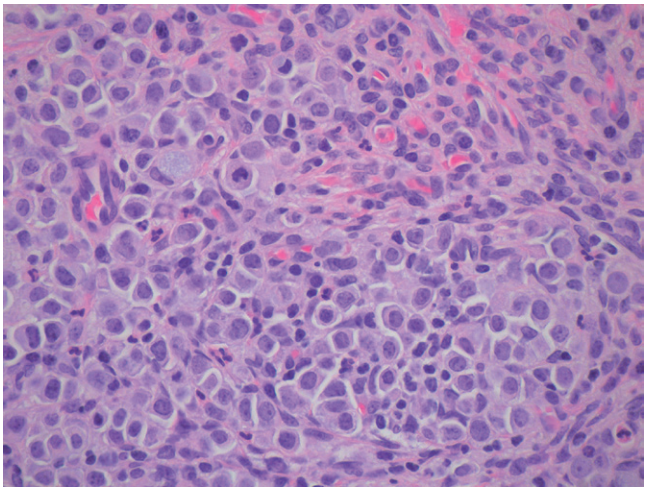


FIGURE 4

Signet-ring cell cervical carcinoma. In another field there is a confluent structureless population of cells forming a pavement with focal mucin droplets.

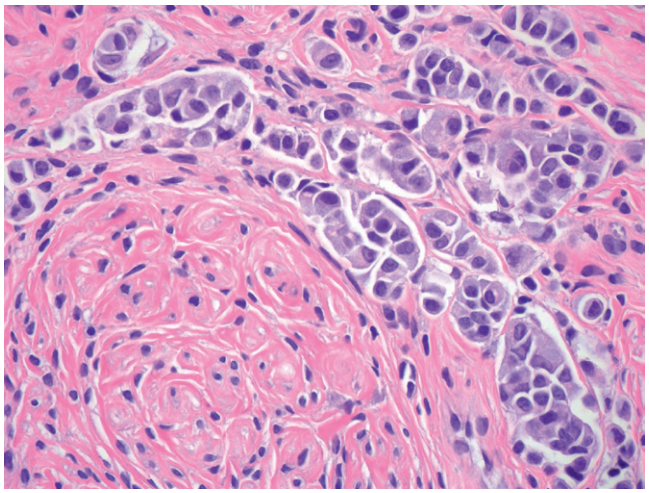


FIGURE 5
Signet-ring cell cervical carcinoma. Classic signet-ring cell differentiation.

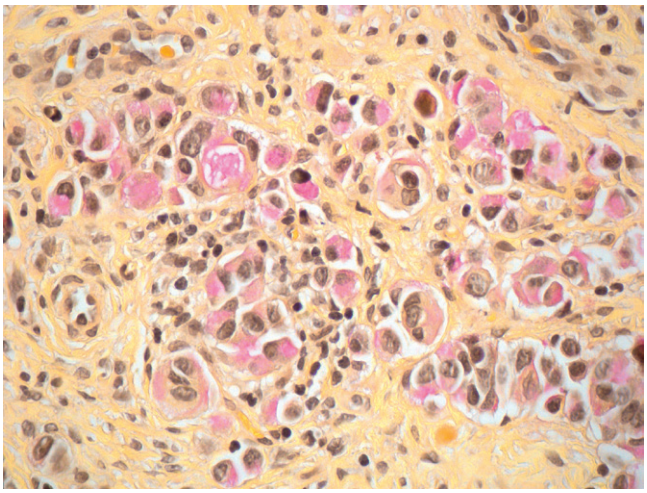


FIGURE 6
Signet-ring cell cervical carcinoma. Strong mucicarmine positivity.

ADENOID BASAL CARCINOMA

Definition—Adenocarcinoma composed of basaloid cells with areas of columnar cell differentiation.

Clinical Features

Epidemiology

- Rare; accounts for less than 5% of cervical carcinomas.
- Usually seen in postmenopausal women.
- Human papillomavirus (HPV) associated.
- African-American women are affected more than other ethnicities.

Presentation

- Most often an incidental finding associated with a high-grade squamous in situ lesion.
- Rarely presents as an abnormal Pap smear.

Prognosis and Treatment

- Excellent when present as a pure adenoid basal carcinoma (ABC) lesion.
- Atypia in the basaloid cells does not alter outcome.
- No recurrences or metastases have been reported in tumors without additional components.

Pathology

Histology

- This lesion is nearly always underlying a typical high-grade squamous in situ lesion.
- Three additional patterns, or components, can be present within the cervical stroma:
  1. Discrete nests of squamoid cells with variable nuclear atypia and pleomorphism, low nuclear-to-cytoplasmic ratio, and a prominent peripheral rim of basal cells.
  2. Small, discrete well-demarcated infiltrating nests composed of basaloid cells with focal cystic change.
  3. Foci of columnar differentiation within small, infiltrating basaloid nests.
- A desmoplastic reaction is notably absent.
- The basaloid cells will vary in degree of atypia. Often they appear monotonous, with only mild nuclear atypia, but in some cases a higher mitotic index with nuclear pleomorphism will be seen. The squamous components often have much more prominent nuclear atypia.
- The ABC pattern may sometimes be focally present as a component of a poorly differentiated carcinoma and adequate sampling should be performed to exclude this possibility.
- In particular, an ABC pattern may be seen associated with patterns suggesting basaloid squamous cell carcinoma, carcinosarcoma, or adenoid cystic carcinoma.

Preferred Diagnostic Term

Adenoid basal carcinoma

Comment (optional): ABC is a rare variant of squamous carcinoma, which is associated with HPV 16 and in its pure form has a favorable outcome without nodal metastases.

Immunopathology (Including Immunohistochemistry)

- Most cases are positive for high-risk HPV, particularly HPV 16.
- p16 immunostaining should be strong.
- Cam 5.2 is positive.

Main Differential Diagnosis

- Adenoid cystic carcinoma—these tumors (if they really exist in the cervix) have additional components including a high-grade gland-forming component.
- Squamous cell carcinoma—these tumors lack the multifaceted picture of ABC.
- Carcinosarcoma—in the cervix rarely can be associated with ABC, but have a prominent spindle cell component.

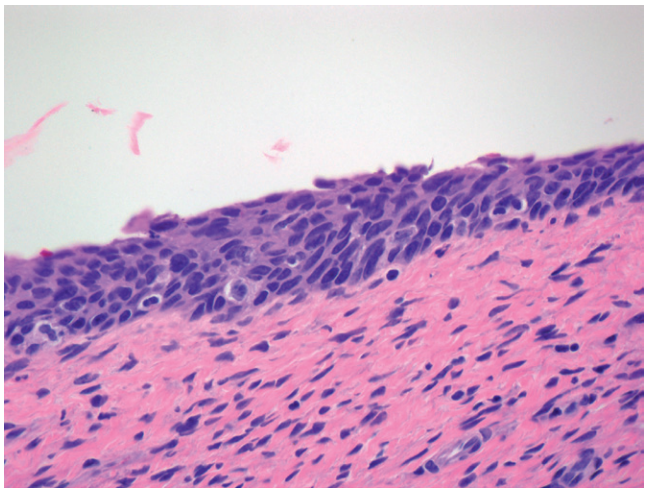


FIGURE 1

ABC. A focus of cervical intraepithelial neoplasia 3 (CIN3) on the surface of the cervix.

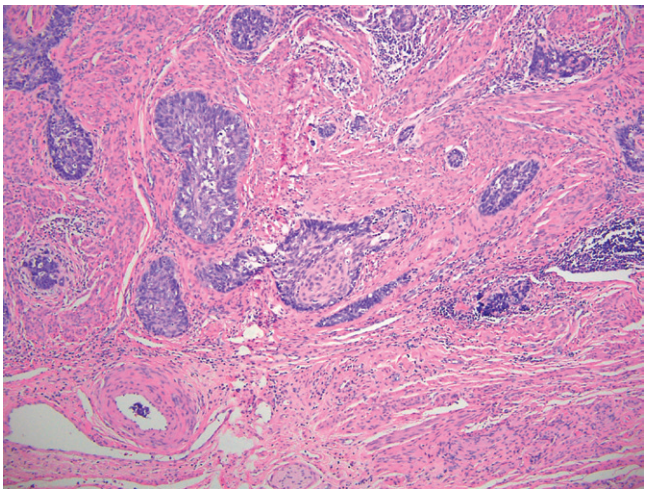


FIGURE 2

A squamoid pattern of infiltration with a combination of squamous differentiation in the center of the invading nest and peripheral basal cells.

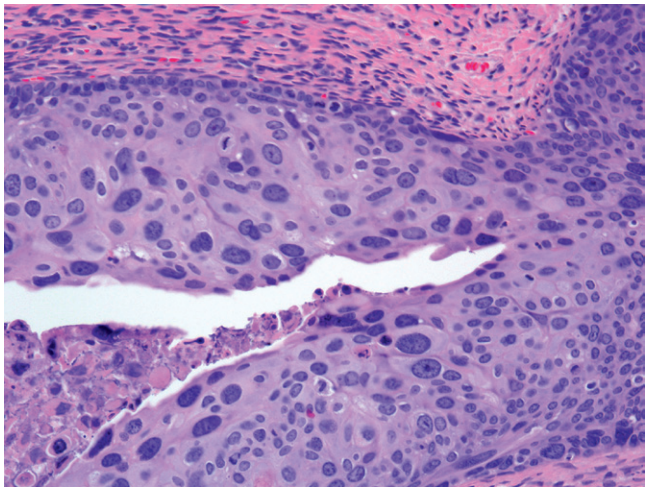


FIGURE 3

Higher magnification showing central squamous differentiation with atypia and a linear row of basal cells at the epithelial-stromal interface *(top).*

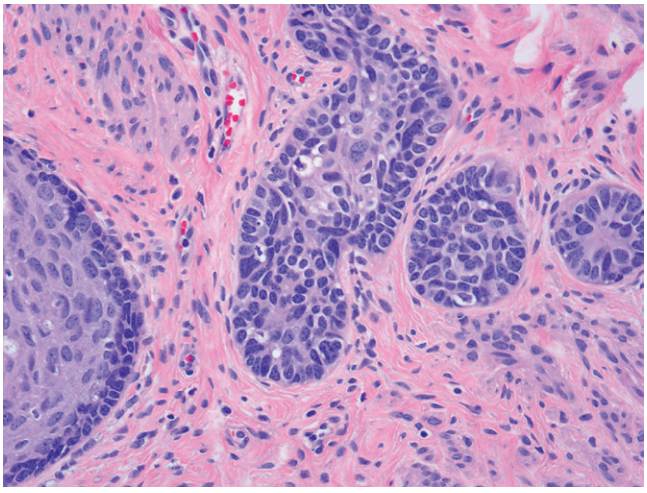


FIGURE 4

A squamous nest *(left)* and small basaloid nests *(right).*

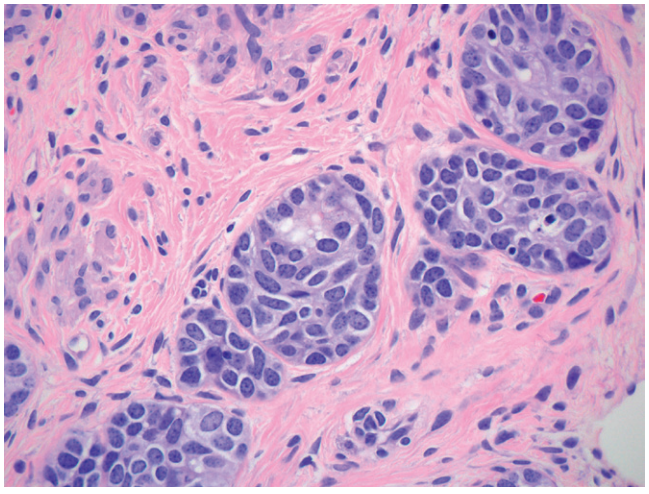


FIGURE 5

These basaloid nests display a hint of columnar differentiation.

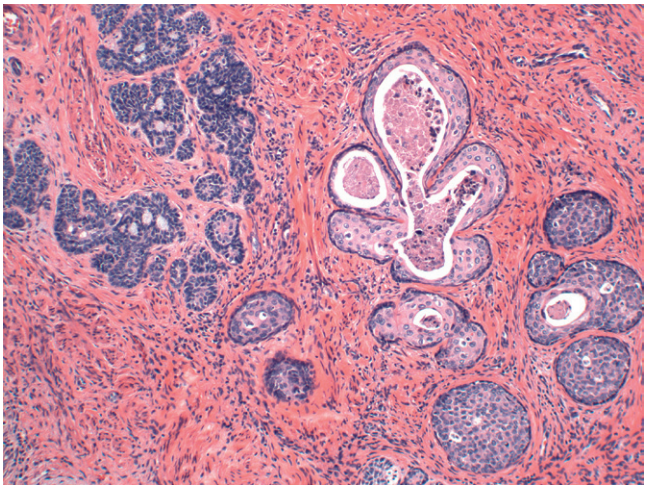


FIGURE 6

Squamoid nests *(right)* and basaloid nests *(left)* of tumor. The latter also shows acinar (adenoid) differentiation.

MESONEPHRIC REMNANTS

Definition—Embryologic remnants of mesonephric differentiation found in the gynecologic tract.

Clinical Features

Epidemiology

- Mesonephric remnants may be identified in up to one fifth of well-sampled cervices.
- No age or demographic predilection has been identified.

Presentation

- Noted incidentally at the time of cervical sampling.

Prognosis and Treatment

- Excellent; no treatment is required.

Pathology

Histology

- Mesonephric remnants are small glandular structures that are typically found in the lateral cervical walls.
- The lining cells are small and cuboidal and lack cilia.
- A dense, eosinophilic intraluminal material is commonly present.
- Multiple clusters of glands may be seen in which case the diagnosis of mesonephric hyperplasia is justified (see differential diagnosis).

Immunopathology (Including Immunohistochemistry)

- PAX2 is strongly positive in mesonephric remnants and mesonephric hyperplasia.

Main Differential Diagnosis

- Endocervical adenocarcinoma—this is not usually a difficult distinction.
- Metastatic endometrial carcinoma—this may closely mimic mesonephric remnants when present in a format of tubular glands. The lining epithelium should demonstrate atypia, albeit subtle, and the distribution will be more haphazard than mesonephric remnants. Moreover, the gland outlines are typically more variable and not exclusively tubular.
- Mesonephric "hyperplasia" versus carcinoma—if the remnants are extensive, the term mesonephric hyperplasia might be entertained, but does not increase the risk of an adverse outcome. However, a careful search for a transition to confluent glands or more striking atypia should be made, and these changes would indicate a coexisting carcinoma.

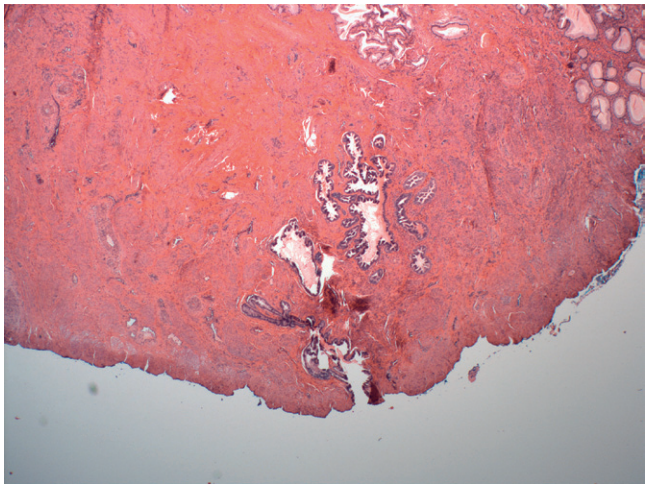


FIGURE 1

Mesonephric remnants in the cervix. Low power reveals the presence of additional glandular structures deep to the usual endocervical glands.

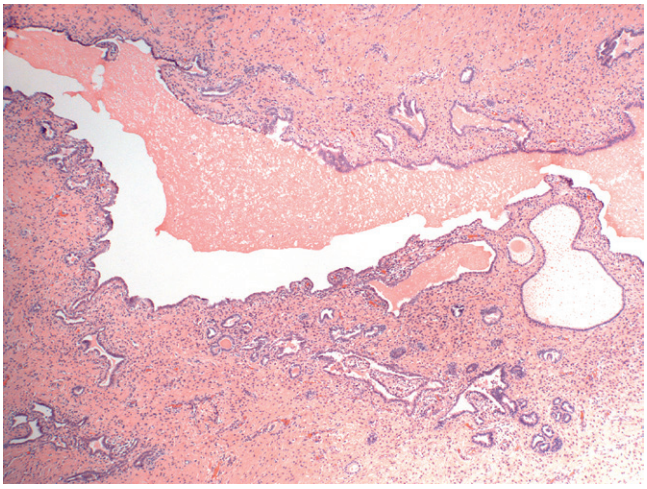


FIGURE 2

Mesonephric remnants in the cervix. In this example small glands appear to emanate from a dilated duct.

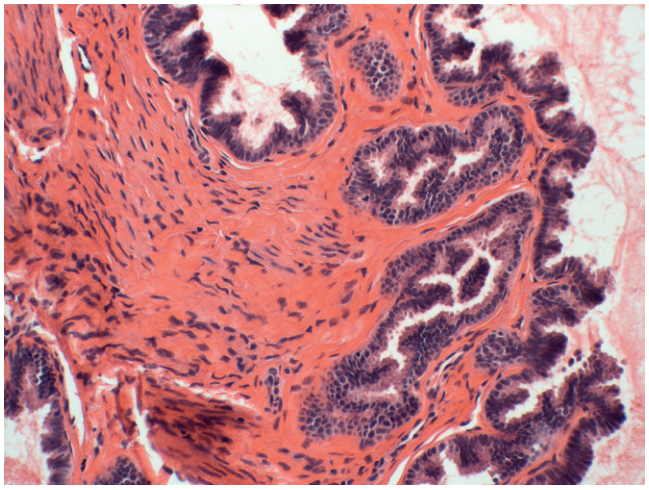


FIGURE 3

Mesonephric remnants in the cervix. At high power the cells comprising the remnants are relatively small and cuboidal. Cilia are not seen. Nuclear atypia is absent. Areas of eosinophilic intraluminal secretions are present.

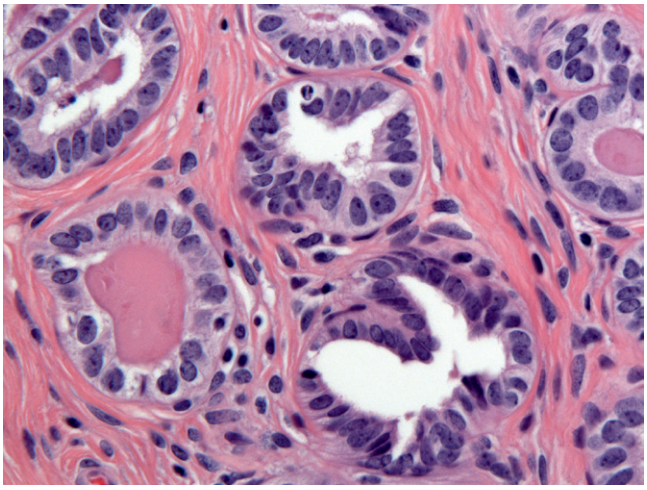


FIGURE 4

Mesonephric remnants of the cervix. Note the intraluminal eosinophilic material.

MESONEPHRIC CARCINOMA

Definition—A carcinoma derived from mesonephric remnants located in the lateral walls of the uterine cervix.

Clinical Features

Epidemiology

- Very rare.
- The mean age at presentation is early 50s.

Presentation

- Abnormal vaginal bleeding.
- Barrel-shaped cervix or a symptomatic cervical mass.

Prognosis and Treatment

- Prognosis is uncertain due to the rarity of this tumor; some reports suggest that it may be an indolent tumor with potential for late recurrence.

Pathology

Histology

- On gross examination, if a discrete mass is present, it is located at the lateral cervical wall.
- The histologic patterns are remarkably variable and may resemble a wide variety of other tumors including carcinomas, malignant mixed müllerian tumor (MMMT), and uterine tumors resembling an ovarian sex cord tumor (UTROSCT).
- Although rare, the histologic patterns seen in this tumor have been well documented and a wide variety of patterns have been described, including tubular, ductal, retiform, and solid.
- Glandlike spaces and intraluminal eosinophilic hyaline secretions are present in all of the histologic patterns.
- The tumor cells are mild to moderately pleomorphic and hyperchromatic, with variably prominent nucleoli.
- The architectural pattern may be solid, with only occasional glandlike spaces, or may be composed of round, variously sized ductlike spaces lined by columnar cells.
- The so-called tubular pattern is identified by the presence of innumerable small, tightly packed gland structures that are lined by flattened to cuboidal epithelial cells; the retiform pattern is similar except that the glandlike spaces are narrow and slitlike.
- Intraluminal papillary projections can be seen in any of the patterns.
- Sex cord–like tumors are composed of cells with minimal amounts of cytoplasm and are arranged in single-file lines of cells.
- The mitotic count is highly variable and can be markedly elevated.
- Occasional heterologous elements, such as cartilage, have been noted.

Immunopathology (Including Immunohistochemistry)

- Positive for Keratin 7, EMA, calretinin, and GATA3.
- Negative for Keratin 20, ER, PR, and WT1.

Main Differential Diagnosis

- Florid mesonephric hyperplasia—this distinction is a matter of degree.
- Metastatic endometrioid adenocarcinoma—this neoplasm can involve the cervix in a unique and subtle pattern in which the glands are uniform, deeply situated, and cytologically bland, resembling mesonephric remnants or mesonephric hyperplasia.

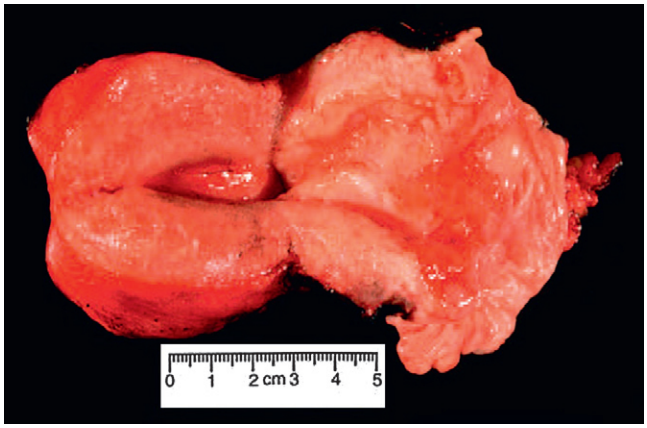


FIGURE 1

Mesonephric carcinoma. In this gross photograph the opened cervix *(right)* is diffusely expanded, with a narrowing at the endocervical-uterine junction. This explains the reported cases of "failure to progress" during labor, as occurred in the patient prior to diagnosis.

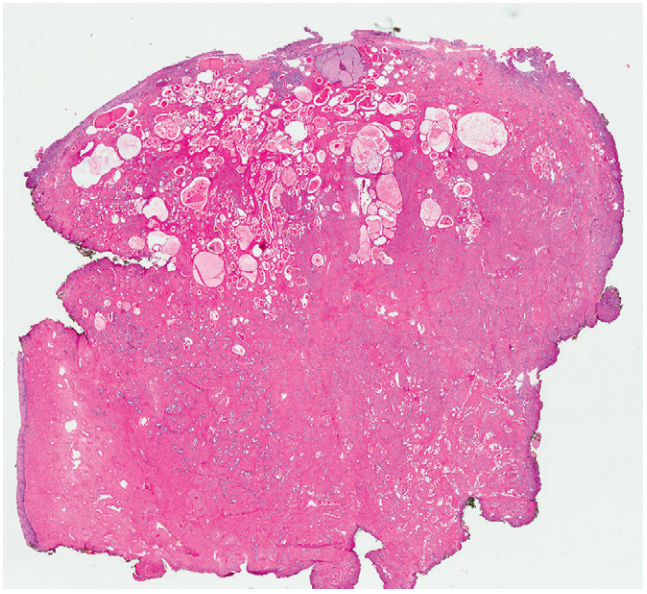


FIGURE 2

Mesonephric carcinoma associated with mesonephric hyperplasia. A classic scanning power appearance of this tumor, with mesonephric remnants in the lower half of the image becoming more cystic and crowded as they approach the lumen.

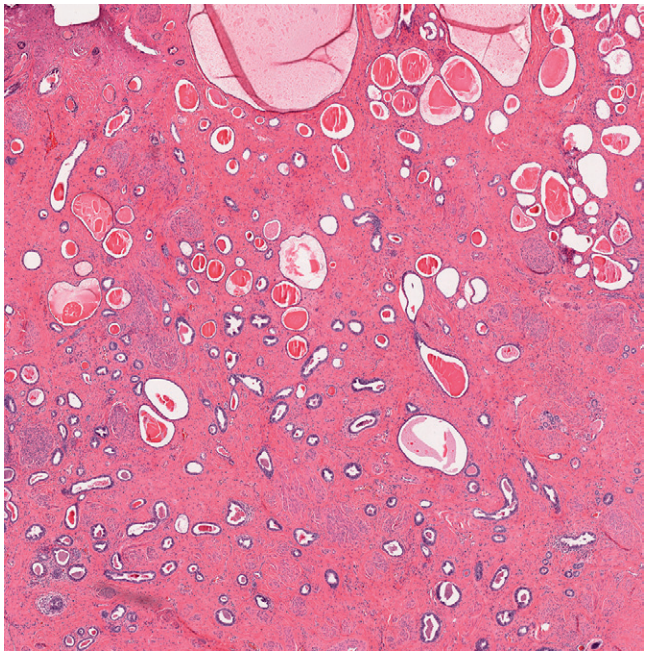


FIGURE 3

Mesonephric hyperplasia. This part of the tumor is identical to mesonephric hyperplasia.

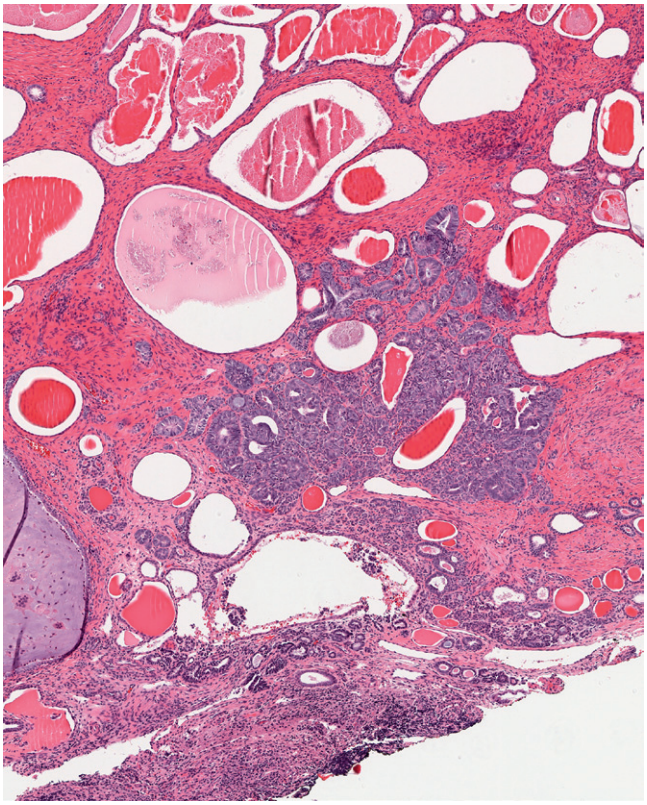


FIGURE 4

Near the endocervical canal the tumor transforms, with a malignant appearing cluster of neoplastic glands. These glands can resemble sex cords or endometrioid carcinoma.

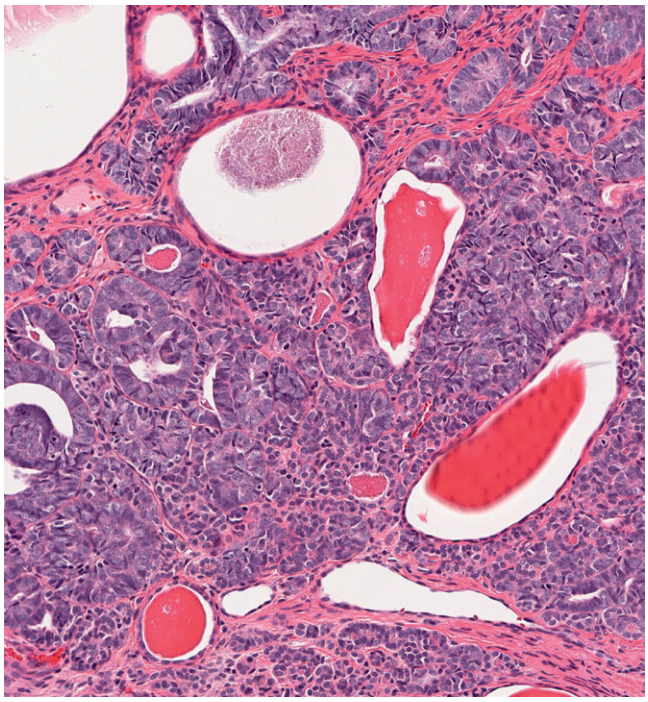


FIGURE 5

Higher magnification of the malignant appearing cluster of neoplastic glands. These glands can resemble sex cords or endometrioid carcinoma.

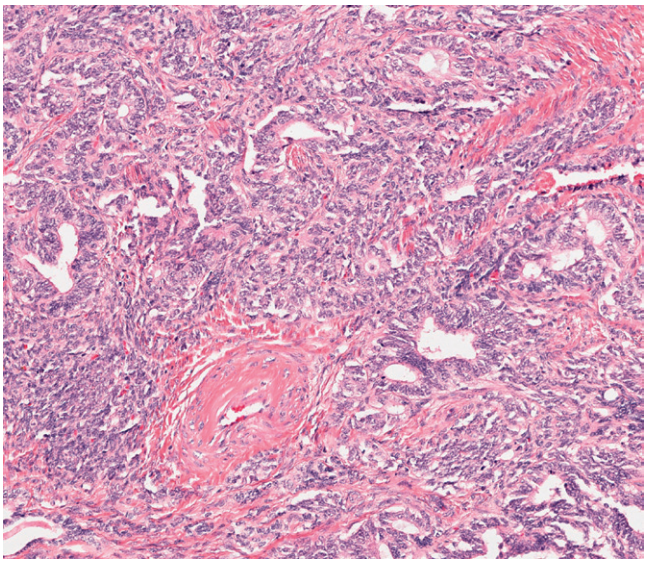


FIGURE 6

Focal spindle cell differentiation in a mesonephric carcinoma. This can be confused with carcinosarcoma or Wilms' tumor of the uterus.

PROSTATIC METAPLASIA OF THE CERVIX

Definition—The histologic appearance of large prostatic duct–like tissue within the cervical stroma.

Clinical Features

Epidemiology

- Prostatic metaplasia is a rare (or possibly underreported) process.
- There is no age predilection.

Presentation

- Prostatic metaplasia is an incidental finding at the time of cervical biopsy or hysterectomy.
- There are no gross findings.

Prognosis and Treatment

- The prognosis is excellent as this process is not associated with neoplasia.
- No treatment is required.

Pathology

Histology

- Microscopically, prostatic metaplasia consists of glands with the appearance of large prostatic ducts set within cervical stroma.
- The nests of glands are well circumscribed and have an identifiable population of reserve cells at the periphery.
- The cells composing the glands consist of cuboidal to columnar mucinous cells with small, bland, uniform nuclei.
- Squamous metaplasia is common.
- The squamous cells within the center are also bland, but these cells typically have clear cytoplasm.

Immunopathology (Including Immunohistochemistry)

- Prostate-specific antigen (PSA) and prostate-specific acid phosphatase (PSAP) are positive in the areas of metaplasia.
- p16ink4 staining will be weak or negative, distinguishing this from either adenoid basal carcinoma (ABC) or adenosquamous carcinoma in situ.

Diagnostic Terminology

- Prostatic metaplasia (benign).

Main Differential Diagnosis

- Adenoid basal carcinomas (ABCs) share with prostatic metaplasia a mixture of immature squamous cells and columnar differentiation as well as an impression of an accentuated perimeter cell layer. However, the situation of the columnar cell acini within the squamous nests or just inside (rather than outside of) the basal layer of squamous is unique to prostatic metaplasia. They are negative or weakly positive for p16ink4 in contrast to ABCs.
- Adenosquamous carcinomas in situ exhibit conspicuous atypia plus strong staining for p16ink4.

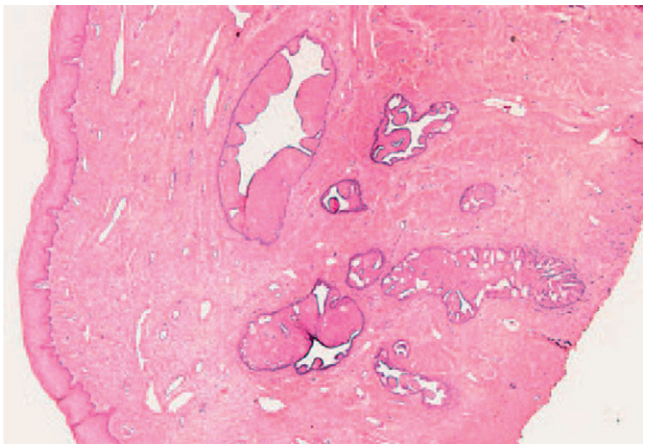


FIGURE 1

Cervical prostatic metaplasia. This focus is rather deeply situated.

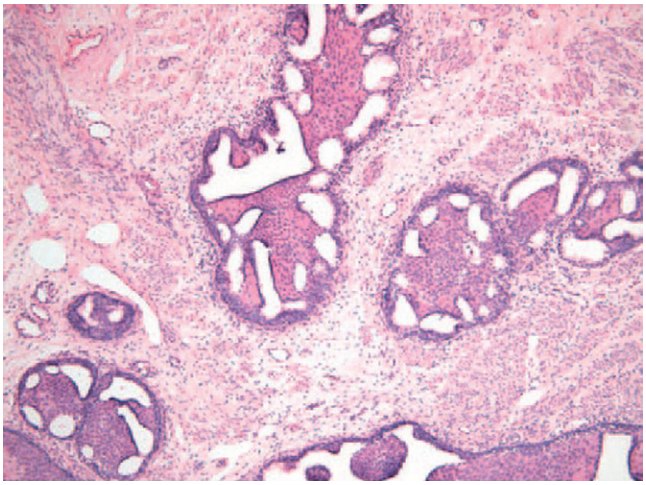


FIGURE 2

Cervical prostatic metaplasia. On higher power, well circumscribed nests squamous epithelium with glandular elements are present within stroma. Note the resemblance to morular metaplasia, where a collar of incomplete acinar architecture merges with central squamous differentiation.

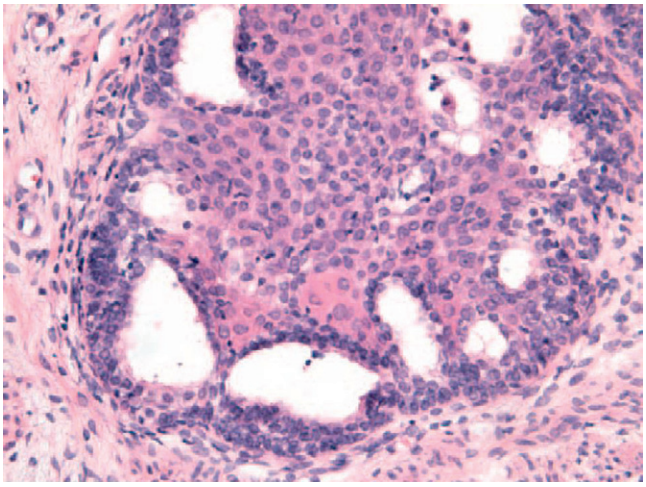


FIGURE 3

At higher magnification, showing the juxtaposition of small columnar acini and bland squamous epithelium.

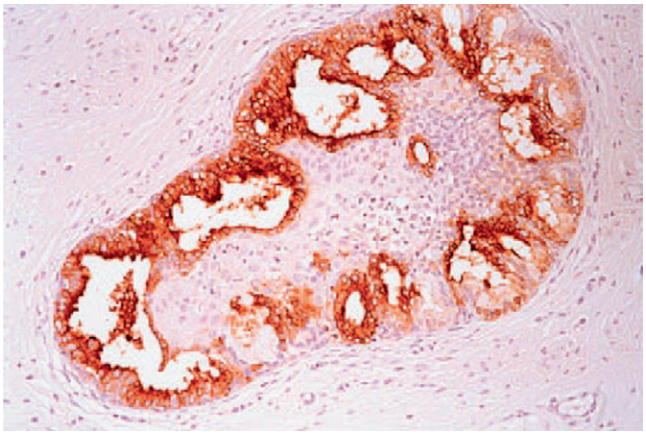


FIGURE 4

Cervical prostatic metaplasia immunostained for prostatic acid phosphatase. Such strong staining is confirmatory, but this biomarker will not always be positive.

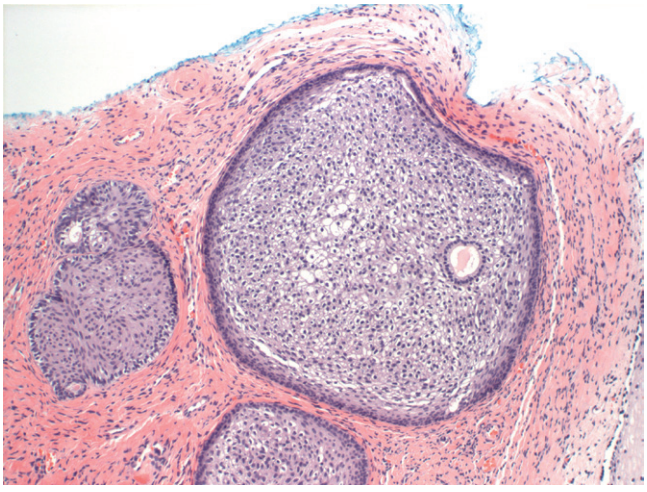


FIGURE 5

Intrasquamous columnar cell acini at low and higher magnifications. This pattern is virtually pathognomonic of prostatic metaplasia.

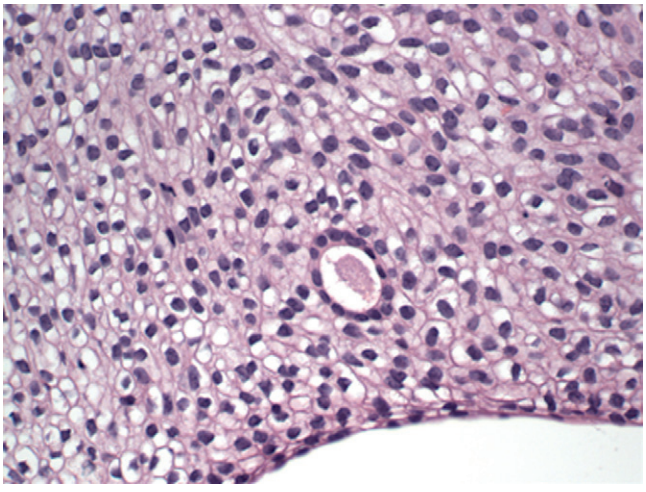


FIGURE 6

Higher magnification of an intrasquamous acinar structure.

ENDOCERVICAL GLANDULAR HYPERPLASIA

Definition—An increase in the number of endocervical glands. May be idiopathic or secondary to increased hormonal stimulation. Some atypical hyperplasias may be associated with minimal deviation adenocarcinomas and Peutz-Jeghers syndrome (see page 300).

Clinical Features

Epidemiology

- Usually seen in reproductive-age women as an incidental finding.

Presentation

- Most patients are asymptomatic and have non–mass-forming lesions.
- One third of patients present with a mass-forming lesion, either with or without clinical symptoms (e.g., pain, bleeding).
- Endocervical glandular hyperplasia, when severe, may be clinically mistaken for a malignant process.

Prognosis and Treatment

- The prognosis is excellent as this is a benign lesion.
- No treatment is typically undertaken, except in cases requiring symptomatic relief.

Pathology

Histology

- **Lobular glandular hyperplasia**
  - An increase in small- to medium-sized glands that maintain a lobular profile.
  - Often, a centrally located, large gland can been identified at low power.
  - The glandular proliferation is usually limited to the inner half of the cervical wall and is sharply demarcated from the cervical stroma.
  - The epithelial cells lining the glands are columnar mucinous cells that have a pyloric gland phenotype.
- **Diffuse laminar glandular hyperplasia**
  - A proliferation of glands similar to the lobular type; however, the glands extend to the same depth within the cervical stroma.
  - The hyperplastic glands involve the entire circumference of the cervix.
  - There is an unusually sharp interface between the glands and the stroma.
  - The glands maintain a round or tubular profile with occasional branching.
  - Inflammation may be present and is typically more prominent in the deeper aspect.
  - Nuclear atypia should be minimal to absent.

Immunopathology (Including Immunohistochemistry)

- p16 is negative. Lobular endocervical hyperplasia may stain for gastric mucins (MUC6) but staining is normally not necessary.

Main Differential Diagnosis

- Endocervical adenocarcinoma.
  - Minimal deviation endocervical adenocarcinoma (adenoma malignum; see page 300).
  - Atypical lobular endocervical glandular hyperplasia (see page 300).

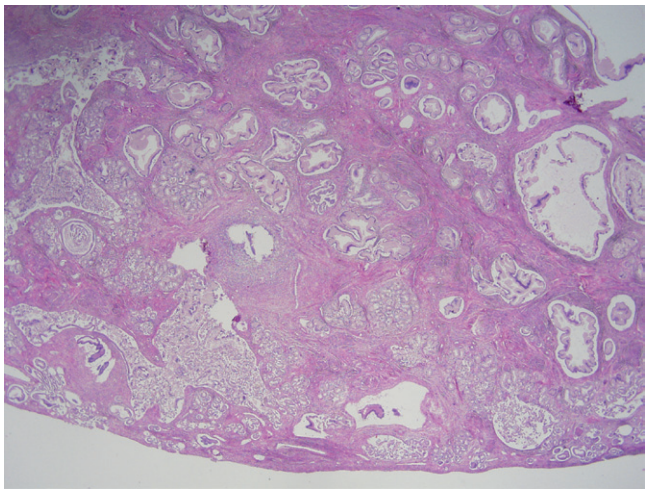


FIGURE 1

Endocervical glandular hyperplasia. Diffuse laminar hyperplasia involving the entire circumference and depth of the cervical stroma. The groups of glands maintain an overall lobular architecture.

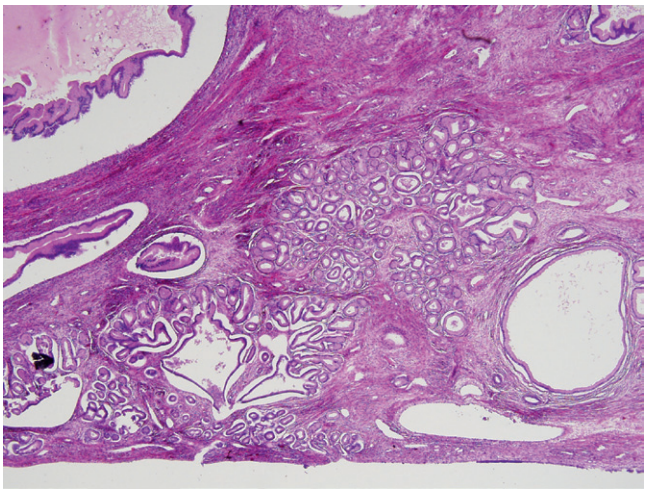


FIGURE 2

Endocervical glandular hyperplasia. The glands are in lobular groups and are tubular with only rare branching glands. A central, larger gland can be seen in some of the groups.

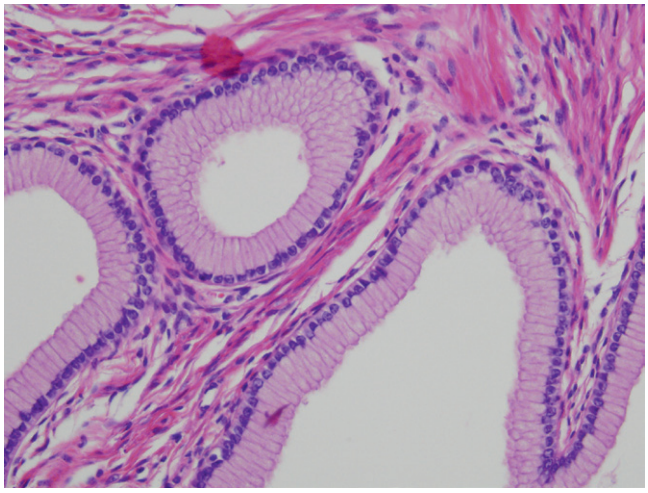


FIGURE 3

Endocervical glandular hyperplasia. At higher power the pyloric (gastric) phenotype of the glands can be seen. Note the lack of nuclear atypia and mitotic activity.

METASTATIC SEROUS CARCINOMA TO THE CERVIX

Definition—Serous carcinoma originating from the upper genital tract involving the cervix (drop metastasis).

Clinical Features

Epidemiology

- Uncommon.
- Women in their 60s to 70s.

Presentation

- Abnormal vaginal bleeding.
- May be present as a clinically identifiable mass or abnormal cervix.
- May be clinically occult and identified only on endocervical brushings.

Prognosis and Treatment

- Poor.
- Treatment is based on tumor stage and may include surgery and/or chemoradiation.
- Workup to determine primary tumor site is the standard of care.

Pathology

Histology

- These tumors are histologically similar to the primary tumor and composed of large pleomorphic cells with vesicular nuclei and prominent nucleoli.
- Neoplastic cells may be present only on the surface, replacing normal cervical epithelium, may form an exophytic mass lesion, or may diffusely invade the cervical stroma.
- Similar to the architecture of the primary tumor, the cells may be arranged in sheets (with characteristic cracks and crevices) or may form papillae and micropapillae.
- Features that favor a metastatic carcinoma include high nuclear grade and complex architecture (papillae).

Immunopathology (Including Immunohistochemistry)

- Positive for p16, p53 (strong, diffuse), and CK7.
- Negative for human papillomavirus (HPV).

Main Differential Diagnosis

- Primary serous carcinoma of the cervix. These women are usually younger and a more conventional cervical adenocarcinoma is also present.
- Adenocarcinoma in situ. These can be difficult. A p53 stain (will be negative in AIS) is helpful.
- High-grade squamous intraepithelial lesion. Rarely may be mimicked by a metastatic carcinoma.

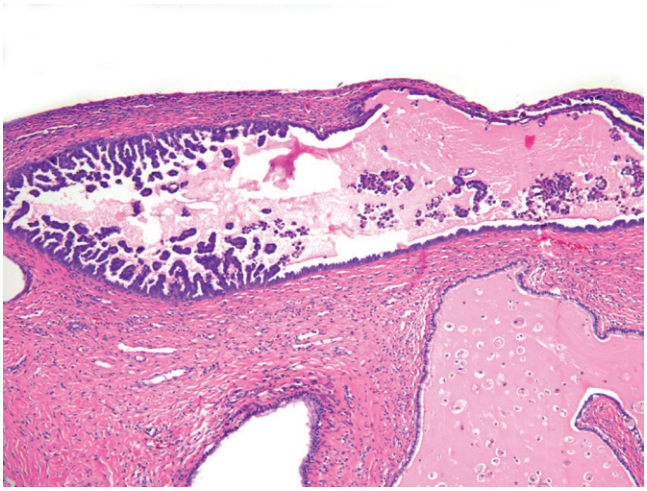


FIGURE 1

Metastatic serous carcinoma to the cervix. Low-power image showing neoplastic papillary epithelium lining mucous cyst.

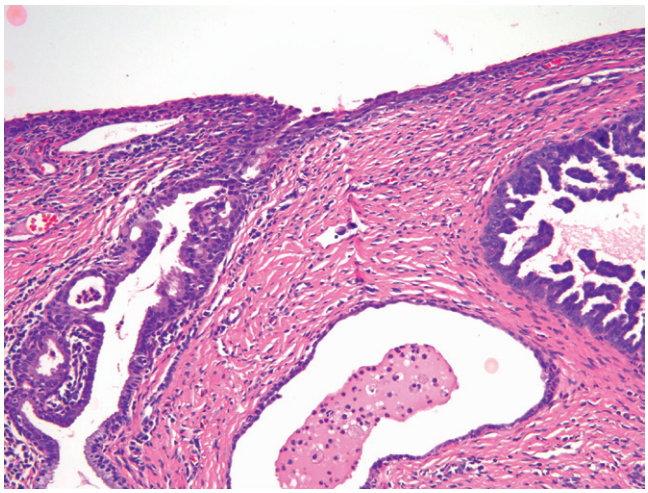


FIGURE 2

Metastatic serous carcinoma to the cervix. At higher power the normal mucosa *(left)* is opposite the involved mucous cyst *(right)*.

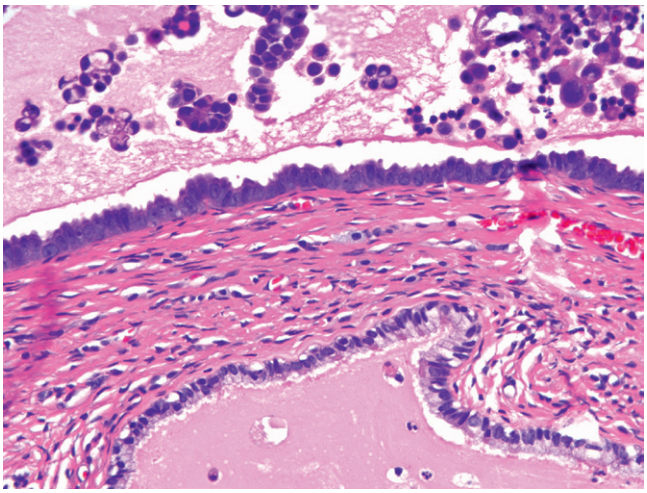


FIGURE 3

Metastatic serous carcinoma to the cervix. At higher magnification the cyst contains free-floating papillae. Note the rather subtle neoplastic epithelium seen here as a cuboidal epithelium with a high nuclear-to-cytoplasmic (N/C) ratio.

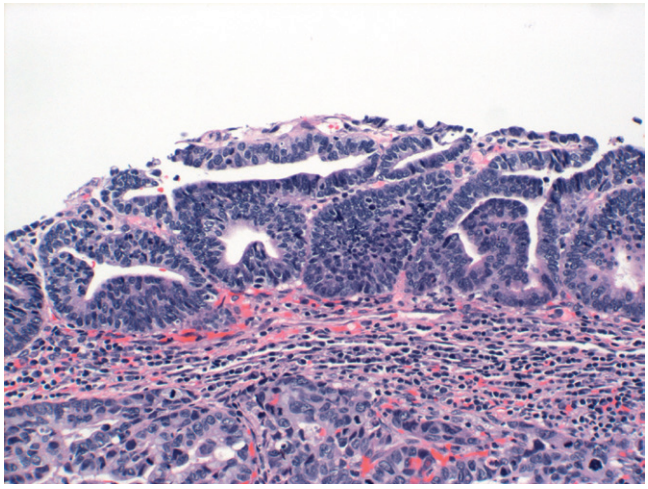


FIGURE 4

In this metastatic focus the glands somewhat resemble a primary glandular neoplasm of the cervix.

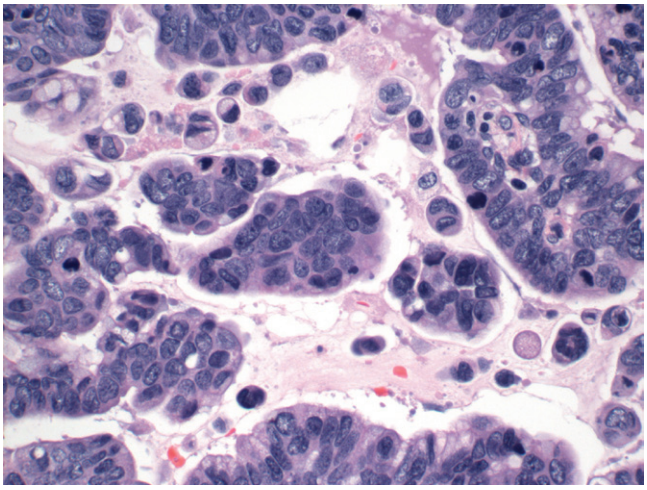


FIGURE 5

The detached fragments are clearly serous in morphology.

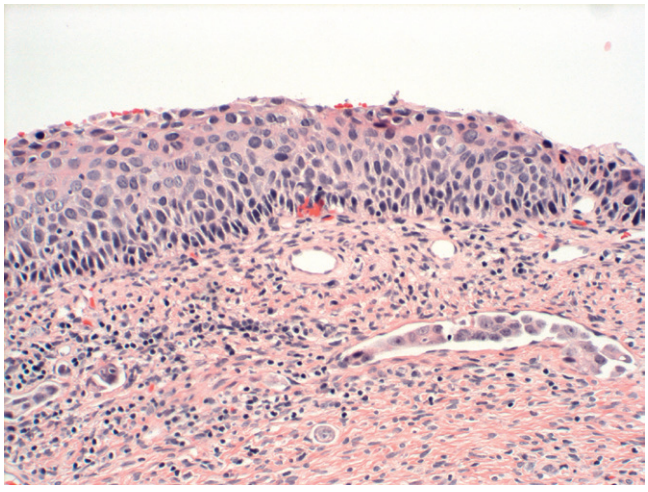


FIGURE 6

Metastatic serous carcinoma in superficial lymphatics. Is that a high-grade squamous intraepithelial lesion (HSIL) above or a metastatic serous carcinoma mimicking an HSIL? Likely the latter!

METASTATIC ENDOMETRIOID CARCINOMA TO THE CERVIX

Definition—Endometrial adenocarcinoma which has spread caudally to involve the cervix.

Clinical Features

Epidemiology

- Varies with the subtype of endometrial adenocarcinoma.

Presentation

- May be identified clinically as a prolapsing cervical mass or as an abnormally firm endocervical canal.
- May be identified at the time of frozen section or upon opening the uterus (tumor grossly extends past the lower uterine segment to the cervix).
- May be identified in routine histologic sections of cervix or in an outpatient cervical biopsy.
- Patients are typically over age 50.

Prognosis and Treatment

- Endocervical *stromal* involvement by endometrial adenocarcinoma increases tumor stage (to stage II).
- Replacement of the endocervical glandular epithelium by carcinoma does not increase tumor stage.
- Involvement of endocervical glands by tumor does not increase tumor stage.
- Overall prognosis and treatment plan is dependent on the characteristics of the primary tumor.

Pathology

Histology

- Tumor involvement may be contiguous with the endometrial mass or may be a discrete focus (drop metastasis).
- The histology varies with tumor subtype (endometrioid, clear cell, mucinous) and may be well or poorly differentiated.
- Features that favor a metastatic endometrioid carcinoma include low-grade nuclei, bland mucinous glands, well-differentiated squamous metaplasia, and lack of concurrent cervical adenocarcinoma in situ.
- Uterine sampling (endometrial biopsy or curettage) is required for complete evaluation of the potential primary site.

Immunopathology (Including Immunohistochemistry)

- The same as the primary uterine tumor, and varies slightly with subtype.
- A panel of stains is sometimes used to distinguish a cervical (p16+, CEA+, vimentin–, ER/PR–) from an endometrial (p16–, CEA–, vimentin+, ER/PR+) primary adenocarcinoma in biopsy samples; however, a degree of skepticism must be employed when interpreting the results as there is significant overlap between the two tumor groups.

Main Differential Diagnosis

- Primary endocervical adenocarcinoma. Look for intense p16 staining, at least moderate nuclear atypia, apical mitoses.
- Adenocarcinoma arising out of cervical endometriosis.

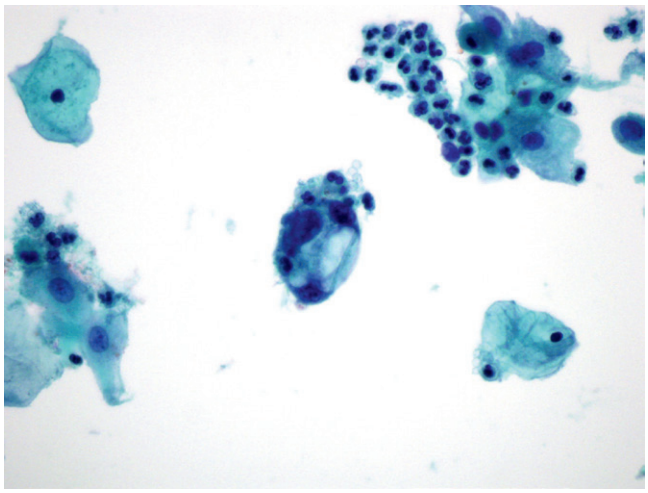


FIGURE 1

Endometrial adenocarcinoma involving the cervix. A single neoplastic cell is seen in the cervical cytology.

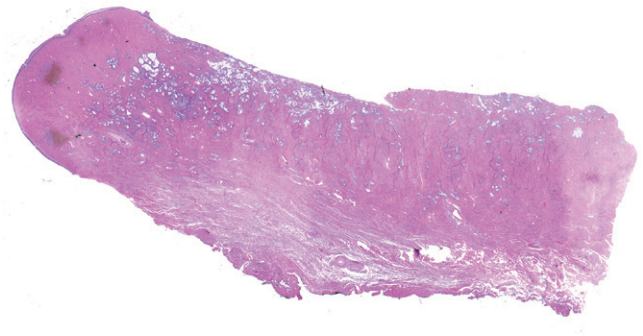


FIGURE 2

Metastatic endometrial adenocarcinoma involving the cervix. This low-power view of the cervix depicts a confluent arrangement of delicate glands mimicking mesonephric hyperplasia or endocervical tunnel clusters.

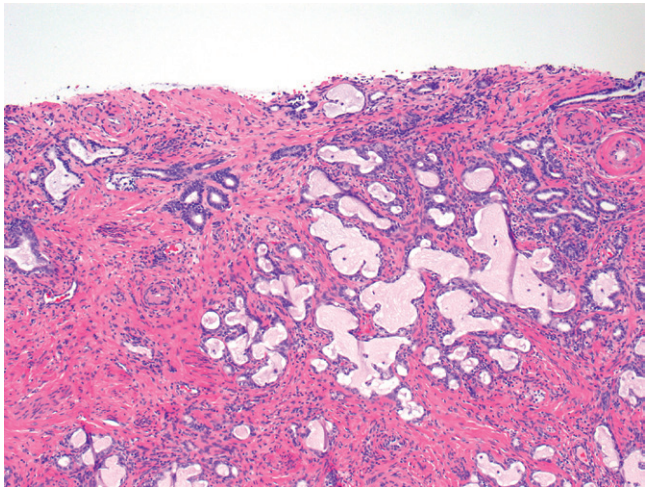


FIGURE 3

Metastatic endometrial adenocarcinoma involving the cervix. This could be confused with tunnel clusters.

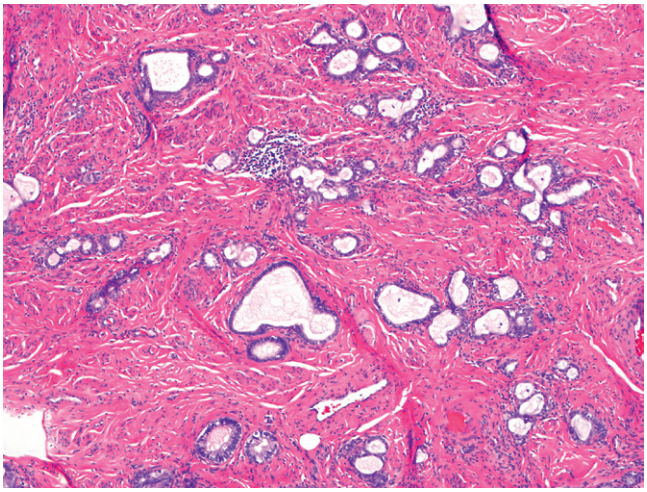


FIGURE 4

Metastatic endometrial adenocarcinoma involving the cervix. A key feature here is the lack of gland crowding.

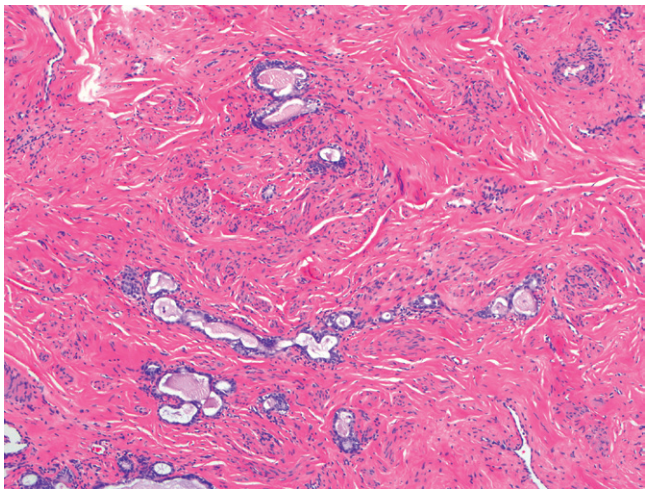


FIGURE 5

Metastatic endometrial adenocarcinoma involving the cervix. Note here the resemblance to mesonephric remnants.

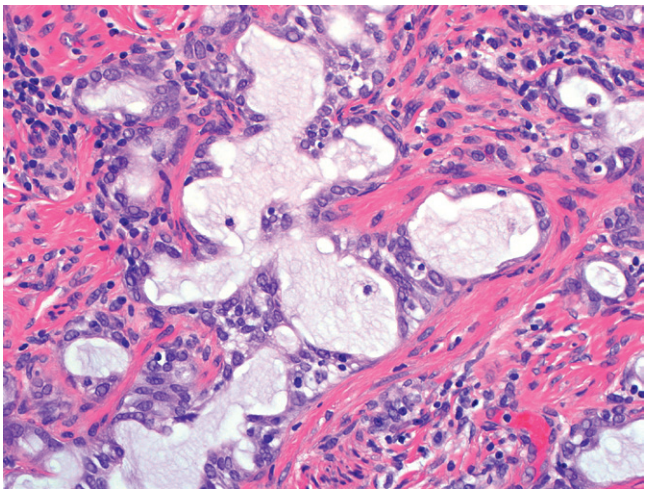


FIGURE 6

Metastatic endometrial adenocarcinoma involving the cervix. At higher magnification the neoplastic glands are deceptively bland appearing. The key is to distinguish them from benign endocervix or mesonephric remnants.

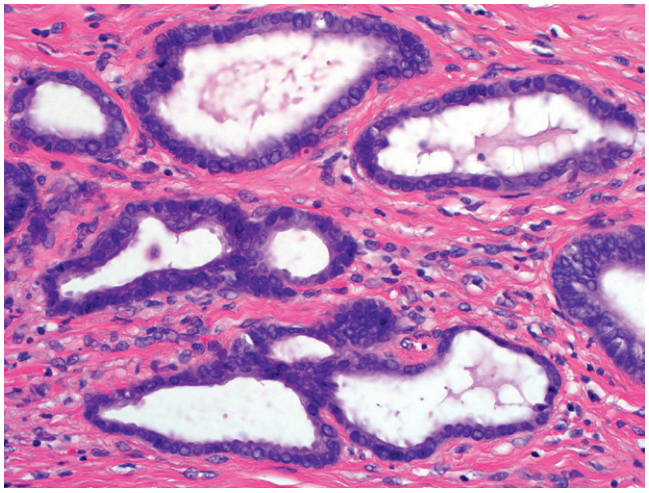


FIGURE 7

Metastatic endometrial adenocarcinoma involving the cervix. Note the lining of the neoplastic glands is a single cell layer in this case, which can be deceptive.

ATYPICAL ENDOCERVICAL POLYP

Brooke E. Howitt, MD

Definition—An endocervical polyp with an atypical epithelial-stromal proliferation that resembles adenosarcoma but is not diagnostic.

Clinical Features

Epidemiology

- Uncommon but will be encountered.
- No predisposing factors have been identified.

Presentation

- Patients present with a cervical polyp or mass.
- Most often asymptomatic, with a polyp identified on routine exam.
- May present with spotting.

Prognosis and Treatment

- Atypical polyps are benign and so have an excellent prognosis,
- Excision of the polyp or mass is required for diagnosis and is also the treatment of choice.
- A small subset of endocervical adenosarcomas are misclassified as polyps initially; thus any atypical polyp should be monitored for regrowth.

Pathology

Histology

- Adenosarcoma-like polyps display some architectural resemblance to low-grade adenosarcoma.
- The most common feature is the presence of irregularly shaped glands with occasional cleftlike, branching spaces that are reminiscent of phyllodes tumor of the breast.
- These irregular glands are best appreciated at low power.
- The area of concern typically occupies only a portion of the polyp.
- High-power examination reveals a notable lack of significant mitotic activity that is usually less than 2 per 10 high powered (400×) fields.
- Periglandular stromal condensation (cuffing) is present to some degree, but there should be minimal or no stromal atypia or nuclear crowding.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Endocervical polyp—typical polyps present no problem given the lack of stromal hypercellularity.
- Low-grade endocervical adenosarcoma—these should have conspicuous nuclear atypia in the periglandular stroma, manifested primarily by nuclear crowding, coupled with mitotic activity.
- Prolapsed endometrial polyp—these can appear atypical, but the classic periglandular cuffing is not seen.
- Adenomyoma—the key to this diagnosis is the presence of smooth muscle fascicles between the endocervical crypts.

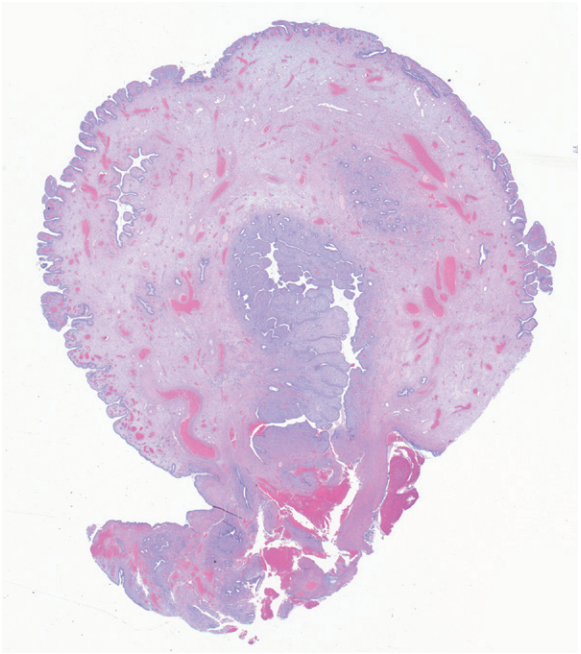


FIGURE 1

Atypical endocervical polyp. Low-power examination shows a cervical polyp with a central focus of leaflike architecture. This is a typical presentation. It could be argued that this is an "early" adenosarcoma arising in a polyp; however, the implication is the same, which is a lesion at low risk for recurrence once excised.

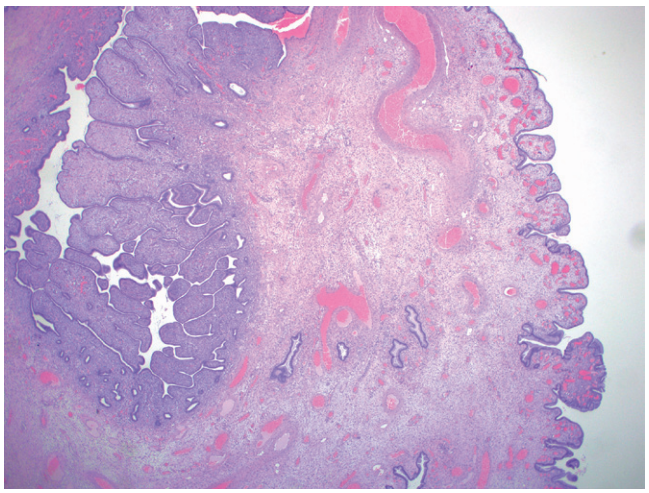


FIGURE 2

Atypical endocervical polyp. At higher magnification there is focal leaflike arrangement of epithelial fronds.

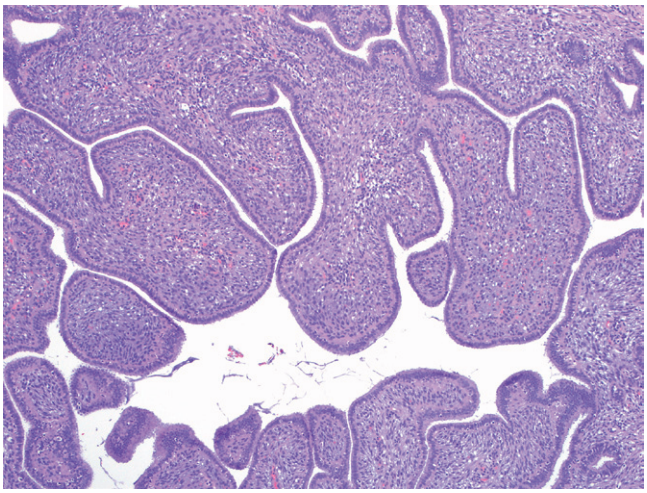


FIGURE 3

Atypical endocervical polyp. At higher magnification there is a leaflike arrangement of epithelial fronds.

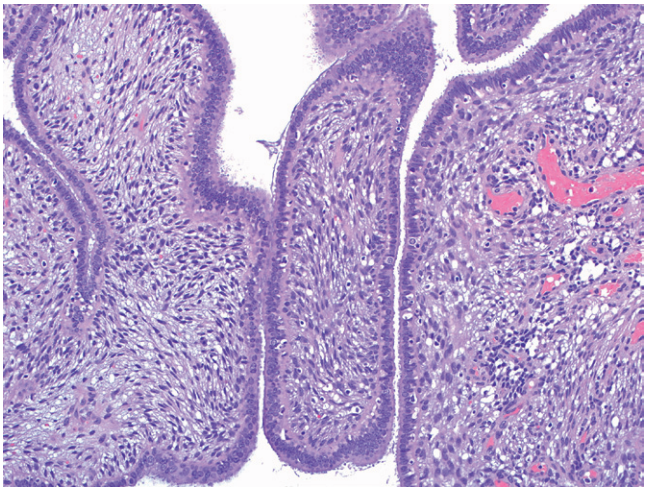


FIGURE 4

Atypical endocervical polyp. At moderate power there is minimal subepithelial stromal condensation seen.

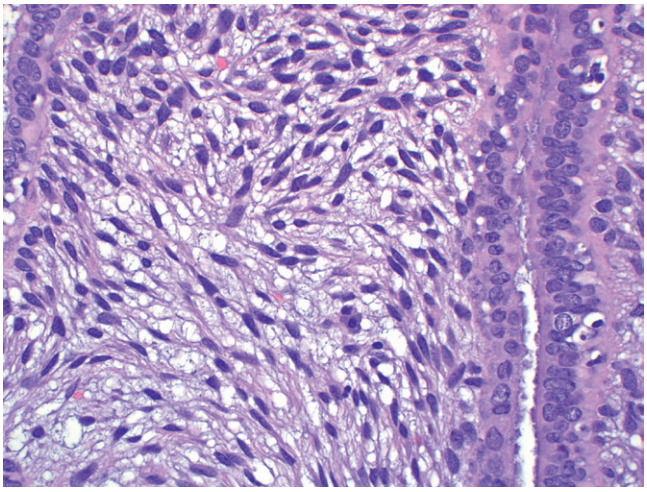


FIGURE 5

Atypical endocervical polyp. At high magnification there is minimal stromal cell atypia.

ADENOMYOMA OF THE CERVIX

Definition—A benign, discrete proliferation of smooth muscle stroma and endocervical glands.

Clinical Features

Epidemiology

- Adenomyomas and polypoid adenomyomas of the cervix are rare.
- The majority of these lesions occur within the uterine cavity, not at the cervix.
- The mean age at diagnosis is 40 years.

Presentation

- Pedunculated or sessile-based cervical masses.
- May be identified as a polyp at routine screening, or patients may report vaginal spotting or complain of symptoms related to mass effect (such as pressure).

Prognosis and Treatment

- Excision of the mass to establish diagnosis is common.
- Cervical adenomyomas have an excellent prognosis, and once completely excised, no further treatment is warranted.
- Incompletely excised lesions may recur locally.

Pathology

Histology

- By definition, adenomyomas are composed of benign glandular elements admixed with smooth muscle–type stroma.
- The glands are lined by bland endocervical cells and may exhibit focally prominent cystic change.
- Clusters of glands have a lobular profile at low power; a stromal reaction should not be present.
- The well-circumscribed, lobular glands are important in distinguishing sessile adenomyomas from the histologically similar minimal deviation adenocarcinoma of the cervix (adenoma malignum).

Immunopathology (Including Immunohistochemistry)

- Endocervical adenomyomas typically stain positive for PAX2. The majority of endocervical adenocarcinomas (particularly adenoma malignum) are negative for PAX2.
- The stroma should be positive for smooth muscle markers (SMA).

Main Differential Diagnosis

- Adenoma malignum variant of endocervical adenocarcinoma: Gland architecture is more complex and rambling rather than tightly arranged as in adenomyoma. Gland epithelium and outlines will appear more complex. Look for a lobular arrangement of glands with a defined smooth muscle–type stroma in the adenomyoma.
- Endocervical polyp: The primary difference is the stromal smooth muscle differentiation in the adenomyoma.
- Adenosarcoma or atypical polyp: Demonstrate both irregular intraglandular polypoid growth and subepithelial stromal condensation.

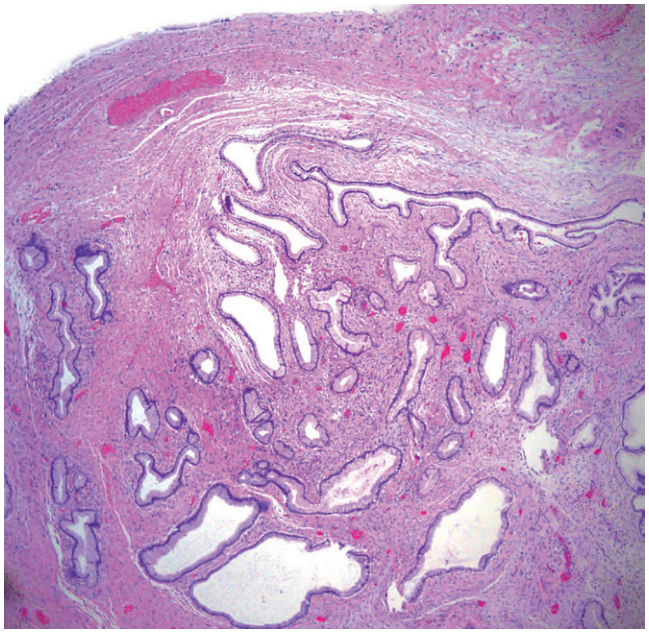


FIGURE 1

Cervical adenomyoma. Low-power examination shows a somewhat discrete, nodular proliferation of endocervical epithelium and myomatous stroma. The glands/crypts are arranged in lobules. A desmoplastic stromal response is not present.

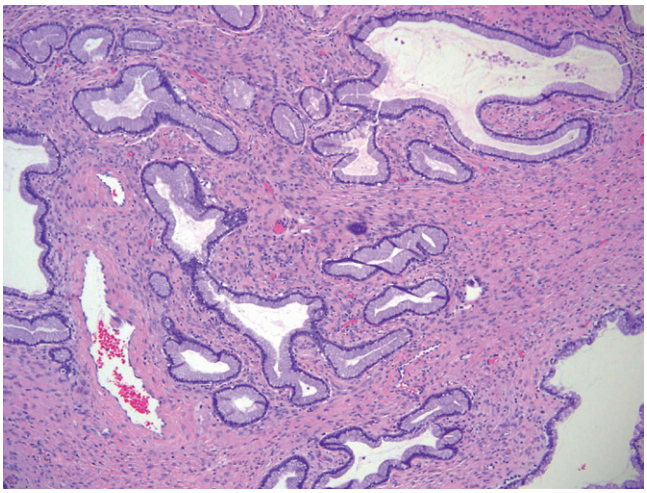


FIGURE 2

Cervical adenomyoma. High-power examination shows bland endocervical epithelium without nuclear atypia. Nuclear stratification and apical mitoses are not seen. The stroma is pink and smooth muscle–like without a desmoplastic reaction.

MICROGLANDULAR HYPERPLASIA OF THE CERVIX

Definition—A proliferation of specialized cuboidal cells derived from the squamocolumnar junction that gives rise to reserve cells, squamous metaplasia, and can harbor squamous intraepithelial lesions (SILs).

Clinical Features

Epidemiology

- Most commonly occurs in young women with an uncertain relationship to hormones.
- Occasionally occurs in women not receiving hormonal therapy, as well as postmenopausal women.
- Likely a proliferation of multipotential squamocolumnar junction–type cells.

Presentation

- Typically incidental at the time of cervical sampling.
- Large lesions may form masses and present with a friable cervix, which may simulate polyps or neoplasia.

Prognosis and Treatment

- Excellent; no treatment is required but can harbor SIL.

Pathology

Histology

- In early forms, low-power evaluation will show an increased number of keratin 7–positive acini lined by cuboidal cells with a well-defined, lobular contour.
- More florid lesions will display loss of intervening stroma with back-to-back acini and cysts. In some forms, acini will be absent and the cuboidal cells will form a near-solid array.
- The cells comprising the glands are bland with cytoplasmic vacuoles, both subnuclear and supranuclear.
- Abundant neutrophilic inflammation is typically present, but apoptotic cells are not typically seen.
- Eosinophilic luminal mucin is often noted.
- The proliferative index is low.
- In more advanced lesions, p63 and krt5 are induced, found first in the acini and later in subcolumnar reserve cells that arise from acini.
- In advanced forms the reserve cells undergo expansion to form metaplasia, and the cuboidal surface cells evolve into mature columnar cells.
- Several variants have been described (hobnailed cells, signet-ring cells, solid pattern, and trabecular patterns) and may lead to diagnostic confusion; however, close attention to the cellular and nuclear morphology should lead to the correct diagnosis.
- SILs can occasionally arise in some cases of microglandular change, seen as an expansion of atypical reserve cells.

Immunopathology (Including Immunohistochemistry)

- Keratin 7 is strongly positive in the acini.
- p63 and krt5 are positive in endocervical reserve cells and immature metaplasia.
- CEA is negative.
- p16 is negative or patchy in distribution.

Main Differential Diagnosis

- Endocervical adenocarcinoma (in situ) can be confused with this entity! However, cellular atypia is usually conspicuous. p16ink4 and MIB1 staining will be markedly increased.
- Clear-cell adenocarcinoma of the cervix does not display reserve cells. Moreover, the nuclei are larger and uniform appearing.
- Endometrial adenocarcinoma (low grade, mucinous type) can present with small groups of microacini and is one of the more difficult distinctions. However, the microacini tend to have a "soft" appearance with less sharply defined vacuoles, and often with minimal intervening stroma.

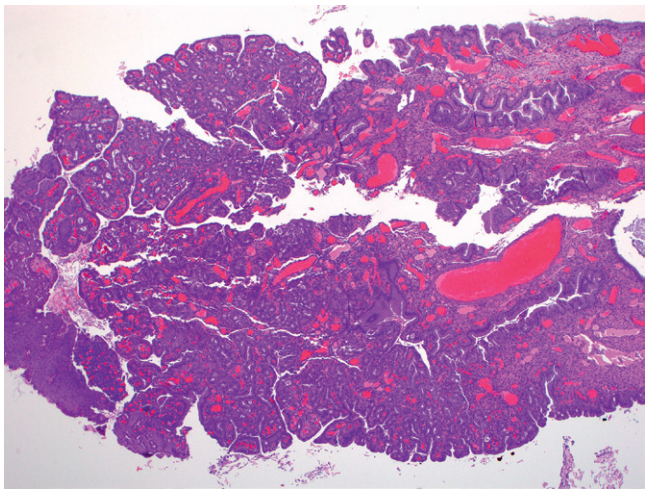


FIGURE 1

Microglandular change. Low-power image showing a polypoid proliferation of epithelial cells. The cells are arranged in a solid pattern, but nuclear atypia, mitotic activity, and nuclear stratification are not seen.

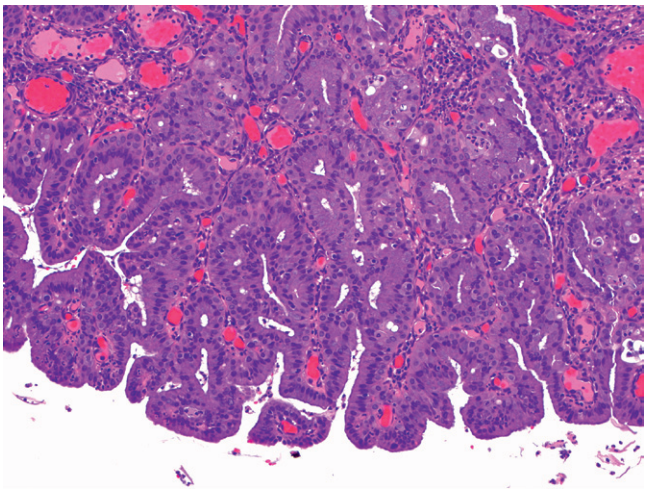


FIGURE 2

Microglandular change. At higher magnification regular acini are seen. Reserve cells are inconspicuous.

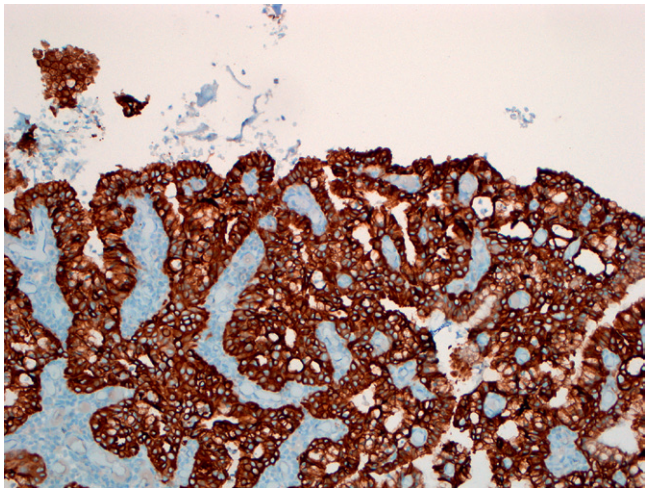


FIGURE 3

Microglandular change. These lesions stain strongly for CK7, a marker of squamocolumnar junction cells and most prominent in immature low-columnar cells.

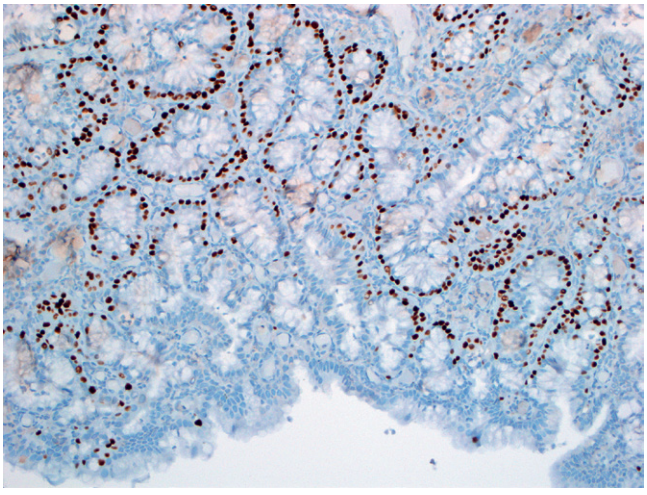


FIGURE 4

p63 highlights reserve cells in microglandular change.

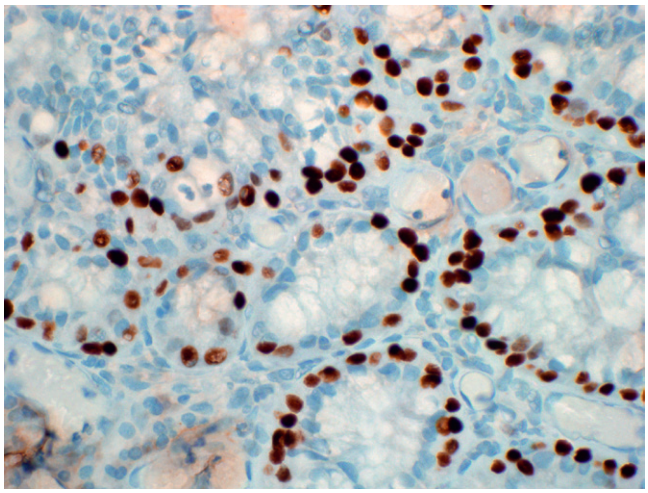


FIGURE 5

At higher magnification p63-positive acini merge with acini in which the reserve cells have segregated beneath the lining cells.

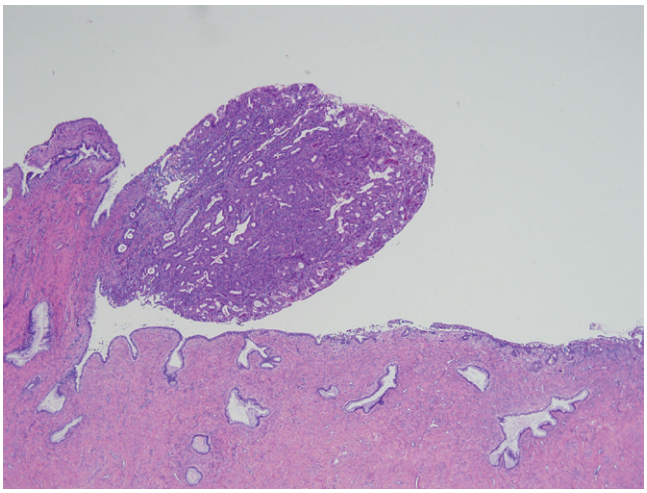


FIGURE 6

Endocervical polyp mimicking a carcinoma due to prominent glandular proliferation.

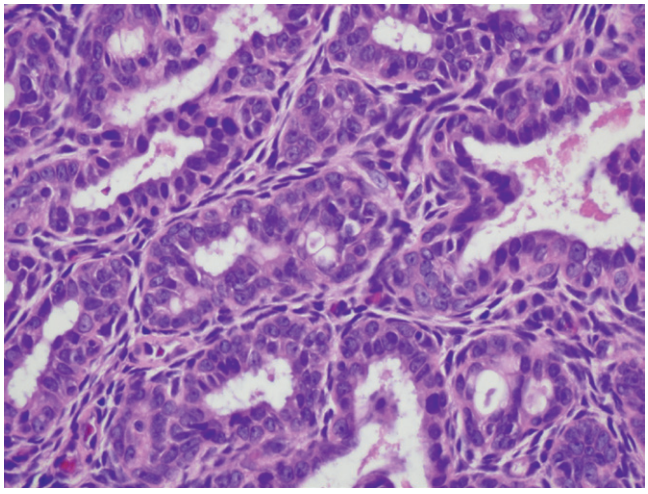


FIGURE 7

Higher magnification of the case in Figure 6. The glands may appear worrisome at first but in this case are associated with a distinct reserve cell layer.

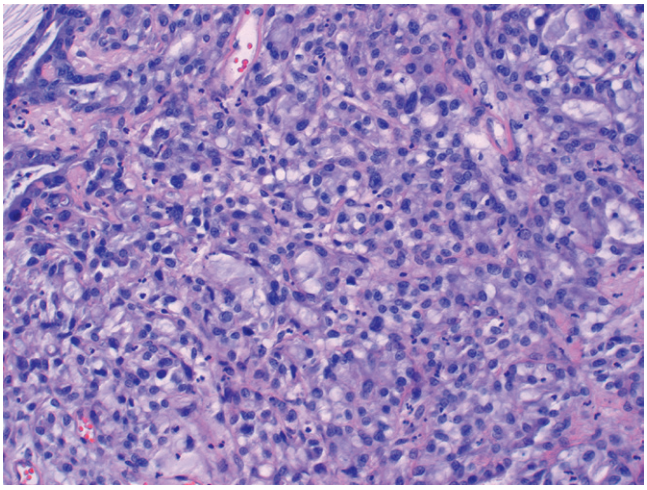


FIGURE 8

An uncommon variant of microglandular change in which the acini are not well formed. This pattern can be more difficult to distinguish from adenocarcinoma.

ADENOSARCOMA OF THE CERVIX

■ **Brooke E. Howitt, MD**

DEFINITION—A bi-patterned low-grade malignancy composed of neoplastic stroma admixed with benign but architecturally unique epithelial elements.

CLINICAL FEATURES

EPIDEMIOLOGY

- Extremely rare; accounts for less than 2% of all müllerian adenosarcomas.
- Average age at presentation is 31 years, with an age range from 11 to 65 years.
- One third of patients are under the age of 15.

PRESENTATION

- Vaginal bleeding is most often the presenting symptom.
- Physical exam often reveals a mass protruding through the cervical os, mimicking a benign endocervical polyp.
- Polyp/mass size is variable and ranges from less than 1 cm to 5 cm.

PROGNOSIS AND TREATMENT

- Prognosis is good, and linked to depth of invasion.
- Up to one third recur, but recurrences are typically locoregional (pelvic).
- Hysterectomy with close clinical observation is the treatment of choice; however, some, particularly those with very bland histology or those particularly polypoid, may be treated with excision alone and close monitoring of the cervix for regrowth.
- Oophorectomy is traditionally performed, but in young women with small or noninvasive lesions some may defer oophorectomy.
- Rare cases exhibit frankly malignant behavior.

PATHOLOGY

HISTOLOGY

- In classic cases the low-power appearance is reminiscent of a phyllodes tumor of the breast, with broad, leaf-shaped stromal proliferations protruding into glandular lumina.
- The glandular spaces may be dilated or slitlike and are distorted by the stromal proliferation, which is often most prominent immediately adjacent to the glands (cuffing).
- The neoplastic stromal cells are spindled, with moderate nuclear-to-cytoplasmic ratios, mild nuclear atypia, and easily identifiable mitoses (>2/10 hpf). Stromal atypia is a cardinal sign of adenosarcoma and most important in distinguishing it from an atypical polyp or adenomyomatous polyp.
- Glandular epithelium often shows altered differentiation, such as ciliated or endometrioid-type epithelium.
- Heterologous elements, such as skeletal muscle or cartilage, are occasionally seen, although well-defined myomatous stroma is not consistent with this diagnosis.

IMMUNOPATHOLOGY (INCLUDING IMMUNOHISTOCHEMISTRY)

- Noncontributory.

MAIN DIFFERENTIAL DIAGNOSIS

- Benign endocervical (atypical) polyp—these usually exhibit stromal condensation and some albeit rather minimal phyllodes-like glandular architecture. They should be devoid of conspicuous stromal atypia.
- Adenomyoma—this tumor will exhibit conspicuous myomatous differentiation.
- Adenosarcoma arising in endometriosis and uterine adenosarcomas metastatic to the cervix are other considerations but can usually be distinguished clinically or by mode of presentation.
- Rare cervical polyps can display bizarre symplastic-like nuclei, but do not otherwise resemble adenosarcoma.
- Embryonal rhabdomyosarcoma—subepithelial cambium layer but no excess benign glands. Typically vaginal in location.

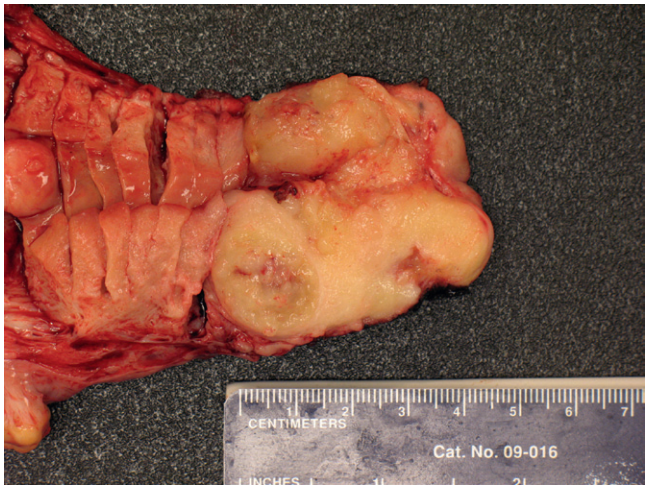


FIGURE 1

Cervical adenosarcoma. Gross examination shows a fleshy mass located in the endocervix and extending nearly to the lower uterine segment. In this example the upper portion of the mass is vaguely polypoid, while other areas are invasive into the cervical stroma.

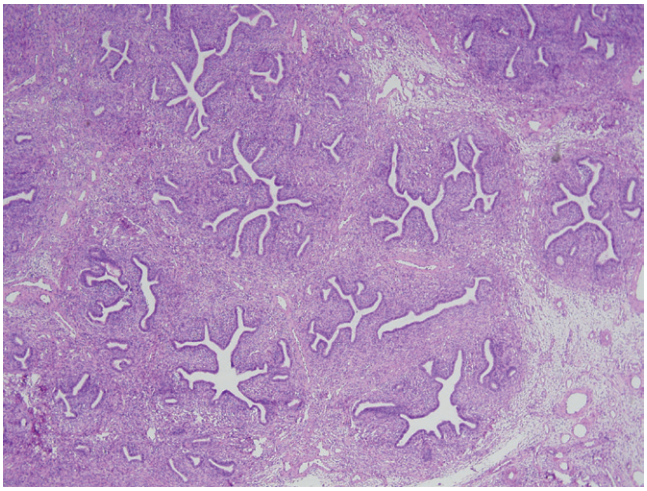


FIGURE 2

Cervical adenosarcoma. This low-power image shows a proliferation of stromal cells surrounding epithelial elements and creating polypoid, vaguely leaflike architecture within the glandular spaces. Periglandular cuffing is prominent.

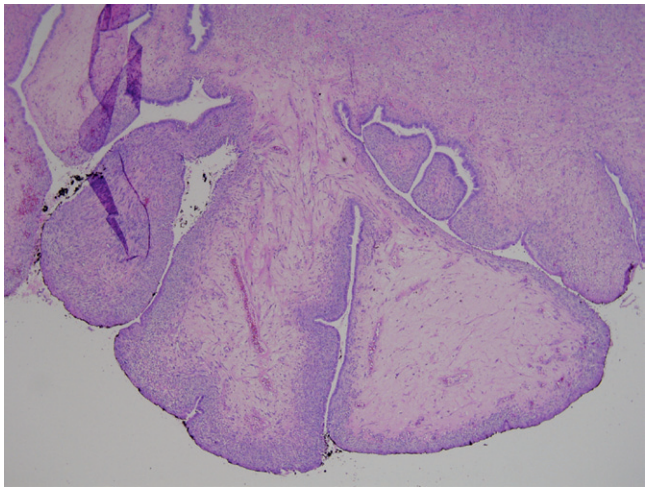


FIGURE 3

Cervical adenosarcoma. Low power of this lesion is characterized by the presence of large, broad leaflike structures. Stromal cuffing or condensation just beneath the epithelium is prominent.

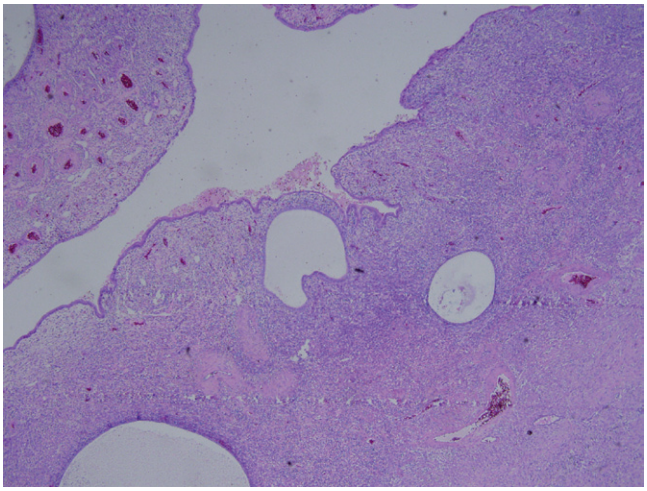


FIGURE 4

Cervical adenosarcoma. This lesion is characterized by dilated, distending glandular structures. Stromal cuffing is subtle, but present.

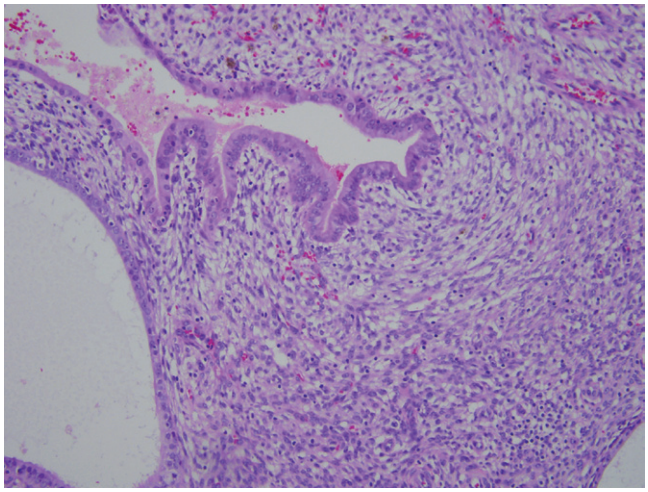


FIGURE 5

Cervical adenosarcoma. High-power examination confirms the benign histology of the epithelial elements. There are small intraluminal polypoid projections. The stromal cells are densely arranged adjacent to the epithelium, with mild nuclear atypia. Mitoses are subtle and infrequent in this example.

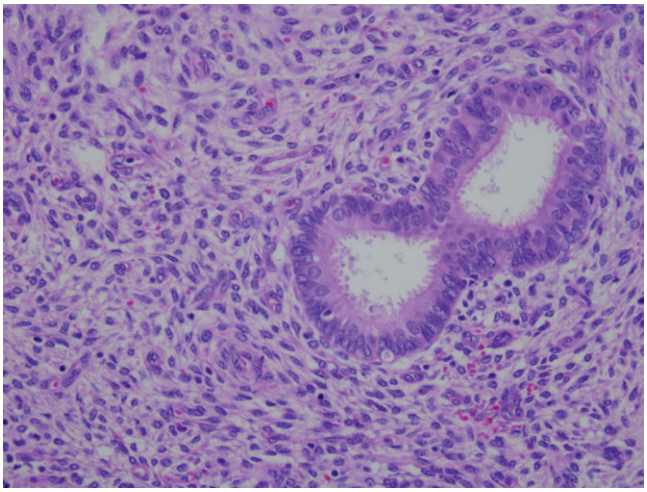


FIGURE 6

Cervical adenosarcoma. The glands in this high-power image are dilated and exhibit altered differentiation (cilia). The stromal cells have mild nuclear atypia, and mitoses are not easily identified.

CERVICAL SCHWANNOMA

Definition—A generally benign, peripheral nerve sheath tumor.

Clinical Features

Epidemiology

- Rare, limited to occasional case reports.
- Most reported cases—benign and malignant—occur in the third to eighth decades.

Presentation

- Vaginal bleeding in many cases.
- May be asymptomatic, detected on routine examination.
- Well-circumscribed cervical mass, usually less than 5 cm.
- Red to gray-white on sectioning.

Prognosis and Treatment

- Excisional therapy is usually adequate.
- Malignant lesions can be cured by excision but occasional recurrences have been reported.

Pathology

Histology

- Spindle cell proliferation.
- Nuclear pallisading.
- Thick-walled hyalinized blood vessels.

Immunopathology (Including Immunohistochemistry)

- Positive for S-100, vimentin.
- Negative for neurofilament protein (NFP), CD34, desmin, actin, chromogranin, synaptophysin, and melanoma markers (MART-1, MelanA, HMB-45).

Main Differential Diagnosis

- Neurofibroma—CD34 and NFP positive.
- Desmoplastic melanoma—positive for melanoma markers.
- Leiomyoma or angiomyomfibroblastoma—negative for S100.

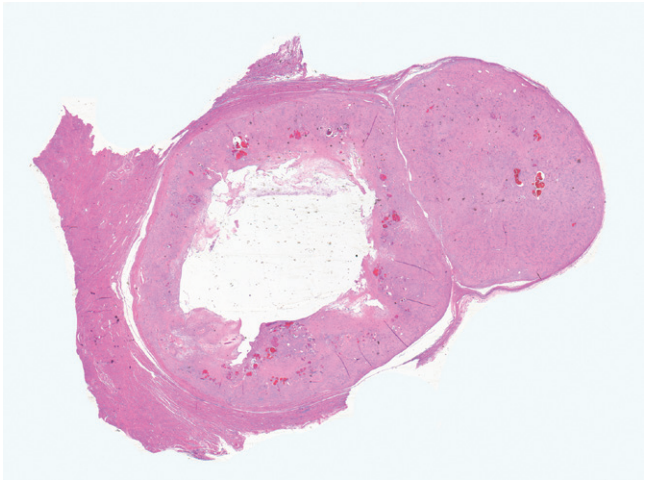


FIGURE 1

Cervical schwannoma. Note the well circumscribed appearance at low magnification.

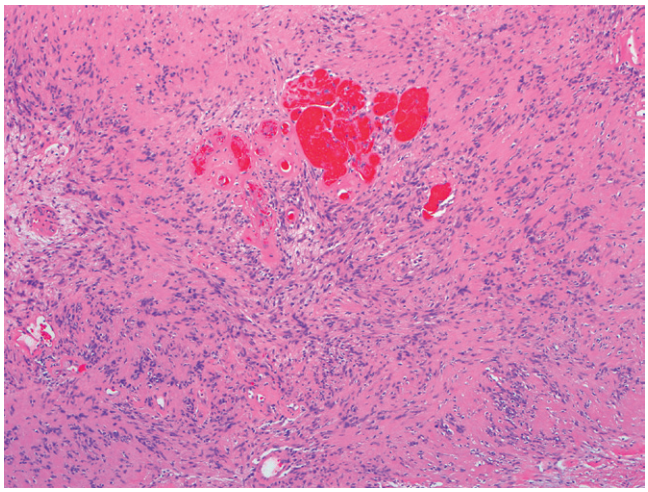


FIGURE 2

Cervical schwannoma. At medium power the pallisaded nuclei and thick-walled vessels can be seen.

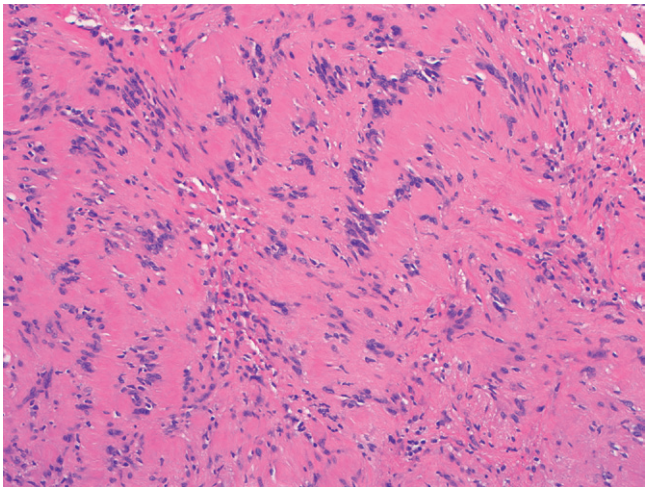


FIGURE 3

Cervical schwannoma. Higher magnification of the pallisaded nuclei.

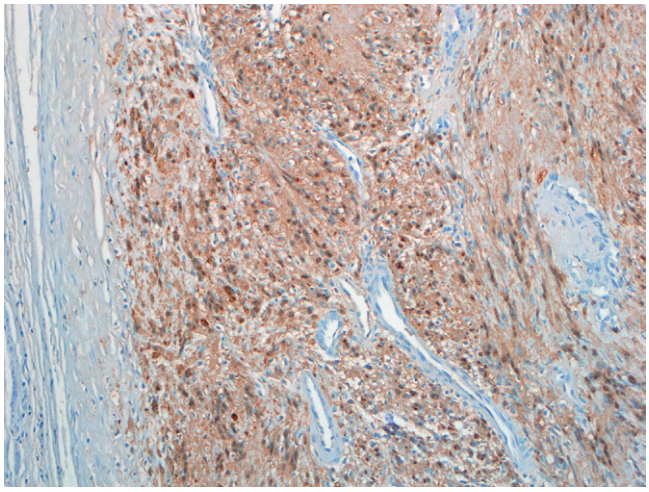


FIGURE 4

Cervical schwannoma. There is strong staining for S-100.

GLIAL POLYP OF THE CERVIX

Definition—A polyp of the cervix composed of mature glial tissue.

Clinical Features

Epidemiology

- Extremely rare.
- Signifies retained glial tissue from a prior pregnancy based on genetic studies.
- Reproductive age group.

Presentation

- Pedunculated or sessile-based cervical masses.
- May be identified as a polyp at routine screening, or patients may report vaginal spotting or complain of symptoms related to mass effect (such as pressure).
- Typically there is a history of pregnancy or spontaneous abortion.

Prognosis and Treatment

- Excision of the mass is curative.

Pathology

Histology

- The polyp consists of glial tissue in a connective tissue matrix.
- Erosion and granulation tissue may also be present.
- Typical features of glial tissue are present, and the glia is sharply demarcated.

Immunopathology (Including Immunohistochemistry)

- Positive for GFAP and S100.

Main Differential Diagnosis

- Schwannoma—this tumor exhibits the characteristic interlaced spindled cells in contrast to the more monotonous array of glia.

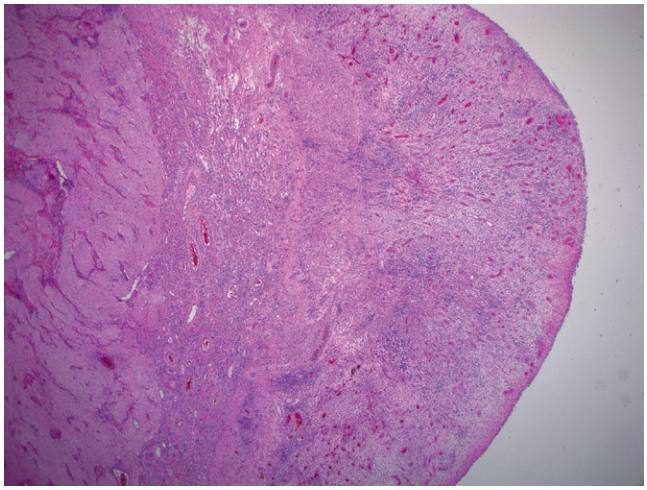


FIGURE 1

Glial polyp of the cervix. At low magnification the glial tissue is seen in the stromal *(left)* and deep to a layer of granulation tissue.

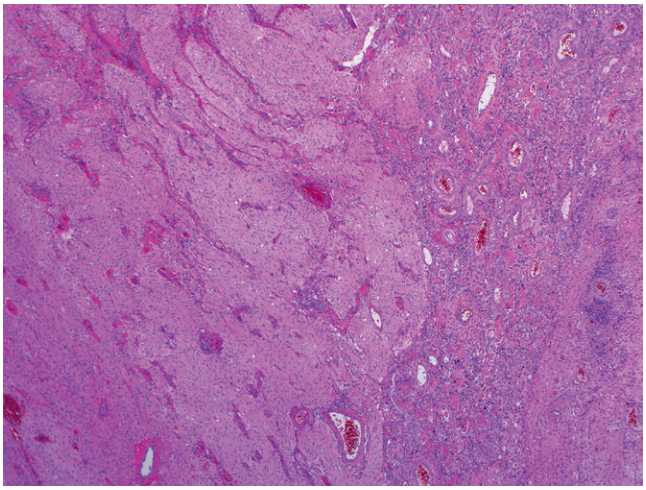


FIGURE 2

Glial polyp of the cervix. At higher magnification the glia is juxtaposed with a vascular stroma.

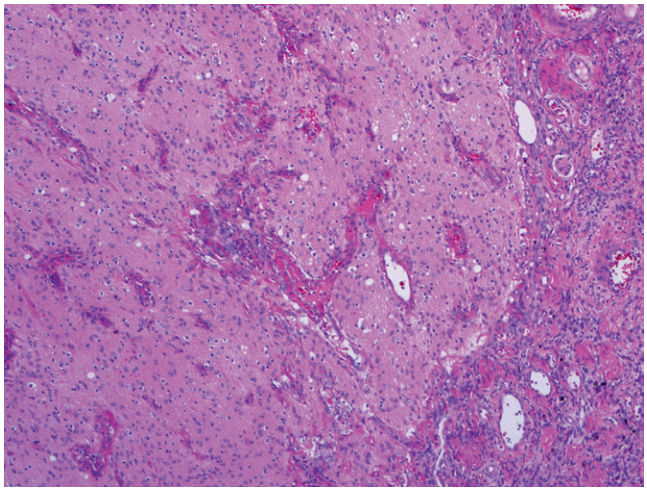


FIGURE 3

At higher magnifications the monotonous array of mature glial cells can be seen within a slightly fibrillar matrix.

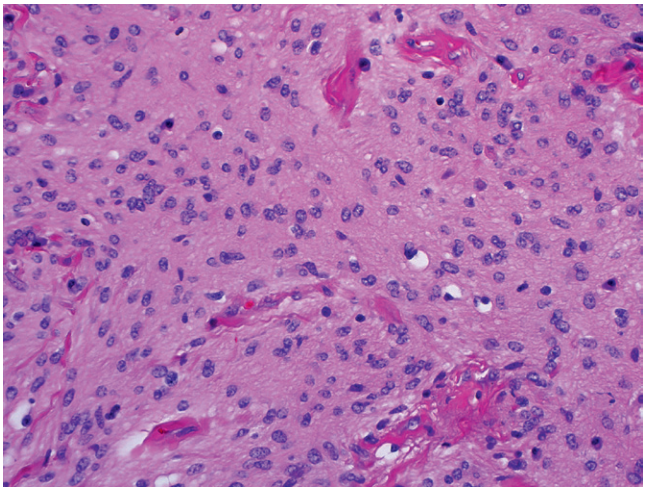


FIGURE 4

At higher magnifications the normal-appearing mature glial cells can be appreciated.