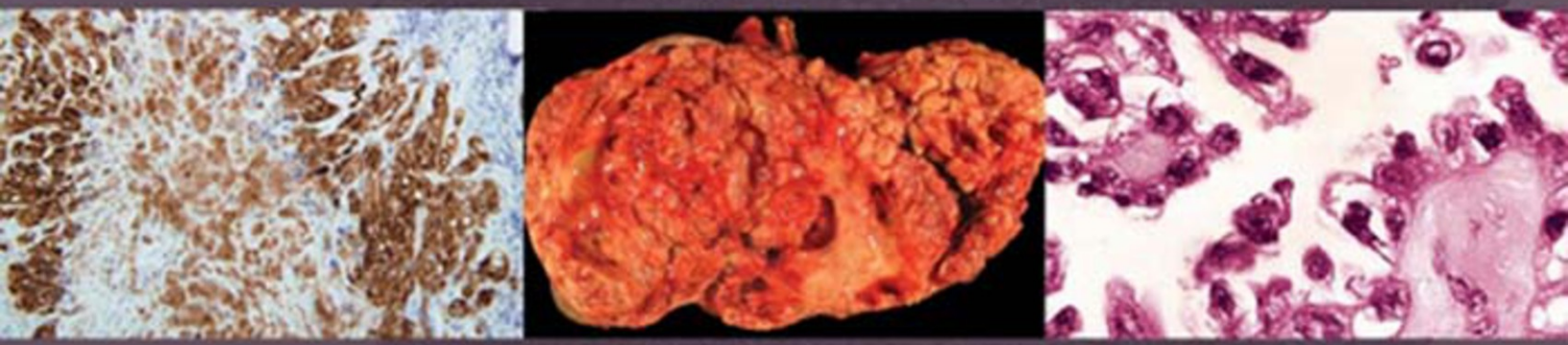
HIGH-YIELD PATHOLOGY

Gynecologic and Obstetric Pathology

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



ELSEVIER

Gynecologic and Obstetric Pathology

HIGH-YIELD PATHOLOGY

Christopher P. Crum, MD
Professor of Pathology, Harvard Medical School
Vice Chair and Director, Women's and Perinatal Pathology
Department of Pathology
Brigham and Women's Hospital
Boston, Massachusetts

Anna R. Laury, MD
Department of Pathology & Laboratory Medicine
Cedars-Sinai Medical Center
Los Angeles, California

Michelle S. Hirsch, MD, PhD
Associate Professor of Pathology
Brigham and Women's Hospital
Department of Pathology
Division of Women's and Perinatal Pathology
Boston, Massachusetts

Charles Matthew Quick, MD
Assistant Professor of Pathology
Director of Gynecologic Pathology
University of Arkansas for Medical Sciences
Little Rock, Arkansas

William A. Peters III, MD
Clinical Professor of Obstetrics & Gynecology, University of Washington
Swedish Medical Center
Seattle, Washington

SAUNDERS
ELSEVIER

ELSEVIER

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

GYNECOLOGIC AND OBSTETRIC PATHOLOGY:
HIGH-YIELD PATHOLOGY

ISBN: 978-1-4377-1422-7

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

International Standard Book Number: 978-1-4377-1422-7

Content Strategist: William R. Schmitt
Senior Content Development Specialist: Jennifer Ehlers
Publishing Services Manager: Catherine Jackson
Design Direction: Paula Catalano

Printed in China.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

CONTRIBUTORS

Odise Cenaj, MD, PhD
Resident in Pathology
Department of Pathology
Brigham and Women's Hospital
Boston, Massachusetts

Brooke E. Howitt, MD
Instructor in Pathology
Department of Pathology
Brigham and Women's Hospital
Boston, Massachusetts

Emily E.K. Meserve, MD, MPH
Fellow in Women's and Perinatal Pathology
Department of Pathology
Brigham and Women's Hospital
Boston, Massachusetts

Jelena Mirkovic, MD, PhD
Fellow in Women's and Perinatal Pathology
Department of Pathology
Brigham and Women's Hospital
Boston, Massachusetts

Bradley J. Quade, MD, PhD
Associate Professor of Pathology
Department of Pathology
Division of Women's and Perinatal Pathology
Brigham and Women's Hospital
Boston, Massachusetts

Kathleen Sirois, BA
Pathology Specialist
Women's and Perinatal Pathology
Brigham and Women's Hospital
Boston, Massachusetts

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 3

Uterus

DYSFUNCTIONAL UTERINE BLEEDING (EARLY OR MID-CYCLE BREAKDOWN)

Definition—Bleeding that occurs in the absence of ovulation and is not associated with an endometrial structural abnormality or other visible cause (fibroid or polyp).

Clinical Features

Epidemiology

- Dysfunctional uterine bleeding (DUB) is common, more frequently seen near menopause.
- Based on histology, the pattern suggests failed follicle and/or the absence of progression to the luteal phase with mid or early cycle shedding.

Presentation

- Patients present with unexplained uterine bleeding in premenopause.

Prognosis and Treatment

- DUB is benign but not associated with a visible cause that can be corrected surgically.
- Management is symptomatic with resampling if bleeding persists or recurs.
- In adolescents, workup and correction of coagulation disturbance as appropriate.

Pathology

Histology

- The pattern is that of a mid-cycle breakdown, with tubular glands and diffuse stromal breakdown.
- Mitoses may or may not be seen depending on interval from cessation of estrogen output and breakdown.
- Relatively normal-appearing luteal phase endometrium may also be seen if there is an extrinsic (coagulopathy) or other cause for bleeding.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis/Associated conditions

- Persistent follicle and benign hyperplasia—cystic glands will be seen.
- Follicular inadequacy and coagulopathy are other potential causes of mid-cycle bleeding.
- A short course of estrogen with withdrawal will produce the same pattern.

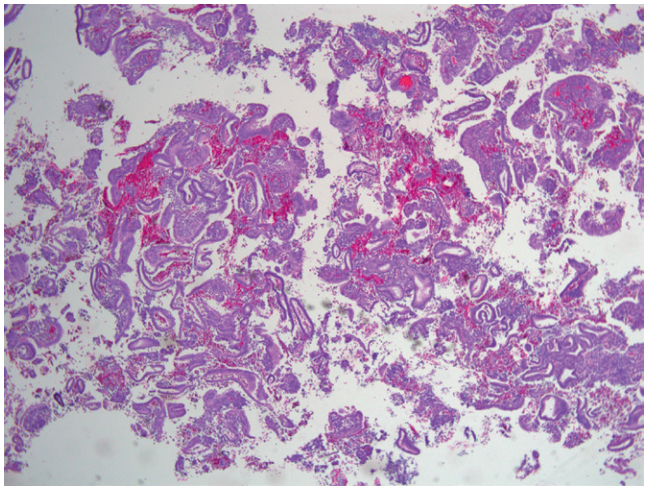


FIGURE 1

DUB. Here is a typical pattern of dysfunctional bleeding, with mostly stromal breakdown and scattered glands and surface epithelium.

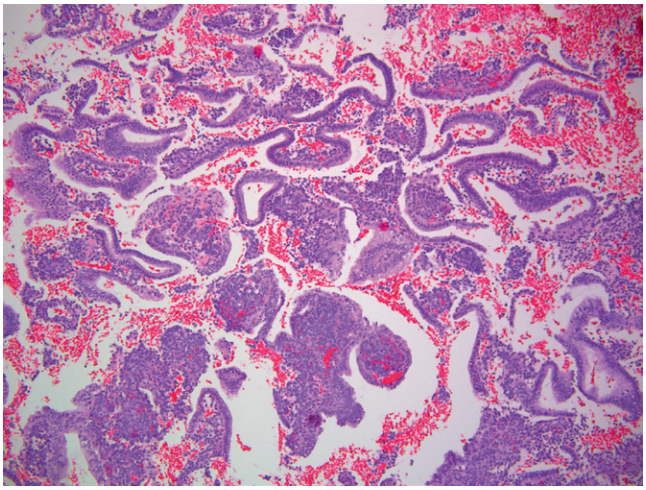


FIGURE 2

DUB. At higher magnification the recognizable glands are nondescript and admixed with stromal breakdown. A similar pattern could be produced by a short course of progestins followed by withdrawal.

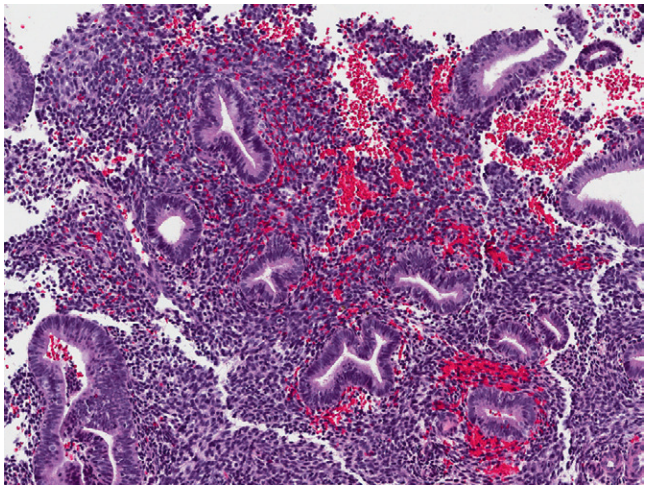


FIGURE 3

DUB. Another example, with proliferative-type glands admixed with a diffuse pattern of stromal breakdown. Note there is evidence of neither persistent follicle (which would produce cystic glands) nor ovulation (which would produce a pseudodecidualized stroma).

BREAKDOWN MIMICKING NEOPLASIA

Definition—Scheduled menstrual breakdown and abnormal stromal breakdown histologically mimicking adenocarcinoma.

Clinical Features

Epidemiology

- The presence of stromal breakdown within an endometrial biopsy is relatively common; fortunately, however, extensive breakdown, mimicking neoplasia, is relatively uncommon.

Presentation

- Patients typically present with abnormal uterine bleeding and are biopsied.
- More typically encountered with unscheduled (anovulatory) bleeding due to the prominent repair and irregular breakdown pattern seen in such cases.

Prognosis and Treatment

- Breakdown and menstruation are normal and carry no adverse prognosis.
- If identified correctly, no treatment is warranted, whereas misdiagnosis may lead to unnecessary surgery.

Pathology

Histology

- Glands may appear crowded due to loss of intervening stroma.
- Aggregates of degenerating stroma may form hyperchromatic, cellular balls and cords, which can simulate poorly differentiated carcinoma.
- Papillary surface (repair) changes may be associated with stromal breakdown and lead to the misdiagnosis of malignancy.
- Alternatively, fragments of carcinoma with loss of architecture may resemble stromal breakdown.

Immunopathology (Including Immunohistochemistry)

- Negative staining for p53 and decreased staining for Ki-67 may be helpful in cases in which serous carcinoma is a concern.

Main Differential Diagnosis

- Adenocarcinoma—the key to this diagnosis is a careful scrutiny of the epithelium, which if neoplastic can be distinguished from necrotic stroma. In rare cases in which small fragments of tumor from either a serous or neuroendocrine carcinoma are encountered, special stains (p53, p16) might be helpful.
- Curettage or procedural artifacts such as telescoping artifact, exfoliation artifact.

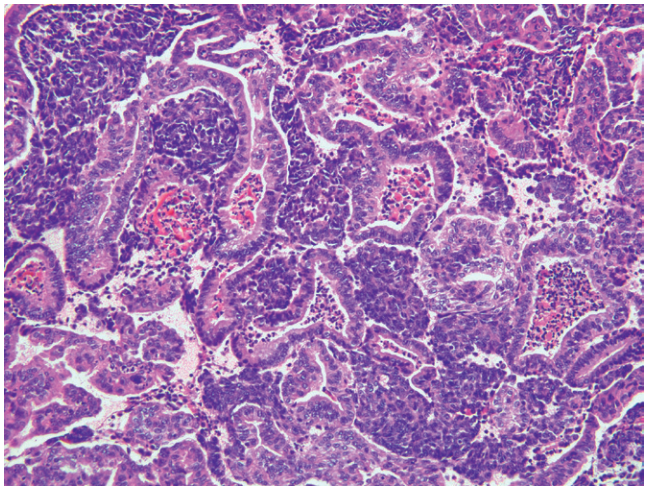


FIGURE 1

Breakdown and menstruation mimicking malignancy. Strips of endometrial glandular epithelium and stromal "blue balls."

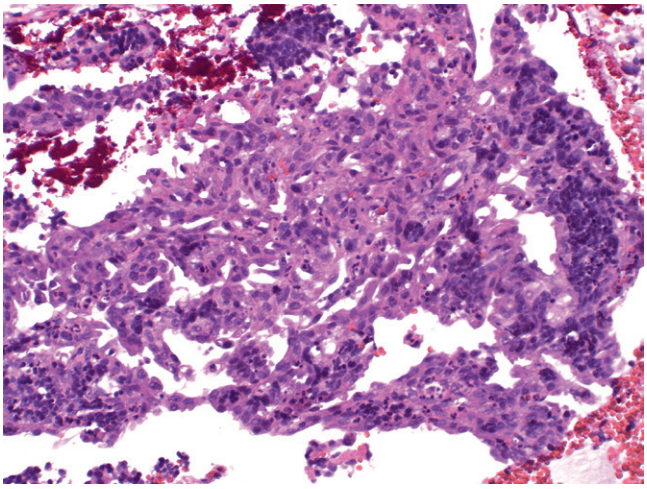


FIGURE 2

Breakdown and menstruation mimicking malignancy. Superficial repair type epithelium with small punched out spaces mimicking carcinoma. Note the stromal breakdown on the right.

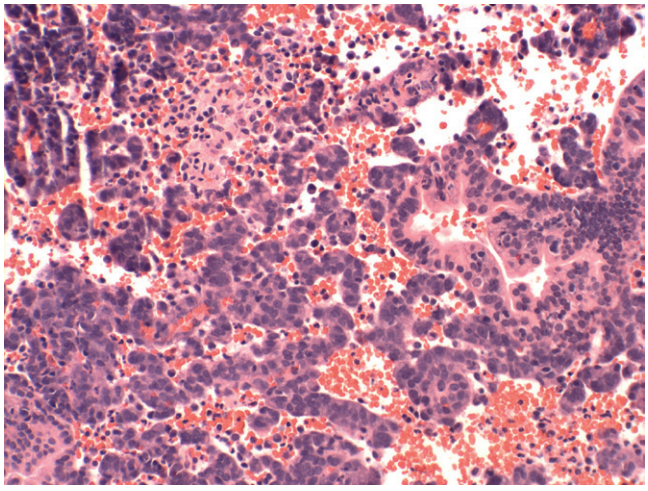


FIGURE 3

Breakdown and menstruation mimicking malignancy. Strips of menstrual endometrium forming cords, which can mimic malignancy.

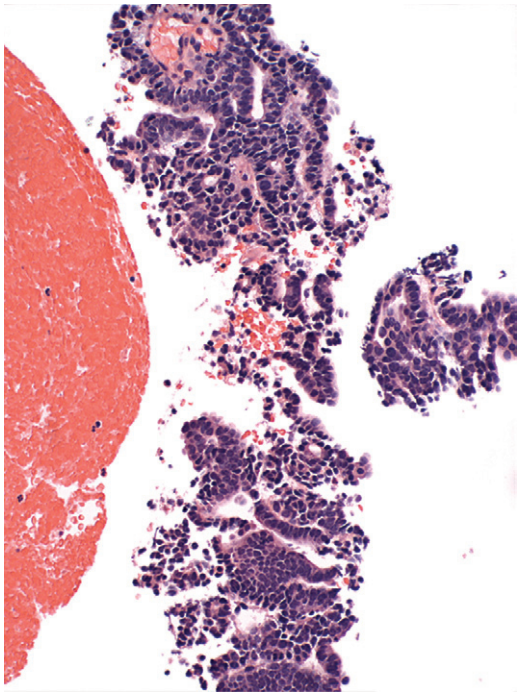


FIGURE 4

Fragments of endometrial adenocarcinoma simulating menstrual endometrium. *(From Crum CP, Nucci MR, Lee KR, editors: Diagnostic Gynecologic and Obstetric Pathology, ed 2, Philadelphia, 2011, Elsevier.)*

ANOVULATORY ENDOMETRIUM WITH PERSISTENT FOLLICLE

Definition—Alterations in the endometrium due to lack of ovulation and estrogenic effects of a persistent follicle.

Clinical Features

Epidemiology

- Most commonly seen at or around menopause with failed ovulation and persistent follicle.
- Common in polycystic ovarian syndrome (PCOS).
- Abnormal uterine bleeding in the fourth or fifth decade is the most common presenting sign.
- Can be mimicked by excessive estrogen administration post menopause.

Presentation

- Unscheduled bleeding.
- Signs of PCOS may be present in younger women.

Prognosis and Treatment

- Usually uneventful in the fifth decade, with bleeding ceasing at menopause.
- Anovulatory bleeding occurring with increased levels of estrogen may lead to benign hyperplasia if estrogen levels are persistently elevated.
- Treatment ranges from clinical follow-up to hormonal therapy.
- Risk of subsequent endometrial cancer estimated at 1%.

Pathology

Histology

- Proliferative endometrium with mitotic figures but may vary as a function of timing of endometrial sampling (during or after cessation of estrogenic stimulation).
- The most pronounced finding is that of uniformly distributed glands with cystic dilatation.
- Glandular karyorrhexis, breakdown, thrombi, repair, and tubal metaplasia will often be present.
- Useful diagnostic terms for this include "altered endometrium with alterations in gland architecture consistent with anovulation" and "disordered proliferative endometrium."

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Recommended Diagnostic Terminology

- Anovulatory-pattern endometrium.
- Proliferative endometrium with alterations in gland architecture consistent with delayed or absent ovulation.
- Disordered proliferative endometrium is another term commonly used albeit less informative.

Main Differential Diagnosis

- Endometrial polyps often display cystic glands but can be recognized by polyp stroma.
- Benign hyperplasia is an exaggerated form of anovulatory change, with slightly higher gland density and undulating gland contours with outpouchings (mouse ears).
- Endometrial intraepithelial neoplasia (atypical hyperplasia) is a clonal expansion of crowded glands that differ in appearance from the background endometrium.
- Basalis or lower uterine segment may display cystic glands as well.

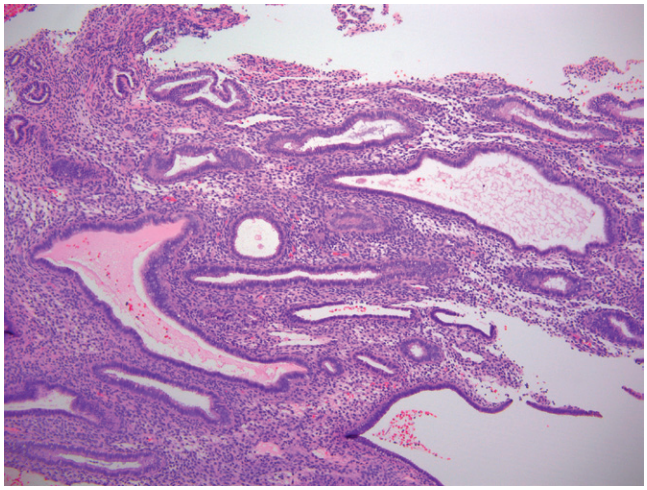


FIGURE 1

Anovulatory endometrium with persistent follicle. Irregularly regular glands with cystic dilatation.

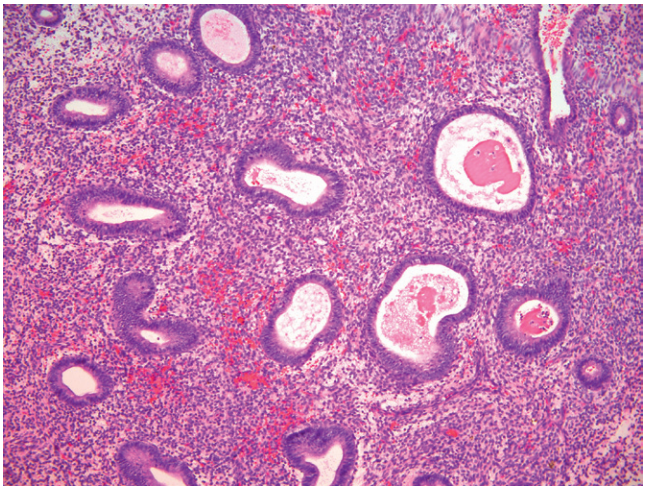


FIGURE 2

Anovulatory endometrium. Variable gland size is the norm. Glands tend to be relatively round without undulating borders.

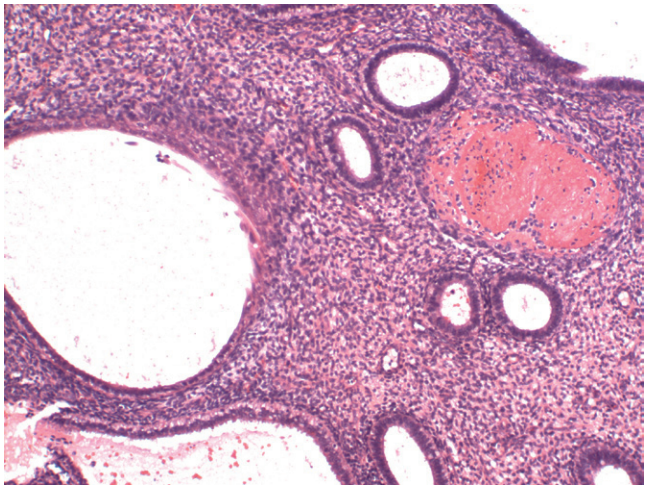


FIGURE 3

Anovulatory endometrium with fibrin thrombi. Gland karyorrhexis will also be common.

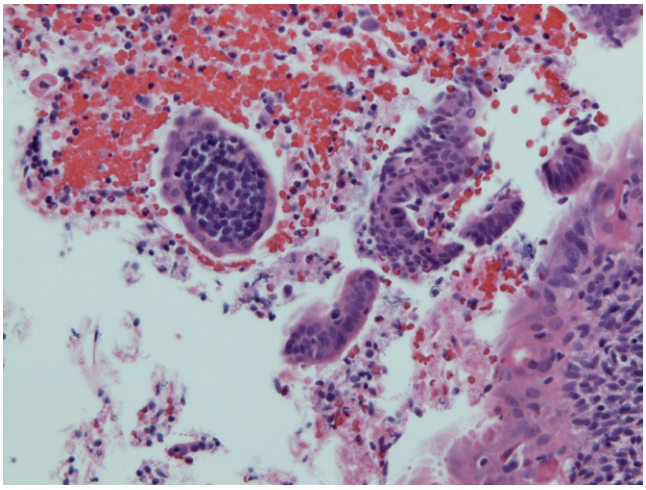


FIGURE 4

Anovulatory endometrium. Reparative epithelial changes adjacent to focal stromal breakdown.

BENIGN ENDOMETRIAL HYPERPLASIA

Definition—An exaggerated response to unopposed estrogen but lacking the features of endometrial intraepithelial neoplasia (EIN) (atypical hyperplasia).

Clinical Features

Epidemiology

- Most commonly seen at or around menopause with failed ovulation and persistent follicle.
- Common in polycystic ovarian syndrome (PCOS).
- Abnormal uterine bleeding in the fourth or fifth decade is the most common presenting sign.
- Can be mimicked by estrogen administration post menopause.

Presentation

- Unscheduled bleeding.
- Signs of PCOS may be present in younger women.

Prognosis and Treatment

- Usually uneventful in the fifth decade, with bleeding ceasing at menopause.
- Anovulatory bleeding occurring with increased levels of estrogen may lead to benign hyperplasia if estrogen levels are persistently elevated.
- Treatment ranges from clinical follow-up to hormonal therapy. Repeat sampling is indicated if clinical circumstances (recurrent bleeding, evidence of an endometrial lesion) dictate.
- Risk of subsequent endometrial cancer estimated at 1%.

Pathology

Histology

- Proliferative endometrium with mitotic figures but may vary as a function of timing of endometrial sampling (during or after cessation of estrogenic stimulation).
- The most pronounced finding is that of uniformly distributed glands with cystic dilatation and groups of glands with irregular contours or outpouchings (ears).
- Glandular karyorrhexis, breakdown, thrombi, repair, and tubal metaplasia will often be present.

Recommended Diagnostic Terminology

- Benign hyperplasia.
- Note: This pattern reflects unopposed estrogen, but there is no evidence of neoplasia (EIN). Repeat sampling is advised if there are clinical concerns (e.g., recurrent bleeding and other abnormal uterine findings).

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Endometrial polyps often display cystic glands but can be recognized by stromal changes. The adjacent endometrium will not contain cystic glands.
- In contrast to the usual changes of persistent follicle, benign hyperplasia is an exaggerated form of anovulatory change, with slightly higher gland density.
- EIN (atypical hyperplasia) is a clonal expansion of crowded glands that differ in appearance from the background endometrium.

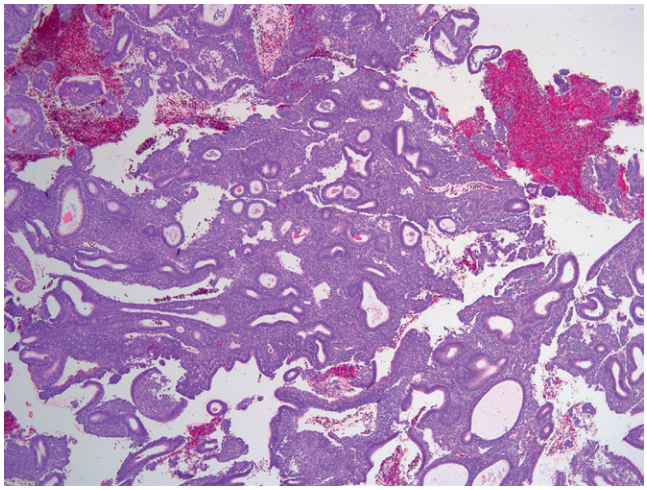


FIGURE 1

Benign hyperplasia at low magnification. Note the relatively high gland density.

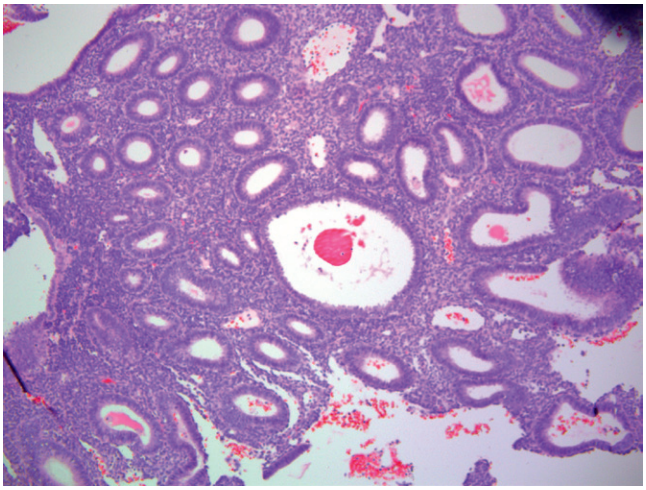


FIGURE 2

Benign hyperplasia at medium magnification. Scattered cystic glands are present.

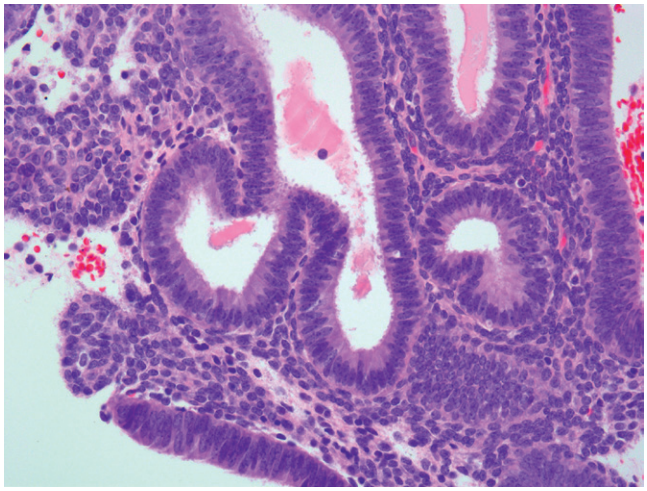


FIGURE 3

Benign hyperplasia. Note the outpouching with "ears" projecting from glands.

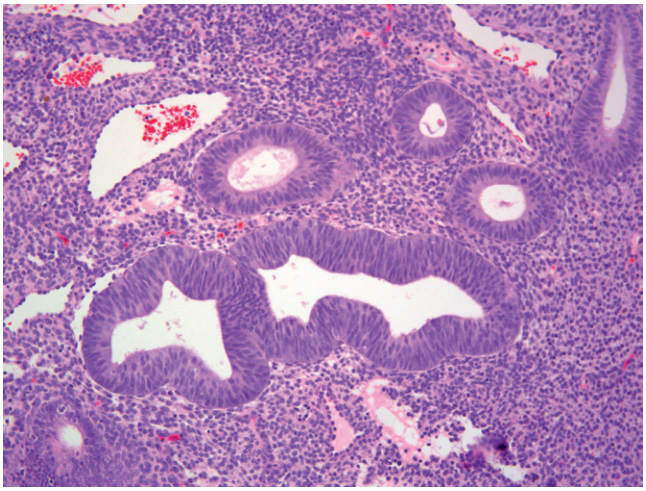


FIGURE 4

Benign hyperplasia. A cluster of glands with more prominent pseudostratification creating some contrast with the other glands. However, other than this there is little difference in cytology between the glands and there is no discrete outgrowth of crowded cytologically altered glands, as seen in EIN.

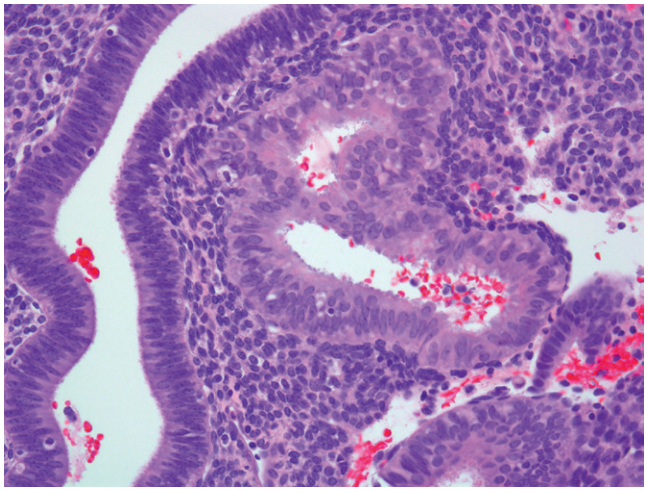


FIGURE 5

Benign hyperplasia. Note the single gland with tubal metaplasia.

TELESCOPING ARTIFACTS MIMICKING NEOPLASIA

Definition—Artifactual compression of glands during the biopsy process.

Clinical Features

Epidemiology

- Telescoping artifact is common and can be identified in a large proportion of endometrial biopsies.

Presentation

- Telescoping artifact is an incidental finding, usually during histologic examination of a sample due to abnormal uterine bleeding.

Prognosis and Treatment

- Gland compression is an artifact and no treatment is required.
- Failure to recognize telescoping artifact may lead to the erroneous diagnosis of endometrial intraepithelial neoplasia (EIN) and further, unnecessary treatment.

Pathology

Histology

- Telescoping of proliferative glands leads to back-to-back glands with little intervening stroma.
- Lack of stroma or stromal fragmentation and hemorrhage are useful clues in ruling out true gland crowding.
- Glandular epithelium is pulled into the lumen causing enlargement of the gland with redundancy of the epithelium.
- Folding of the epithelium may lead to pseudopapillary structures.
- This artifact is also common in the early secretory phase.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- EIN or well-differentiated carcinoma—these two lesions are characterized by closely arranged glands with altered cytology. The glands in telescoping artifact are typically no different in appearance from the surrounding epithelium.
- Secretory hyperplasia or EIN—this entity will display an altered epithelium, usually with prominent pseudostratification or some atypia (see secretory EIN). Telescoping artifacts in early secretory endometrium will not appreciably alter the cytology of the lining epithelium.

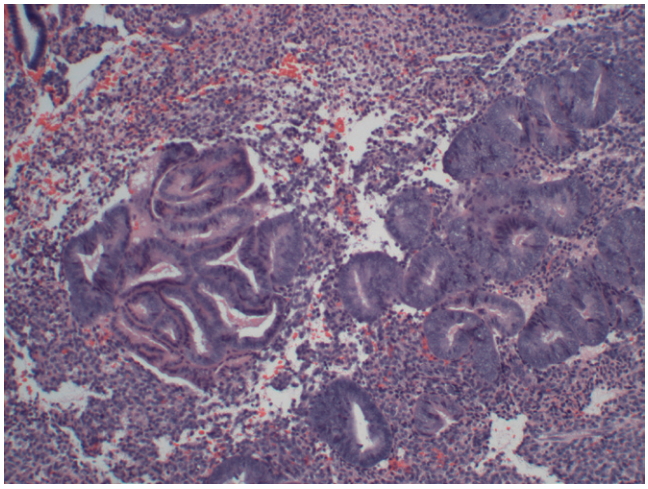


FIGURE 1

Telescoping artifact. Glands on the left are compressed within one gland tract; those on the right are compressed longitudinally.

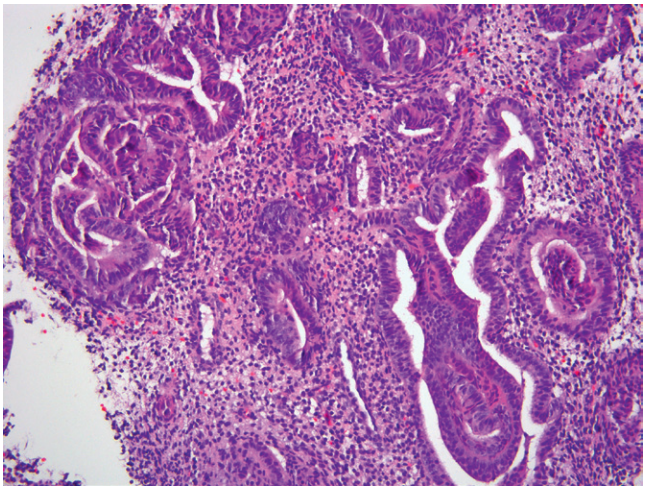


FIGURE 2

Telescoping artifact. Large glands with redundant epithelium. Note that the telescoped gland is at the edge of the tissue fragment.

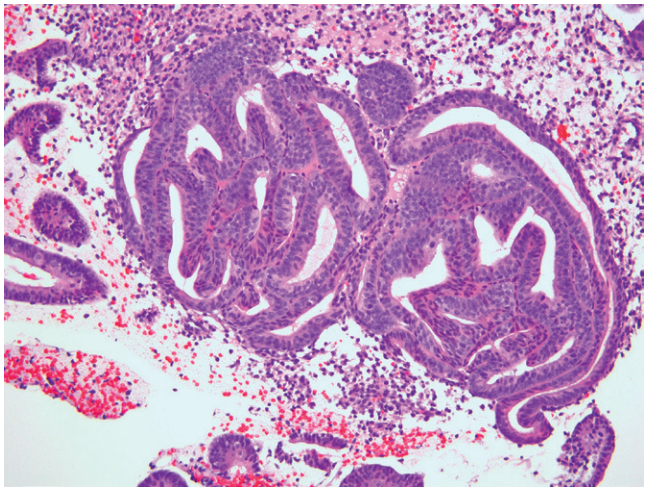


FIGURE 3

Telescoping artifact. Gland in gland formation with pseudopapillae. Stromal fragmentation is readily apparent.

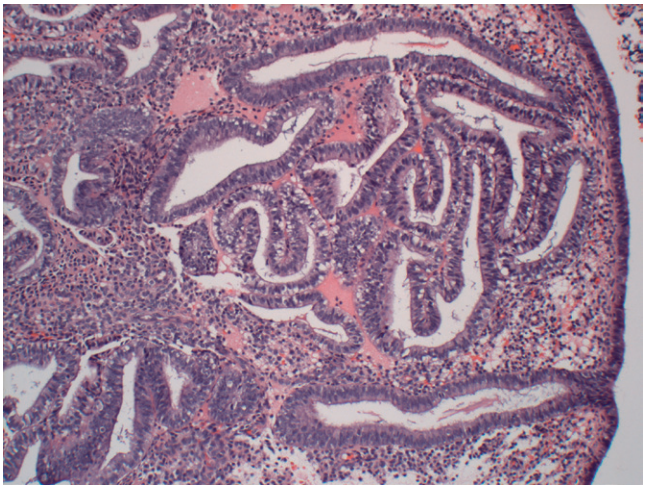


FIGURE 4

Telescoping or compression artifact in secretory endometrium can cause conspicuous crowding. Note the normal appearance of the glandular epithelium.

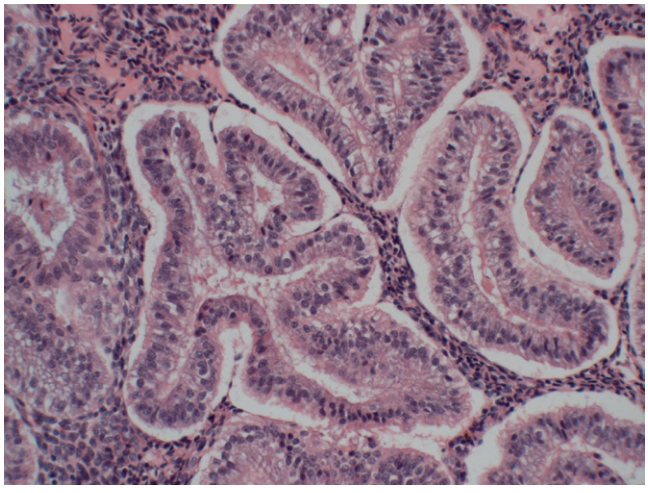


FIGURE 5

Telescoping or compression artifact in early secretory endometrium is common.

MIXED-PATTERN ENDOMETRIUM

Definition—Endometrium with both secretory and proliferative pattern glands.

Clinical Features

Epidemiology

- True mixed-pattern endometrium is relatively uncommon and can be attributed to four likely causes:
  1. Hormonal imbalance (therapy)
  2. Irregular ovulation
  3. Defects in follicle development
  4. Clonal lesions
- The most common cause of a mixed pattern is hormonal imbalance secondary to therapy or assisted reproduction.

Presentation

- Typically found at the time of endometrial sampling for abnormal uterine bleeding.
- May be discovered in biopsies utilized in fertility workups.

Prognosis and Treatment

- Mixed-pattern endometrium is benign and carries no adverse prognosis.
- Hormone therapy may be used to attempt to restore normal ovulation.

Pathology

Histology

- Mixture due to hormonal therapy presents with cystically dilated, tubular glands and prominent stromal changes (pseudodecidualization).
- Cases of irregular ovulation (anovulation followed by ovulation) lead to glands with a marked discrepancy in size. Stromal edema is typically present, and the glands may display secretory features. Cystic dilation and tubal metaplasia are typically present.
- Mixture in the presence of a follicular failure shows quiescent, tubular glands persisting into the secretory phase.
- Clonal causes of a mixed pattern may be identified by the presence of two physiologic states of endometrium in close apposition. The histology is variable, but may consist of a population of stratified glands with (or without) mitotic activity or a "lagging secretory phase."

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Hormonal effect—hormonal treatment often will produce a mixed pattern, including cystic endometrial glands and the illusion of polyp, and must be taken into account when considering this diagnosis.
- Follicular dysfunction—this is a generic term for midcycle bleeding that occurs without a clear cause (dysfunctional bleeding). The glands will appear tubular but may lack mitoses after cessation of estrogen stimulation, thus giving the appearance of a mixed pattern.
- Luteal phase defect—this term implies delayed secretory maturation (early for stated date) but presumably a normal morphology.
- Clonal evolution (endometrial intraepithelial neoplasia [EIN])—when a component of the mixed pattern consists of crowded glands with altered cytology, EIN must be excluded.

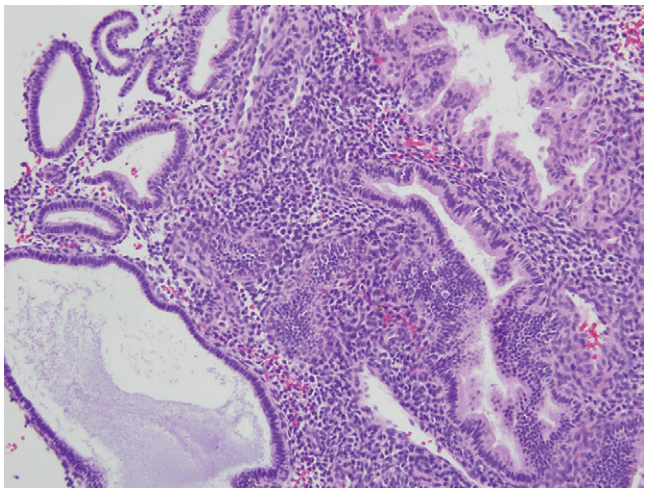


FIGURE 1

Mixed-pattern endometrium. Anovulatory endometrium showing a diversity of secretory maturation varying from hypersecretory *(center)* to less so *(left)*.

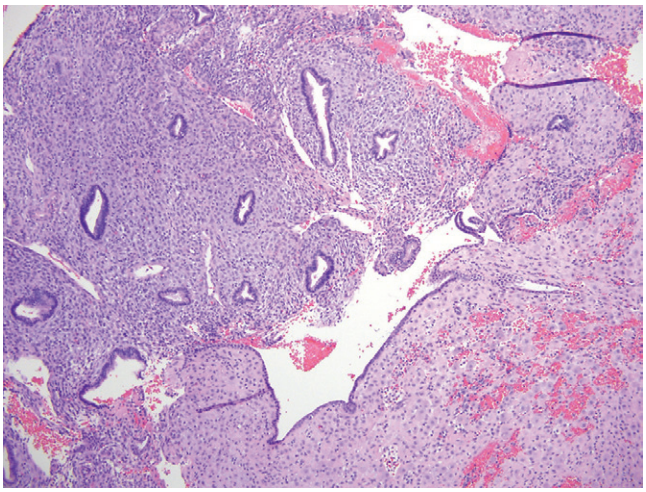


FIGURE 2

Mixed-pattern endometrium. Hormonally treated endometrium with quiescent tubular (proliferative pattern) glands set in a pseudodecidualized stroma.

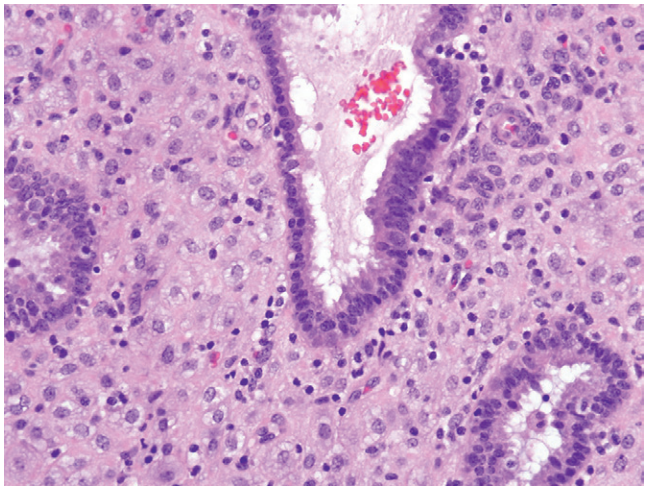


FIGURE 3

Mixed-pattern endometrium. Higher magnification of the case shown in Figure 2 shows the prominent pseudodecidualized stroma.

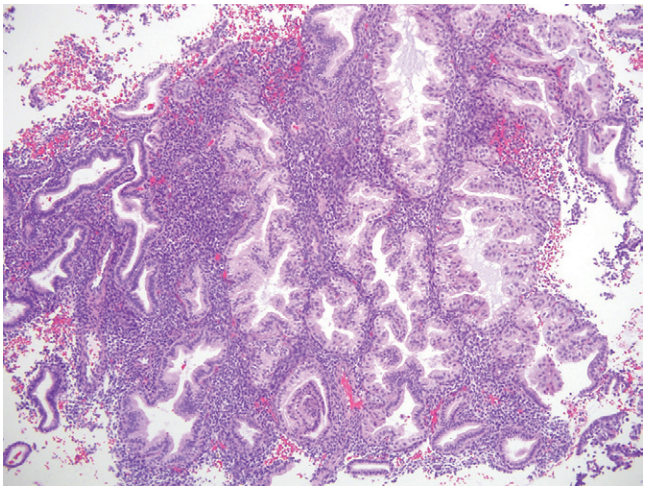


FIGURE 4

Mixed-pattern endometrium. A "clonal mixed pattern" showing secretory glands *(bottom)* and a population of glands with pseudostratification above. This implies that one or more mutations occurred in a clone that led to a difference in response to progestins.

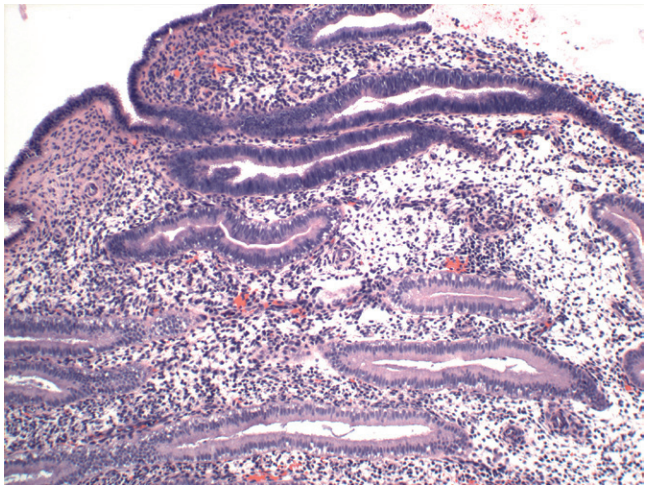


FIGURE 5

Anovulation with superimposed progestin therapy or ovulation. In this scenario, glands have become cystic due to persistent estrogen stimulation, followed by ovulation or progestin therapy. The latter imparts a superimposed secretory phenotype.

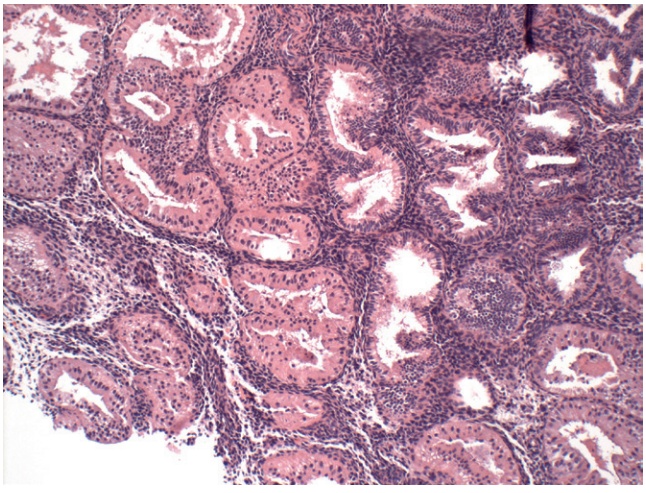


FIGURE 6

"Clonal mixed-pattern" endometrium. In this case a population of eosinophilic glands are situated in the midst of a secretory endometrium. Note the normal distribution of these glands, in keeping with the surrounding secretory glands. These are not always straightforward, and may at times require a follow-up endometrial sampling.

ADENOMYOMATOUS POLYP

Definition—An endometrial polyp composed of benign smooth muscle and glands.

Clinical Features

Epidemiology

- Adenomyomatous polyps are a variant of endometrial polyp with smooth muscle differentiation. They are often found in association with conventional polyps.

Presentation

- Patients may be asymptomatic or present with abnormal uterine bleeding.
- Large polyps may prolapse through the cervical os, mimicking malignancy.

Prognosis and Treatment

- Adenomyomatous polyps are benign, and no treatment is warranted other than to manage uterine bleeding.

Pathology

Histology

- Variable amounts of myomatous stroma and endometrial glands are present.
- Glands may display irregular glandular contours.
- The polyp stroma is composed of smooth muscle versus the fibrous stroma that can be seen in typical endometrial polyps.
- No glandular atypia should be present.

Immunopathology (Including Immunohistochemistry)

- The stromal component should be diffusely positive for smooth muscle markers (SMA, Desmin).
- The stromal component of the polyp should be negative for CD10 (endometrial stroma marker) and CD34.

Main Differential Diagnosis

- Endometrial polyp—the stroma lacks the compact bundles of smooth muscle.
- Atypical polypoid adenomyoma (APA)—this is essentially a sessile adenomyomatous polyp with two differences. The first is abnormal gland growth and squamous morules. The second is the smooth muscle differentiation, which is more mature, with conspicuous cytoplasmic differentiation, akin to what would be seen in a leiomyoma.

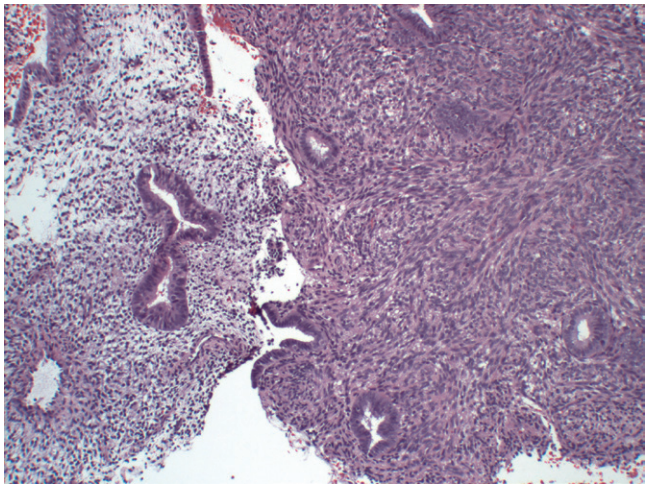


FIGURE 1

Adenomyomatous polyp. Smooth muscle and glands, composing an adenomyomatous polyp, are seen on the right. Normal endometrium is on the left for comparison.

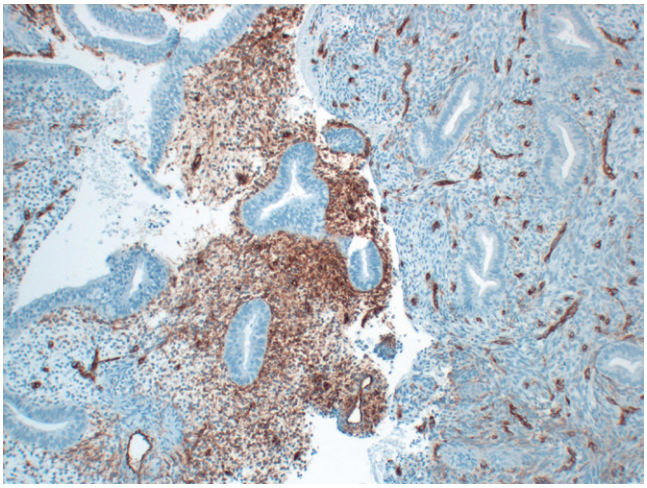


FIGURE 2

Adenomyomatous polyp. Immunostain for CD34 showing positivity in the endometrial stroma and negativity in the polyp.

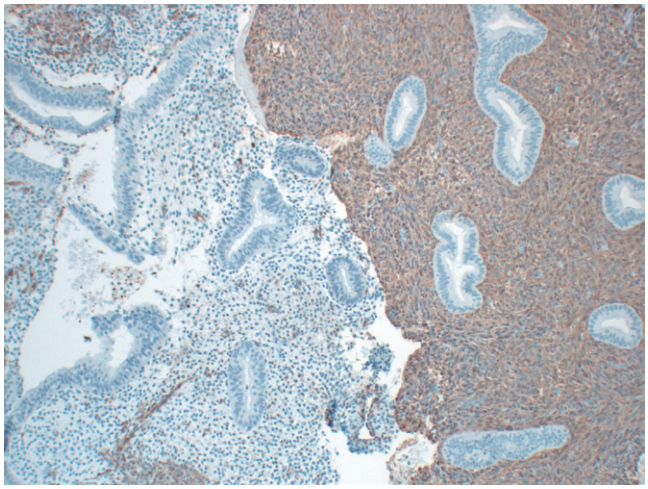


FIGURE 3

Adenomyomatous polyp. Immunostain for SMA showing diffuse positivity in the adenomyomatous polyp.

CHRONIC ENDOMETRITIS

Definition—Chronic inflammatory process within the uterus often associated with infection.

Clinical Features

Epidemiology

- Chronic endometritis (CE) is thought to represent an infectious process.
- CE is strongly associated with the presence of pelvic inflammatory disease and acute salpingitis.
- Virtually all organisms described that can cause sexually transmitted diseases have been implicated in CE.
- In young patients the most common cause is infection during a recent pregnancy/delivery.

Presentation

- In all age groups CE is a common cause of abnormal uterine bleeding but is generally seen in the fifth decade.
- Patients may present with obstructive symptoms (concurrent pyometra).
- A large number of patients are asymptomatic other than abnormal bleeding. It is important to emphasize that abnormal bleeding is among the most common signs of chlamydial endometritis, hence the importance of pathologic examination.

Prognosis and Treatment

- CE has a favorable prognosis when treated. It may be idiopathic in older women.
- Treatment usually consists of removal of the inciting agent (if present), such as an intrauterine device (IUD) and antibiotics if indicated.
- Pyometra in postmenopausal women may signal a malignancy, and repeated sampling may be indicated to exclude this possibility.

Pathology

Histology

- Stromal condensation, spindling, and cellularity (attributed to an increased mononuclear cell infiltrate) are typically the easiest to recognize signs of CE.
- Reactive alterations in the normal endometrial glands may be present (typically proliferative phase).
- Lymphoid follicles may be increased in number or easily identifiable.
- Acute inflammatory debris, eosinophilic "repair" epithelium, focal breakdown, and surface squamous metaplasia may be present.
- Plasma cells can be seen within the endometrial stroma, particularly surrounding blood vessels.
- Lymphoid follicles can be seen in normal endometrium and are not diagnostic; likewise, plasma cells may be seen in endometrial polyps, during menstruation, and near submucosal leiomyomas, and by themselves are not diagnostic of CE.

Immunopathology (Including Immunohistochemistry)

- Much is sometimes made of performing special stains for plasma cells. CD138 immunostaining or other stains may be helpful in identifying plasma cells in difficult cases. However, in general, a reasonable search (2 to 3 minutes) should turn up plasma cells if they are in the field of examination.

Main Differential Diagnosis

- Endometrial polyps often display plasma cells, and unless prominent are not classified as CE.
- Stromal breakdown, particularly in late menstrual endometrium, will occasionally display plasma cells. Menstruation is associated with inflammatory cells, but not plasma cells. Postpartum endometrium will contain lymphocytes and macrophages; the presence of plasma cells warrants a diagnosis of CE.

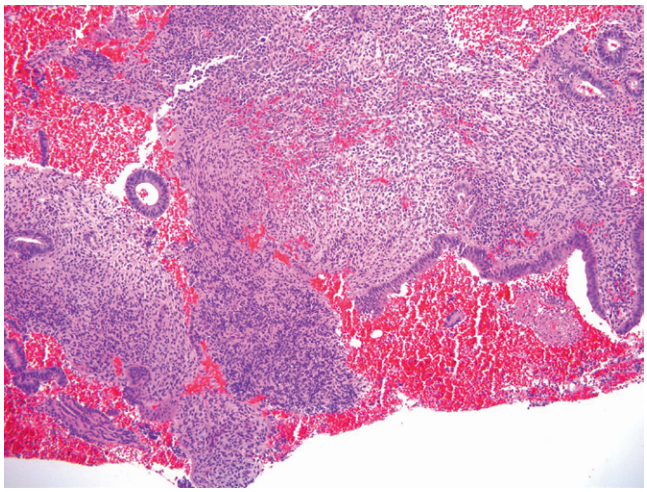


FIGURE 1

CE. Increased stromal cellularity and lymphoid aggregates can be seen at low power.

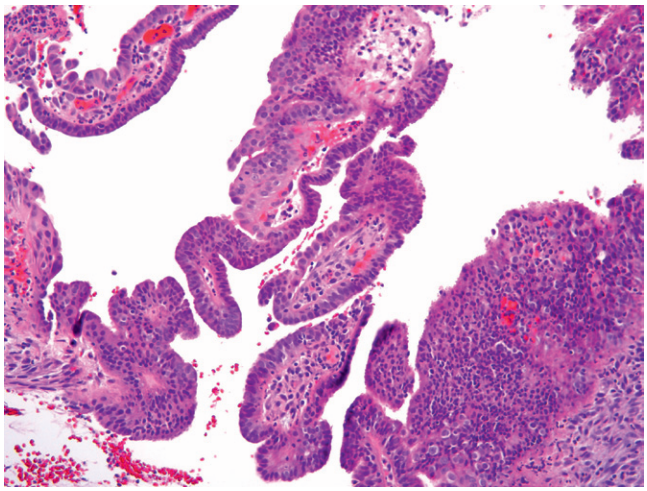


FIGURE 2

CE. The surface endometrium may display reactive, repair-type epithelial changes.

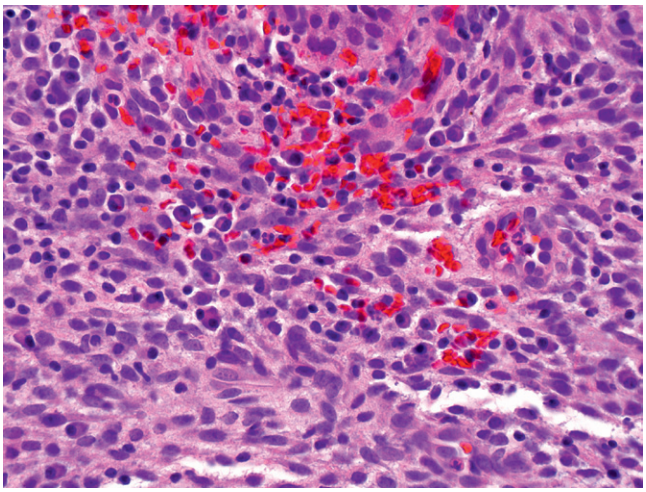


FIGURE 3

CE. Scattered plasma cells can be found, often in the areas surrounding vessels or near breakdown and hemorrhage.

PSEUDOACTINOMYCOTIC RADIATE GRANULES

Definition—Granular material that may be found in association with intrauterine devices.

Clinical Features

Epidemiology

- The finding of granular material associated with intrauterine device (IUD) use is not uncommon, happening in slightly less than 10% of patients.
- To date, no microbial association has been made with pseudoactinomycotic radiate granules (PAMRAGs).

Presentation

- Patients may be asymptomatic or may be experiencing adverse symptoms from IUD use (prompting removal).

Prognosis and Treatment

- PAMRAGs are not associated with microbial organisms, and no treatment is needed.
- Misdiagnosis of a PAMRAG as a sulfur granule (actinomycotic granule) may lead to unnecessary treatment.

Pathology

Histology

- PAMRAGs typically demonstrate radiant filamentous structures with blunted ends.
- The majority of PAMRAGs have a glassy, coarse eosinophilic appearance.

Immunopathology (Including Immunohistochemistry)

- Special stains for organisms will be negative.
- Cultures of the IUD will be negative.

Main Differential Diagnosis

- Actinomycosis—here the fine detail of the organisms can be appreciated.

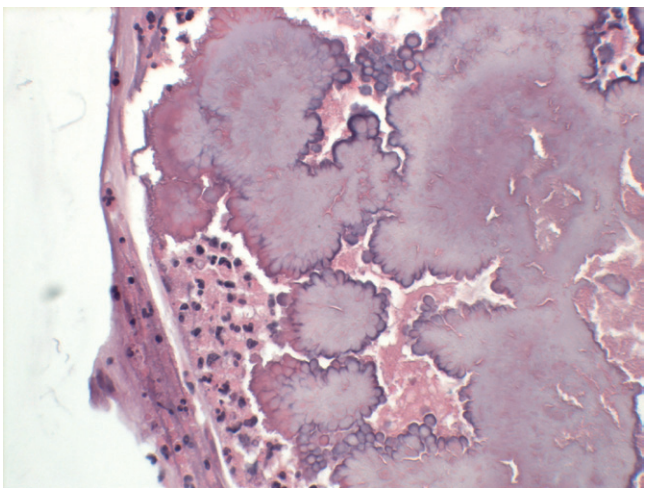


FIGURE 1

PAMRAG. Acellular, eosinophilic material with blunted ends characterizes this deposit, which is virtually exclusive to endometria with IUDs.

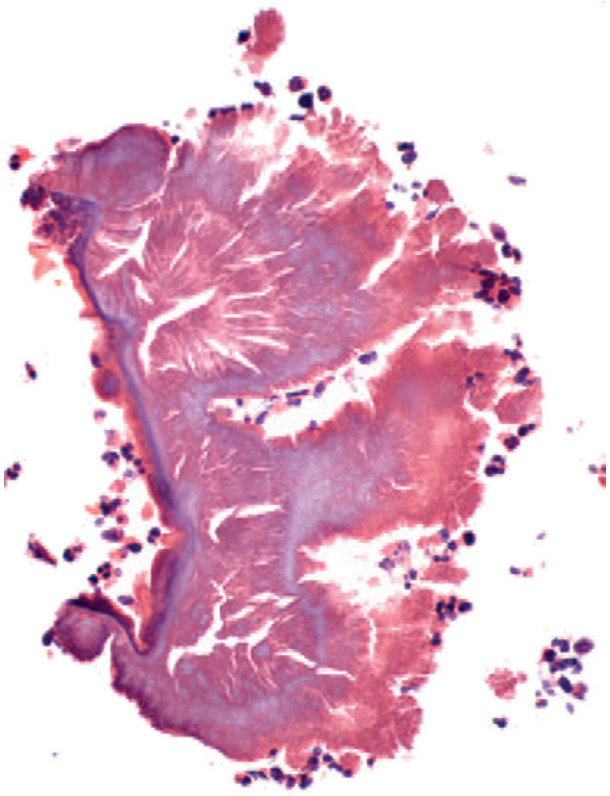


FIGURE 2

PAMRAG. *(From Crum CP, Nucci MR, Lee KR, editors: Diagnostic Gynecologic and Obstetric Pathology, ed 2, Philadelphia, 2011, Elsevier, Figure 16-30C.)*

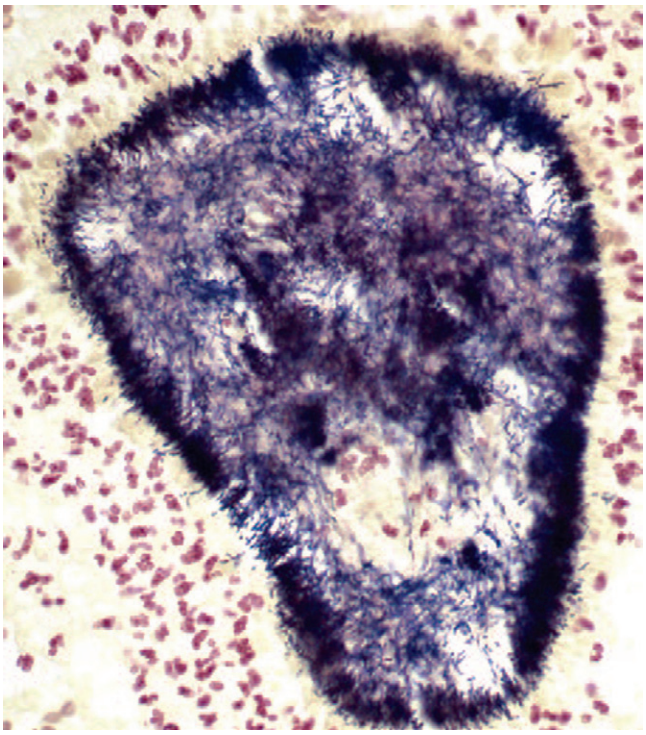


FIGURE 3

Actinomycosis for comparison. *(From Crum CP, Nucci MR, Lee KR, editors: Diagnostic Gynecologic and Obstetric Pathology, ed 2, Philadelphia, 2011, Elsevier, Figure 16-30B.)*

PYOMETRA

Definition—Extensive necroinflammatory debris within the uterine cavity.

Clinical Features

Epidemiology

- Overall rare (0.1% to 0.5% of women) but more commonly occurs in postmenopausal women.
- Associated with a wide range of disorders, including cervical stenosis, leiomyomata, retained IUD, and prior radiotherapy. There is a small but significant risk (5% to 10%) of associated malignancy.

Presentation

- Patients may be asymptomatic or present with abdominal pain with or without spotting. Additional symptoms/findings include nausea and uterine enlargement.

Prognosis and Treatment

- Management is based on either treating the infection or malignancy or hysterectomy. Resampling may be necessary if malignancy is a concern.

Pathology

Histology

- Sampling reveals abundant neutrophilic inflammation, fragments of necrotic tissue, and superficial endometrium with features of repair.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Endometrial carcinoma (must be ruled out). The most common conundrum is distinguishing reactive epithelial changes from malignant epithelium.

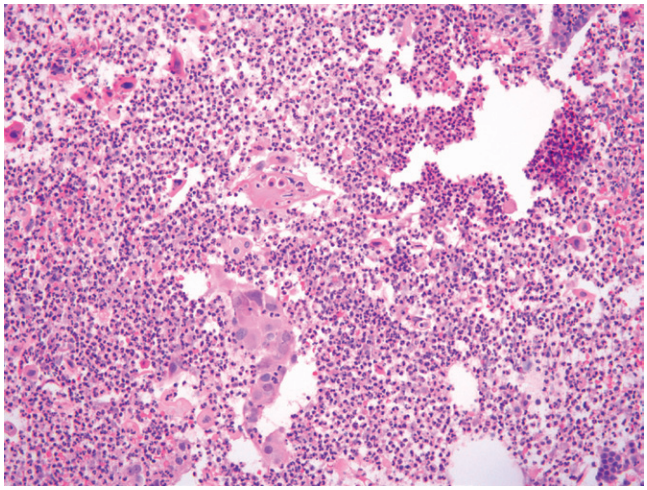


FIGURE 1
Pyometra. Sheets of neutrophils and scattered reactive, atypical epithelial cells.

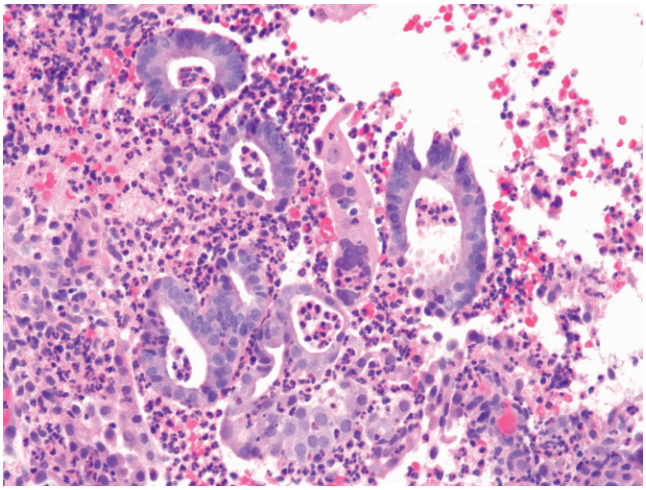


FIGURE 2
Pyometra. Reactive atypia may be marked.

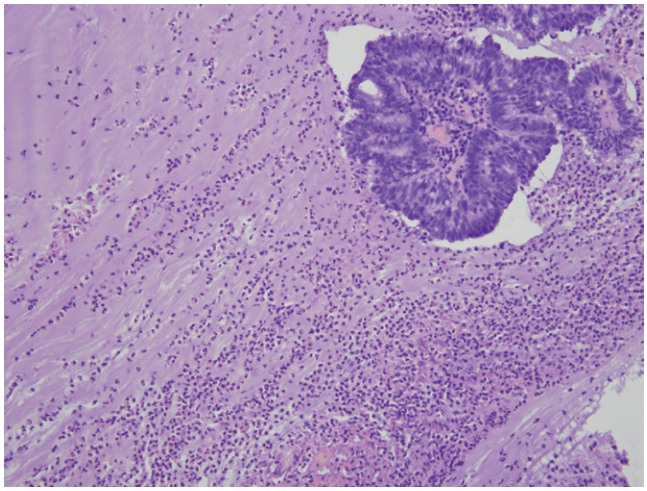


FIGURE 3
Pyometra. A dense neutrophilic infiltrate, note the adenocarcinoma in the upper right.

TUBERCULAR ENDOMETRITIS

Definition—Infection of the uterus (endometrium) by *Mycobacterium tuberculosis*.

Clinical Features

Epidemiology

- Involvement of the uterus by tuberculosis (TB) is exceedingly rare, due to modern treatment.
- Patients with uterine involvement often have systemic (or miliary) disease.
- Uterine involvement is most commonly seen in immunocompromised patients.

Presentation

- Patients may present with systemic symptoms of illness.
- Abnormal uterine bleeding is common.

Prognosis and Treatment

- Prognosis is variable based on the immunologic state of the patient and the extent of their infection.
- Multiple-drug cocktails are typically used to treat systemic TB infection.
- Severe cases of granulomatous endometritis may require hysterectomy.

Pathology

Histology

- Caseating granulomas may be identified in the endometrium or myometrium.
- The granuloma is composed of a central necrotic core, surrounded by multinucleated giant cells, lymphocytes, plasma cells, and histiocytes.
- Characteristic viral inclusions suggestive of cytomegalovirus or herpes should be sought for and be absent.

Immunopathology (Including Immunohistochemistry)

- Special stains (AFB) are required for visualization of the mycobacteria.
- Corresponding PPD (skin test) may be helpful.

Main Differential Diagnosis

- Sarcoid—this may closely mimic TB. Granulomas should be nonnecrotic; however, special stains and other tests to exclude TB may be needed as clinically appropriate.
- Granulomatous endometritis following ablation—clinical history and other features of ablation (tissue necrosis) should be present.
- Microbial infections (cytomegalovirus, herpes virus, toxoplasmosis, schistosomiasis) should be excluded in the appropriate clinical setting.

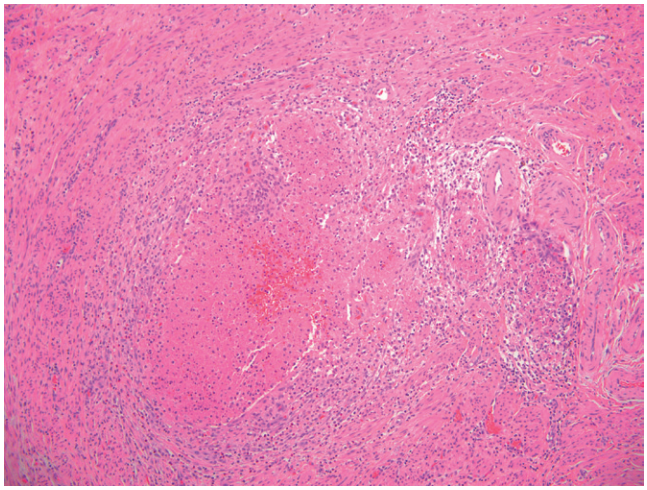


FIGURE 1

Uterine TB. A granuloma with a necrotic core surrounded by a mononuclear cell infiltrate.

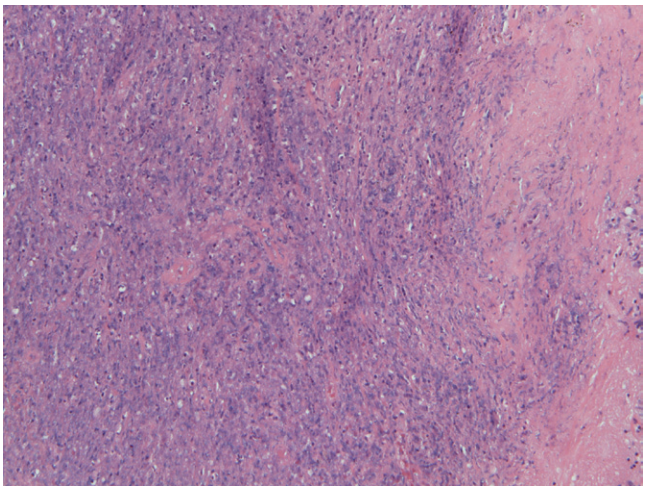


FIGURE 2

Uterine TB. A dense rim of lymphohistiocytic inflammation can be seen surrounding the necrotic core *(right). (Courtesy Matthew R. Lindberg, M.D.)*

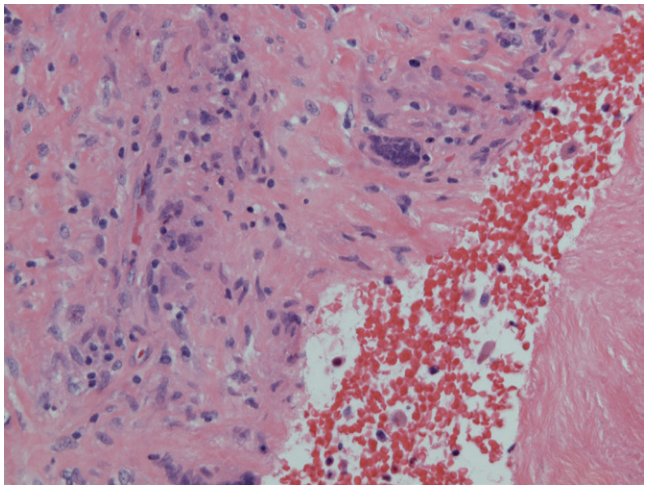


FIGURE 3

Uterine TB. Multinucleated giant cell and surrounding lymphohistiocytic inflammation. *(Courtesy Matthew R. Lindberg, M.D.)*

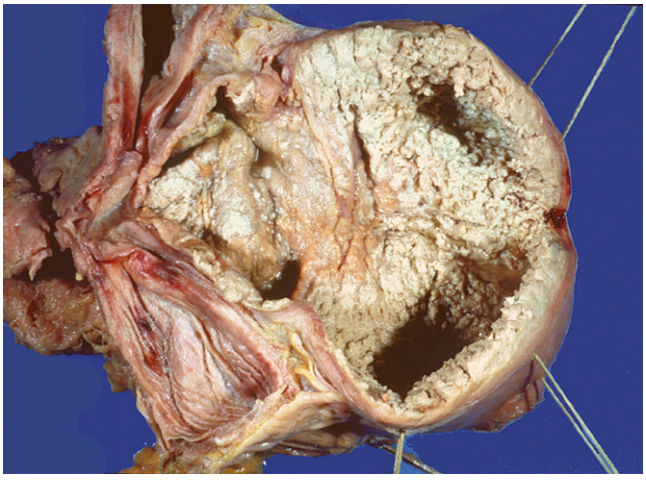


FIGURE 4

Gross pathology of endometrial tuberculosis with caseous necrosis filling the endometrial cavity. *(From Crum CP, Nucci MR, Lee KR, editors: Diagnostic Gynecologic and Obstetric Pathology, ed 2, Philadelphia, 2011, Elsevier.)*

SUBMUCOSAL LEIOMYOMA

Definition—Attenuation of the functionalis due to compressing smooth muscle tumor.

Clinical Features

Epidemiology

- Similar to uterine leiomyomas.
- Frequently associated with uterine polyps.

Presentation

- Abnormal uterine bleeding is the most common presenting symptom.
- History of uterine leiomyomata.
- Appearance of a polyp on ultrasound or hysteroscopy.

Prognosis and Treatment

- Predicated on size and extent of bleeding.
- Hysteroscopic-guided removal is the preferred approach.

Pathology

Histology

- The endometrial specimen contains a proliferative- or secretory-phase endometrium, with strips of surface functionalis showing a paucity of glands (aglandular functionalis).
- Reactive stromal changes with old hemorrhage may also be encountered if there has been prior endometrial injury with bleeding.
- Fragments of submucosal leiomyoma may or may not be present.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Diagnostic Terminology

- Strips of aglandular functionalis, see comment.
- Comment: This finding is not diagnostic but can be seen with submucosal leiomyoma.

Main Differential Diagnosis

- Endometrial polyp—these may display aglandular functionalis.
- Progestin therapy—aglandular functionalis may be seen. For this reason, a diagnosis of possible submucosal leiomyoma should not be made in the setting of progestin therapy.
- Hormone replacement therapy, tamoxifen therapy, or menopausal endometrium—any scant endometrial sample will exhibit functionalis without glands.
- Endometrial stromal tumor—another cause of aglandular functionalis. Look for stromal cellularity and atypia.

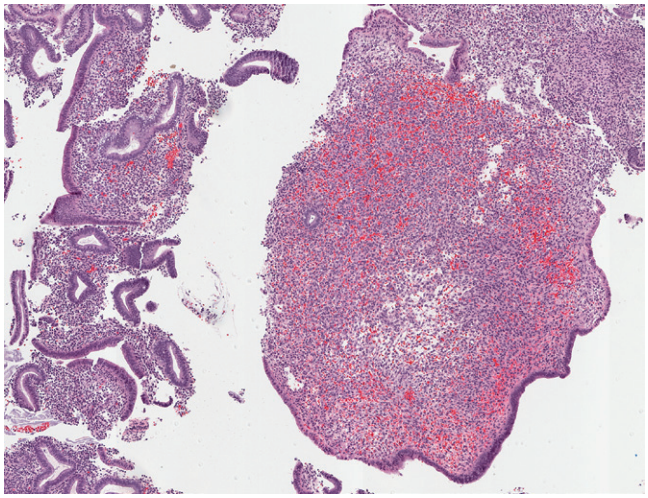


FIGURE 1

Strip of aglandular functionalis next to normal-appearing endometrium.

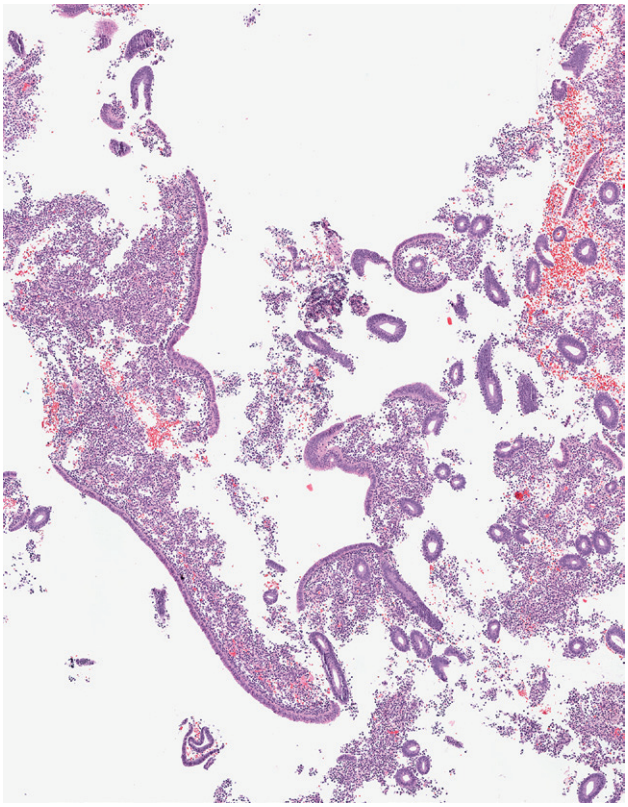


FIGURE 2

A strip of aglandular functionalis with proliferative endometrium on the right. This suggests a submucosal leiomyoma may be nearby.

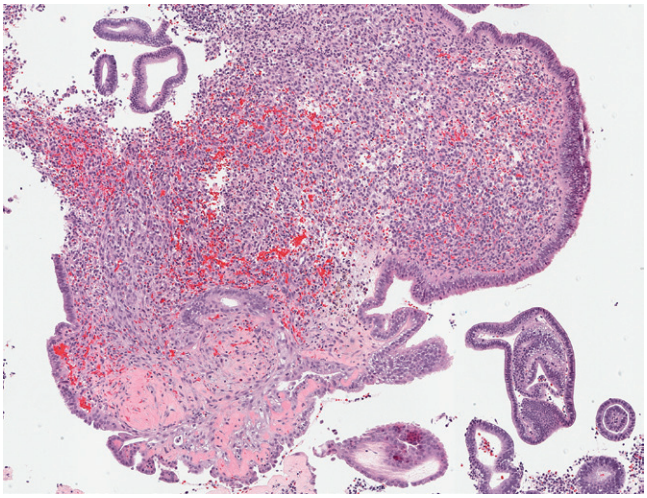


FIGURE 3

This fragment of aglandular functionalis displays some ischemic changes *(lower left)*.

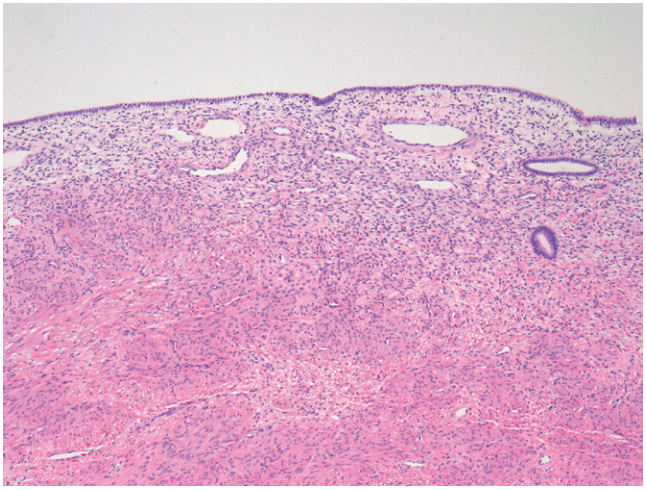


FIGURE 4

Leiomyoma-endometrial interface showing attenuated functionalis with few glands.

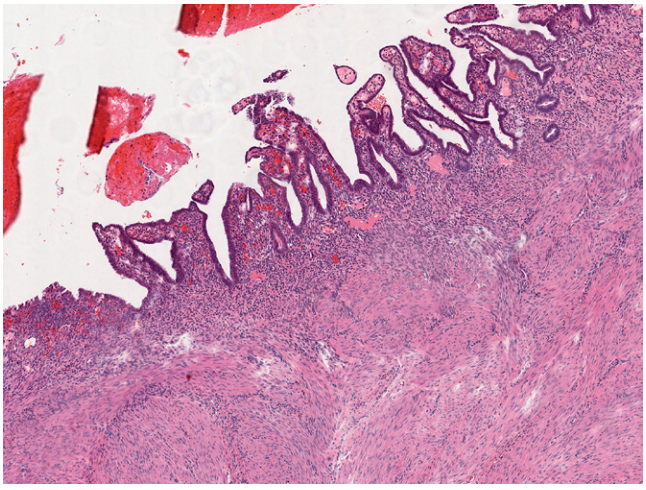


FIGURE 5

A fragment of endomyometrium with a submucosal leiomyoma. Note the unusual villiform reparative surface changes in the attenuated endometrium.

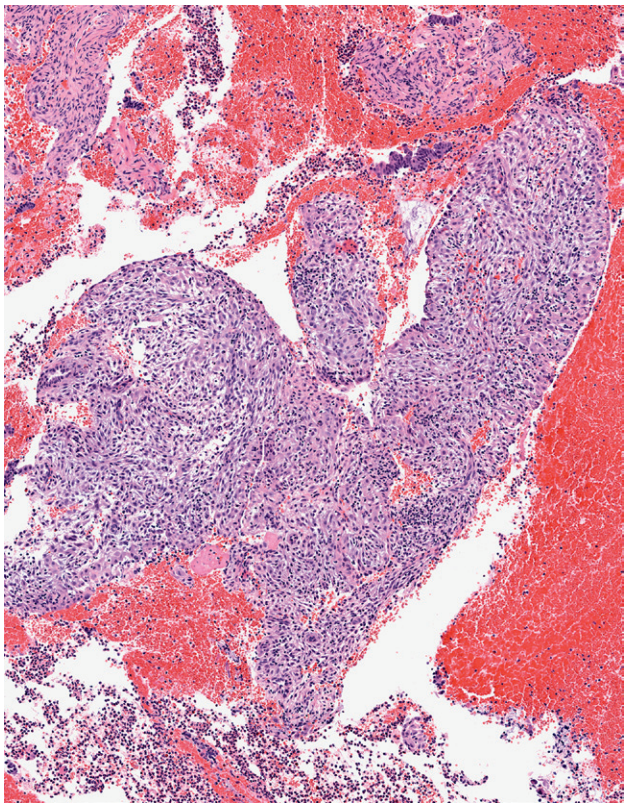


FIGURE 6

A fragment of aglandular functionalis associated with progestin therapy. This does not exclude a submucosal leiomyoma, but the latter cannot be confirmed on histology alone if the progestin has been administered for a prolonged period of time.

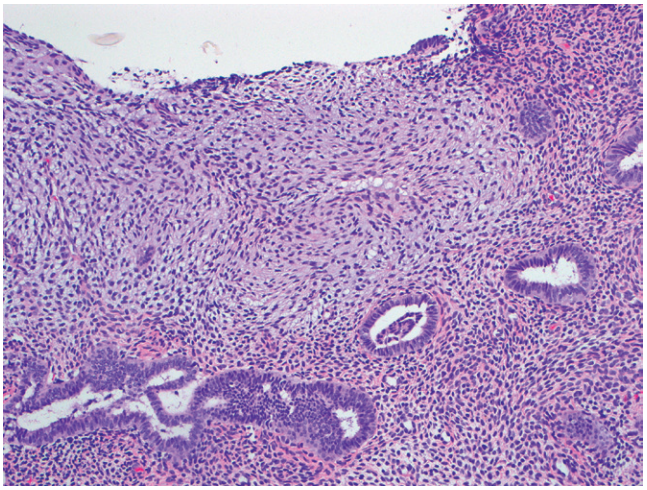


FIGURE 7

Aglandular functionalis associated with polyp.

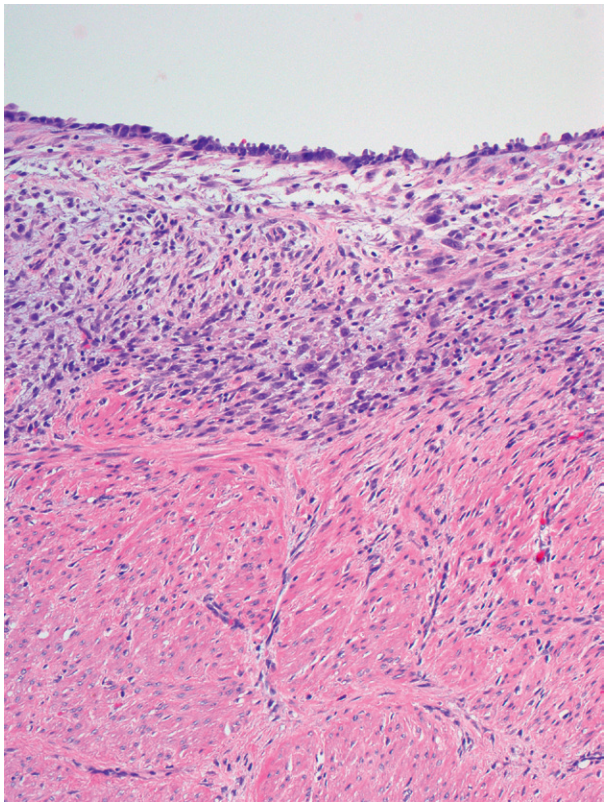


FIGURE 8

A thin strip of stromal sarcoma on the surface of a curetting fragment mimicking aglandular functionalis.

EXFOLIATION ARTIFACT

Definition—A preservation artifact in the endometrial epithelium leading to epithelial discohesion and exfoliation.

Clinical Features

Epidemiology

- Exfoliation artifact has been noted in association with hysteroscopic biopsies secondary to fluid instillation during the procedure.

Presentation

- Found incidentally at the time of histologic examination of the endometrial tissue.

Prognosis and Treatment

- Exfoliation artifact carries no adverse outcome and requires no treatment.

Pathology

Histology

- Superficial endometrial epithelium shows disaggregation, which leads to pseudomicropapillary clusters of epithelial cells protruding into the lumen.
- Occasionally the cells become "hobnailed" and mimic serous or clear-cell carcinoma. They may also mimic secretory epithelium due to the appearance of a nonlayered epithelium (due to exfoliated cells). However, the presence of mitoses will confirm the diagnosis of a proliferative-phase endometrium.
- The adjacent stroma typically reinforces the diagnosis, showing various degrees of preservation artifact, with indistinct nuclei and loosely disaggregated cells.
- Malignancy can be excluded based on the adjacent degenerative changes in the stroma, blending of the artifact with normal adjacent glands, a low nuclear-to-cytoplasmic ratio, and the absence of nuclear atypia.

Immunopathology (Including Immunohistochemistry)

- A negative p53 stain may be helpful in cases in which serous carcinoma is a concern and should be normal.

Main Differential Diagnosis

- Secretory endometrium—some exfoliation artifacts in proliferative-phase endometrium will mimic secretory endometrium, but the presence of mitoses will distinguish.
- Clear-cell or serous carcinoma—these entities might be expected with prominent hobnail patterns due to disaggregation of the epithelial cells; however, with exfoliation artifact there should be no atypia.

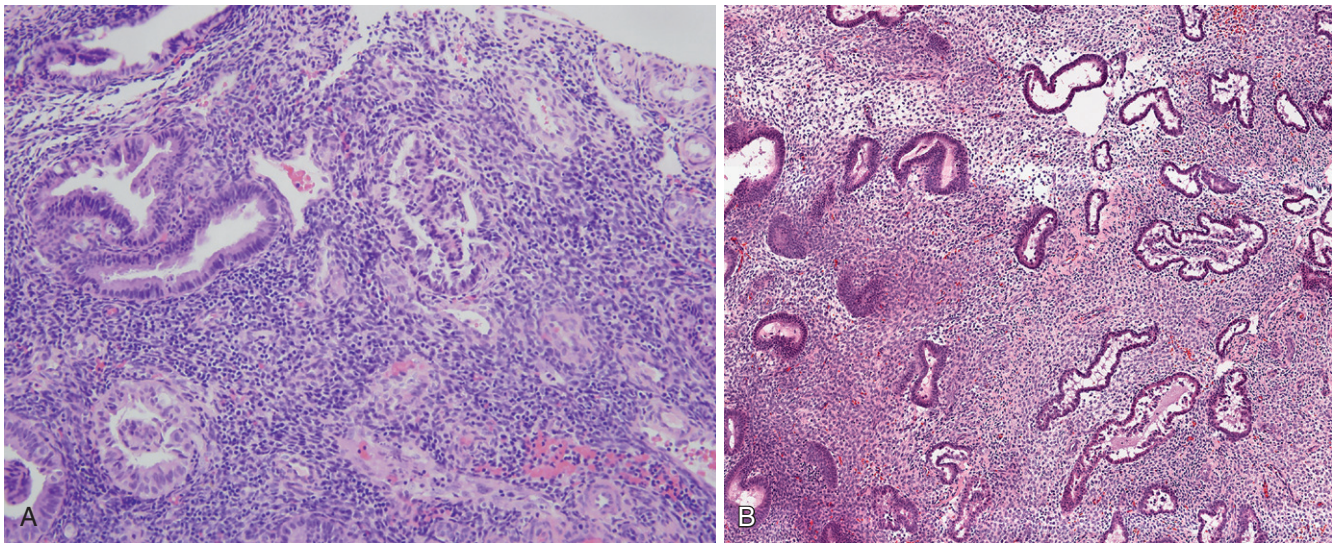


FIGURE 1A AND 1B

Exfoliation artifact. These lower-power images of the endometrium show a transition from well-preserved glands to poorly preserved glands and stroma with disaggregated epithelial cells in the gland lumens. Note how in 1B the proliferative glands on the right appear secretory.

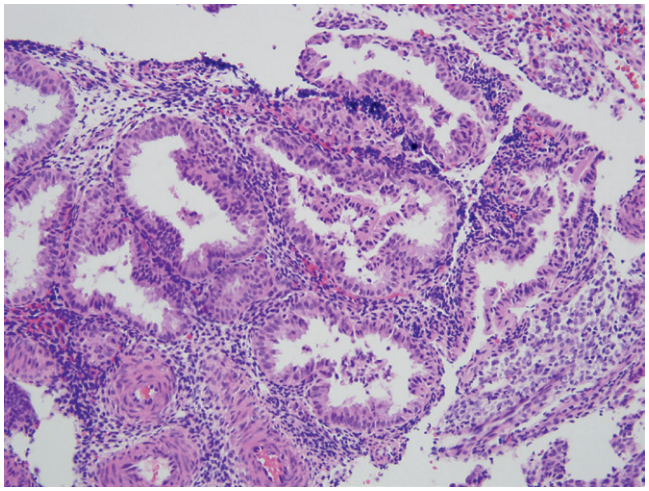


FIGURE 2

Exfoliation artifact. A cluster of endometrial glands with exfoliative epithelium. Note the somewhat poorly preserved stroma with mildly disaggregated cells and lightly staining nuclei.

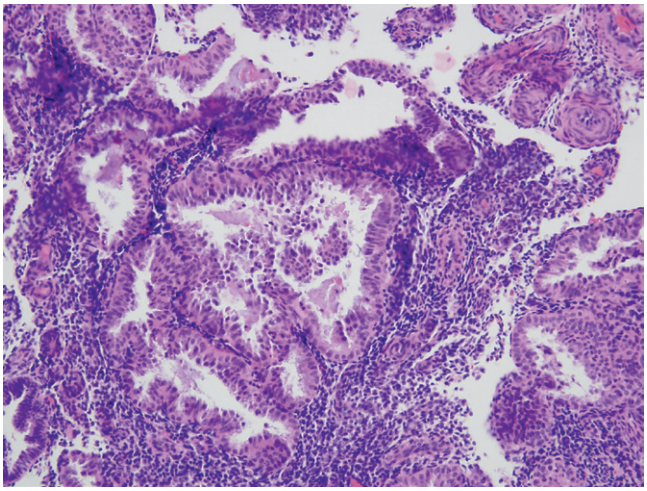


FIGURE 3

Exfoliation artifact. Higher-power image of proliferative endometrium with luminal exfoliation.

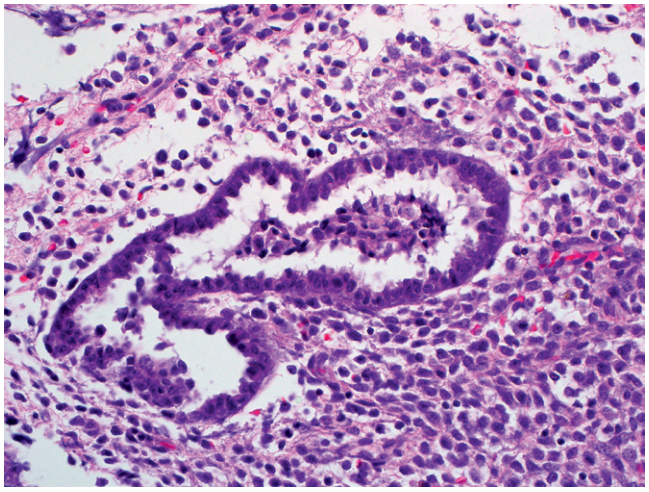


FIGURE 4

Exfoliation artifact in proliferative endometrium. Note the resemblance to secretory-phase endometrium.

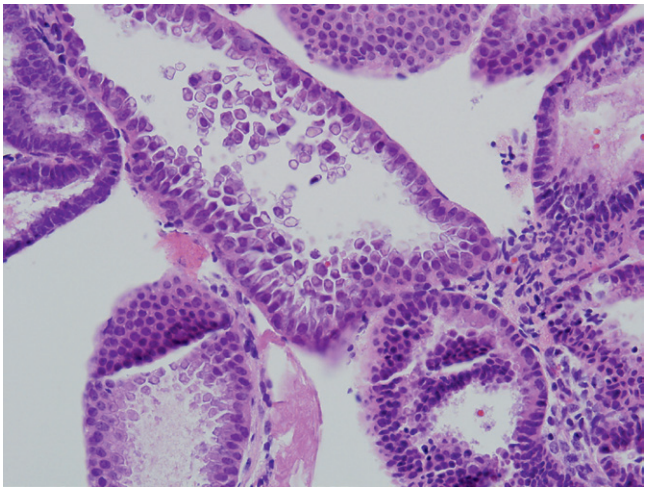


FIGURE 5

Exfoliation artifact. The exfoliated cells in this gland exhibit a hobnail appearance and could be confused with serous intraepithelial carcinoma.

PERFORATION

Definition—Perforation of the uterus, usually during endometrial sampling.

Clinical Features

Epidemiology

- Perforation is a rare complication of endometrial sampling.

Presentation

- Clinical suspicion of perforation may or may not be present.
- Pathologic evidence of perforation may be the first sign.
- Patients may be asymptomatic (usually) or present with an "acute abdomen."

Prognosis and Treatment

- The prognosis is variable.
- Cases with perforation range from asymptomatic to surgical emergencies.
- Repair of the defect or hysterectomy may be indicated based on severity.

Pathology

Histology

- Typically the presence of adipose tissue is the indication that perforation has occurred.
- Occasionally bladder, bowel, or other abdominal tissue may be identified.

Immunopathology (Including Immunohistochemistry)

- S100 will be positive in adipose tissue, differentiating adipose tissue from fatlike spaces in blood clot.

Main Differential Diagnosis

- Blood clot with artifactual fatlike spaces.

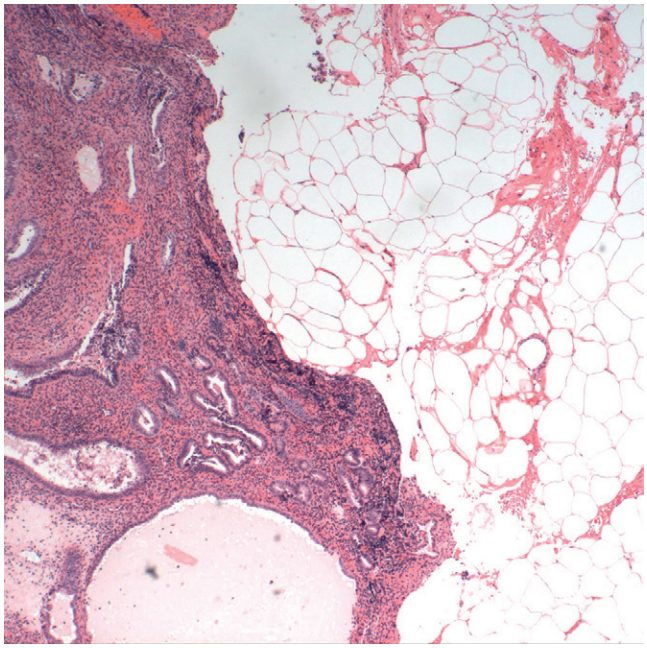


FIGURE 1

Uterine perforation. Adipose tissue adjacent to an endometrial polyp.

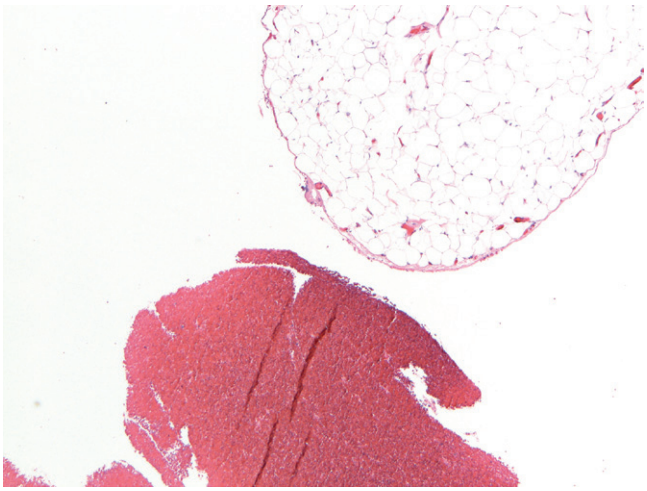


FIGURE 2

Uterine perforation. Blood clot and adipose tissue.

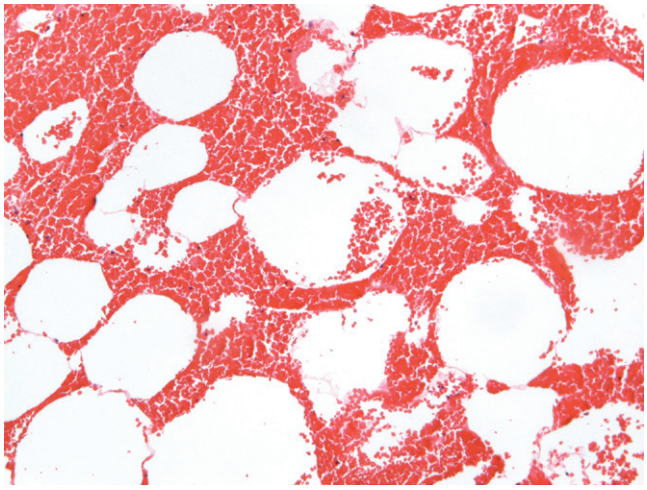


FIGURE 3

Blood clot as a mimic of uterine perforation. The lack of adipocyte nuclei is helpful in identifying fatlike spaces. Note the variability in size and shape of the spaces.

ABLATION ARTIFACT

Definition—Morphologic changes secondary to medical therapy that destroys the endometrial lining.

Clinical Features

Epidemiology

- Seen in patients who undergo endometrial ablation for dysfunctional uterine bleeding.

Presentation

- Found during sampling of the uterus after ablative therapy.

Prognosis and Treatment

- The most common consequence of ablation is a perplexed pathologist who may not be aware that ablation had been previously attempted. We occasionally see ablation artifact in uteri without a clinical history.
- Occasionally a curetting performed at the time of ablation may show an abnormality, which may lead to hysterectomy and a specimen with ablation artifact.

Pathology

Histology

- Following ablation the endometrial lining becomes necrotic and "devitalized" then hyalinized.
- "Ghosted" endometrial glands may be present.
- Deep endometrial glands (endometrial basalis) may be viable in occasional cases.
- A prominent giant cell reaction may be present.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Necrotic endometrial polyps or submucosal leiomyomas can be impossible to distinguish from necrotic endomyometrium, but the clinical history will be helpful.

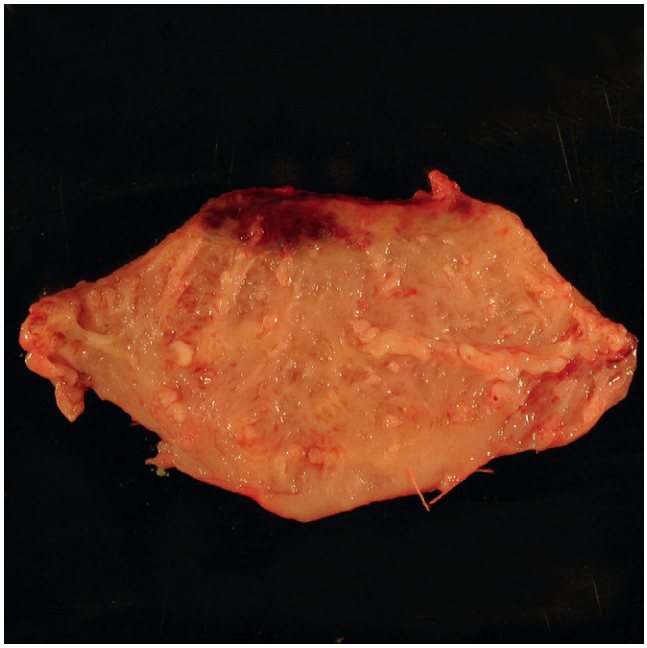


FIGURE 1

Endometrial ablation artifact. Gross image of endometrium and myometrium after ablation. Note the absence of abundant functionalis and the mottled appearance consistent with coexisting hemorrhage.

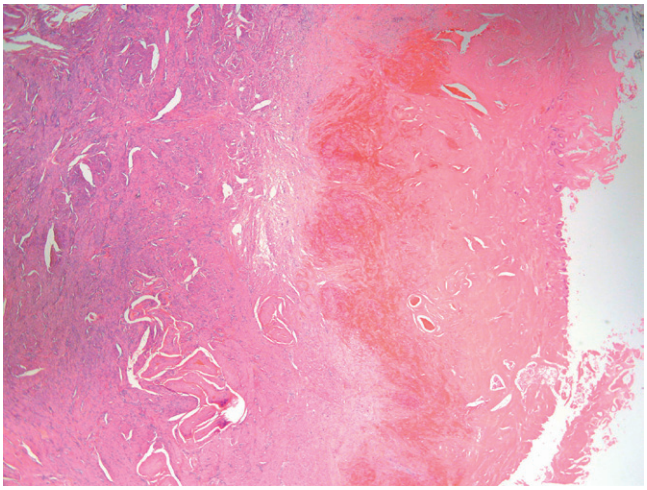


FIGURE 2

Endometrial ablation artifact. Necrosis and extensive hyaline change involving the endometrium.

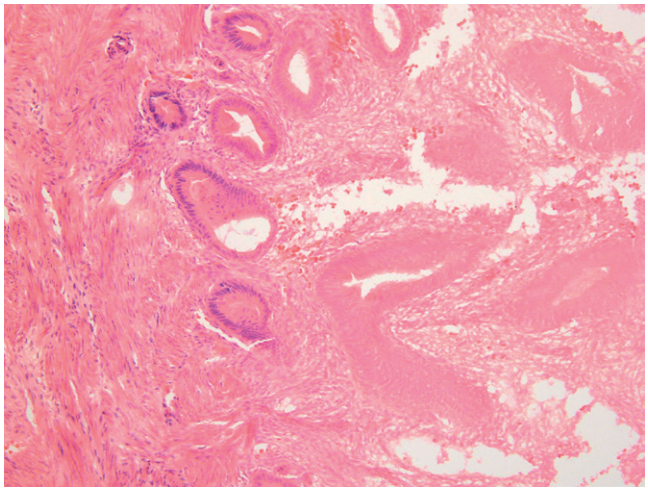


FIGURE 3

Endometrial ablation artifact. Necrotic or "ghosted" endometrial glands on the right. Note the presence of histologically recognizable, deep endometrial glands on the left.

ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA (ATYPICAL HYPERPLASIA)

Definition—A premalignant clonal expansion of altered endometrial glands.

Clinical Features

Epidemiology

- Endometrial intraepithelial neoplasia (EIN) is relatively common and carries an increased risk of development of type 1 endometrial adenocarcinoma.
- Women with excess estrogen (whether exogenous or endogenous) are at increased risk.
- Because of the production of excess estrogens, obese women are at an increased risk.
- Patients with hereditary nonpolyposis colorectal cancer (HNPCC) (Lynch syndrome) and Cowden syndrome are at an increased risk.
- Patients taking tamoxifen are at an increased risk of the development of EIN.

Presentation

- Patients typically present with abnormal or postmenopausal uterine bleeding.

Prognosis and Treatment

- EIN carries 46-fold increased risk of concurrent or future adenocarcinoma.
- In women who do not wish to preserve fertility, hysterectomy is the treatment of choice.
- Patients desiring fertility or poor surgical candidates may undergo hormonal therapy with progestins, although some patients may not respond.

Pathology

Histology

- The accurate diagnosis of EIN requires fulfillment of the following histologic criteria:
  1. Area of the glands exceeds that of the endometrial stroma. This does not apply toward cystically dilated, atrophic glands and in glands with squamous morular metaplasia.
  2. Altered cytologic features of the crowded focus of glands. No fixed features defining nuclear atypia are utilized in the diagnosis of EIN; instead, cytologic demarcation of the "atypical" glands from the background "normal" endometrial glands should be sought.
  3. The size of the focus of crowded glands must exceed 1 mm (not including scattered, cytologically altered glands). Lesions failing to meet these criteria are best given a descriptive diagnosis and follow-up is recommended.
  4. The exclusion of benign mimics of EIN (including polyps, metaplasia, endometrial basalis, repair, telescoping, and fragmentation artifact).
  5. The exclusion of low-grade adenocarcinoma.
- Several recognizable patterns of glandular alteration have been described including
  - Intraglandular papillary formations
  - EIN with extensive mucinous differentiation
  - EIN with secretory differentiation
  - EIN with squamous morular metaplasia
  - EIN with eosinophilic or tubal metaplasia

- In cases of suspected EIN arising within an endometrial polyp, comparison with the "background" glands within the polyp is required as all glands in a polyp may be altered compared with the nonpolyp endometrium.

Preferred Diagnostic Terminology

- EIN (atypical hyperplasia).

Immunopathology (Including Immunohistochemistry)

- Loss of PTEN and PAX2 has been described in EIN and endometrial adenocarcinoma; however, reliance on these markers over histologic criteria is not recommended.

Main Differential Diagnosis

- Reactive epithelial changes (repair) occur on the endometrial surface and are degenerative in nature. They must be distinguished though from surface growth of an EIN.
- Gland compression or telescoping artifact due to procedure effect. The glands are folded and compressed in the gland tract but are not altered cytologically.
- Benign hyperplasia may show crowding but no discrete cytologically altered population.
- Secretory endometrium can contain crowded glands and mild variations in cytologic appearance. A key discriminator is the normalcy of the secretory maturation as opposed to EIN.
- Endometrial polyps will show some gland heterogeneity and minor gland crowding.
- Endometrial breakdown will push glands together.
- Endometrioid adenocarcinoma must fulfill the criteria including one of the following: loss of gland integrity, papillary architecture, cytologic atypia (beware serous intramucosal [intraepithelial] carcinomas!).
- Gland crowding with altered cytologic can occur in very small foci, in which case a repeat sample is advised.

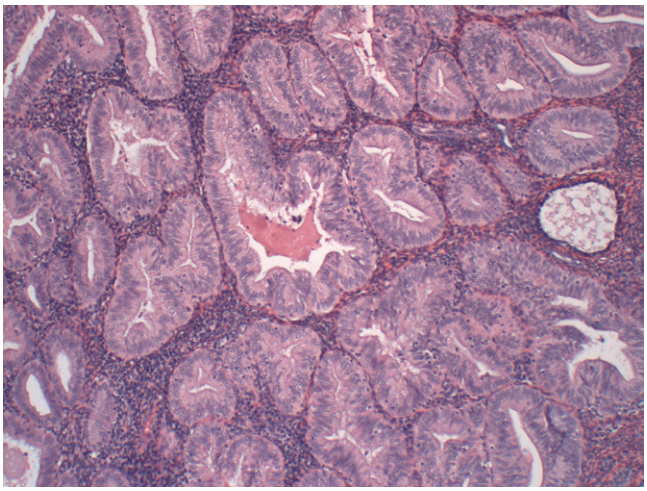


FIGURE 1

EIN. Crowded endometrial glands that are cytologically altered when compared with the cystic gland on the right.

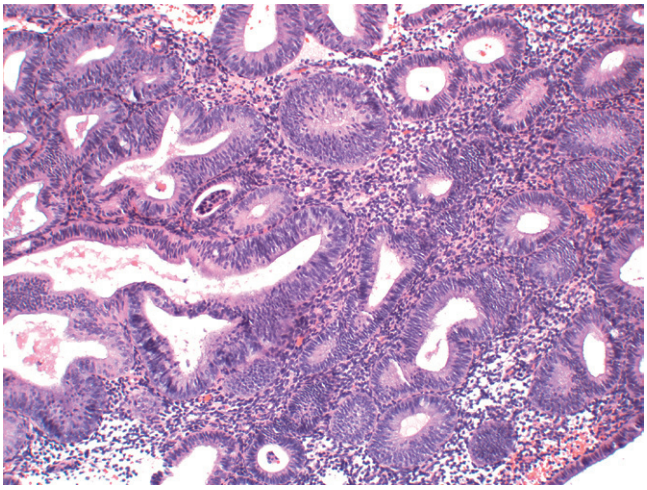


FIGURE 2

EIN. Note the interspersed, cytologically normal glands.

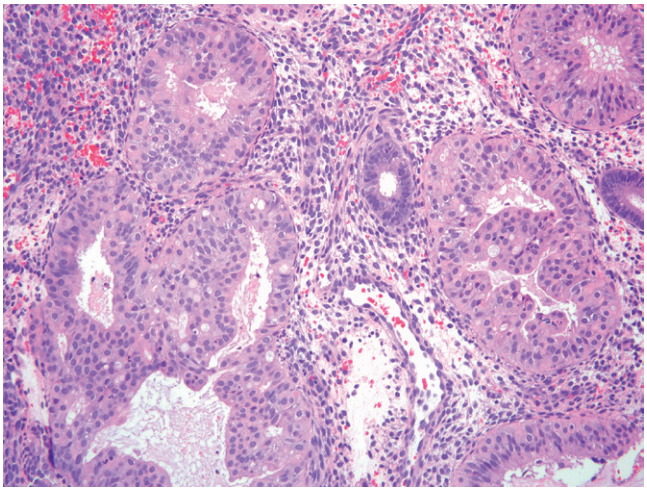


FIGURE 3

EIN. Increased intraglandular complexity justifies the diagnosis of EIN, even in the absence of crowding.

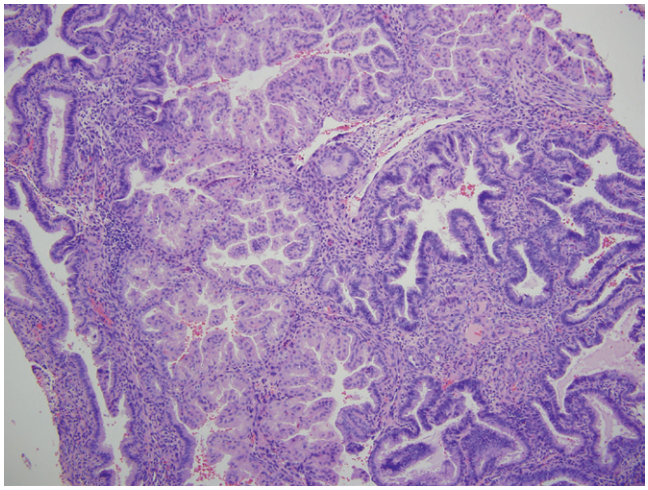


FIGURE 4

EIN. Crowded glands with extensive intraglandular papillae formation. Note the sharp cytologic demarcation between the background and EIN-containing glands.

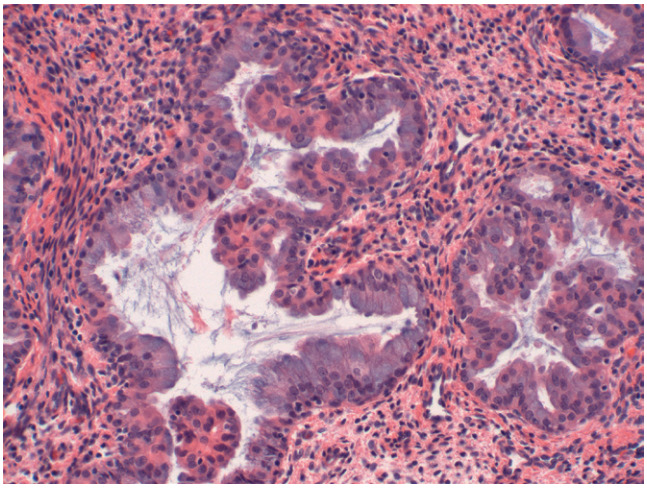


FIGURE 5

EIN. Mucinous metaplasia within EIN. Note the small papillary tufts.

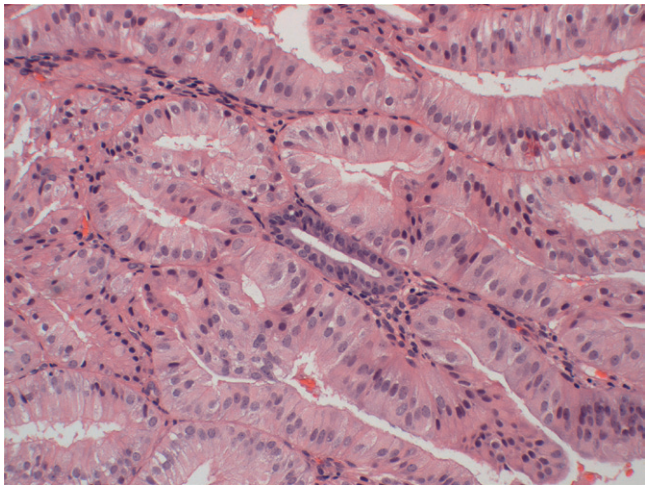


FIGURE 6

EIN. Eosinophilic EIN, with a single, entrapped background gland *(center)*.

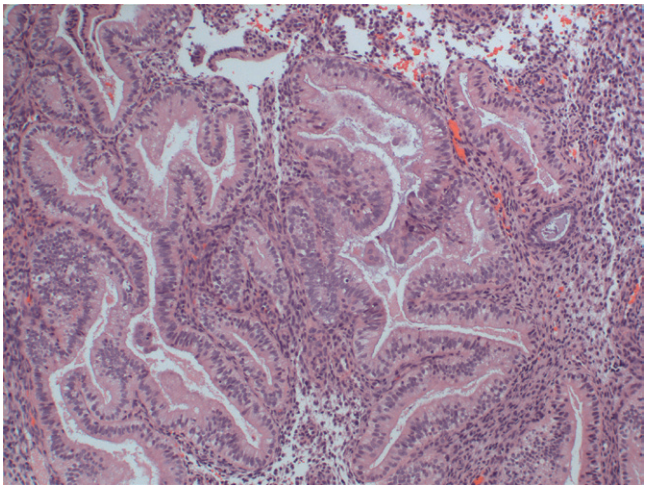


FIGURE 7

EIN. Secretory EIN denoted by scattered cytoplasmic vacuoles. A normal gland can be seen on the right.

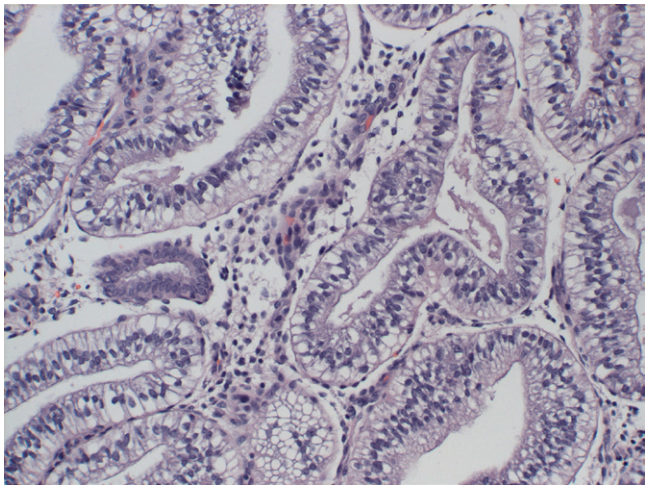


FIGURE 8

EIN. Secretory EIN with extensive vacuole formation.

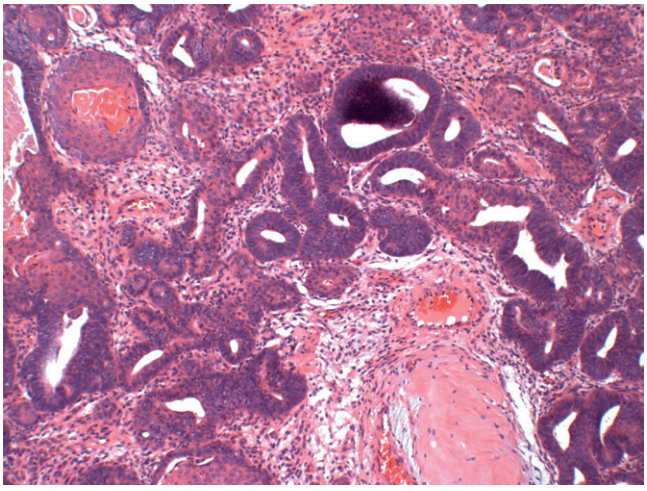


FIGURE 9

EIN. Squamous morular metaplasia within a focus of EIN.

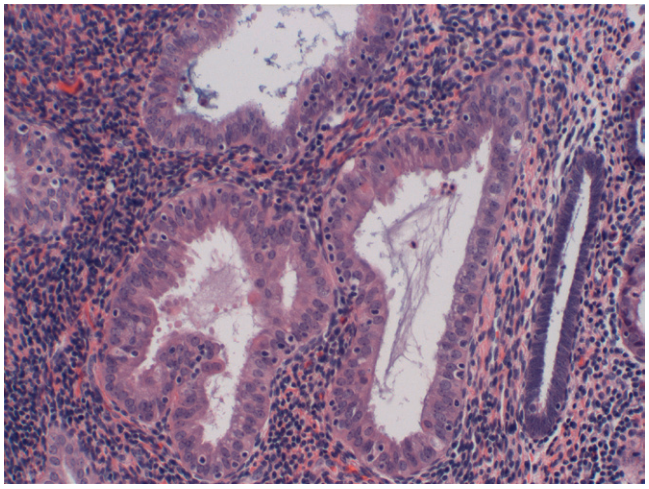


FIGURE 10

EIN. Tubal metaplasia within a focus of EIN. Note the normal gland on the right.

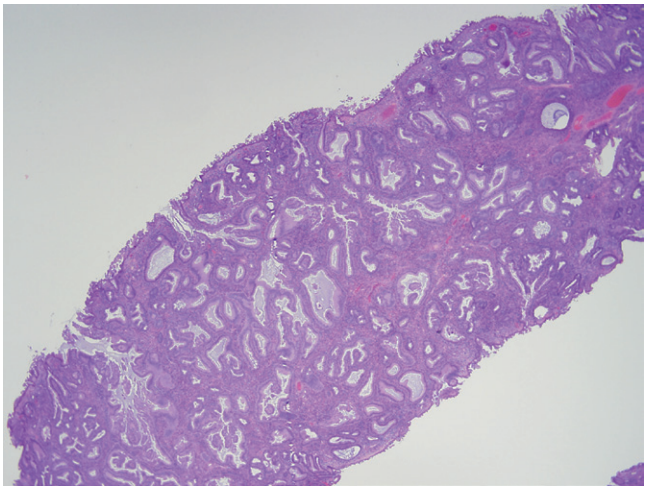


FIGURE 11

EIN. Low-power view of an endometrial polyp containing EIN. Intraglandular papillary tufts are prominent.

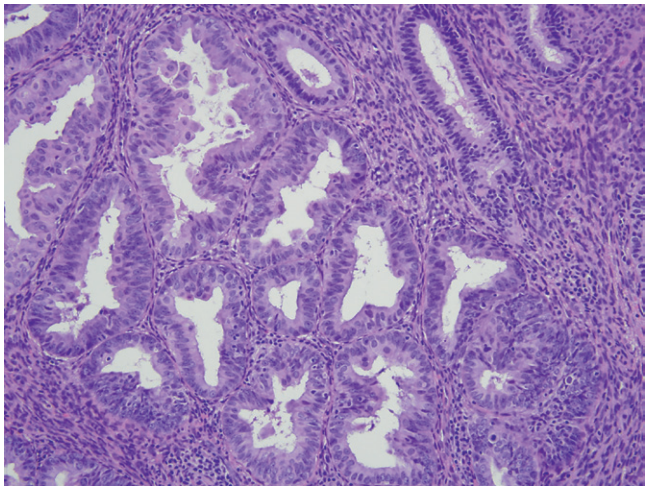


FIGURE 12

EIN. A higher-power view of the polyp in Figure 11. Cytologic demarcation can be seen between the EIN *(left)* and the background glands *(right).*

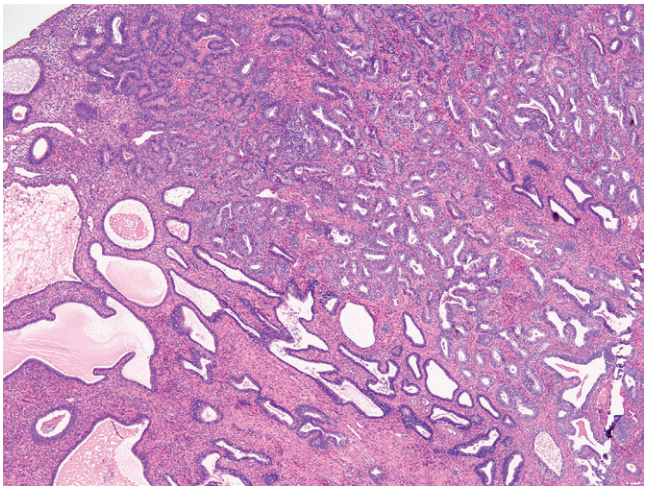


FIGURE 13

Another polyp showing crowded altered glands *(upper).*

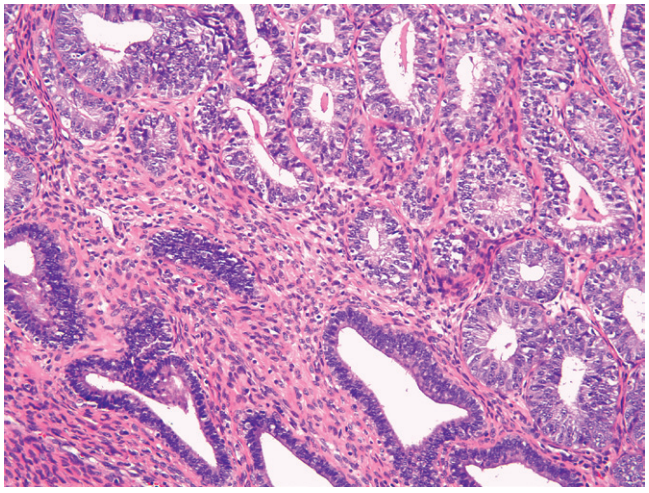


FIGURE 14

Note the sharp contrast between the normal glands *(lower)* and EIN.

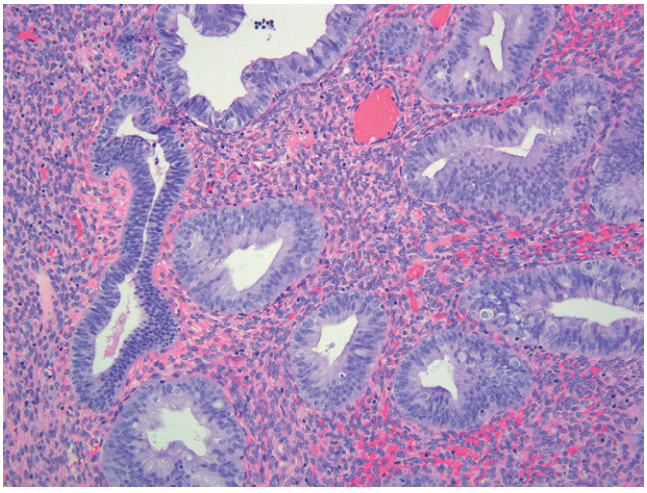


FIGURE 15

Small foci of gland crowding and altered cytology may not fulfill the criteria for EIN, but must be followed with a repeat sample since the risk of EIN on follow-up approaches 25%.

ATYPICAL POLYPOID ADENOMYOMA

Definition—A polypoid neoplasm composed of atypical glands and smooth muscle stroma.

Clinical Features

Epidemiology

- Atypical polypoid adenomyomas (APAs) are rare neoplasms.
- Typically seen in the fifth decade.

Presentation

- Patients present with abnormal uterine bleeding or may be asymptomatic.

Prognosis and Treatment

- APAs appear to carry a very low risk of adverse outcome.
- However, they may be difficult at times to distinguish from adenocarcinomas and thus have a guarded prognosis.
- In patients who do not desire hysterectomy, conservative excision has been undertaken with pregnancy outcomes. However, complete removal of these tumors may be difficult because of their sessile nature.

Pathology

Histology

- APAs typically appear as sessile, broad-based polyps. Some may be more pedunculated, others ensconced in the endomyometrium.
- Glands tend to be regular in appearance with mild atypia, consistent with those seen in endometrial intraepithelial neoplasia.
- Well-defined squamous morules are virtually always present and usually abundant and regularly distributed throughout the tumor. There will be rare instances, however, when they will be absent, in which case the distinction between APA and an adenomyomatous polyp may be difficult.
- The glandular complexity may border on well-differentiated adenocarcinoma, and in some cases foci indistinguishable from adenocarcinoma may be present.
- The stroma is a key feature and should be composed of regular fascicles of smooth muscle without a fibrotic or desmoplastic appearance.
- In many cases the smooth muscle stroma may blend imperceptibly with the myometrium.

Diagnostic Terminology

- Atypical polypoid adenomyoma. (Clinician should be made aware that although not considered malignant, APA may nonetheless recur and develop considerable atypia that may make it difficult to distinguish from malignancy. Thus it should be monitored by repeated sampling if preservation of childbearing potential is desired.)

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Endometrial intraepithelial neoplasia (atypical hyperplasia) does not exhibit myomatous stroma.
- Well-differentiated adenocarcinoma (with myometrial invasion)—this may be difficult to exclude and if not, should be mentioned in the report.
- Adenomyomas are often encountered in the myometrium. The glands are not atypical, and squamous morules are not seen.
- Adenomyomatous polyps do not typically display squamous morules. They can, however, and the distinction from APA depends somewhat on whether the polyp is pedunculated or sessile. APA also tends to exhibit large well-developed fascicles of smooth muscle, whereas the muscle in adenomyomatous polyps has a finer consistency.

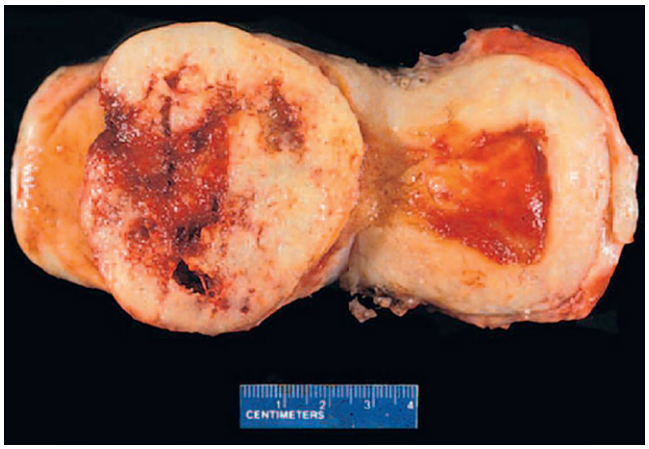


FIGURE 1

APA. A discrete mass in the lower uterine segment occludes the endometrial cavity.

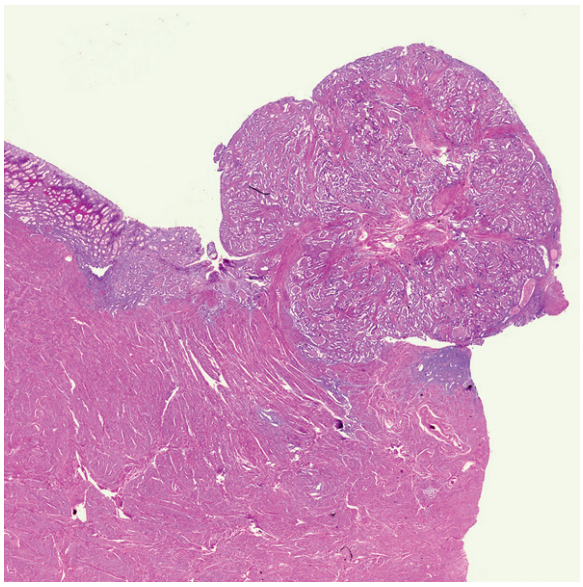


FIGURE 2

APA. This small lesion presents as a polyp.

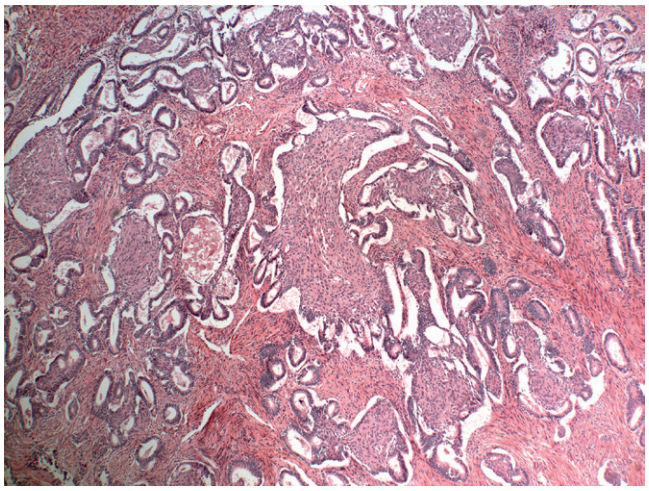


FIGURE 3

APA. Numerous glands with extensive squamous morular metaplasia. Note the smooth muscle stroma.

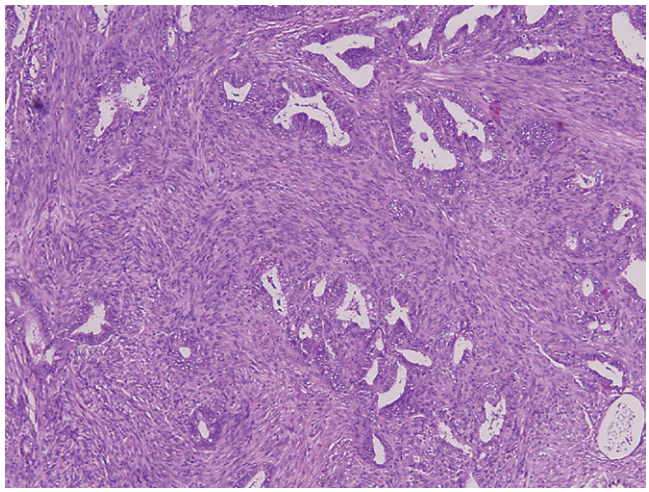


FIGURE 4

APA. Scattered glands separated by well-defined fascicles of smooth muscle. Note the absence of a desmoplastic stromal change.

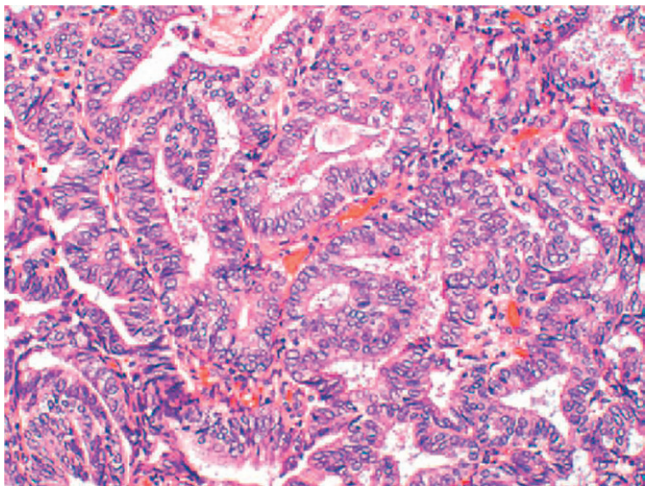


FIGURE 5

Proliferation in an APA may resemble an adenocarcinoma.

ENDOMETRIAL INVOLVEMENT BY ENDOCERVICAL GLANDULAR NEOPLASIA

Definition—Involvement of the endometrium by endocervical glandular neoplasia, either by direct extension or by contamination during sampling.

Clinical Features

Epidemiology

- True endometrial involvement (direct extension) by endocervical adenocarcinoma is rare.
- Not uncommonly, endometrial biopsies in patients with endocervical neoplasia may contain fragments of endocervical adenocarcinoma.

Presentation

- Patients present with signs and symptoms of cervical adenocarcinoma, typically abnormal spotting or bleeding and pain.
- Patients may be asymptomatic or present with atypical glandular cells on Pap smear.

Prognosis and Treatment

- True endometrial extension of endocervical adenocarcinoma denotes a higher-stage disease and thus has a more adverse outcome (vs. localized endocervical disease).
- Artifactual contamination of an endometrial biopsy does not increase the surgical stage and is not associated with an adverse outcome.
- Treatment of endocervical adenocarcinoma consists of a radical hysterectomy (or trachelectomy) with or without lymph node dissection.
- Adjuvant therapy may be indicated in advanced cases of invasive carcinoma.

Pathology

Histology

- Tumor fragments will display histologic features similar to those seen in endocervical adenocarcinoma, including pseudostratification, apical mitotic figures, and apoptotic debris.
- The presence of stromal plasma cells may be helpful in indicating a cervical primary.
- Well-defined, crisp, glandular contours are more commonly seen in endocervical primaries, whereas endometrial primaries have less well-defined, punched-out glands.
- Stromal foam cells are more commonly seen in endometrial primaries.

Immunopathology (Including Immunohistochemistry)

- p16 will show strong, diffuse positivity in endocervical adenocarcinoma versus patchy staining in low-grade endometrial adenocarcinoma.
- Vimentin is negative in endocervical adenocarcinoma and positive in a pericellular (piano-key) fashion in endometrial adenocarcinoma.
- ER and PR are diffusely positive in low-grade endometrial adenocarcinoma and typically negative (or only focally positive) in endocervical primaries.
- CEA is positive in cervical lesions and negative in endometrial primaries.

Main Differential Diagnosis

- Low-grade endometrioid adenocarcinoma—this can be distinguished histologically by the more pseudostratified appearance of endometrioid neoplasia and the greater hyperchromasia seen in the endocervical neoplasm, often with coarse chromatin, apical mitoses, and mucin production. A p16 immunostain will be diffusely positive in the endocervical neoplasm.

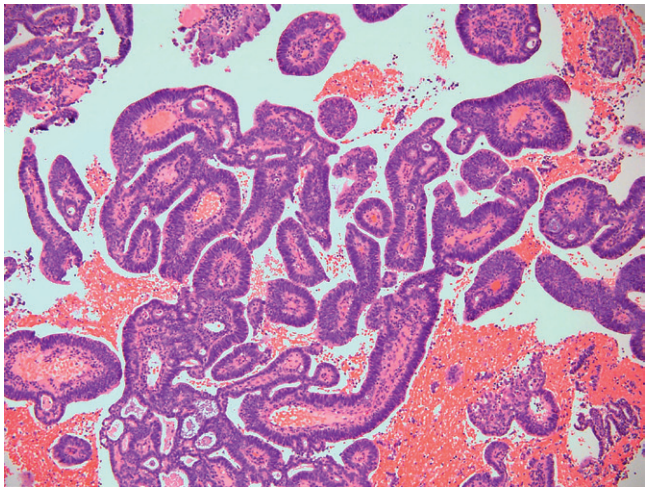


FIGURE 1

Endometrial involvement by endocervical adenocarcinoma. Predominantly papillary growth of endocervical adenocarcinoma in an endometrial biopsy.

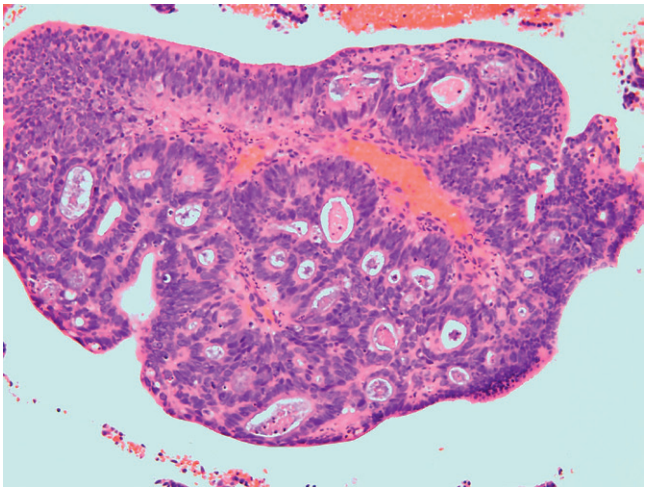


FIGURE 3

Endometrial involvement by endocervical adenocarcinoma. Endocervical adenocarcinoma; note the well-circumscribed, "punched-out," glandular spaces.

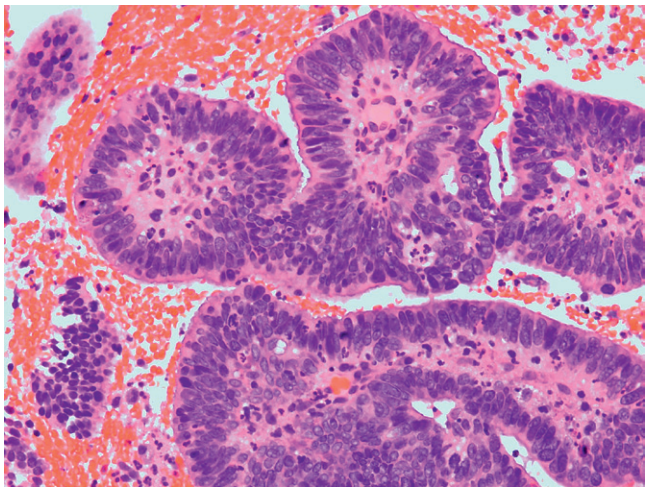


FIGURE 2

Endometrial involvement by endocervical adenocarcinoma. Endocervical adenocarcinoma displaying apical mitoses, pseudostratified nuclei, and apoptotic debris.

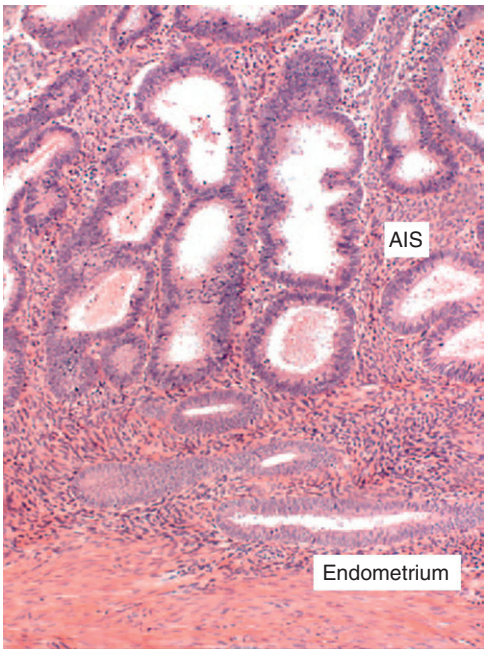


FIGURE 4

Endometrial involvement by adenocarcinoma in situ (AIS). The lesion is in the functionalis, replacing the glands *(left)*. Normal basal endometrium is on the right.

DEGENERATIVE REPAIR

Definition—Degenerative changes of the surface epithelium associated with breakdown and ischemia.

Clinical Features

Epidemiology

- Most commonly occurs in the fifth decade.
- Associated with anovulatory bleeding or other unscheduled breakdown, including polyps and submucosal leiomyomas.

Presentation

- Typically in curettings for abnormal uterine bleeding.

Prognosis and Treatment

- Considered benign. Management is predicated on the underlying disturbance.

Pathology

Histology

- Admixed blue clusters of degenerating stroma and epithelium.
- Pseudopapillary architecture, absence of gland differentiation.
- Ill-defined, slit-forming spaces between epithelial cells with a low nuclear-to-cytoplasmic (N/C) ratio.
- Exuberant reparative changes (papillary syncytial metaplasia) occasionally seen.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Endometrial intraepithelial neoplasia (EIN) and adenocarcinoma—both might exhibit some degree of surface or intraglandular papillary changes. The latter should always raise suspicion for malignancy. The surface changes typically will be both multilayered and microacinar in some fashion, too complex for a degenerative or simple proliferative process.
- Proliferative repair—pseudostratification is the rule, with a picture of healthy appearing mucosa. A regenerative rather than degenerative process.

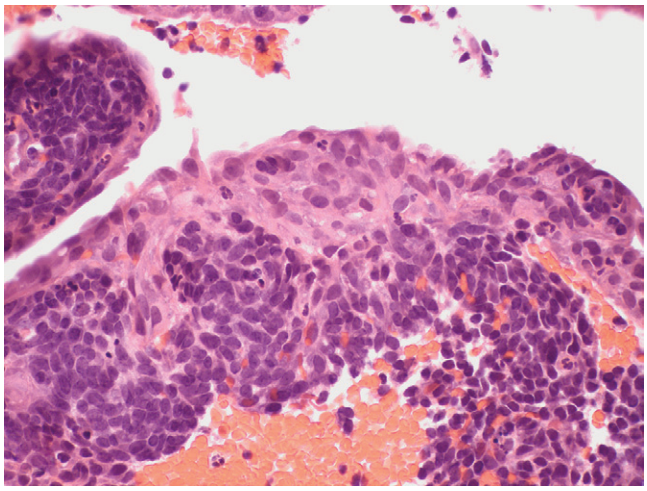


FIGURE 1

Degenerative repair associated with breakdown.

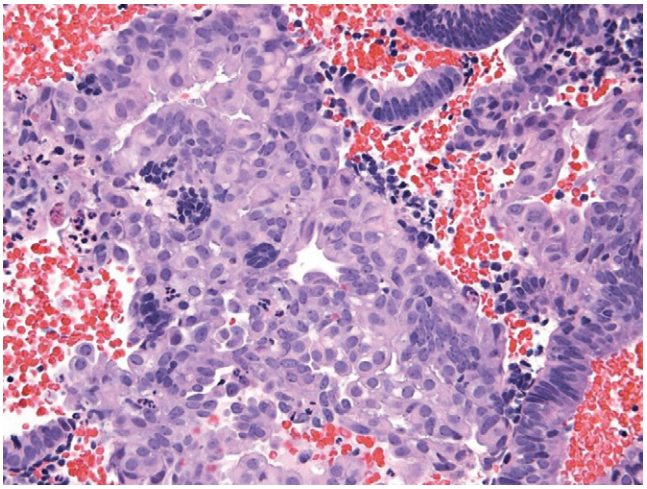


FIGURE 2

Degenerative repair with mild stratified appearance. Note the absence of any true papillary or glandlike architecture.

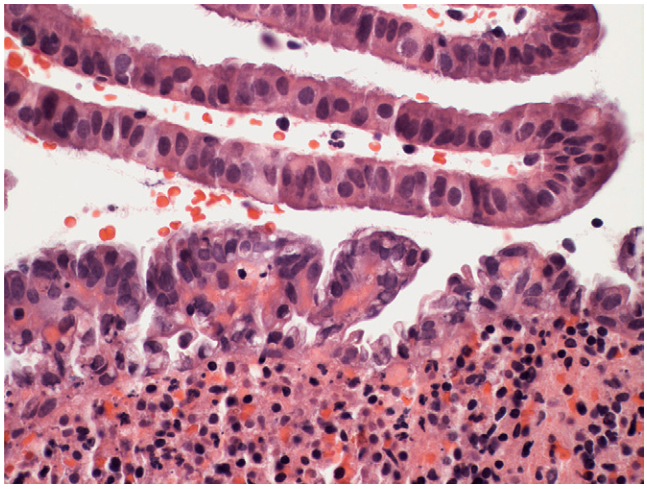


FIGURE 3

Degenerative epithelial changes associated with necrotic polyp.

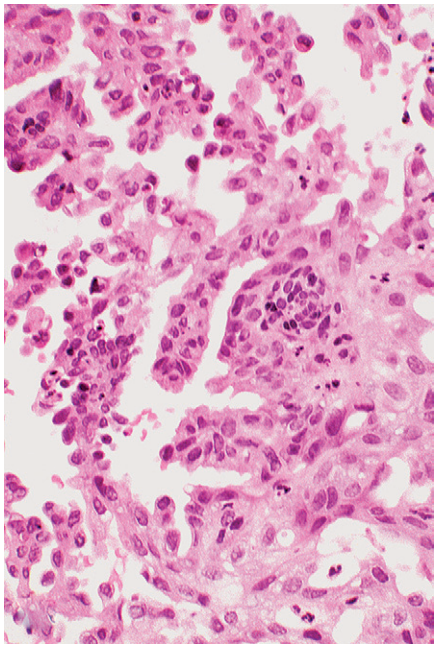


FIGURE 4

Exaggerated repair (papillary syncytial metaplasia) associated with breakdown.

PROLIFERATIVE REPAIR

Definition—Surface changes in the endometrium associated with breakdown and injury.

Clinical Features

Epidemiology

- Most commonly occurs in the fifth decade associated with endometrial breakdown or injury (submucosal leiomyoma or polyp).

Presentation

- Typically abnormal uterine bleeding; however, patients may be asymptomatic.

Prognosis and Treatment

- Considered a benign condition.
- Management is tailored to the underlying cause of the bleeding (submucosal leiomyoma, polyp, altered cycle).

Pathology

Histology

- Surface changes characterized primarily by multilayered epithelium with pseudostratified appearance.
- Tubal or mucinous metaplasia is not uncommon.
- More complex features, such as a highly stratified epithelium or true papillary or microacinar architecture, should not be present, but proliferative repair could coexist with these features in cases of neoplasia.

Immunopathology (Including Immunohistochemistry)

- Noncontributory, although stains for p53 might be employed if serous neoplasia is suspected.

Main Differential Diagnosis

- Endometrial neoplasia—either adenocarcinoma or endometrial intraepithelial neoplasia (EIN) will display more complex surface epithelial architecture.
- Reactive epithelial changes—these will be characterized by nuclear enlargement and some hyperchromasia.

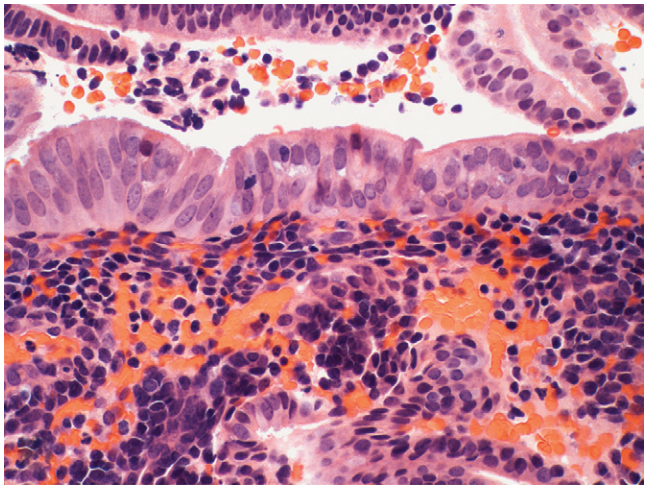


FIGURE 1

Proliferative surface epithelial changes associated with breakdown. Mild changes resemble tubal metaplasia.

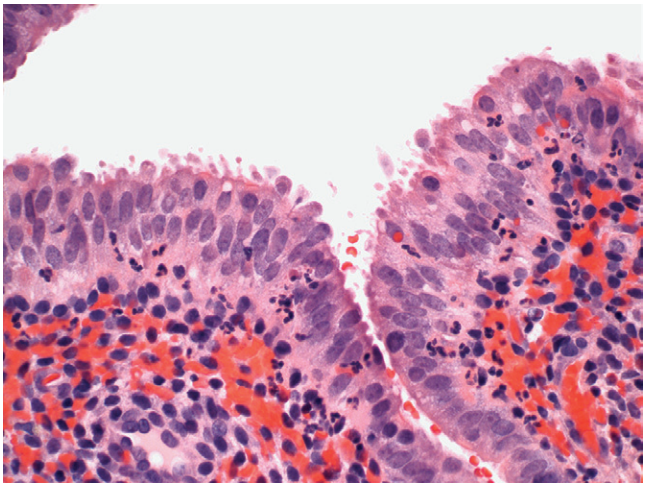


FIGURE 2

Proliferative surface epithelial changes associated with breakdown. Pseudostratified epithelial changes.

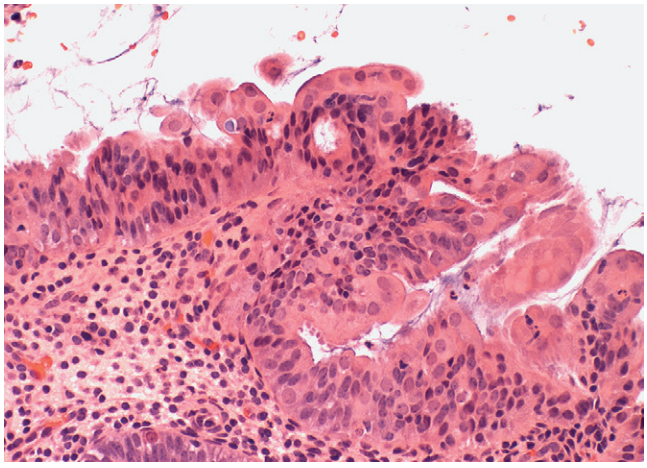


FIGURE 3

Complex "metaplastic" surface changes with stratified appearance and glandlike structures associated with endometrial adenocarcinoma.

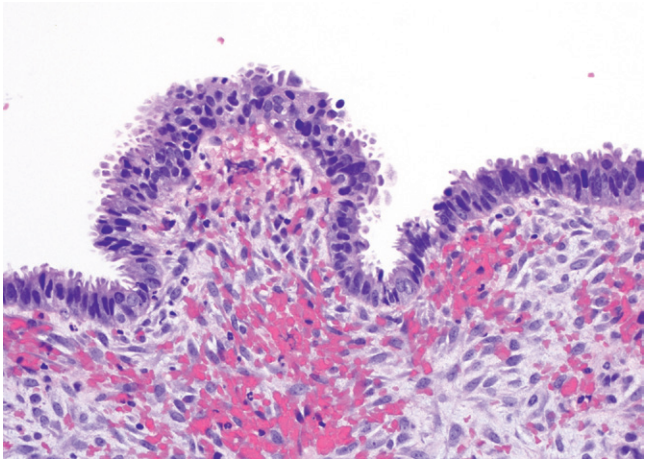


FIGURE 4

Another example of "proliferative repair," possibly overlying a submucosal leiomyoma and bordering on reactive epithelial changes.

MUCINOUS METAPLASIA OF THE ENDOMETRIUM

Definition—Change of the epithelium of the endometrium to a mucinous phenotype.

Clinical Features

Epidemiology

- Most commonly occurs in the perimenopausal to postmenopausal years.
- Papillary and microglandular forms are associated with a significantly increased risk of a coexisting endometrioid adenocarcinoma.

Presentation

- Typically abnormal uterine bleeding; however, patients may be asymptomatic.

Prognosis and Treatment

- Simple, nonstratified (or at most tufting) surface mucinous metaplasia is not significantly associated with an increased cancer risk and may be followed up routinely.
- Any intraglandular mucinous epithelium with stratification or tufting should be viewed as a possible endometrial intraepithelial neoplasia (EIN).
- Mucinous metaplasia with well-developed stromal cores or possessing microglandular or microacinar architecture should be treated according to EIN-hyperplasia protocols.
- True *intestinal* mucinous metaplasia (or rarely gastric metaplasia) of the endometrium is rare and may be found in isolation. The risk of malignancy is unknown, and follow-up is required.

Pathology

Histology

- The mucinous epithelium may range from simple, cuboidal to columnar and stratified. A classification scheme based on the amount of epithelial complexity has been described:
  - Type A—cuboidal, endocervical-like epithelium involving the surface of polyps or glands.
  - Type B—mild, increased complexity with pseudopapillary formations.
  - Type C—cribriform mucinous epithelium or free-floating mucinous epithelium with microglandular or villous architecture (discussed in greater detail under microglandular variants of endometrioid adenocarcinoma in the following).
  - A rare variant of intestinal-type mucinous metaplasia has been identified by the presence of goblet cells or intracytoplasmic *O*-acetylated sialomucins (which may be seen in the absence of morphologic evidence of intestinal metaplasia).

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Endocervical microglandular hyperplasia—look for reserve cells, cervical stroma, etc.

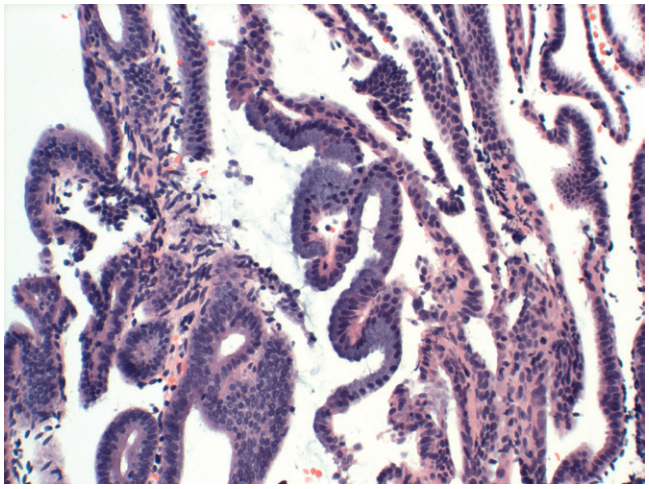


FIGURE 1

Mucinous metaplasia. Type A mucinous metaplasia consisting of a single layer of mucinous epithelium. This does not require further action.

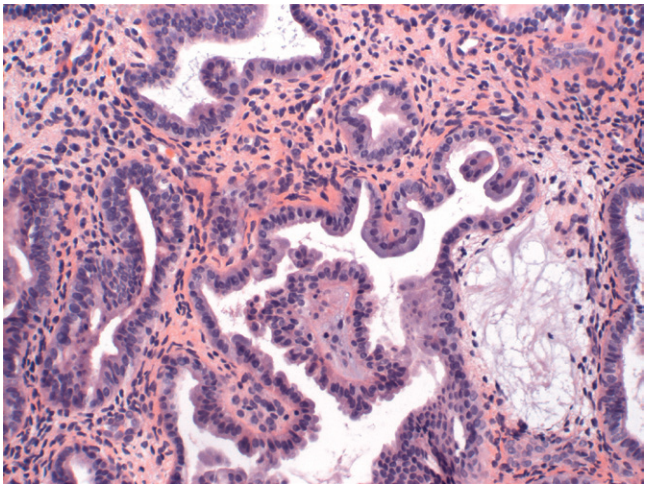


FIGURE 2

An endometrial polyp with focal mucinous differentiation in a papillary structure (Type B mucinous metaplasia). These changes can be managed with a follow-up office endometrial sampling if there are clinical concerns.

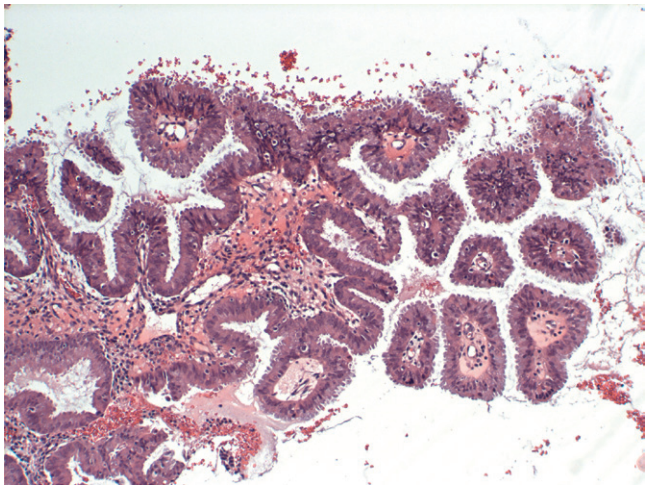


FIGURE 3

Mucinous metaplasia. Increased complexity with small papillae. This should be managed with follow-up sampling to exclude EIN or a subtle adenocarcinoma.

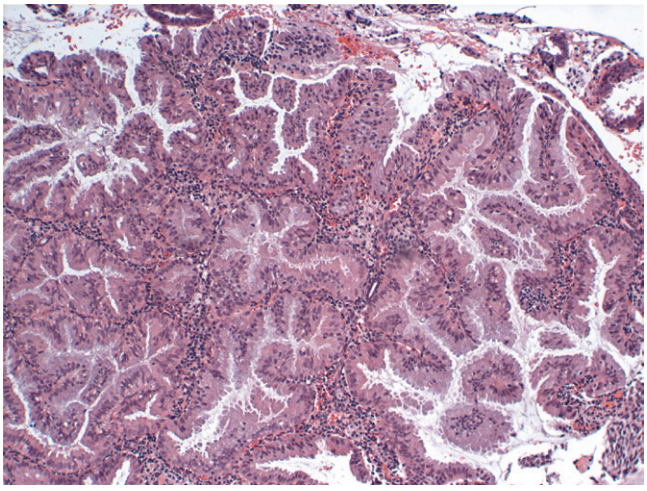


FIGURE 4

Mucinous metaplasia. True papillae with mucinous metaplasia in the background of an endometrial polyp. Followup sampling is needed.

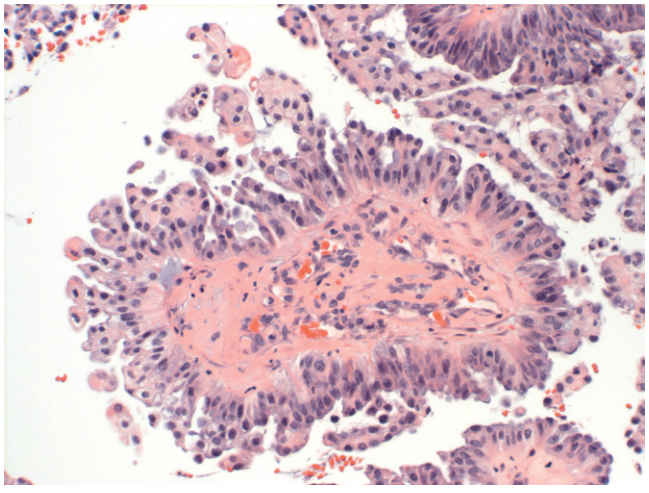


FIGURE 5

Mucinous differentiation. This surface change is associated with an obvious papillary structure with a stromal core. This requires close follow-up with repeat sampling to exclude neoplasia.

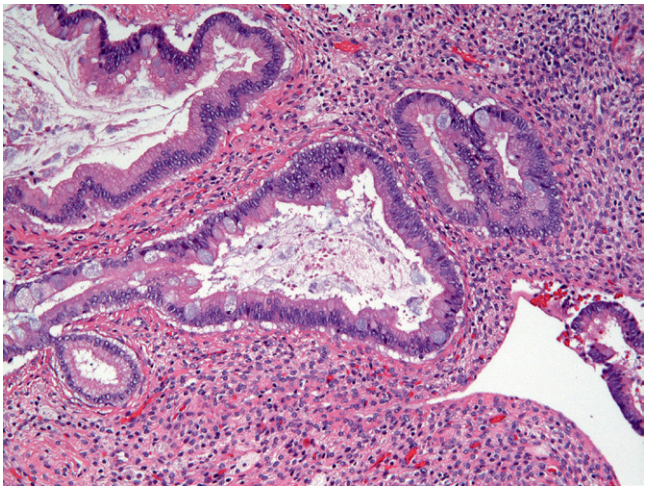


FIGURE 6

Mucinous metaplasia. A rare example of intestinal-type mucinous metaplasia displaying occasional goblet cells. This may be benign but should be followed with repeat sampling to exclude neoplasia.

SQUAMOUS AND MORULAR METAPLASIA

Definition—Partial or complete replacement of an endometrial gland tract by a generally nonkeratinizing squamous metaplasia.

Clinical Features

Pathogenesis

- Squamous morules are seen at all ages, mostly in the fifth decade.
- Can be isolated, associated with minor gland proliferations, seen with endometrial intraepithelial neoplasia (EIN) and cancers.

Presentation

- Patients may be asymptomatic or present with abnormal uterine bleeding.
- Commonly seen in association with otherwise normal-appearing cyclic endometrium.

Prognosis and Treatment

- Risk of developing an adenocarcinoma with isolated morules or morules accompanied by mild gland proliferations is low (less than 5%). High rate of resolution on follow-up sampling.
- Risk of carcinoma increases to 20% when morules are associated with EIN.
- Treatment ranges from repeat sampling when EIN is not present to hysterectomy or hormonal therapy when EIN is present.

Pathology

Histology

- Morules consist of well-demarcated if somewhat irregularly shaped aggregates of uniform nonkeratinizing squamoid cells having an almost granuloma appearance. They typically are found in the center of (or entirely replace) glands and unlike conventional cervical squamous metaplasia appear often to arise by direct transdifferentiation from glandular epithelium rather than from reserve cells. Central necrosis is common and of no significance.
- Morules fall into four general categories short of adenocarcinoma:
  1. Isolated morules without appreciable glandular proliferation. These carry a low risk of progression and are managed by a follow-up sampling.
  2. Morules associated with mild glandular proliferation. In contrast to EIN, these glands do not differ appreciably from the surrounding proliferative endometrium. The glands may form a ringlet or garland around the morule. Like the first category the risk of carcinoma on follow-up is no more than 5%.
  3. Morules associated with EIN, with a 20% or higher risk of adenocarcinoma.
  4. Confluent morular metaplasia without visible EIN or adenocarcinoma. These can be diagnostically confusing, and a careful search for EIN is necessary. However, if not present, they are simply designated as extensive morular metaplasia.

Immunopathology (Including Immunohistochemistry)

- Squamous metaplasia shows some positivity for p63.
- Morules are hormonally inert, as shown by their typically negative staining for ER and PR.

Diagnostic Terminology

- Morular metaplasia (if isolated or accompanied by mild gland proliferation) with a comment: Morular metaplasia, in the absence of EIN, often resolves and carries a low (~5%) risk of adenocarcinoma on follow-up. However, a follow-up sample in 6 months is advised to exclude persistence.
- EIN with morular metaplasia (if associated with EIN).

Main Differential Diagnosis

- Other forms of squamous metaplasia associated with chronic endometritis (morular metaplasia may be associated with plasma cells).
- Endometrial adenocarcinoma with squamous metaplasia. If bizarre keratinization is seen, this must be excluded.
- Squamous carcinoma or high-grade adenocarcinoma with a predominantly squamous component is usually easily distinguished. Nevertheless, any squamous differentiation on the surface of the endometrium requires excluding this entity, inasmuch as even the most malignant squamous lesions can harbor deceptively benign foci.
- Occasionally, cohesive clusters of macrophages will mimic morules.

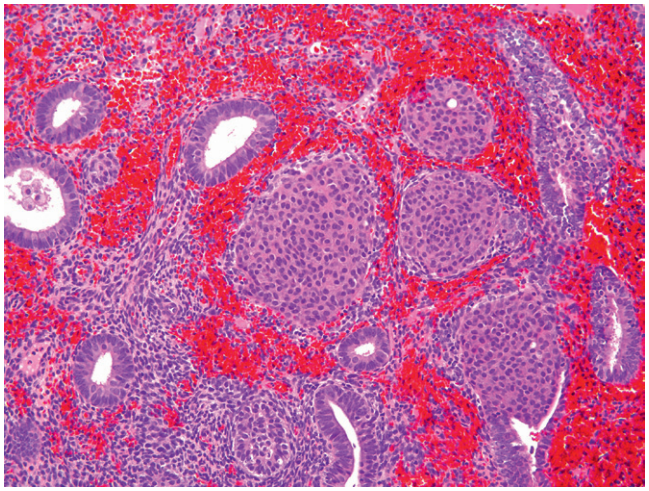


FIGURE 1
Isolated squamous morules. These often resolve on follow-up.

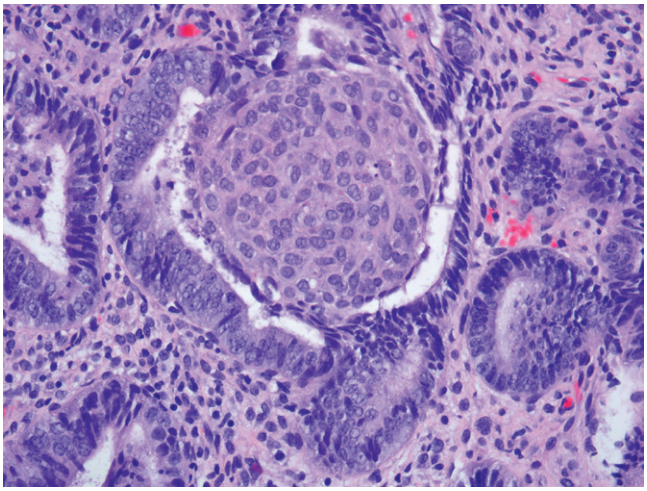


FIGURE 3
Higher magnification of a squamous morule. Note the bland cytology and collar of normal-appearing glandular epithelium.

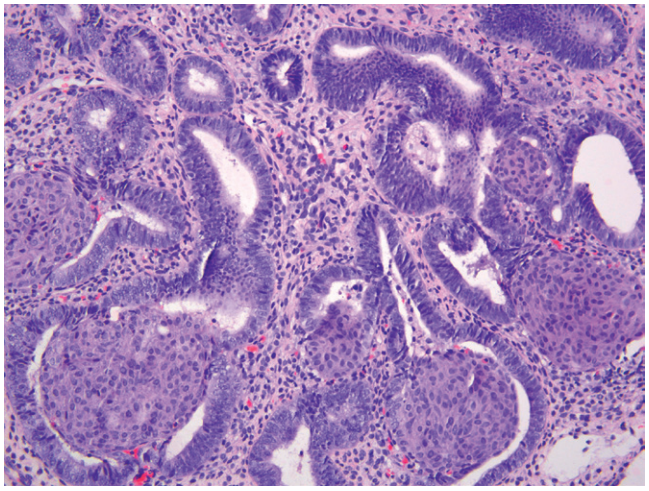


FIGURE 2
Squamous morules in the center of gland tracts. Note the mild degree of adjacent gland cell proliferation and lack of appreciable change in gland cytology relative to normal proliferative endometrium.

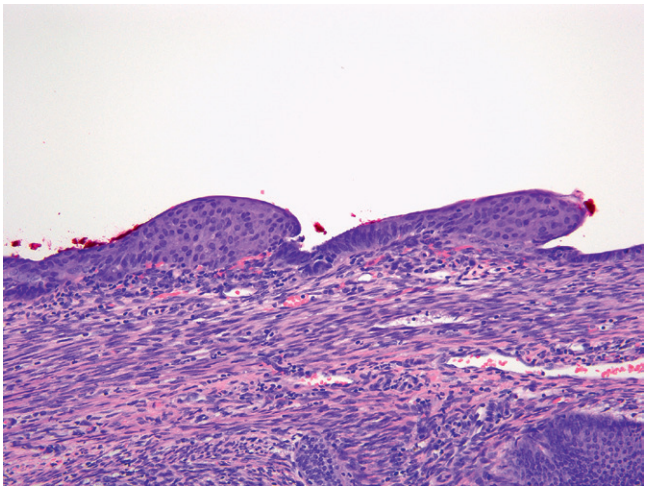


FIGURE 4
Superficial squamous metaplasia in a case of squamous morules.

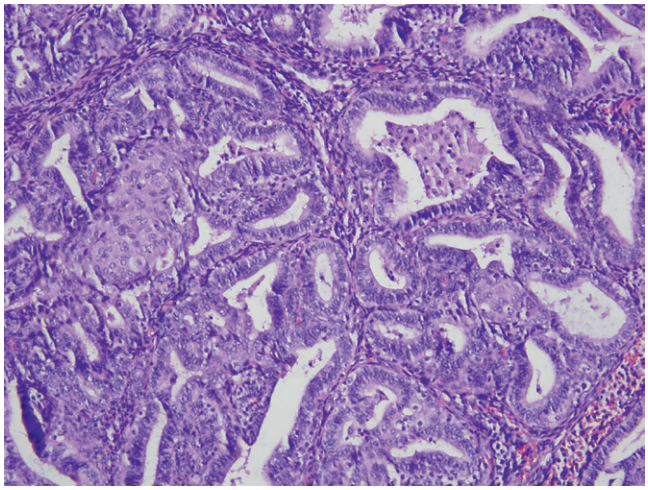


FIGURE 5

Near back-to-back glands with morular metaplasia (EIN). This form of EIN often differs somewhat from usual EIN by a lesser degree of cytologic demarcation relative to the adjacent endometrium. However, the level of gland density warrants a diagnosis of EIN.

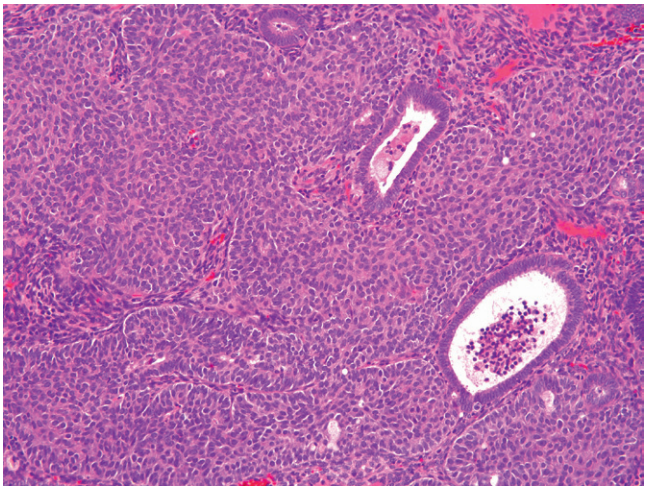


FIGURE 6

Confluent morular metaplasia. Note the absence of any visible EIN or adenocarcinoma. Nevertheless, caution is advised in managing this and additional sampling warranted.

ICHTHYOSIS UTERI

Definition—Extensive, superficial endometrial squamous (nonmorular) metaplasia.

Clinical Features

Epidemiology

- Ichthyosis uteri is rare. It is seen in patients with long-standing irritation of the endometrium (intrauterine device [IUD] or chronic endometritis). In postmenopausal patients care should be exercised in order to exclude concurrent adenocarcinoma.

Presentation

- Patients may be asymptomatic or present with abnormal uterine bleeding.

Prognosis and Treatment

- Ichthyosis uteri is a benign condition; however, whenever a deceptively bland-appearing squamous epithelium is seen on the endometrial surface, an associated adenocarcinoma must be excluded. Removal of the irritant may lead to reversal. In cases clinically or histologically worrisome for carcinoma, hysterectomy may be necessary.

Pathology

Histology

- Confluent, superficial squamous metaplasia, usually with striking differentiation and sometimes hyperkeratosis. Additional features that may be seen include large cysts, necrosis, and acute inflammation. The process may extend into the myometrium. Squamous cell carcinoma and adenocarcinoma should be searched for and excluded in every case.

Immunopathology (Including Immunohistochemistry)

- Markers for squamous differentiation will be positive, but stains are not necessary.

Main Differential Diagnosis

- Squamous cell carcinoma of the endometrium (rare).
- Endometrial adenocarcinoma with squamous differentiation—this must always be excluded although the squamous differentiation will usually be more bizarre (but not always).
- Involvement of the endometrium by squamous cell carcinoma of the cervix—unlikely if the squamous differentiation is not atypical. Paradoxically normal-appearing squamous differentiation in the endometrium is the property of endometrial carcinomas.

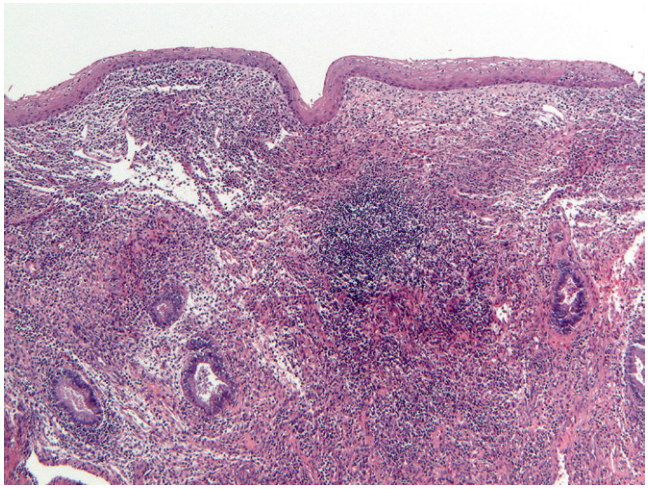


FIGURE 1

Ichthyosis uteri. Low-power view showing bland, confluent squamous metaplasia of the endometrium.

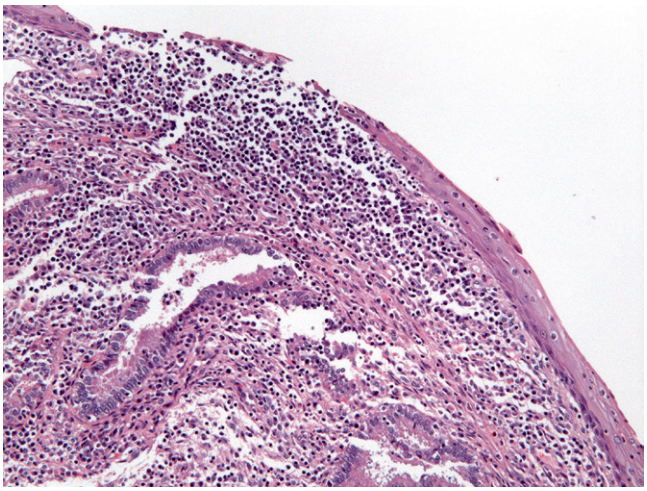


FIGURE 2

Ichthyosis uteri. Confluent squamous metaplasia of the superficial endometrium overlying endometrial glands and stroma with marked inflammation.

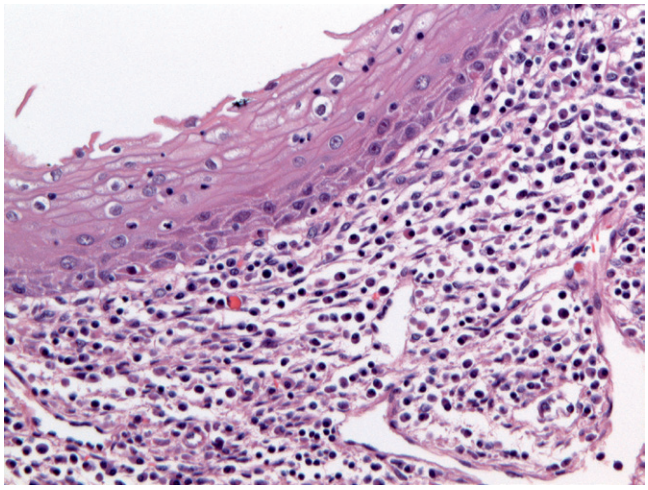


FIGURE 3

Ichthyosis uteri. Squamous metaplasia and an underlying, intense chronic inflammatory infiltrate.

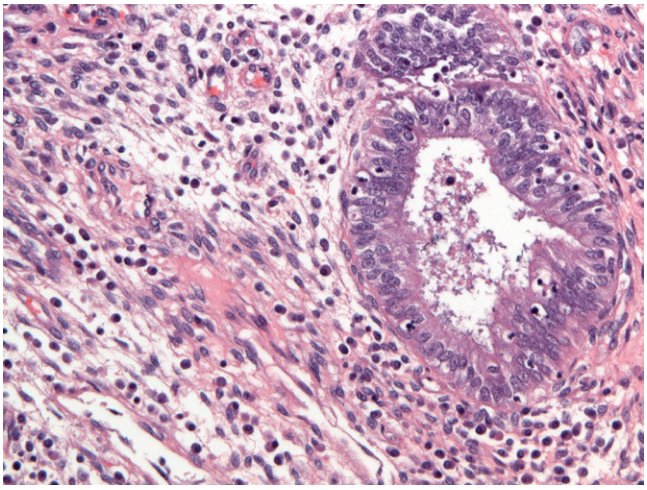


FIGURE 4

Ichthyosis uteri. An endometrial gland and stroma with marked chronic inflammation with numerous plasma cells seen in a case of ichthyosis uteri.

SQUAMOUS CARCINOMA OF THE ENDOMETRIUM

Definition—An endometrial malignancy composed almost entirely of squamous carcinoma.

Clinical Features

Epidemiology

- Rare, comprises less than 1% of uterine endometrial carcinomas.
- Most commonly occurs in postmenopausal women in their seventh and eighth decades.
- Usually not associated with human papillomavirus (HPV), although rare reports have linked HPV to some cases.

Presentation

- Seen in endometrial curettings or biopsies of women with abnormal bleeding.

Prognosis and Treatment

- Prognosis is similar to other endometrial carcinomas and is comparable to the stage at the time of diagnosis.
- Managed with combined surgery, chemotherapy, and radiation as determined by stage.

Pathology

Histology

- Classic features of squamous cell carcinoma with keratin formation and sheetlike growth.
- Papillary architecture is common.
- Differentiation may vary from well (or verrucous) to poor.
- Not infrequently, some foci exhibit deceptively bland histology, a feature not common in cervical carcinomas.

Immunopathology (Including Immunohistochemistry)

- Positive for p53 in some reports.
- High proliferative index.

Recommended Diagnosis

- Squamous cell carcinoma.

Main Differential Diagnosis

- Conventional endometrial carcinoma with squamous differentiation—these tumors usually display squamous differentiation that is rather low grade.
- Squamous cell carcinoma of the cervix—typically more moderately to poorly differentiated. p16 stains should be strong in contrast to the endometrial primary.

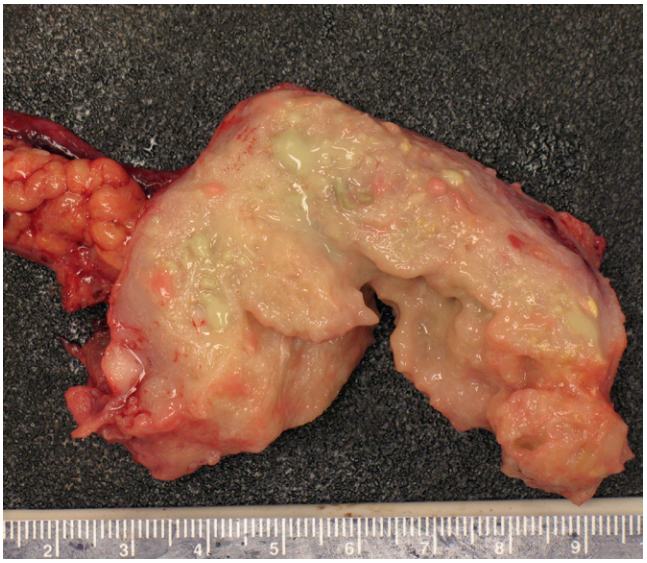


FIGURE 1

Squamous carcinoma of the endometrium. This cross section shows the endometrium and myometrium to be replaced by a necrotic tumor mass.

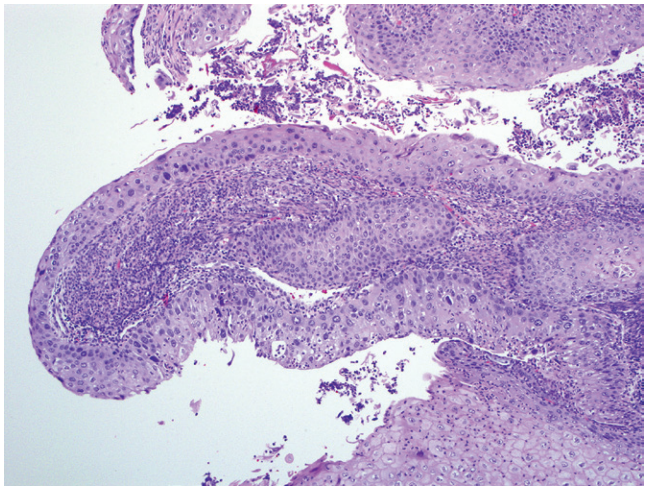


FIGURE 2
Squamous carcinoma of the endometrium with papillary architecture.

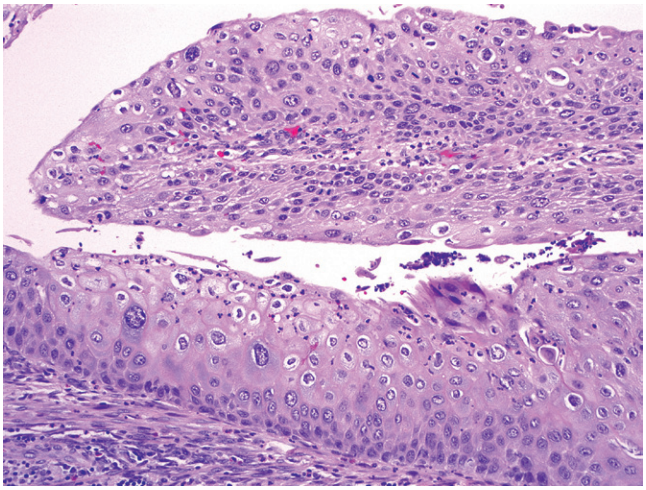


FIGURE 3
Squamous carcinoma of the endometrium. There is moderate atypia.

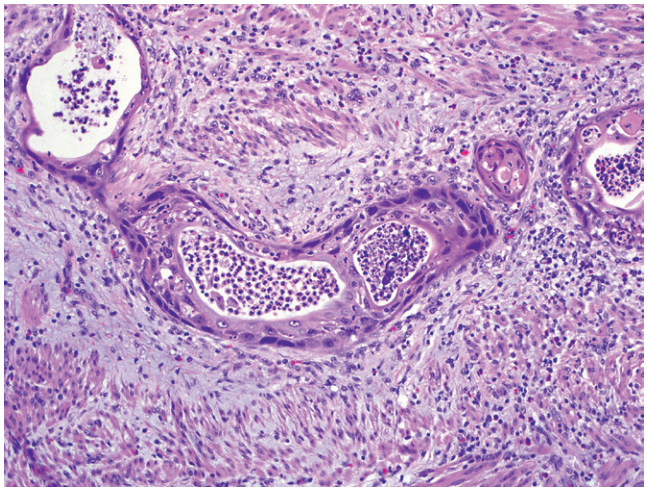


FIGURE 4
Squamous carcinoma of the endometrium infiltrating fibrous tissue.

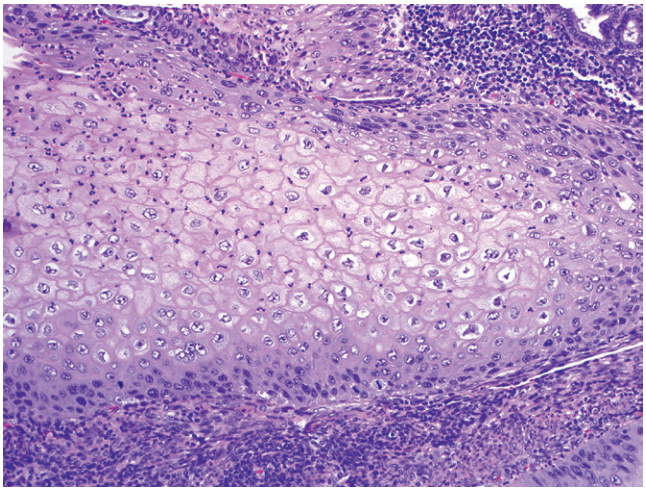


FIGURE 5
Squamous carcinoma of the endometrium. In this field the epithelial cells demonstrate pallor and minimal superficial atypia. This pale appearance to the neoplastic epithelium is more typical of endometrial versus cervical carcinomas.

TUBAL AND EOSINOPHILIC (OXYPHILIC) METAPLASIA

Definition—Alteration of the epithelial cells consisting of tubular differentiation, including oxyphilic cytoplasm.

Clinical Features

Epidemiology

- Tubal metaplasia is common, although clonal expansions of tubal metaplasia are less so. Eosinophilic metaplasia is an uncommon entity.
- Both tubal and eosinophilic metaplasia have been described in conjunction with endometrial intraepithelial neoplasia (EIN) and endometrial adenocarcinoma.

Presentation

- Patients may be asymptomatic or present with abnormal uterine bleeding.

Prognosis and Treatment

- Isolated tubal or eosinophilic metaplasia limited to one or a few glands needs no additional management.
- Either tubal or eosinophilic metaplasia in a crowded expanded gland population should be managed as possible EIN.

Pathology

Histology

- Cells composing eosinophilic metaplasia are typically large, polygonal cells with abundant oxyphilic cytoplasm, arranged in a single layer.
- The nuclei are uniform and round.
- Cells appear similar to those seen in tubal metaplasia, but without the apical cilia.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Reactive-reparative changes can exhibit cytoplasmic eosinophilia and are managed similarly, depending on the complexity of gland architecture.

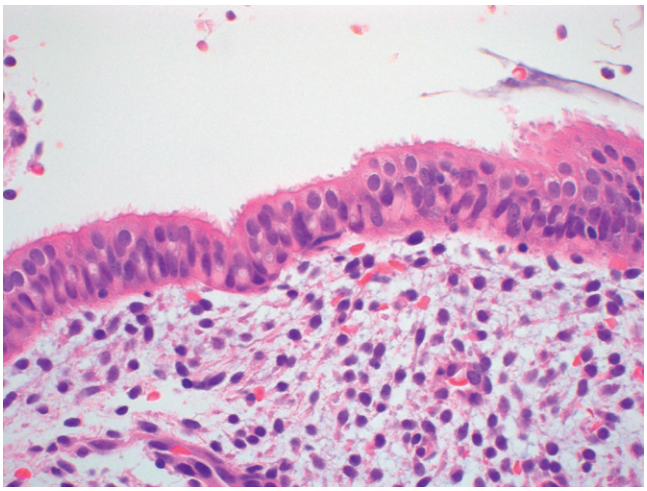


FIGURE 1

Noncomplex tubal metaplasia, typically seen on the endometrial surface epithelium.

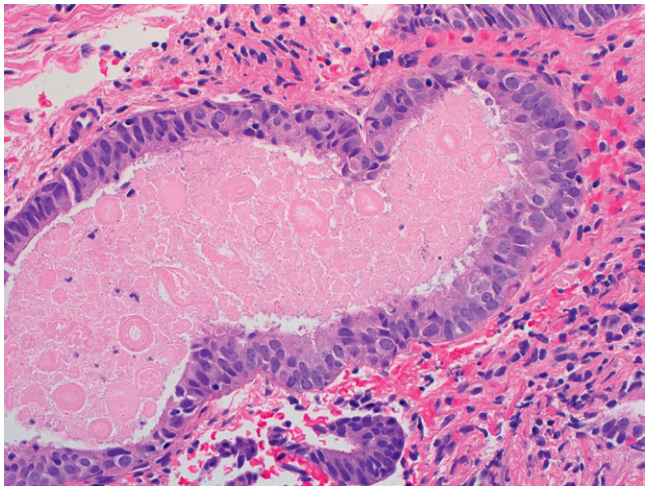


FIGURE 2

Tubal metaplasia with mild anisokaryosis, a benign feature.

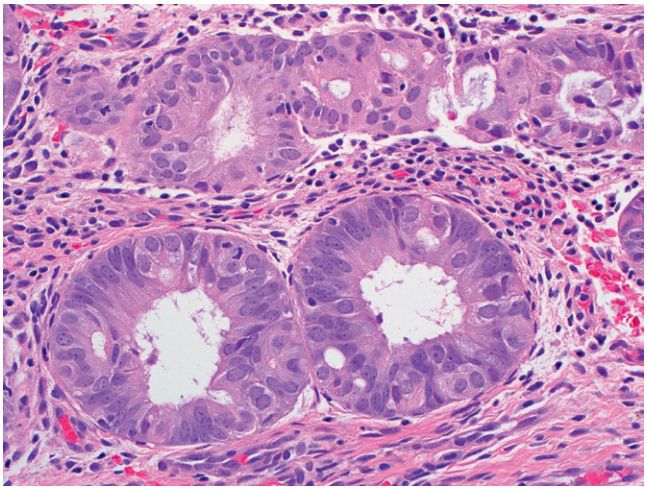


FIGURE 3

Tubal metaplasia *(center)* with mild complexity *(upper)*. This was associated with EIN.

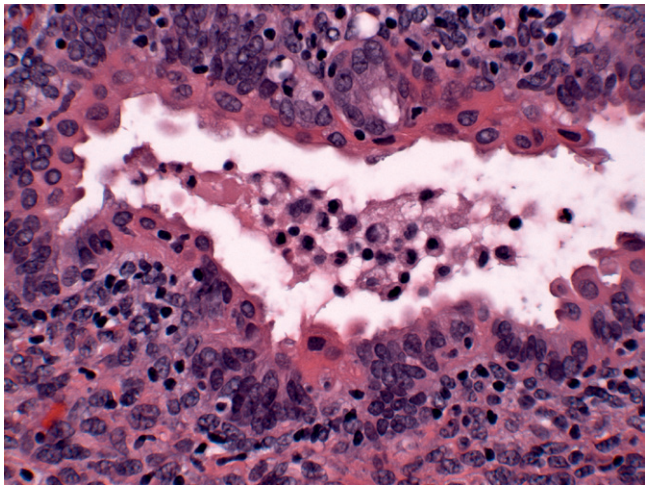


FIGURE 4

Eosinophilic metaplasia. Large, eosinophilic cells lining a normal endometrial gland. This is considered a form of tubal metaplasia.

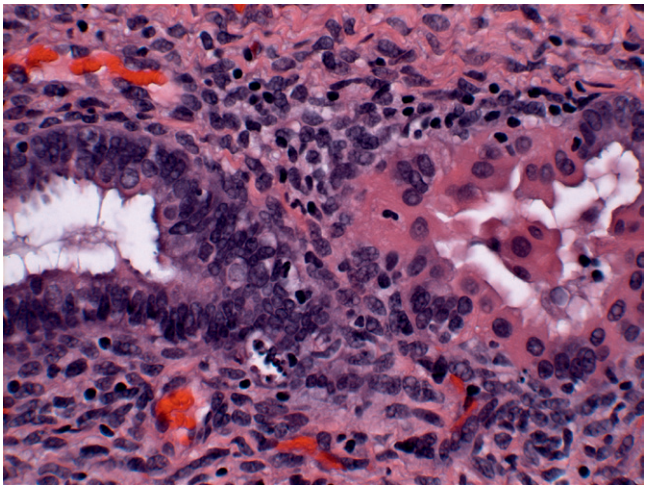


FIGURE 5

Eosinophilic metaplasia. Large, eosinophilic cells lining a normal endometrial gland. This is considered a form of tubal metaplasia.

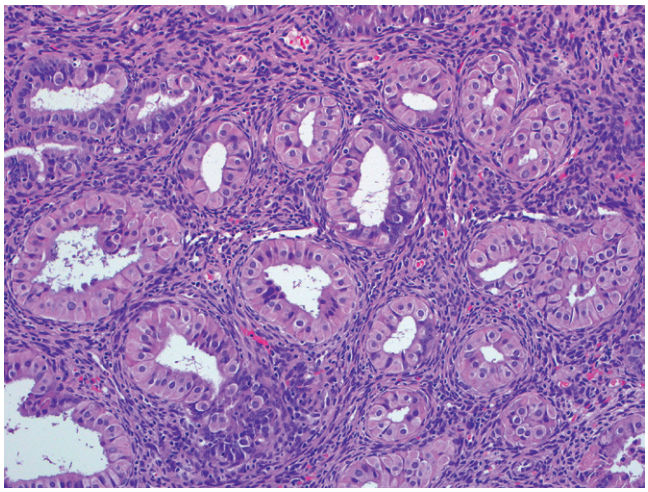


FIGURE 6

Glands showing a blend of tubal and eosinophilic metaplasia.

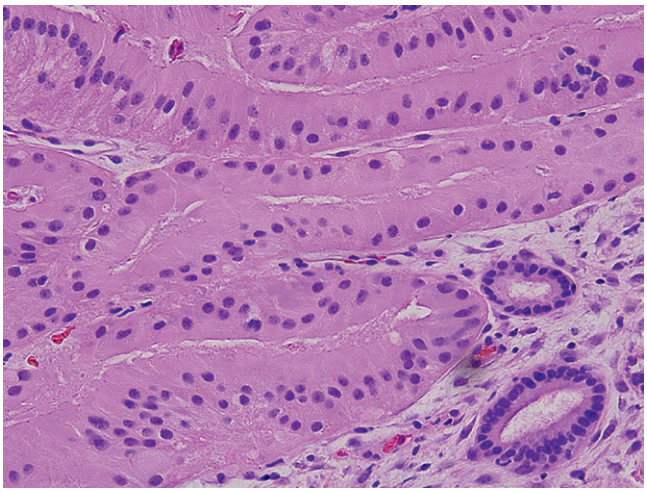


FIGURE 7

EIN with eosinophilic metaplasia. Note normal glands for reference.

MICROGLANDULAR ENDOMETRIAL ADENOCARCINOMA IN CURETTINGS

Definition—A microacinar arrangement of endometrioid epithelium seen in endometrial biopsies/curettings that signifies the presence of endometrial neoplasia.

Clinical Features

Epidemiology

- Most commonly occurs in postmenopausal women in their sixth and seventh decades.

Presentation

- Seen in endometrial curettings or biopsies of women with abnormal bleeding.
- Not infrequently identified in relatively scant curettings.

Prognosis and Treatment

- A "red flag" for the presence of endometrial cancer, typically endometrioid with mucinous differentiation.

Pathology

Histology

- Low-power examination reveals slightly irregular clusters of epithelial cells that do not exhibit the usual simple linear configuration.
- The most obvious finding is aggregated microacini with a slightly "soft" appearance relative to typical microglandular change of the cervix. However, some aggregates can be crisp appearing with vacuoles.
- Nuclei are slightly enlarged, and the mitotic index is low.
- Some neutrophils might be present.
- In their most subtle presentation they appear as small abortive acini ensconced in a linear stretch of columnar epithelium. Intervening stroma is minimal; the eosinophilic stroma seen in microglandular change is not present.
- Subcolumnar cells are inconspicuous.
- Some fine papillary architecture might be seen as well, but by itself is less specific.

Immunopathology (Including Immunohistochemistry)

- Vimentin should be positive.
- ER and PR often positive.
- p63 will be more likely positive in microglandular change of the cervix but is not invariably negative in the endometrial lesion.

Recommended Diagnosis

- Atypical endometrial glandular epithelium consistent with endometrial neoplasia.
- Well-differentiated endometrial adenocarcinoma (if sufficient).
- Comment: The curetting/biopsy specimen contains microacinar clusters of endometrial glandular epithelium. Although there is minimal cytologic atypia, this architecture is worrisome for a well-differentiated endometrial adenocarcinoma. Further tissues studies are recommended to exclude malignancy.

Main Differential Diagnosis

- Endocervical microglandular change—the lining cells are typically small and cuboidal appearing rather than taller columnar cells; reserve cells are often present; intervening stroma is distinctly cervical (if present).

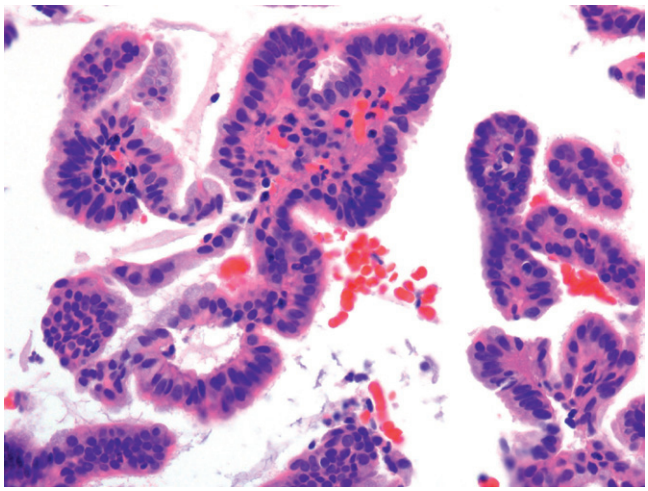


FIGURE 1

Small papillary clusters in the endometrium are relatively nonspecific but can be associated with microacinar clusters. A repeat sample would be prudent.

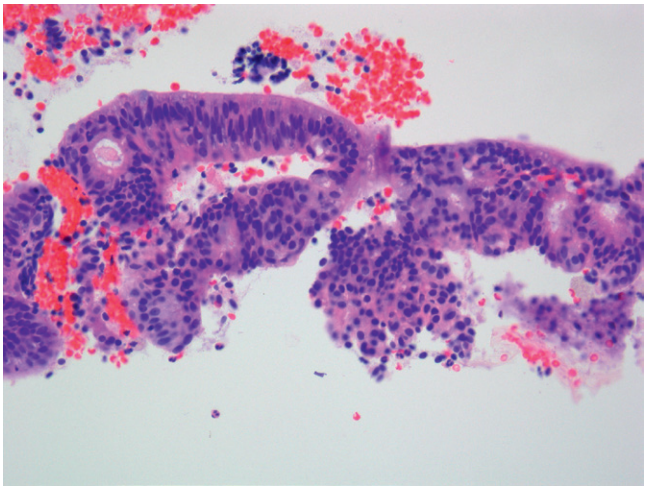


FIGURE 2

Subtle microacinar change in an endometrial biopsy. This is consistent with endometrial neoplasia (well-differentiated adenocarcinoma).

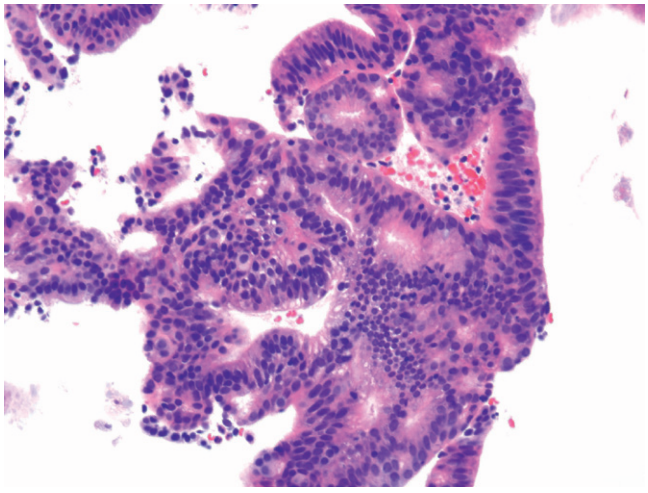


FIGURE 3

A more conspicuous cluster of microacini.

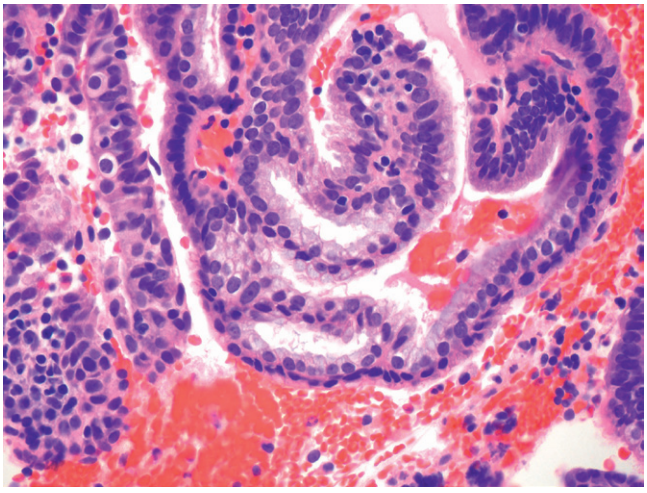


FIGURE 4

Prominent mucinous differentiation in a microacinar cluster.

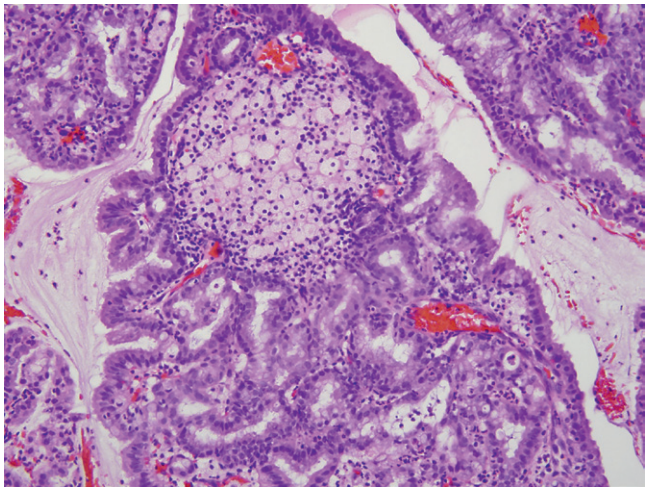


FIGURE 5

This microacinar cluster mimics endocervix. Note the foamy stromal cells.

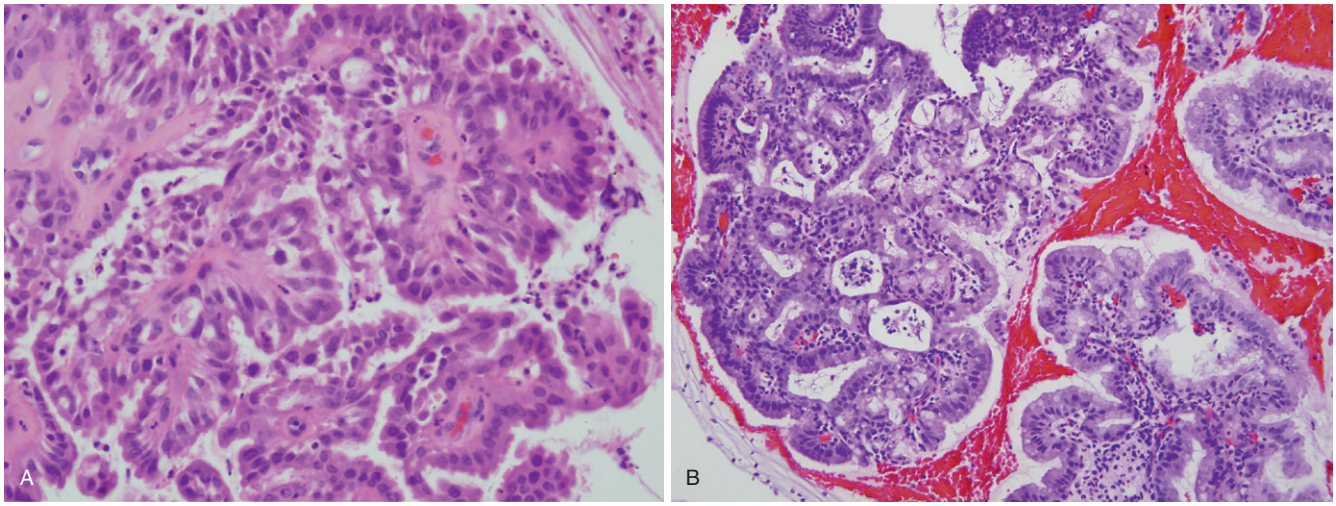


FIGURE 6

A, Microglandular change of the cervix. Note the intervening dense eosinophilic stroma, which is often seen in these cervical lesions. **B,** For comparison, microglandular adenocarcinoma.

ENDOMETRIOID ADENOCARCINOMA

Definition—Adenocarcinoma of the endometrium that maintains some histologic features of normal endometrium.

Clinical Features

Epidemiology

- Endometrioid endometrial carcinoma (EMCA) is the most common form of gynecologic malignancy.
- The overall lifetime incidence is between 2% and 3%.
- The majority of patients are between 55 and 65 years of age at the time of diagnosis; however, cases can occur at almost any age.
- Women with excess estrogen (whether exogenous or endogenous) are at increased risk.
- Because of the production of excess estrogens, obese women are at an increased risk.
- Patients with hereditary nonpolyposis colorectal cancer (HNPCC) (Lynch syndrome) and Cowden syndrome are at an increased risk. Approximately 4% of women with EMCA will score positive for HNPCC.
- Family history of EMCA, nulliparity, early menarche, and late menopause have all been associated with increased risk as well.
- Patients taking tamoxifen are at an increased risk of the development of endometrial intraepithelial neoplasia (EIN), which carries a 46-fold increased risk of subsequent (or concurrent) EMCA.

Presentation

- Abnormal uterine bleeding or postmenopausal bleeding is the most common presenting sign.
- Increased age at the time of postmenopausal bleeding is associated with increased incidence of carcinoma. The risk of endometrial cancer may be as high as 40% 10 years out from menopause.

Prognosis and Treatment

- No further treatment for Stage IA, grade 1 or 2. Vaginal cuff radiation for Stage IB, grade 1 or 2, and Stage IA, grade 3. Chemotherapy +/– directed radiation for Stages III and IV. Stage IC, grade 3, and all Stage II are evolving toward chemotherapy and vaginal cuff radiation.
- Stage I, grade I or II carcinomas are associated with cure rates of ~90% or better.
- High-grade, high-stage tumors, especially undifferentiated or pleomorphic variants, have a dismal prognosis (stage III 20% to 30% 5-year survival, stage IV ~0% 5-year survival).
- Tumors exceeding 50% myometrial invasion as determined intraoperatively will usually receive lymph node dissection in the United States. However, staging is not as aggressively pursued in Europe.

Pathology

Histology

- Tumor grade: FIGO grading is based on the percentage of nonsquamous, solid glandular component:
  - Grade 1: less than 5% solid growth
  - Grade 2: 5% to 50% solid growth
  - Grade 3: more than 50% solid growth
- Severe nuclear atypia may increase the FIGO grade by a factor of 1; however, these criteria are highly subjective and a point of controversy.
- Traditional low-grade EMCA is composed of irregular endometrioid glands with columnar cells with "cigar-shaped" nuclei, resembling the glands of proliferative endometrium. The nuclei are typically pseudostratified and have a fine, powdery chromatin with occasional small nucleoli.
- Enlarged polygonal cells with eosinophilic cytoplasm and vesicular, hyperchromatic nuclei and prominent nucleoli are signs of severe nuclear atypia.
- Numerous morphologic patterns arising in and associated with EMCA have been described:
  - Squamous differentiation is frequently found in EMCA. A wide range of squamous differentiation has been described, ranging from histologically benign squamous morules to markedly atypical

squamous epithelium indistinguishable from squamous cell carcinoma. The amount and degree of atypia of the squamous component have no effect on patient outcome.
- Mucinous differentiation is commonly identified as a minor component in many EMCA. Occasional tumors may be predominantly mucinous, prompting the diagnosis of "mucinous adenocarcinoma"; however, this has no effect on patient outcome. Morphology may range from focal columnar cell change to complete mucinous change with cribriforming or papillary growth. Cribriforming mucinous differentiation may bear a striking resemblance to microglandular hyperplasia of the cervix. Rare intestinally differentiated mucinous carcinomas have been identified. The amount and degree of atypia of the mucinous component have no effect on patient outcome.
- Secretory change, noted by scattered subnuclear or supranuclear vacuoles, can be seen in many tumors. When extensive, secretory endometrium can be ruled out by noting the enlarged glands, atypia, and loss of intervening stroma. Clear-cell carcinoma is a consideration, but the cells composing clear-cell carcinoma are typically cuboidal, lack stratification, and display marked atypia.
- Ciliated cells are common in both normal endometrium and neoplasia. Tumors composed of ciliated epithelium have been described and are termed "ciliated carcinoma."
- Villoglandular carcinoma is a term used to describe tumors composed of well-defined, slender papillae with discrete fibrovascular cores.
- Occasional tumors may display extensive eosinophilic (oxyphil) change. These tumors typically display abundant brightly eosinophilic cytoplasm and a mild degree of nuclear atypia.
- Biphasic carcinoma, composed of two distinct elements, has been reported. Commonly these tumors are composed of distinct areas of low-grade and undifferentiated carcinoma or adenocarcinoma and neuroendocrine carcinoma. Treatment and outcome are dependent on the most poorly differentiated component.
- Poorly differentiated, pleomorphic variants composed of markedly atypical cells are rare.

Immunopathology (Including Immunohistochemistry)

- The diagnosis of EMCA is typically based on histologic findings; however, several stains may be helpful:
  - p53: Lack of diffuse, strong p53 staining is seen in most low-grade EMCAs. High-grade EMCA (FIGO grade 3) may display strong, diffuse staining similar to that seen in serous carcinoma.
  - Ki-67: Higher levels of proliferative activity are noted in more poorly differentiated cancers.
  - p63: Squamous differentiation (denoted by p63 positivity) can commonly be seen in endometrioid adenocarcinomas. Positive p63 staining may be especially helpful in identifying abortive squamous morular metaplasia.
  - Cytokeratin: Positive staining for cytokeratins can help distinguish undifferentiated carcinoma from conventional grade 3 endometrioid carcinomas.
  - CD10: Can help to identify endometrial stroma; however, care must be used as artifactual staining has been described surrounding frankly invasive glands.

Main Differential Diagnosis

- Benign endometrium (telescoping artifact).
- EIN.
- Stromal breakdown.
- Tangential sectioning.
- Microglandular hyperplasia (cervix).
- Endocervical adenocarcinoma (including in situ).
- Repair (papillary syncytial metaplasia).
- Hobnail metaplasia.
- Arias-Stella effect.
- Radiation-related changes.
- Exfoliation artifact.
- Metastasis from other sites.

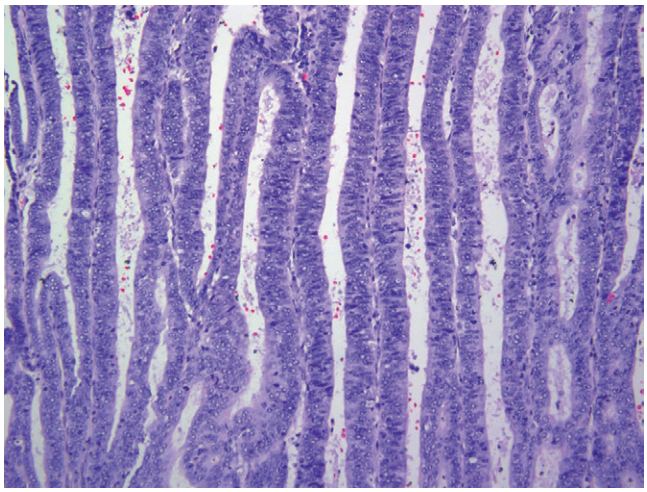


FIGURE 1

EMCA. Well-differentiated endometrial carcinoma composed exclusively of glands (FIGO grade 1).

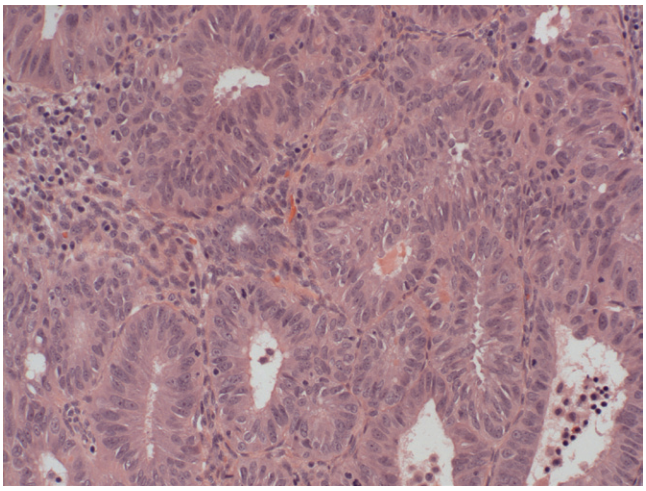


FIGURE 2

EMCA. Typical low-grade EEC morphology.

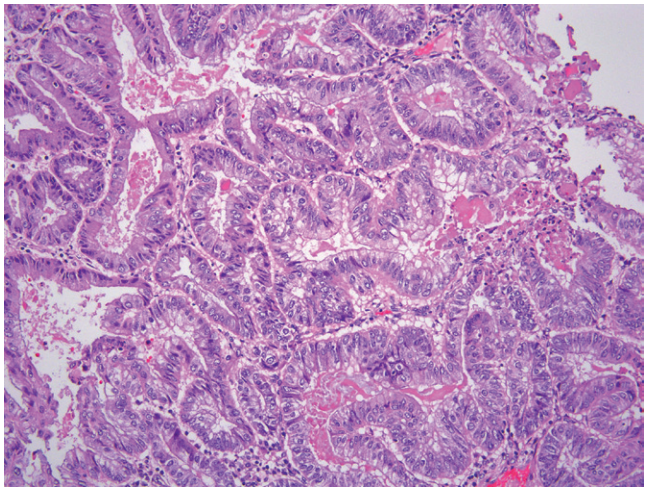


FIGURE 3

EMCA. Glands are irregular and there is minimal supporting stroma.

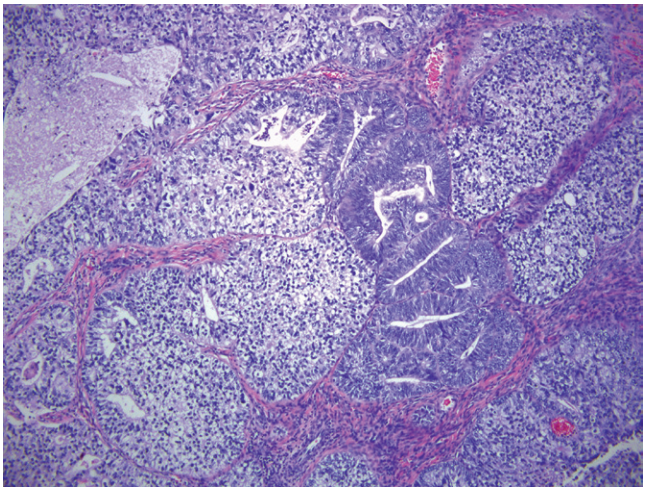


FIGURE 4

EMCA. Focal secretory change is seen here with numerous vacuoles.

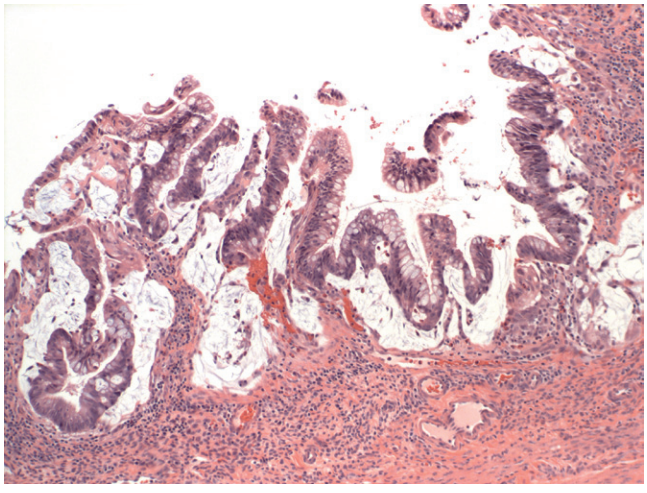


FIGURE 5

EMCA. This focus has rare intestinal differentiation.

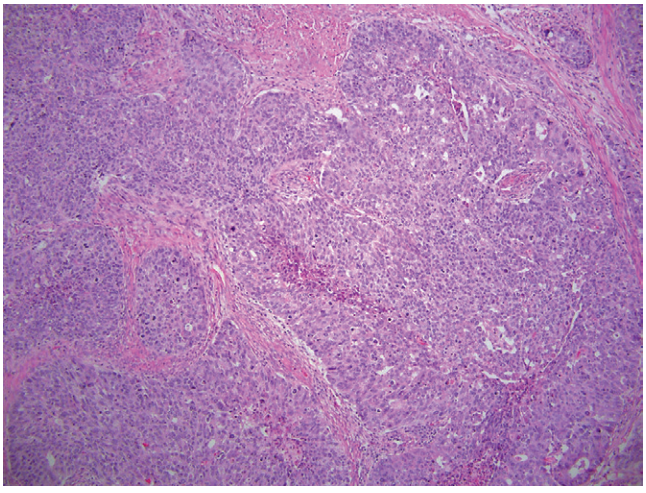


FIGURE 6

EMCA. FIGO grade 2 carcinoma based on solid growth. Note the well-differentiated component in the lower half.

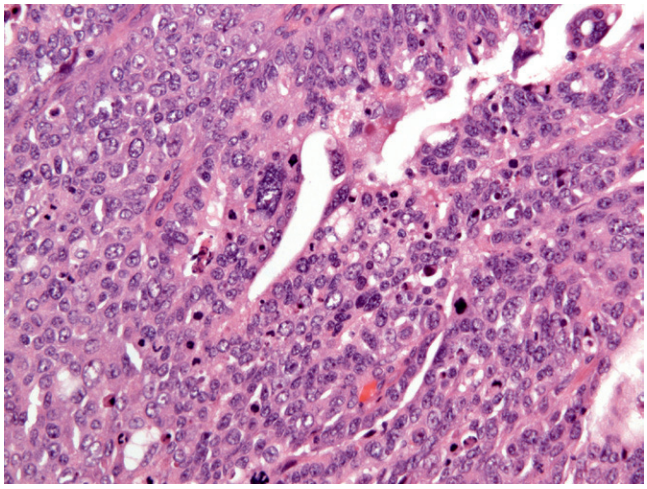


FIGURE 7

EMCA. FIGO grade 3 EEC composed almost exclusively of solid tumor growth with nuclear atypia.

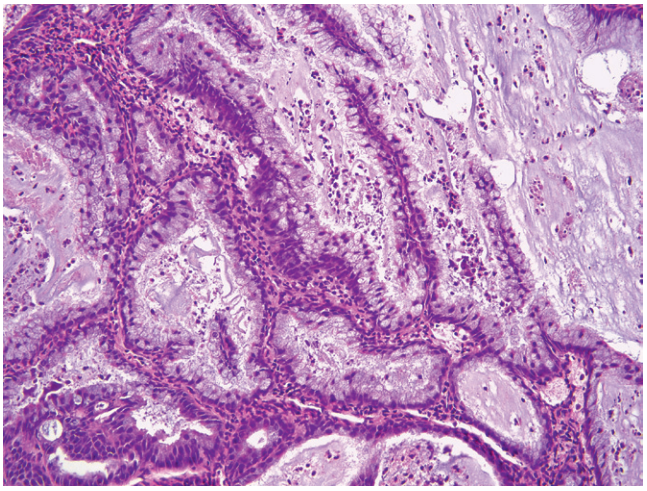


FIGURE 8

EMCA. High-grade adenocarcinoma with mucinous differentiation.

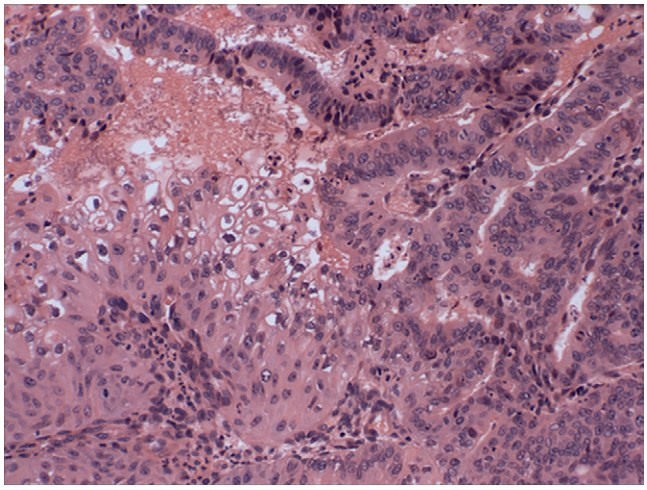


FIGURE 9

EMCA. Squamous differentiation *(lower left)*; note the presence of vacuoles and mild nuclear atypia.

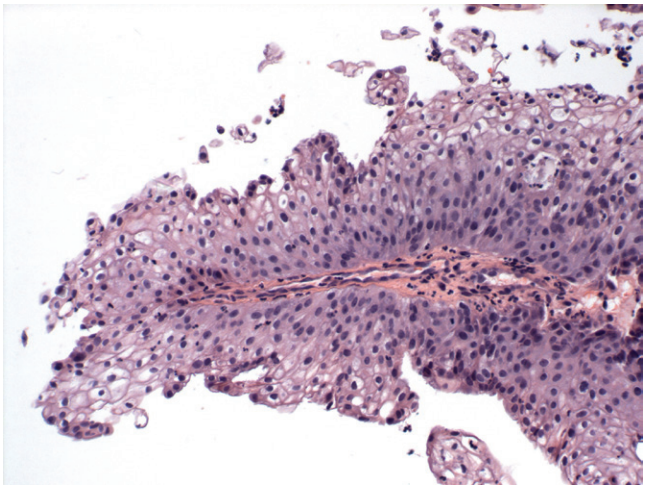


FIGURE 10

EMCA. Papillary architecture is seen here.

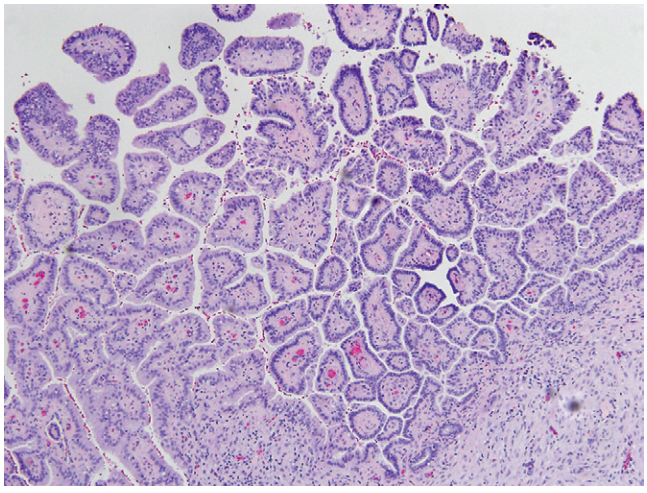


FIGURE 11

EMCA. This focus is markedly papillary; serous carcinoma must be excluded by careful histologic exam and immunostaining for p53, if deemed necessary.

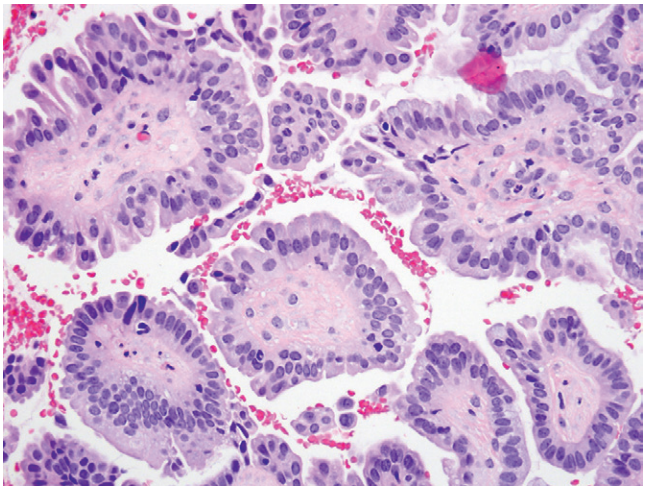


FIGURE 12

EMCA. Mucinous differentiation composed of a single layer of columnar mucinous cells simulating endocervix.

LOWER UTERINE SEGMENT ADENOCARCINOMA

Definition—Adenocarcinoma arising in the lower uterine segment (LUS).

Clinical Features

Epidemiology

- Uncommon variant of endometrial adenocarcinoma, accounting for from 3% to 6%.
- Associated with Lynch syndrome in up to 29% versus approximately 2% of conventional endometrial adenocarcinoma. A higher frequency of MSH2 loss has been reported by some.
- More commonly associated with higher-grade, deep myometrial invasion and less likely to have an associated endometrial intraepithelial neoplasia (atypical hyperplasia) or reproductive risk factors (such as parity and polycystic ovaries).

Presentation

- Abnormal uterine bleeding or postmenopausal bleeding is the most common presenting sign.
- Imaging studies will often depict a mass in the region of the cervix, and distinction from cervical carcinoma may be difficult.

Prognosis and Treatment

- The prognosis is generally stage and grade dependent. Management is similar to other uterine carcinomas.
- Tumors may be more poorly differentiated and thus have a more adverse outcome.
- LUS involvement in conventional adenocarcinomas is associated with decreased survival, although in some studies this is not an independent prognostic factor.

Pathology

Histology

- Tumor in the LUS with lesser involvement of the corpus and often extending into the endocervix.
- Higher-grade variants are common, including poorly differentiated endometrioid and serous subtypes.
- Mixed patterns with squamous, neuroendocrine carcinosarcomas have been described. Poorly differentiated, pleomorphic variants composed of markedly atypical cells have also been occasionally seen.

Immunopathology (Including Immunohistochemistry)

- Vimentin might be helpful in confirming endometrial origin versus cervix.
- Should routinely be negative for human papillomavirus (HPV).
- p16 usually heterogeneous (as opposed to diffuse) excepting cases with serous histology.

Main Differential Diagnosis

- Cervical cancer—this can usually be excluded because although high-grade elements can be found, including squamous differentiation and neuroendocrine differentiation, these components are more haphazardly distributed in the LUS carcinomas.

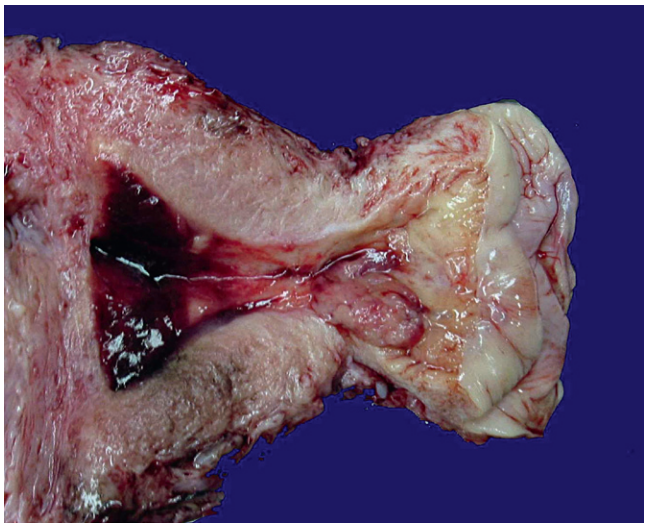


FIGURE 1

LUS carcinoma seen here as a small mass with involvement of the high endocervix.

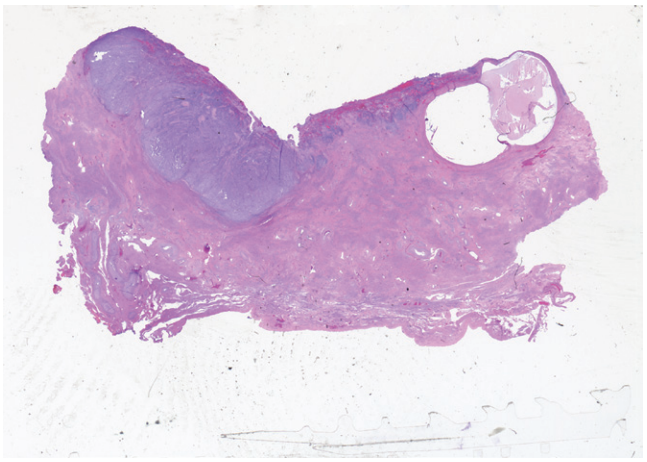


FIGURE 2

Poorly differentiated LUS carcinoma *(left)*. The endocervix is to the right.

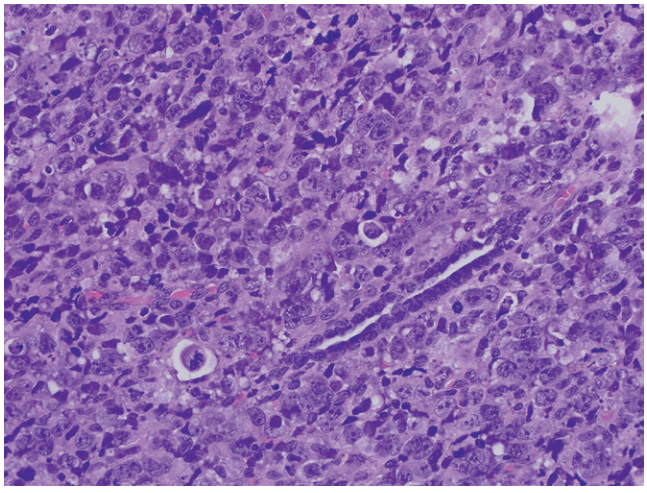


FIGURE 3

Higher magnification of the tumor in previous figure. Note the tumor is essentially undifferentiated.

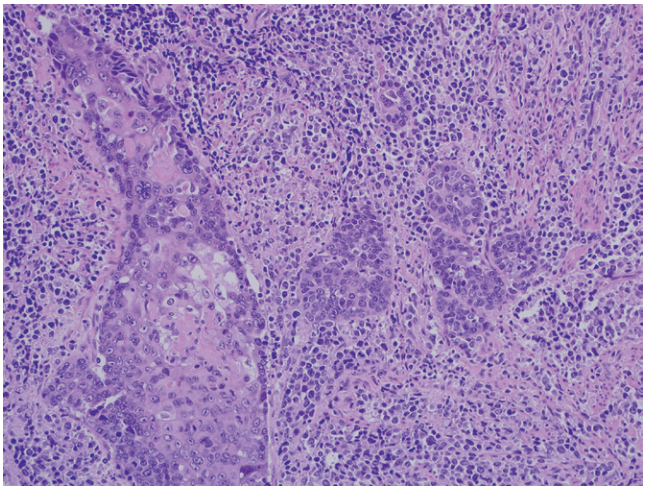


FIGURE 4

Another LUS carcinoma composed of squamous differentiation with an undifferentiated component.

LYNCH SYNDROME SCREENING

■ **Brooke E. Howitt, MD**

DEFINITION—Detecting abnormalities in immunohistochemical expression of mismatch repair proteins to identify patients at risk of harboring germline mutations in these genes (i.e., Lynch syndrome).

CLINICAL FEATURES

EPIDEMIOLOGY

- Lynch syndrome results from a germline mutation in a mismatch repair gene (MLH1, PMS2, MSH2, MSH6). The lifetime risk of colonic or endometrial cancer is from 40% to 60%.
- Approximately 60% of initial tumors in Lynch syndrome are endometrial in origin.
- Approximately 2% to 4% of endometrial carcinomas will have mismatch repair gene mutations.
- Risk of Lynch syndrome increases for women under age 50 who develop endometrial carcinomas, but can be seen at any age.
- Lifetime endometrial cancer risk of women with MLH1 or MSH2 mutations is about 40%, for PMS2 15%, and for MSH6 17% to 44%.
- Lifetime ovarian cancer risk is 6% to 8% for women with Lynch syndrome.

PRESENTATION

- Virtually any endometrial adenocarcinoma can be associated with Lynch syndrome.
- Most Lynch syndrome–associated tumors are endometrioid, but serous, poorly differentiated, and even carcinosarcoma subtypes may occur. Lower uterine segment carcinomas (up to 29%) are associated with Lynch syndrome. Lower uterine segment involvement is the only factor significantly separating Lynch syndrome–associated tumors from the general population.

PROGNOSIS AND TREATMENT

- The prognosis is generally stage and grade dependent like any endometrial cancer.

SCREENING

IMMUNOHISTOCHEMISTRY

- Sequencing of the MMR genes is the most sensitive approach and can be based on a strong family history of colon or endometrial cancer under age 60. However, the most cost-effective approach is immunohistochemical staining of all cases with triage to sequencing if staining is lost (abnormal).
- A panel of immunostains targeting the four genes (PMS2, MSH2, MSH6, MLH1) is employed.
- Loss of staining for MSH2 and/or MSH6 strongly correlates with a germline mutation. If no signal is detected, screening will then typically proceed to sequence analysis.
- Loss of staining for PMS2 and MLH1 is usually (but not always) a result of methylation of these genes. The next step is promoter methylation analysis, which if positive will generally exclude Lynch syndrome. If negative, sequencing will be offered.

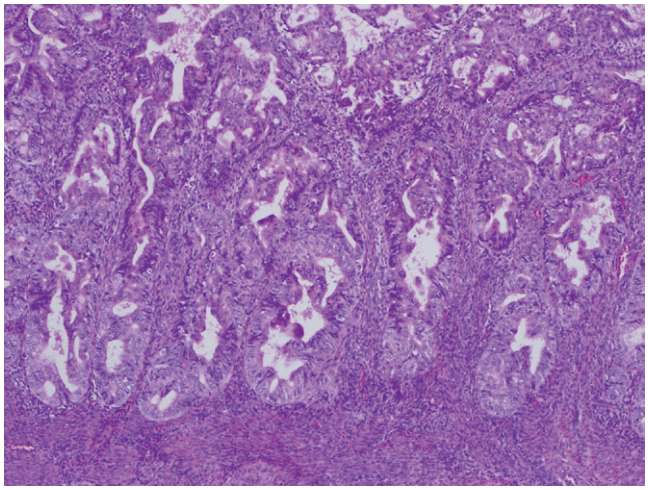


FIGURE 1
An endometrial endometrioid carcinoma.

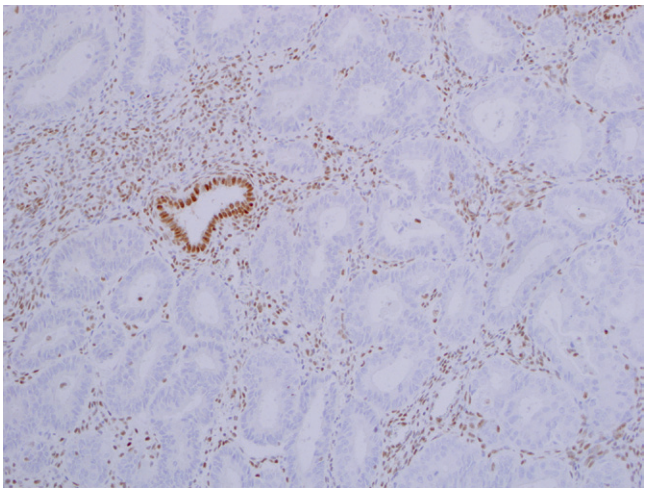


FIGURE 2
Loss of staining for MSH2.

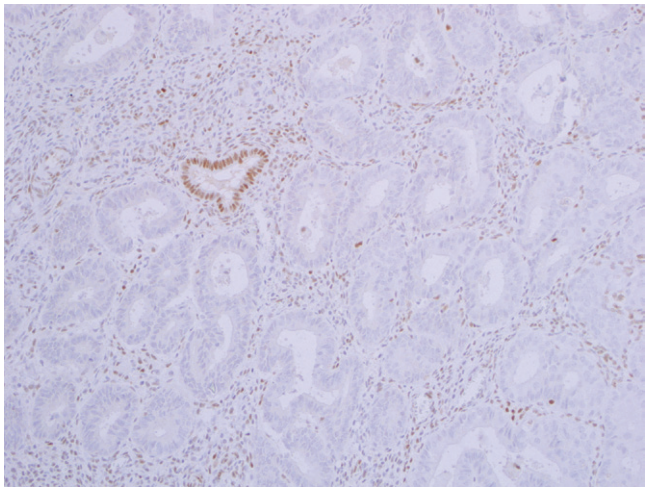


FIGURE 3
Loss of staining for MSH6.

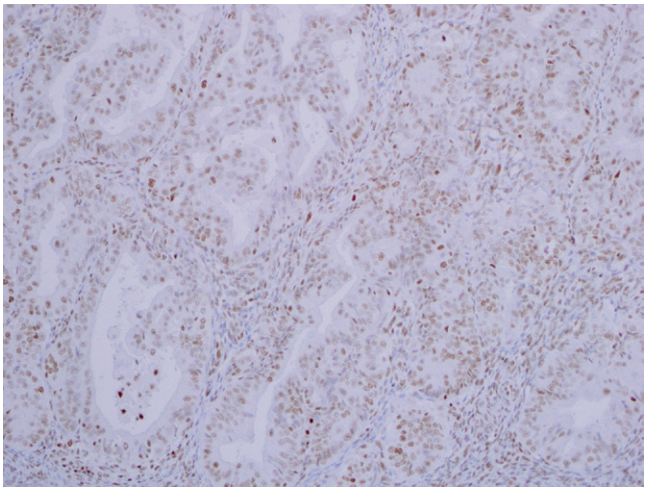


FIGURE 4
Retained staining for PMS2. MLH1 staining was also retained. This case was confirmed to be Lynch syndrome following sequencing.

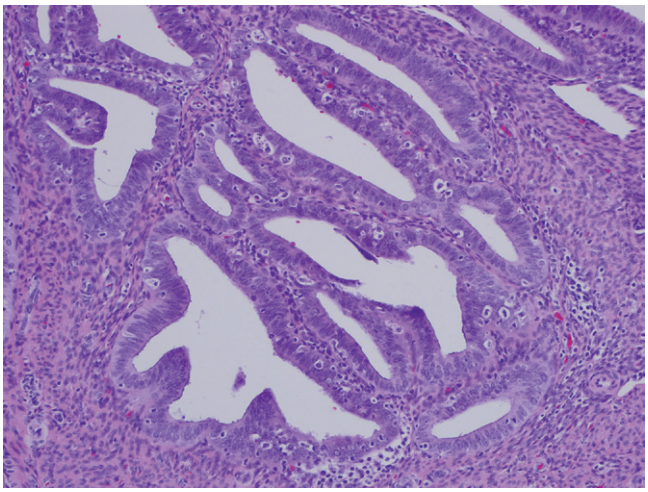


FIGURE 5
Another endometrial adenocarcinoma.

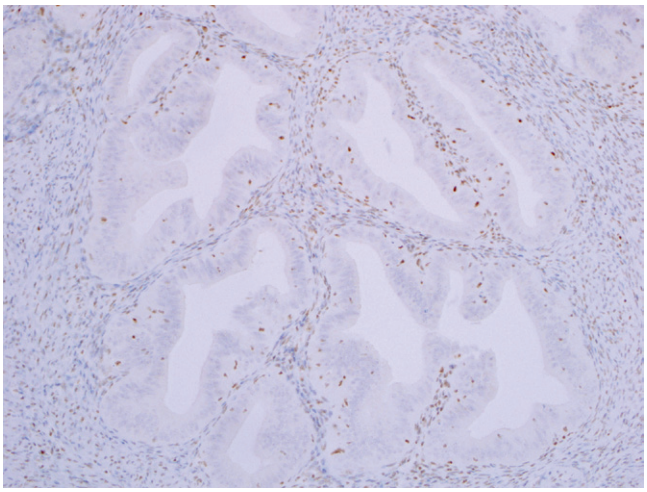


FIGURE 6
Absence of staining for PMS2.

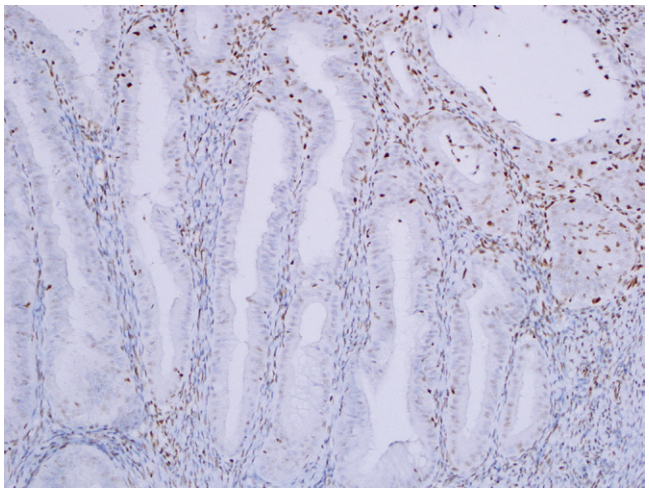


FIGURE 7

Absence of staining for MLH1.

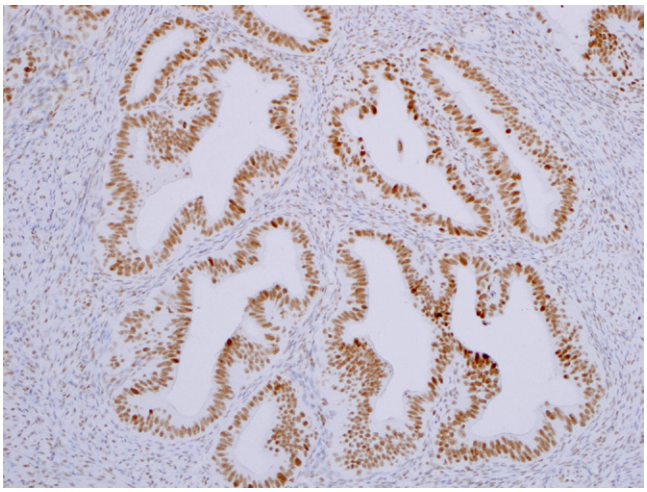


FIGURE 8

Intact staining for MSH2. Staining for MSH6 was also intact. This case was subjected to promoter methylation analysis, which was negative, a rather uncommon occurrence but one that justifies this confirmatory test. This case was subsequently confirmed to be Lynch syndrome following sequencing.

MYOINVASION IN ENDOMETRIAL ADENOCARCINOMA

Definition—A diagnostic conundrum influencing management and outcome.

Presentation

- Abnormal uterine bleeding or postmenopausal bleeding is the most common presenting sign.
- Increased age at the time of postmenopausal bleeding is associated with increased incidence of carcinoma. The risk of endometrial cancer may be as high as 40% 10 years out from menopause.

Prognosis and Treatment

- The prognosis is stage and grade dependent.
- Stage I, grade 1 carcinomas are associated with cure rates exceeding 90%.
- High-grade, high-stage tumors, especially undifferentiated or pleomorphic variants, have a dismal prognosis (stage III 20% to 30% 5-year survival, stage IV ~0% 5-year survival).
- Tumors exceeding 50% myometrial invasion will usually receive radiation therapy or lymph node dissection.

Pathology

Histology

- Several patterns of myoinvasion have been described:
  - Infiltrating glands: The most common pattern of myoinvasion. This pattern is composed of a single gland to small clusters of glands that infiltrate the myometrium with or without a desmoplastic response.
  - Adenomyosis like: A pattern of invasion composed of large islands of malignant glands set in the myometrium. This pattern may be confused for malignant involvement of adenomyosis; however, the presence of irregular outlines and the lack of normal endometrial glands and stroma can aid in this distinction.
  - Broad front: Also known as a pushing border. Broad front invasion is composed of sheets of malignant glands that push into the myometrium. If present, adjacent normal endometrium can help to estimate the depth of invasion.
  - Microcystic elongated and fragmented glands (MELF): MELF is composed of small, fragmented clusters of eosinophilic cells set in a myxoid, desmoplastic stroma. Accompanying inflammatory cells, notably neutrophils, are typically seen. This pattern is believed to be the result of a stromal response to the infiltrating glandular pattern.
  - Adenoma malignum: A rare pattern of myoinvasion comprised of histologically unremarkable glands that infiltrate the myometrium with no surrounding tissue response.
- Issues concerning the diagnosis and staging of EEC are discussed in the following:
  - Carcinoma involving adenomyosis is a common occurrence that can be confused with adenomyosis-like tumor infiltration. Several features can help distinguish adenomyosis including the presence of normal (usually compressed) glands and stroma surrounding the malignant glands and a smooth interface between the adenomyotic nest and the surrounding endometrium. Invasion occurring at the edge of an area of adenomyosis is measured from the edge of the adenomyosis, as adenomyosis is seen as a direct extension of endometrium that can communicate with the surface.

Immunopathology (Including Immunohistochemistry)

- CD10—can help to identify endometrial stroma; however, staining has been described surrounding invasive glands. For this reason, CD10 staining must be viewed critically.

Main Differential Diagnosis

- Myometrial invasion.

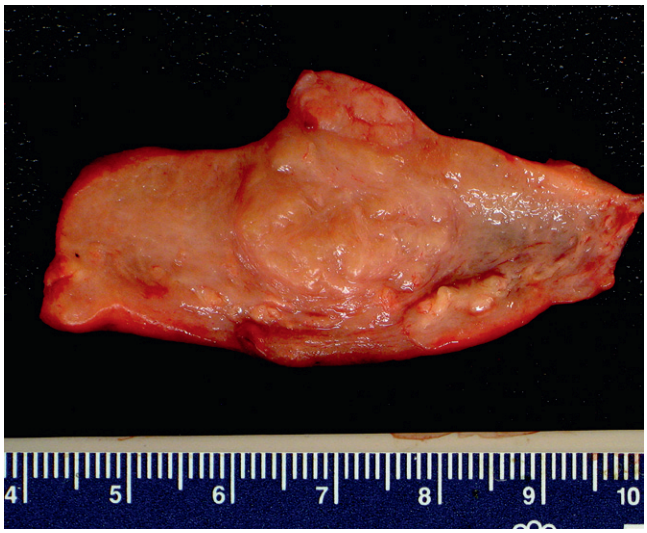


FIGURE 1

Gross image of adenocarcinoma involving adenomyosis, seen here as a nodular focus in the myometrium.

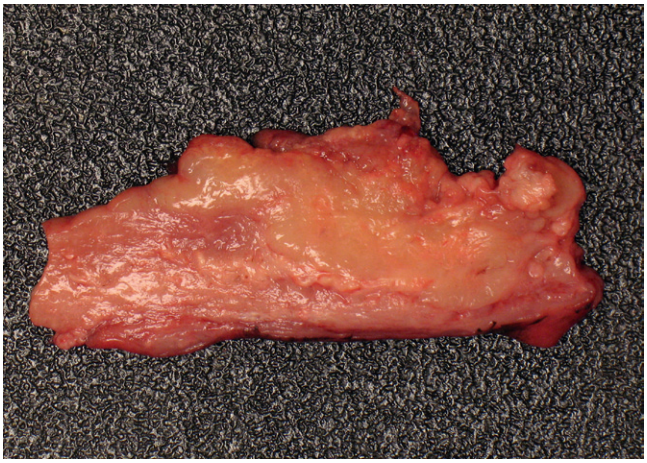


FIGURE 2

Gross image of myoinvasion. Note the less well-demarcated, yellowish thickening that is nearly transmural in this section.

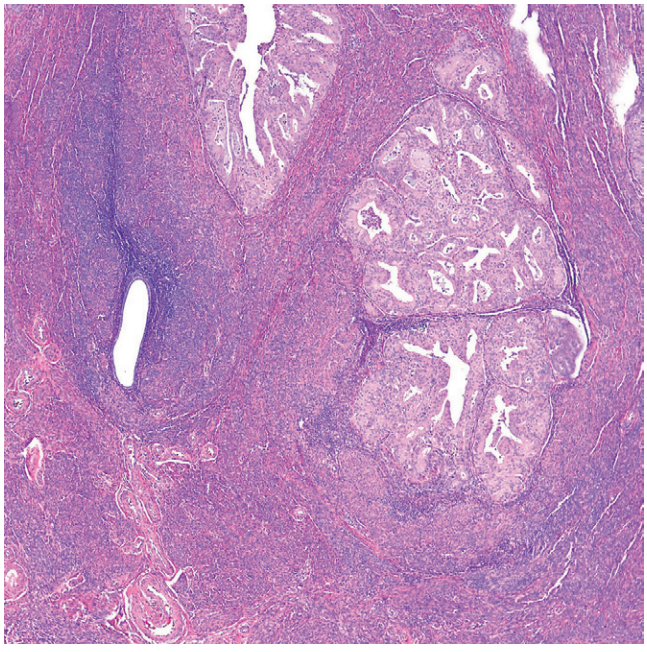


FIGURE 3

Endometrioid endometrial carcinoma involving adenomyosis. Here the stroma can be appreciated at the interface of the neoplasm and the myometrium.

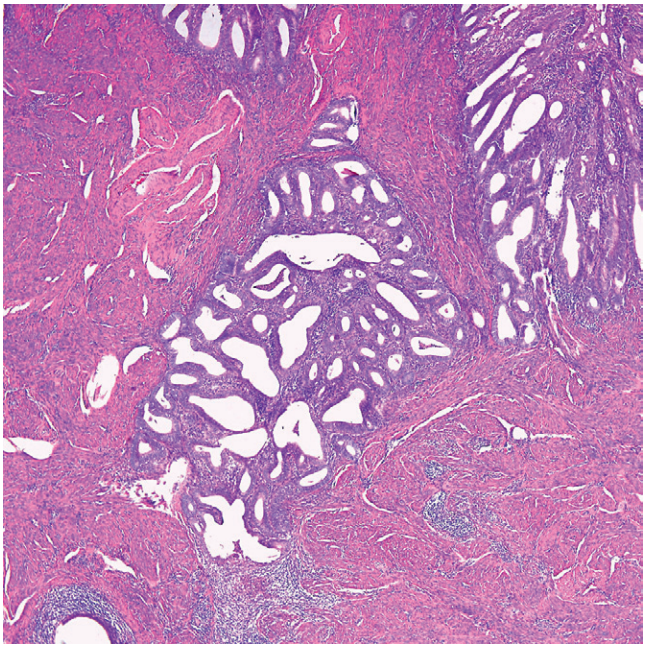


FIGURE 4

Endometrioid endometrial carcinoma involving adenomyosis. This is similar to the prior image except note the stromal reaction at the bottom, suggesting invasion developing from adenomyosis.

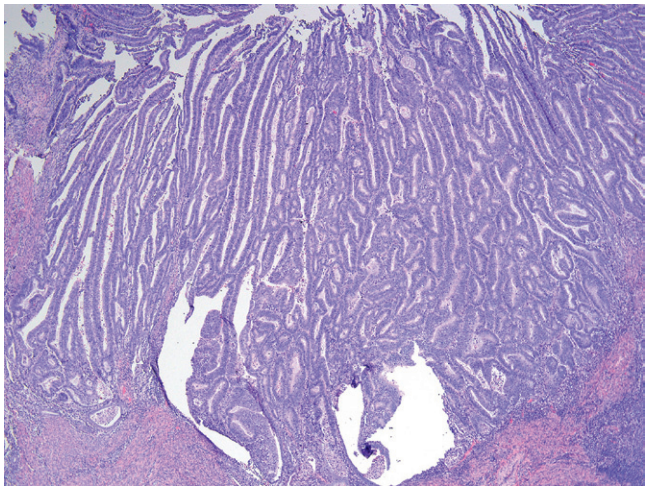


FIGURE 5

Confluent endometrioid endometrial carcinoma with a uniform epithelial stromal interface. Presumably the degree of invasion is slight.

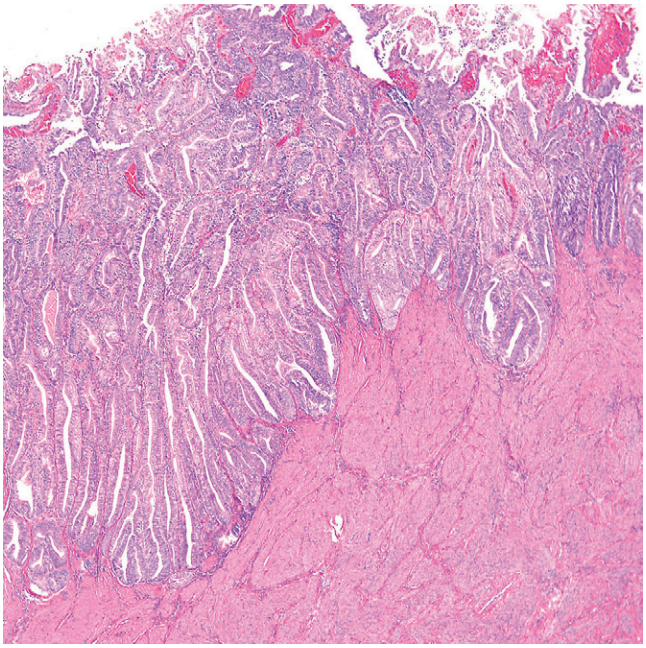


FIGURE 6

Confluent endometrioid endometrial carcinoma with a uniform epithelial stromal interface. Presumably the degree of invasion is slight.

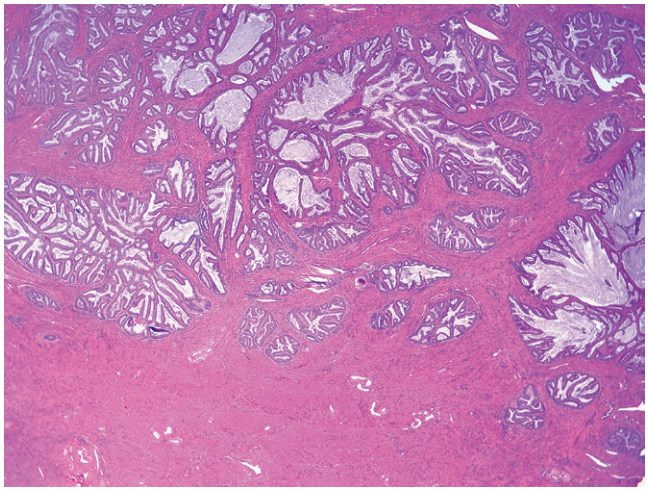


FIGURE 7

An adenomyosis-like pattern of myometrial invasion. Note the extent and downward direction of the growth pattern are characteristic of myoinvasion.

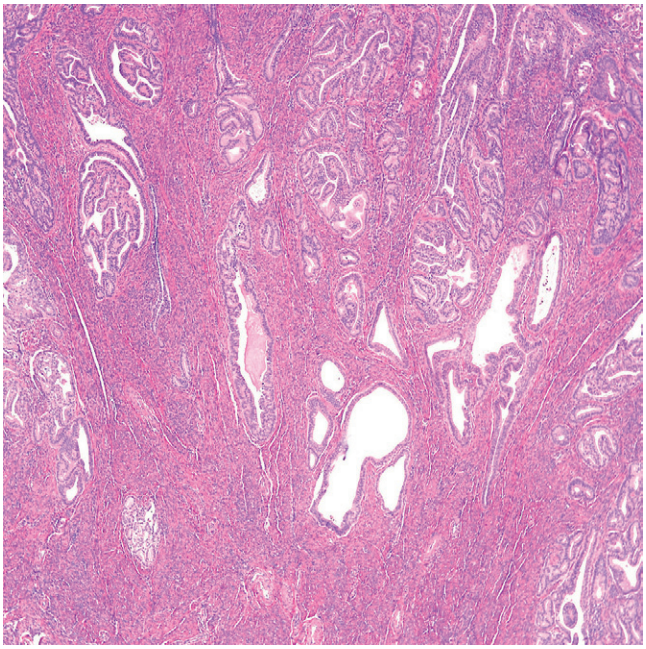


FIGURE 8

An adenomyosis-like pattern of myometrial invasion. Note the extent and downward direction of the growth pattern are characteristic of myoinvasion.

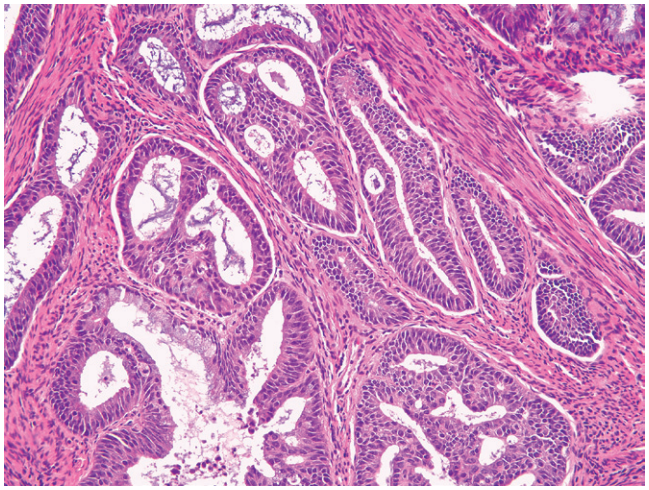


FIGURE 9

An adenomyosis-like pattern of myometrial invasion. Note the extent and downward direction of the growth pattern are characteristic of myoinvasion.

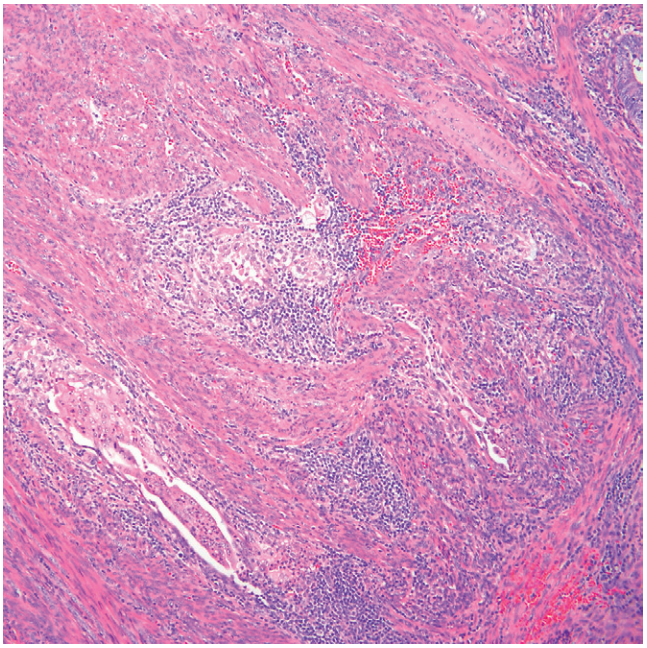


FIGURE 10

MELF-like invasion with subtle myxoid stromal changes and inconspicuous nests of epithelium. This pattern increases the risk of lymph node metastases.

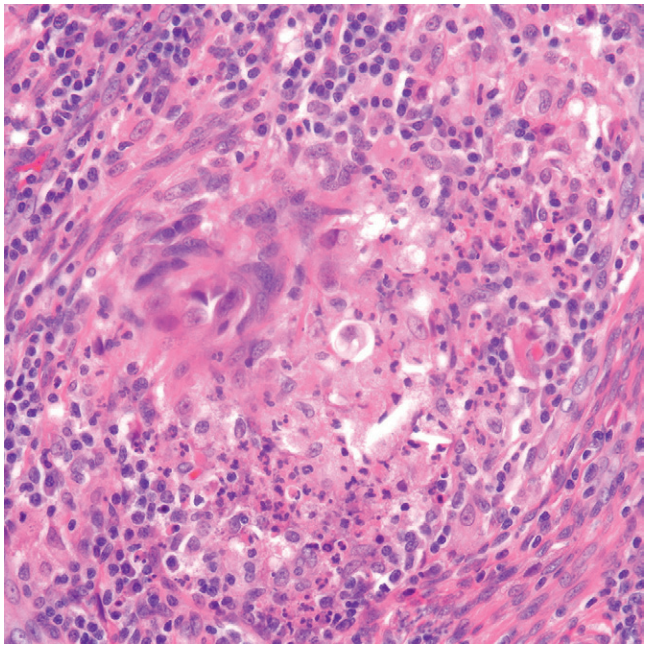


FIGURE 11

MELF-like invasion with subtle myxoid stromal changes and inconspicuous nests of epithelium. This pattern increases the risk of lymph node metastases.

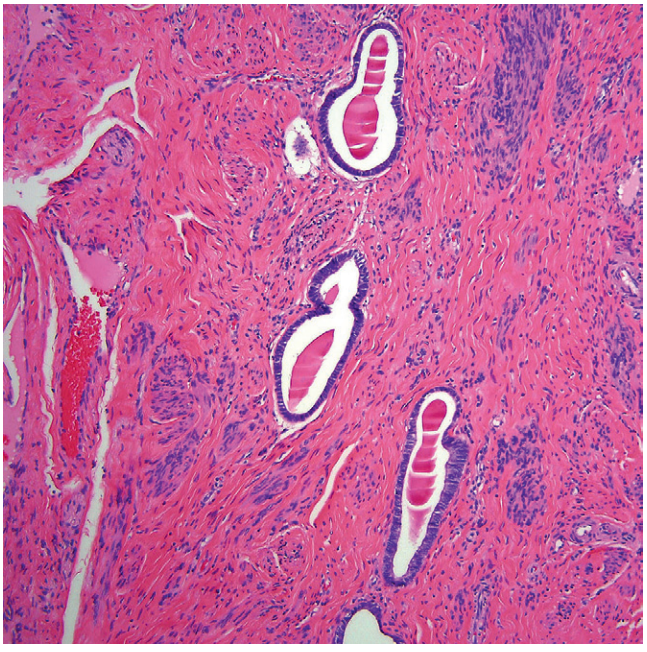


FIGURE 12

Adenoma malignum–like invasion. Uniform glands invade stroma without a desmoplastic response.

INTRAPERITONEAL KERATIN GRANULOMA

Definition—Implants of keratinous material within the peritoneal cavity causing an associated granulomatous response.

Clinical Features

Epidemiology

- Overall, peritoneal keratin granulomas are an uncommon finding; however, they most commonly occur in patients with gynecologic tumors.
- The most common associated tumor is endometrioid adenocarcinoma with squamous differentiation, but squamous cell carcinoma, atypical polypoid adenomyomas, and ruptured dermoid cysts have been known to cause this finding as well.

Presentation

- Typically found at the time of surgery.
- If widely disseminated, it may mimic peritoneal metastasis.

Prognosis and Treatment

- Peritoneal keratin granulomas have not been associated with an adverse outcome, and no additional treatment is required.

Pathology

Histology

- Microscopic examination of the small nodules reveals keratinous debris, necrotic keratinocytes (ghost cells) and surrounding foreign body giant cells, and chronic inflammatory cells.
- Variable amounts of fibrosis will be seen encasing the granulomas.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Metastatic carcinoma—this will exhibit neoplastic glandular epithelium.
- Other causes of granulomatous disease (i.e., sarcoid, tuberculosis (TB), fungal infection, foreign material such as talc)—these should not exhibit keratin debris.

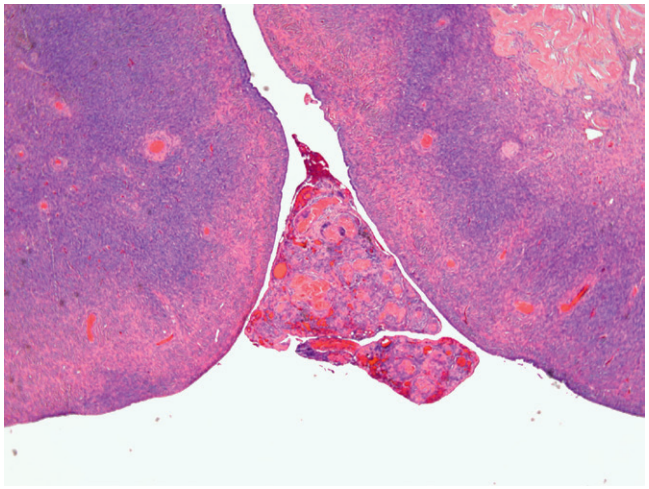


FIGURE 1

Keratin granuloma. A nodule of amorphous, eosinophilic material present on the ovarian surface.

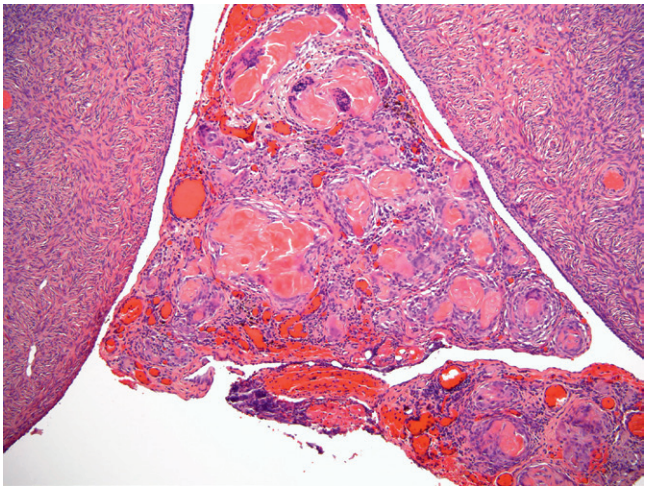


FIGURE 2

Keratin granuloma. Granulomatous inflammation and associated chronic inflammatory cells.

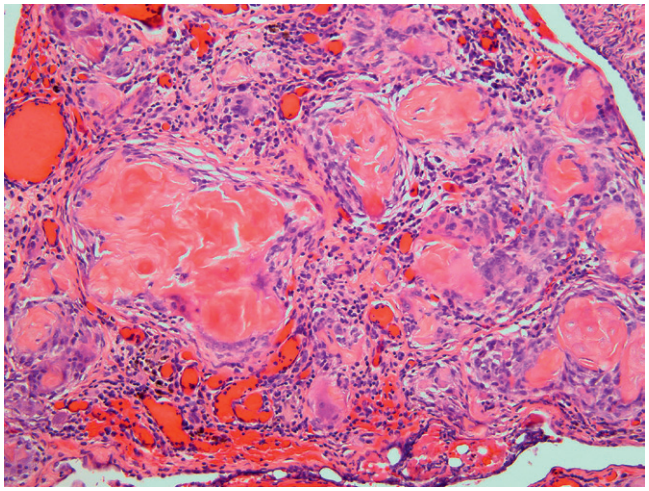


FIGURE 3

Keratin granuloma. Amorphous keratinous material and associated foreign body giant cells.

ENDOMETRIAL HISTIOCYTES AND FOAMY STROMAL MACROPHAGES

Definition—Nonepithelial cells present during both benign and neoplastic conditions.

Clinical Features

Epidemiology/Significance

- Histiocytes are common in postmenopausal endometrial samples, often associated with surface injury or erosion. They do not confer an increased risk of malignancy.
- Foamy stromal macrophages are commonly associated with, although not specific for, well-differentiated endometrial adenocarcinomas.

Presentation

- Typically found in curettings and hysterectomy specimens.
- Associated with a polyp (histiocytes) or malignancy (foamy macrophages).

Prognosis and Treatment

- Management is tailored to the underlying disorder.

Pathology

Histology

Histiocytes

- Loosely cohesive aggregates of small cells with slightly irregular nuclei.
- Often admixed with fibrin or hyaline stromal changes when degenerated polyp is present.
- Cohesive sheets may mimic epithelium.
- Cytoplasmic borders are vague.
- Mitotic figures and eosinophils may be present.

Foamy macrophages

- Discrete sharply demarcated groups of foamy cells.
- May be adjacent to neoplasia (endometrial intraepithelial neoplasia [EIN] or carcinoma).

Immunopathology (Including Immunohistochemistry)

- Keratin or macrophage markers will help in distinguishing histiocytes from epithelial cells.

Main Differential Diagnosis

- Carcinoma—macrophages can mimic carcinoma, but can be distinguished by immunohistochemical stains (cytokeratins) if needed.

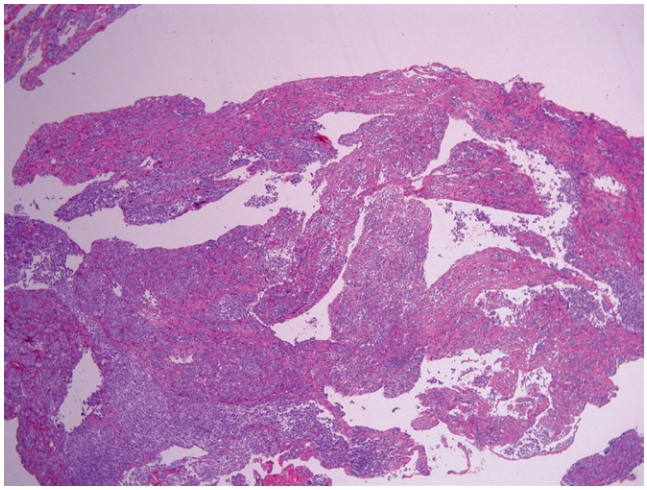


FIGURE 1

Endometrial histiocytes. A typical low-power image.

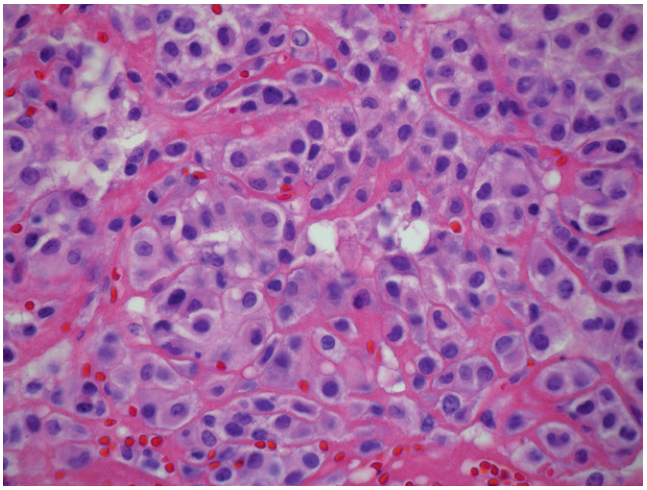


FIGURE 2

Endometrial histiocytes. At higher magnification the polyhedral cells seem to form an epithelial structure and may mimic small tumor cells. Note in particular the small nuclei with uniform chromatin.

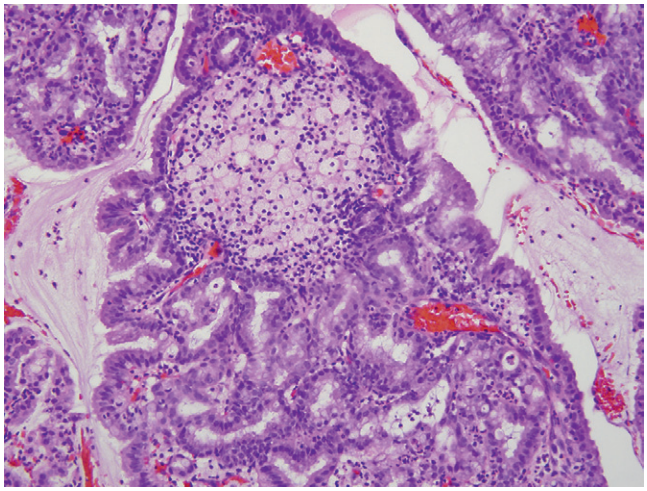


FIGURE 3

Foamy stromal macrophages. This image shows discrete clusters adjacent to endometrial neoplasms.

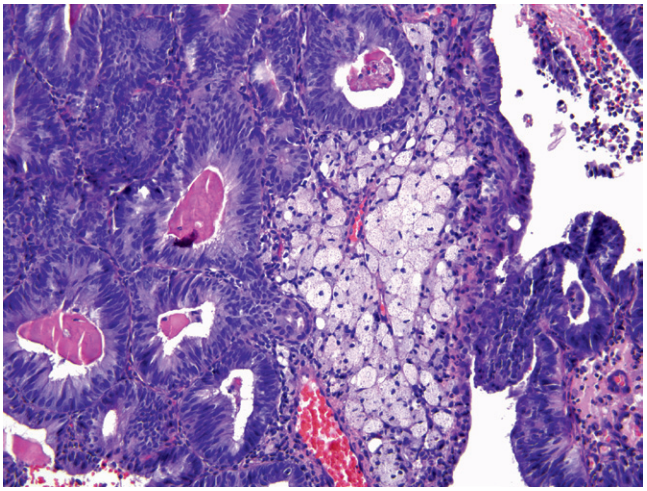


FIGURE 4

Another example of foamy stromal macrophages in a glandular neoplasm.

SEROUS CANCER PRECURSORS

Definition—Epithelial proliferations with evidence of p53 mutations that do not fulfill the criteria for intramucosal carcinoma.

Clinical Features

Epidemiology

- These lesions are rare and occur around menopause.
- Occasionally seen in endometrial polyps.
- Link between p53 positive epithelium with minimal atypia and cancer risk (of subsequent serous cancer) unknown.

Presentation

- Typically detected in biopsies or curettings of menopausal or postmenopausal women.
- May be associated with abnormal bleeding by default.
- A subset present incidentally, in an endometrial polyp.

Prognosis and Treatment

- Management of a histologically normal endometrium should not include immunostaining for p53. However, positive staining for p53 might be encountered accidentally.
- So-called p53 signatures (benign appearing p53-positive mucosa) should be managed as clinically appropriate (i.e., repeat sampling if there are clinical indications such as abnormal bleeding).
- More extensive proliferations with evidence of clonal expansion but lacking marked atypia and substantially increased proliferative activity should be managed with repeat sampling and consultation as needed.

Pathology

Histology

- p53 signatures: These are localized, histologically normal expansions of cells with a clonal p53 mutation. They are encountered in less than 2% of endometrial polyps.
- Atypical proliferations (so-called endometrial glandular dysplasia). These are multilayered populations of cells with strong p53 (or completely absent p53) staining. Proliferative index is usually low (less than 20%).
- Both p53 signatures and endometrial glandular dysplasia can be associated with serous carcinoma including intramucosal (or intraepithelial) carcinoma.

Immunopathology (Including Immunohistochemistry)

- Strong, diffuse (or completely null) staining for p53 should be seen in the cells. Some will have a deletion mutation and
- Ki-67 index is low.

Preferred Diagnostic Terms (When an Isolated Finding)

- For p53 signature: Benign endometrium with a comment that focal p53 staining is present, but there is no evidence of malignancy. Suggest repeat sampling if clinically indicated.
- For atypical proliferations that are p53 positive: Glandular atypia, possibly early serous neoplasia, with a comment that while serous endometrial intraepithelial carcinoma (EIC) is not seen, follow-up sampling is advised to exclude this possibility.

Main Differential Diagnosis

- Serous EIC—this entity will display multilayered atypia with an increased proliferative index and greater loss of polarity.

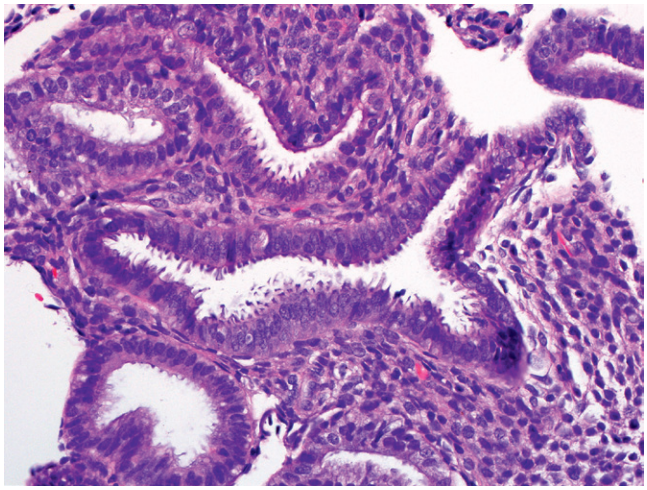


FIGURE 1

p53 signature in the endometrium discovered incidentally. Note the normal appearing mucosa. There is no current evidence that this is a risk factor for subsequent serous carcinoma.

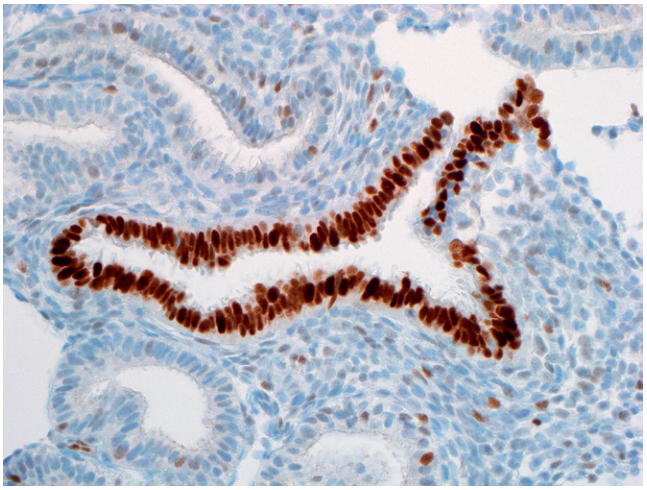


FIGURE 2

p53 immunostain of Figure 1.

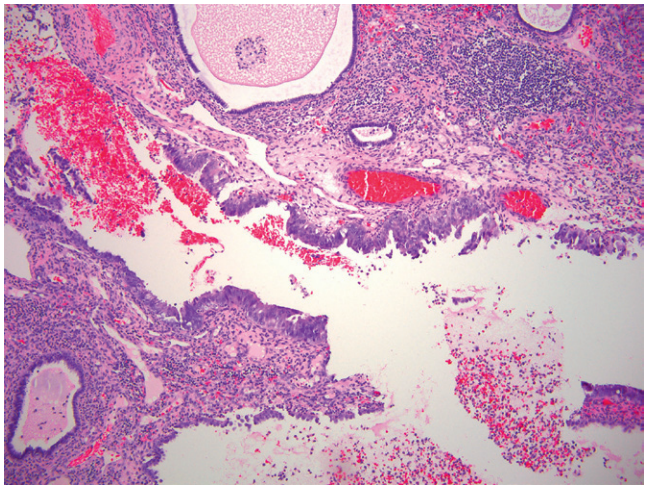


FIGURE 3

Endometrial glandular dysplasia showing multilayered epithelium with a relatively low nuclear-to-cytoplasmic (N/C) ratio.

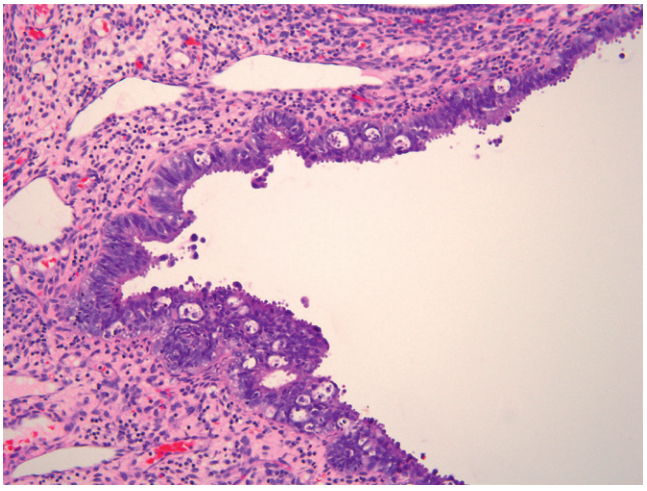


FIGURE 4

Endometrial glandular dysplasia showing multilayered epithelium with a relatively low nuclear-to-cytoplasmic (N/C) ratio.

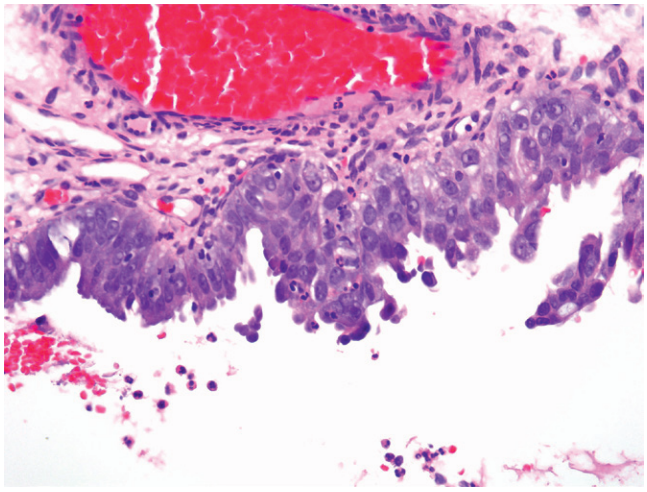


FIGURE 5

Endometrial glandular dysplasia. There is moderate atypia with some multilayering of the epithelium.

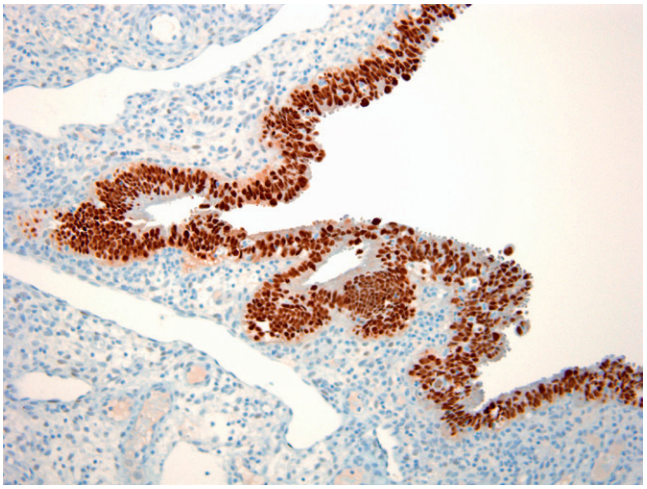


FIGURE 6

Endometrial glandular dysplasia. There is strong staining for p53.

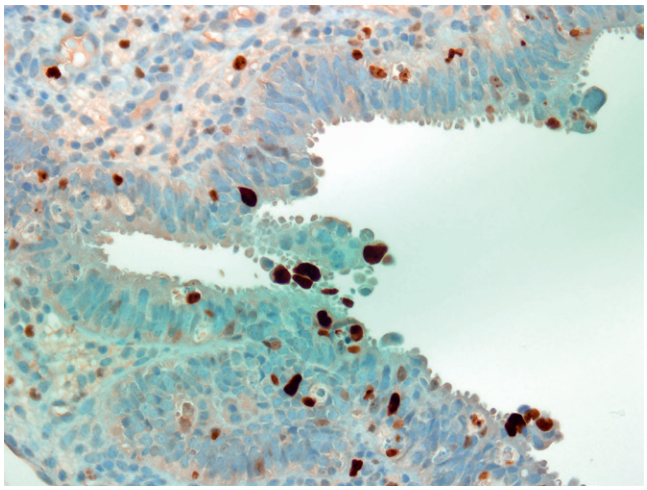


FIGURE 7

Endometrial glandular dysplasia. Note the low proliferative index.

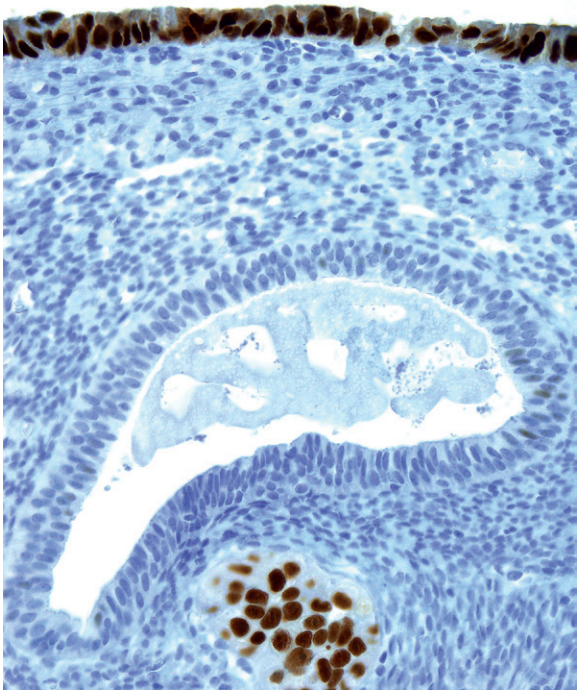


FIGURE 9

Both epithelia in Figure 8 stain strongly for p53. Note, however, that the surface epithelium is deceptively bland and would not by itself justify a diagnosis of serous EIC (see Figure 9).

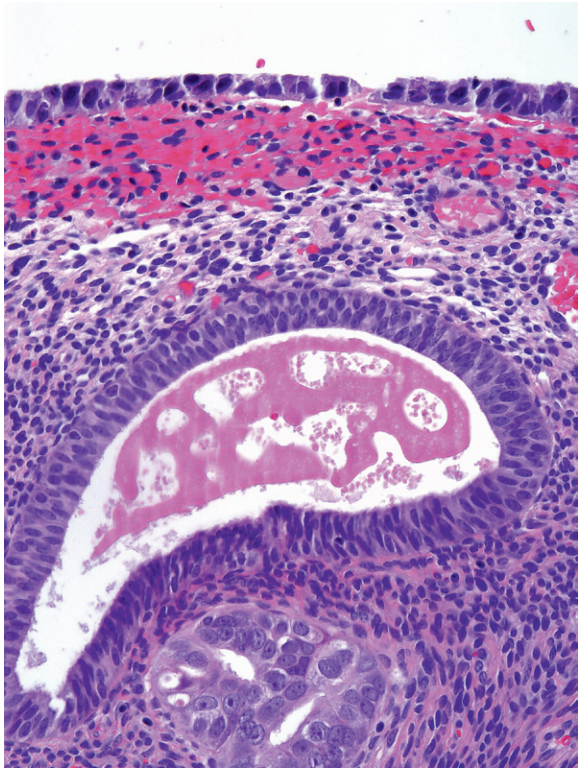


FIGURE 8

A small gland *(bottom center)* contains atypia befitting a serous EIC. Note the contrast with the surface epithelial changes, which are not diagnostic for malignancy.

SEROUS ENDOMETRIAL INTRAEPITHELIAL CARCINOMA

Definition—An early, noninvasive form of serous adenocarcinoma of the endometrium.

Clinical Features

Epidemiology

- Serous endometrial intraepithelial carcinoma (EIC) is a rare neoplasm.
- The vast majority of patients are postmenopausal.
- EIC is most commonly seen in a background of endometrial atrophy and associated with endometrial polyps.

Presentation

- Patients may present with abnormal bloody or blood-tinged discharge.
- Patients may be asymptomatic or present with signs and symptoms of lower genital tract or abdominal spread of tumor.
- A subset present incidentally in an endometrial polyp.

Prognosis and Treatment

- The prognosis in serous EIC is guarded. Notably patients who are completely staged and found to have low-stage disease have a favorable prognosis with a relapse rate of approximately 5%.
- Serous EIC does display metastatic potential.
- Primary therapy includes full surgical staging.
- The value of chemotherapy in an intramucosal carcinoma without spread is controversial.

Pathology

Histology

- Nuclear enlargement, hyperchromasia, and pleomorphism of the endometrial glandular cells are prominent.
- No increase in the gland density should be appreciated as serous EIC spreads along the surface of the endometrium and into existing gland tracts.
- Prominent exfoliation of cells may be present (mechanism of early spread).
- Increased mitotic figures with atypical forms are easily identifiable.
- A background of cystic atrophy or endometrial polyp (or both) is common.
- *A subset of these lesions are subtle.* Careful inspection of the surface epithelium may disclose an increased nuclear-to-cytoplasmic (N/C) ratio with mild nuclear enlargement only.

Immunopathology (Including Immunohistochemistry)

- Strong, diffuse (or completely null) staining for p53 should be seen in the malignant cells. Some will have a deletion mutation and exhibit no staining.
- Increased but often quite variable proliferative index with Ki-67.

Preferred Diagnosis (When an Isolated Finding)

- Serous intramucosal (intraepithelial) carcinoma, see comment.
- Comment: This serous carcinoma is confined to the mucosa (in this specimen) without stromal invasion. Appropriate clinical management is recommended to exclude extrauterine (tubes, ovaries, peritoneal surfaces) disease.

Main Differential Diagnosis

- Surface repair; the N/C ratio is typically low, but the nuclear atypia can be striking. This paradoxical finding (atypia, low N/C ratio) is not typical of early serous carcinoma, which can show deceptively uniform nuclei.

- Papillary syncytial metaplasia can mimic serous carcinoma, but true papillary architecture is absent.
- Arias-Stella (like) effect has pronounced atypia but should have weak to patchy p53 staining.
- Metastasis (from the upper genital tract/tube) is possible in very superficial involvement, hence the necessity for full staging.
- Exfoliation artifact produces a hobnail pattern in the endometrium resulting from discohesion of the lining cells brought about by preservation artifacts. Look for a regional distribution of the changes and evidence of preservation artifact in the adjacent stroma.
- Benign (ischemic) atypia associated with polyps can show marked nuclear changes. This may mimic both serous intramucosal carcinoma and clear-cell carcinoma.
- Lower-grade precursors to serous cancer, including atypias that border on serous EIC (akin to endometrial glandular dysplasia). These can display a lower proliferative index and less atypia, suggesting that they are precursors to EIC. Their management is problematic.

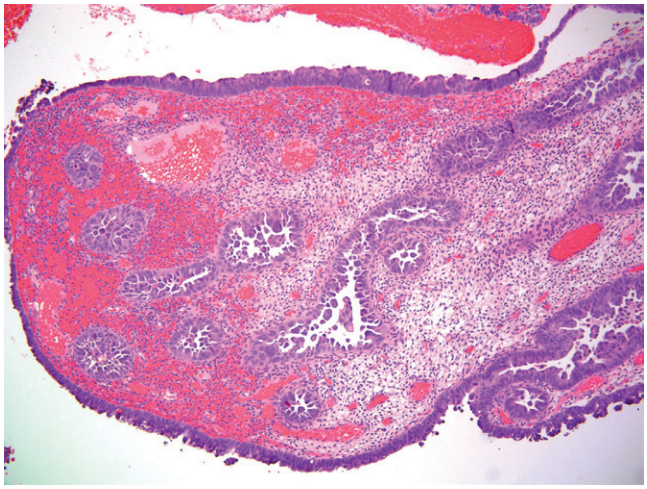


FIGURE 1

Serous EIC. At low power the process involves an endometrial polyp. The lesion conforms to existing glands but note the marked nuclear atypia.

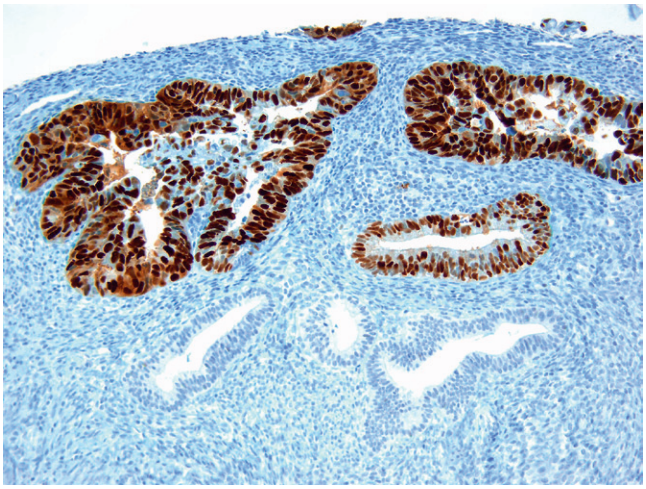


FIGURE 3

Serous EIC. p53 staining highlights the neoplastic epithelial cells with strong nuclear signal.

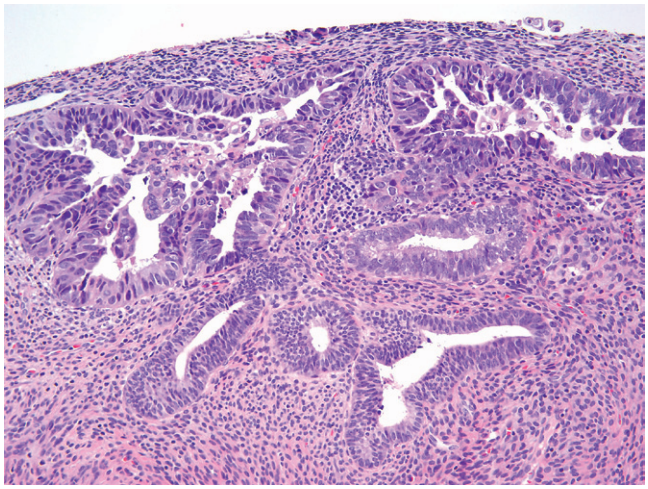


FIGURE 2

Serous EIC. Note the contrast with underlying benign glands.

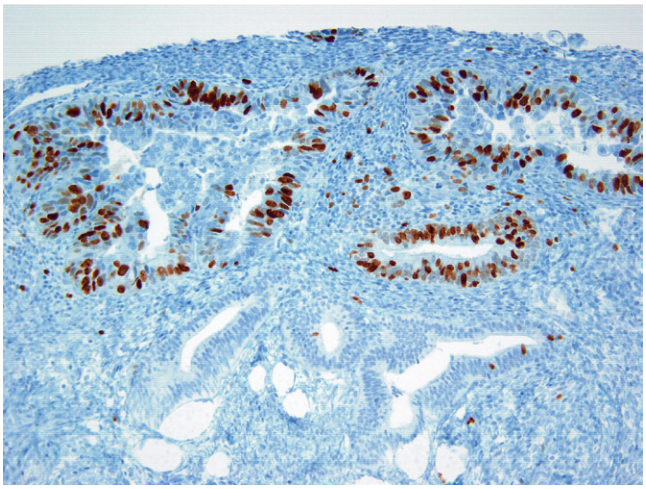


FIGURE 4

Serous EIC. A high proliferative index (MIB1) is the usual finding.

ISCHEMIC ATYPIAS OF THE ENDOMETRIUM

Definition—A form of hobnail atypia associated with adjacent necrosis or hyaline degeneration signifying regional ischemia.

Clinical Features

Epidemiology

- Most commonly occurs in women in their fifth to seventh decades who have endometrial polyps.

Presentation

- Seen in endometrial curettings or biopsies of women with abnormal bleeding.

Prognosis and Treatment

- Inconsequential by itself. Management is directed to the underlying condition (e.g., polyps).

Pathology

Histology

- The presence of endometrial polyps is common.
- Background of ischemic changes, with hemorrhage or hyaline stromal changes, either in the polyp or adjacent endometrium.
- Striking "hobnail" metaplasia.
- Often a noticeable transition from normal to hobnail changes.
- Relatively low nuclear-to-cytoplasmic (N/C) ratio and mild nuclear enlargement.

Immunopathology (Including Immunohistochemistry)

- p53 staining is weak to heterogeneous.
- Low Ki-67 index.

Recommended Diagnosis

- Reactive epithelial changes associated with infarction/ischemic change.

Main Differential Diagnosis

- Clear-cell carcinoma—nuclear enlargement and high N/C ratio with prominent nuclear enlargement.
- Serous carcinoma—high N/C ratio and high p53 and Ki-67 indices.
- Arias-Stella effect—appropriate clinical setting (pregnancy or progestin therapy) and the absence of stromal necrosis.

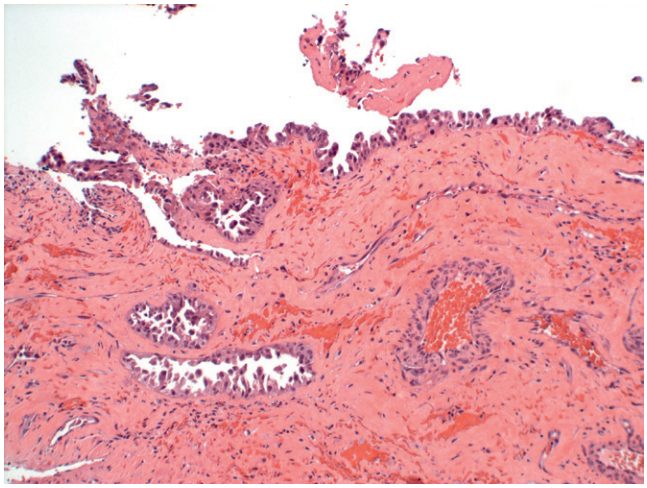


FIGURE 1

Ischemic atypia. This polyp is infarcted with prominent hobnail changes in the glands.

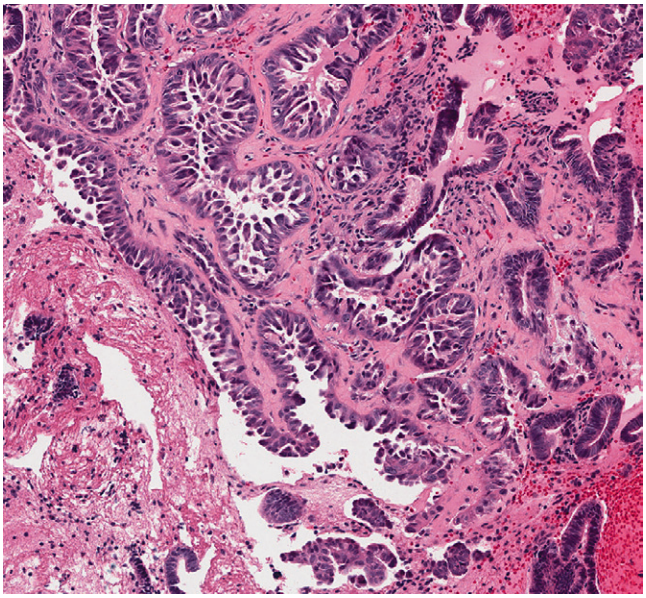


FIGURE 2

Ischemic atypia. Note the transition from nonischemic *(upper right)* to ischemic *(lower left)* zones with hyaline stromal changes.

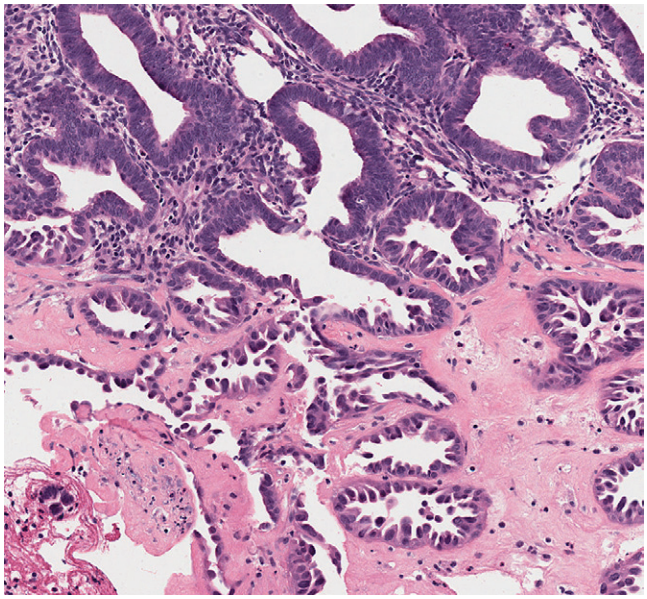


FIGURE 3

Ischemic atypia. In this field the preserved glands *(upper)* merge with the ischemic area *(lower)* with hyaline stromal changes and hobnail features.

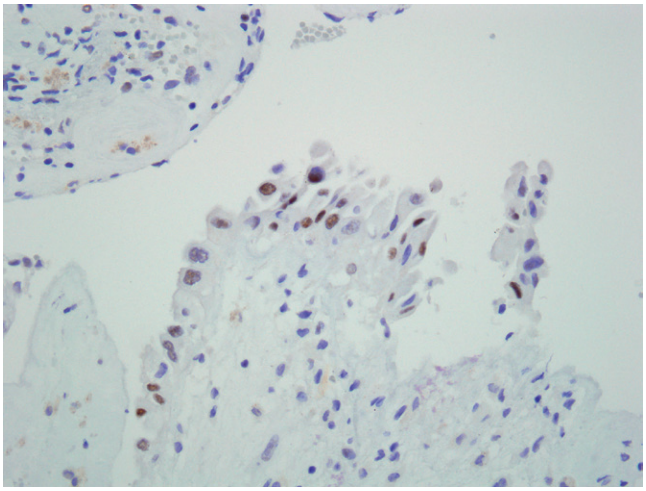


FIGURE 4

p53 staining of ischemic atypia displays heterogeneous distribution consistent with normal expression.

REACTIVE ATYPIA IN THE ENDOMETRIUM

Definition—A form of atypia associated with abnormal bleeding.

Clinical Features

Epidemiology

- Most commonly occurs in women in their fifth to seventh decades.

Presentation

- Seen in endometrial curettings or biopsies of women with abnormal bleeding.

Prognosis and Treatment

- Inconsequential by itself. Management is directed to the underlying condition (e.g., polyps).

Pathology

Histology

- The presence of endometrial polyps is common.
- Background of breakdown, with or without repair but might be seen in isolation.
- Nuclear enlargement, hyperchromasia, and in some cases multinucleation.
- Relatively low nuclear-to-cytoplasmic (N/C) ratio and mild nuclear enlargement.

Immunopathology (Including Immunohistochemistry)

- p53 staining is weak to heterogeneous.
- Low Ki-67 index.

Recommended Diagnosis

- Reactive epithelial changes associated with infarction/ischemic change.

Main Differential Diagnosis

- Clear-cell carcinoma—nuclear enlargement and high N/C ratio with prominent nuclear enlargement.
- Serous carcinoma—high N/C ratio and high p53 and Ki-67 indices. Notably many early intramucosal serous carcinomas display less variation in nuclear size, albeit a much higher N/C ratio.
- Arias-Stella effect—appropriate clinical setting (pregnancy or progestin therapy) and the absence of stromal necrosis.
- Ischemic atypia—this is probably a related entity, albeit more pronounced and described in association with infarcted endometrium or polyps.

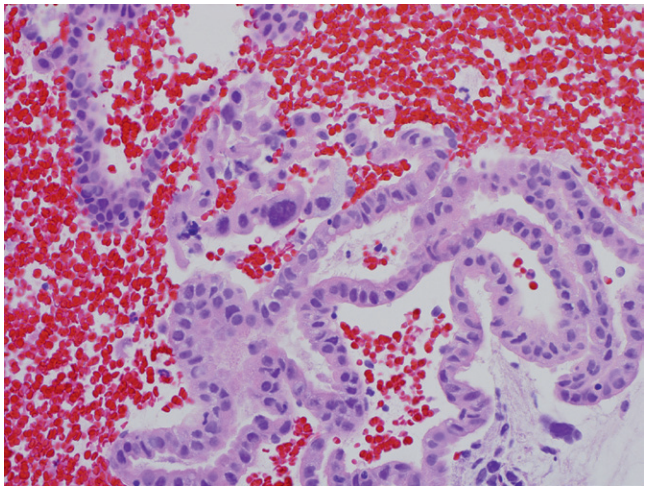


FIGURE 1

Typical reactive atypia in surface endometrium. Note the nuclear enlargement, uniform chromatin (smudged) and relatively low N/C ratio.

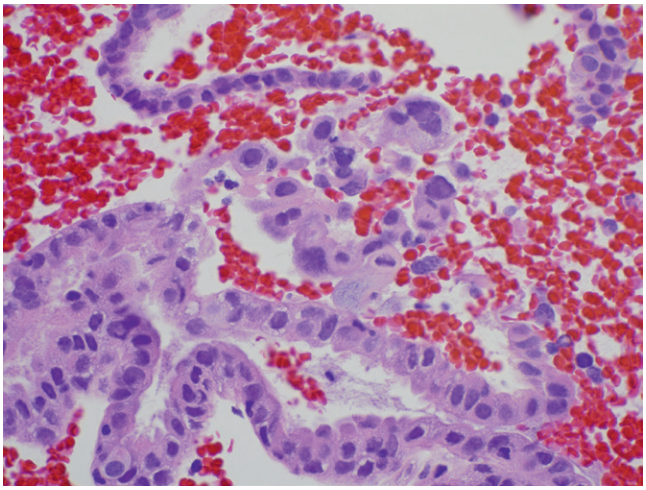


FIGURE 2

Another focus of reactive atypia *(center)* in strips of benign-appearing endometrial lining.

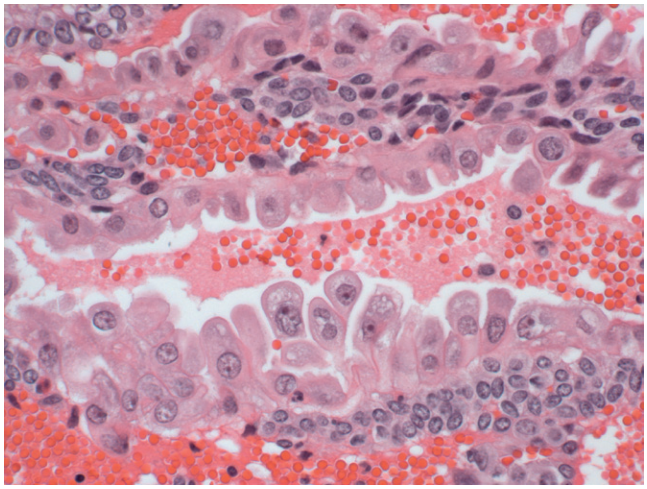


FIGURE 3

Another example of reactive atypia with breakdown. This overlaps with so-called ischemic atypia.

UTERINE SEROUS CARCINOMA

Definition—High-grade adenocarcinoma arising from the endometrium and invariably associated with mutations in the p53 tumor suppressor gene.

Clinical Features

Epidemiology

- Uterine serous carcinoma is relatively uncommon, comprising around 10% of endometrial primaries.
- Patients are most commonly in their seventh or eighth decade.
- Uterine serous carcinoma is not associated with obesity, diabetes, or estrogen excess.
- Precursors to serous carcinoma have been described (endometrial glandular dysplasia) and are being studied.

Presentation

- Abnormal uterine bleeding, abnormal cervical cytology.

Prognosis and Treatment

- Serous carcinoma is automatically considered high grade and carries a worse prognosis for similarly staged endometrioid tumors.
- Tumor cell exfoliation may occur early in the course of disease and lead to pelvic or abdominal metastasis.
- Lymph node or peritoneal metastasis can be seen in over one third without myometrial invasion.
- Treatment consists of total abdominal hysterectomy with bilateral salpingo-oophorectomy and omental sampling. Some stage IA cases might be managed by observation alone but otherwise vaginal brachytherapy and platinum-based chemotherapy are frequently employed.
- Recurrence rates for stage I are approximately 15% to 20%; 5% or less for tumors confined to the endometrium with no residual disease following surgery. Three-year survival for advanced disease (Stage III or greater is 40%).

Pathology

Histology

- Cells composing serous carcinoma are cuboidal to stratified, with marked nuclear pleomorphism, a high nuclear-to-cytoplasmic (N/C) ratio, and prominent nucleoli.
- Different patterns of growth have been described:
  1. Broad papillary projections lined by malignant cells
  2. Micropapillae, which consist of shed cells and lack fibrovascular cores
  3. Slit-forming glandular spaces.
  4. Solid growth (typically seen in more poorly differentiated/large cell serous carcinomas)
  5. Scattered angular glands with abundant fibrous stroma (so-called carcinofibroma).
  6. Microcystic growth (more common in ovarian/tubal primaries)
  7. Superficial epithelial growth, which commonly occurs in the setting of an (atrophic) endometrial polyp. These tumors may spread early and carry a poor prognosis, despite being noninvasive.

Immunopathology (Including Immunohistochemistry)

- Serous carcinoma shows strong, diffuse positivity for p53. Occasional cases (~15%) may be completely negative for p53 (relative to the background), consistent with a p53 null mutant.
- Ki-67 is markedly increased in serous carcinoma.
- p16 (as in diffuse and intense) and IMP4 are also positive in most. Combined p16 and p53 positivity correlates strongly with serous carcinoma but does not exclude a small percentage of higher-grade endometrioid carcinomas.

Main Differential Diagnosis

- Metastatic serous carcinoma from fallopian tube or ovary—the general consensus is that most combined endometrial and tubal/ovarian carcinomas arose in the uterus; however, it may be difficult to determine primary site, since in some cases there may be multiple primary tumors. In general an invasive or large serous carcinoma in the uterus is assigned as the primary.
- Poorly differentiated endometrioid carcinoma—these tumors can be immunophenotypically identical to serous carcinoma. The distinction is primarily histological, based on lower N/C ratio, greater nuclear uniformity.
- Clear-cell carcinoma—these are relatively uncommon in the uterus. Some tumors will have features of both clear-cell and serous carcinomas. p53 immunostaining should be heterogeneous; HINF1B, Napsin A, and AMACR staining might be helpful as well.
- Undifferentiated carcinoma—these tumors typically have a very monomorphic population of undifferentiated epithelioid cells with prominent nucleoli. Some can be highly pleomorphic. In either case the necessary architectural features of serous carcinoma should be absent. In fact, many undifferentiated carcinomas will be near a small component of lower-grade endometrioid carcinoma.

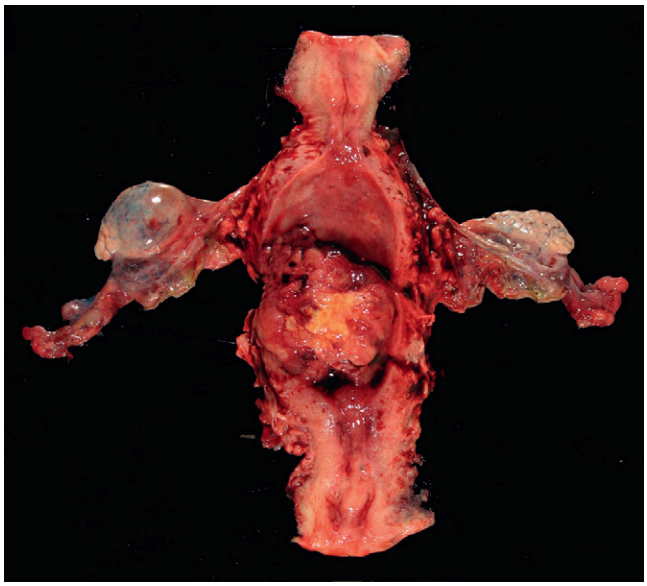


FIGURE 1

Uterine serous carcinoma. Gross photo of serous carcinoma forming a polypoid endometrial lesion.

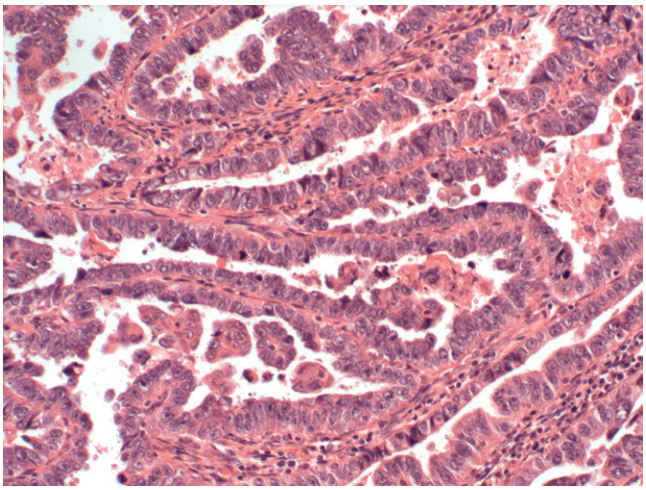


FIGURE 3

Uterine serous carcinoma. Angulated, slitlike glands with tumor cell exfoliation forming micropapillae.

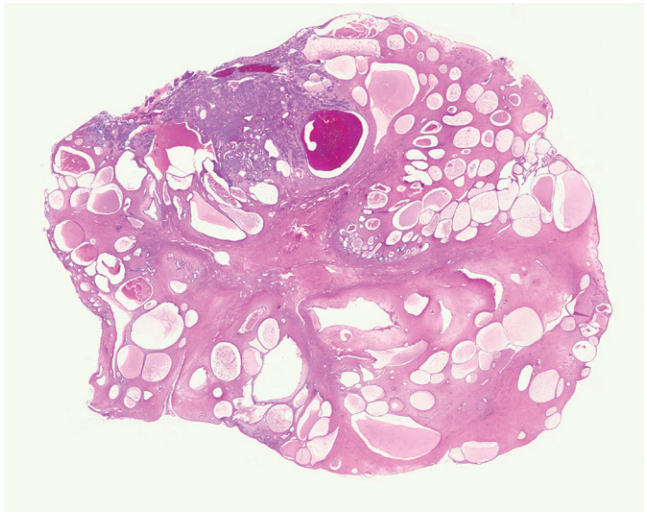


FIGURE 2

Uterine serous carcinoma. An atrophic polyp with a focus of serous carcinoma *(top half).*

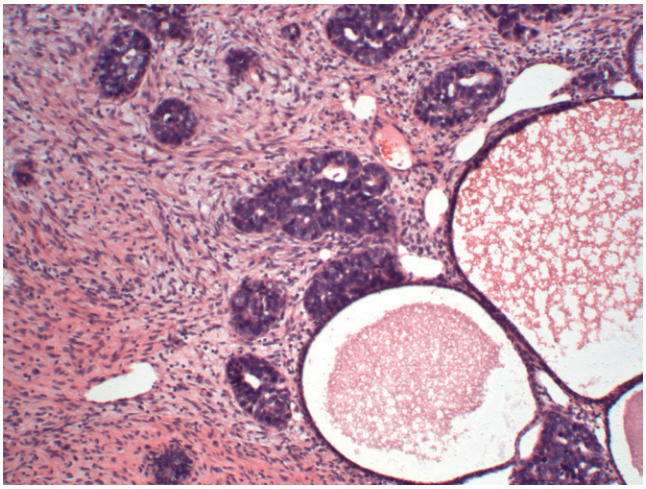


FIGURE 4

Uterine serous carcinoma. Nests of serous carcinoma with a markedly increased N/C ratio. Note the presence of cystic atrophic endometrial glands.

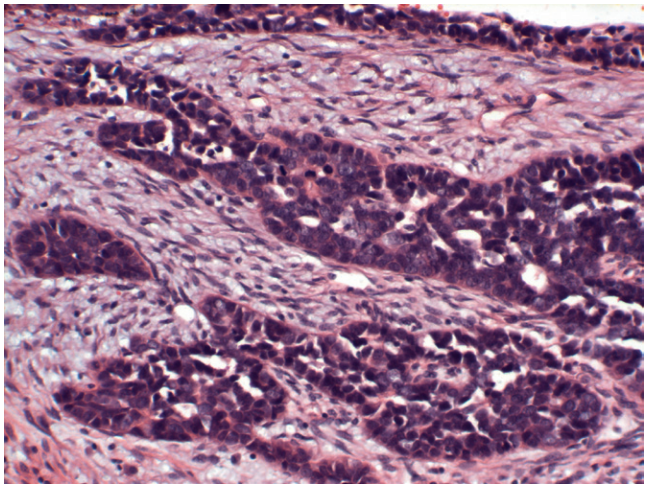


FIGURE 5

Uterine serous carcinoma. Increased N/C ratio and numerous slitlike spaces.

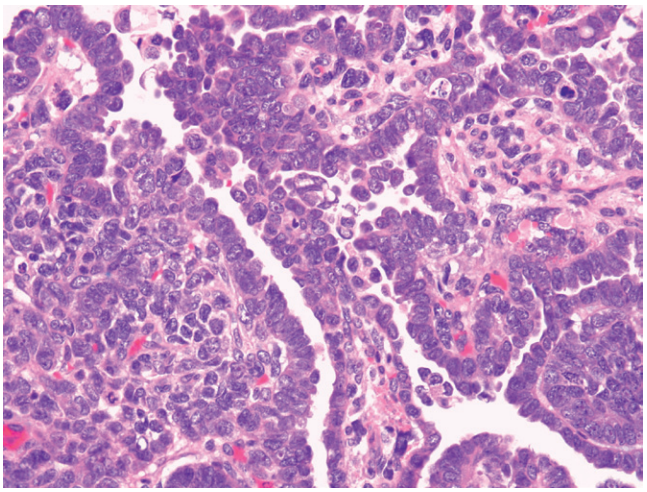


FIGURE 6

Uterine serous carcinoma. Cuboidal to low-stratified epithelium with marked nuclear pleomorphism and prominent nucleoli.

MIXED-PATTERN ADENOCARCINOMA

Definition—A variant of endometrial carcinoma with two distinct differentiation patterns, usually separated, with minimal evidence of a histologic transition.

Clinical Features

Epidemiology

- Relatively uncommon.
- Can occur at any age.
- Presumed to be a single original clone followed by divergence into two distinct phenotypes.

Presentation

- Similar to any endometrial carcinoma.
- May be a component of a diffusely undifferentiated carcinoma or part of a biphasic carcinoma that includes a conventional endometrioid component.

Prognosis and Treatment

- Prognosis is poor in cases in which there is undifferentiated carcinoma or serous carcinoma as the higher-grade component. Prognosis is not affected when the second component is a lower-grade spindle cell carcinoma.
- Managed as undifferentiated carcinoma if this is the second component.

Pathology

Histology

At least two patterns can be encountered, but any combination is possible:

- Combined endometrioid and high-grade serous carcinoma, with divergent immunophenotypes.
- Combined well-differentiated and undifferentiated carcinomas, including neuroendocrine differentiation in the latter. Neuroendocrine differentiation is common in these poorly differentiated areas but does not justify classification of the tumor as a neuroendocrine carcinoma.

Immunopathology (Including Immunohistochemistry)

- Immunostains may be necessary to exclude carcinosarcoma.
- p53 staining will highlight the more aggressive serous component when suspected.

Preferred Diagnosis (When an Isolated Finding)

- Biphasic endometrial carcinoma with a note specifying the different components.

Main Differential Diagnosis

- Grade II endometrioid carcinoma—this diagnosis is based on amount of solid growth, but two distinct patterns are not seen.
- Carcinosarcoma—excluded when necessary by cytokeratin stains.
- Stromal sarcoma or sarcomas with sex cord–like differentiation.

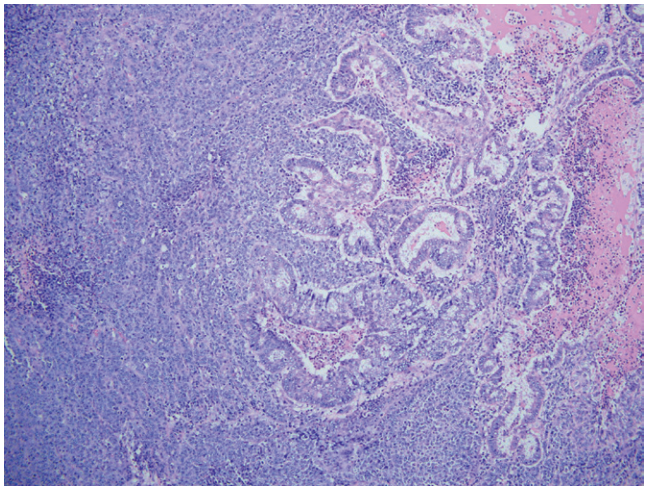


FIGURE 1

Biphasic carcinoma of the endometrium. Here a well-differentiated component on the right suddenly merges with an undifferentiated carcinoma on the left.

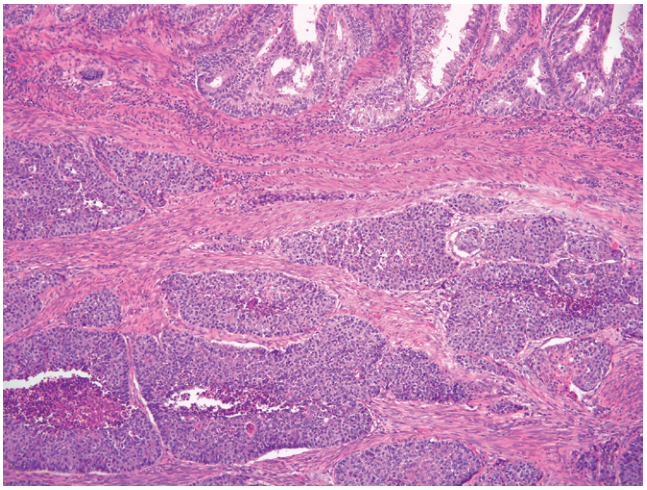


FIGURE 2

This biphasic carcinoma depicts a well-differentiated adenocarcinoma above, and a poorly differentiated carcinoma with neuroendocrine features below.

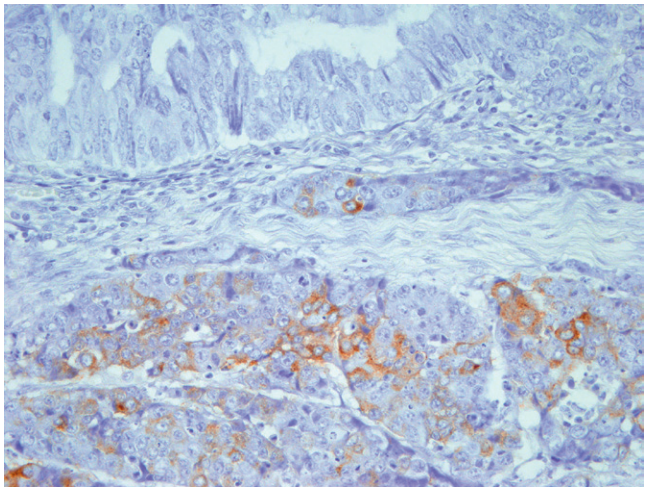


FIGURE 3

The interface of the lesion in the previous figure, with synaptophysin staining in the lower neuroendocrine component.

p53-POSITIVE ENDOMETRIOID ADENOCARCINOMA

Definition—A common conundrum in endometrial cancer classification in which an endometrioid histology coexists with strong p53 staining.

Clinical Features

Epidemiology

- Outcomes for serous carcinoma are distinctly less favorable relative to both low- and high-grade endometrioid carcinomas.
- Some tumors do not readily fall into either category, specifically those with both endometrioid histology and a high level of p53 expression.

Presentation

- Abnormal uterine bleeding and abnormal cervical cytology.

Prognosis and Treatment

- High (more than 50%) expression of p53 is independently associated with a worse clinical outcome in patients with endometrioid adenocarcinomas.
- In serous carcinomas, p53 expression is not independently associated with survival.
- Cases with ambiguous results, either histologically or diagnostically (i.e., interobserver disagreement), are more likely to be p53 positive.
- p53 immunohistochemistry might provide prognostic information in cases that would otherwise be classified as endometrioid adenocarcinomas.

Pathology

Histology

- Diagnostically ambiguous, p53-positive tumors fall into three general categories:

1. Tumors with variable histology, part of which is classically serous carcinoma. The latter exhibits the typical papillary, micropapillary, and slit-forming glandular growth with conspicuous nuclear atypia.
2. Tumors with endometrioid glandular morphology but increased (grade 2) nuclear atypia. The latter may take the form of less stratified more cuboidal cells, higher nuclear-to-cytoplasmic (N/C) ratio, and nuclear enlargement.
3. Rare tumors that are indistinguishable from endometrioid adenocarcinomas. These may not prompt suspicion but are nonetheless diffusely positive for p53.

Immunopathology (Including Immunohistochemistry)

- p53 staining is most useful in delineating these tumors and should be found in at least 50% of the tumor cells and typically is higher.

Recommended Diagnostic Terminology

- Endometrial adenocarcinoma, endometrioid-type grade (specify 1, 2, or 3).
- Comment: Immunostain for p53 is positive (more than 50% of cells). p53 has been independently associated with a more adverse outcome in endometrioid adenocarcinoma. Clinical correlation is advised.

Main Differential Diagnosis

- Serous carcinoma is the obvious exclusion and is done by the application of histologic criteria.

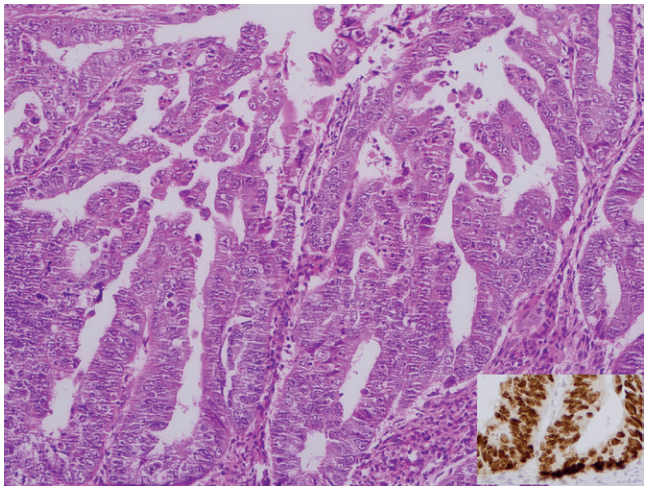


FIGURE 1

p53-Positive endometrioid adenocarcinoma. There is mild cell discohesion in an otherwise pseudostratified epithelium.

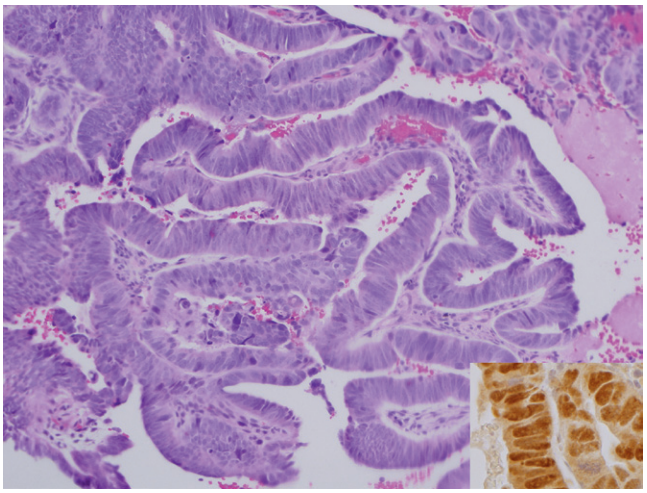


FIGURE 2

p53-Positive endometrioid adenocarcinoma. This endometrioid gland population demonstrates a higher N/C ratio.

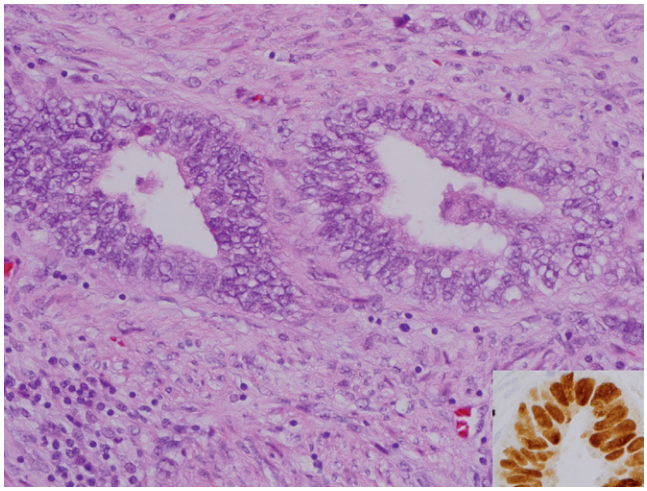


FIGURE 3

p53-Positive endometrioid adenocarcinoma. Another endometrioid glandular lesion with strong p53 staining.

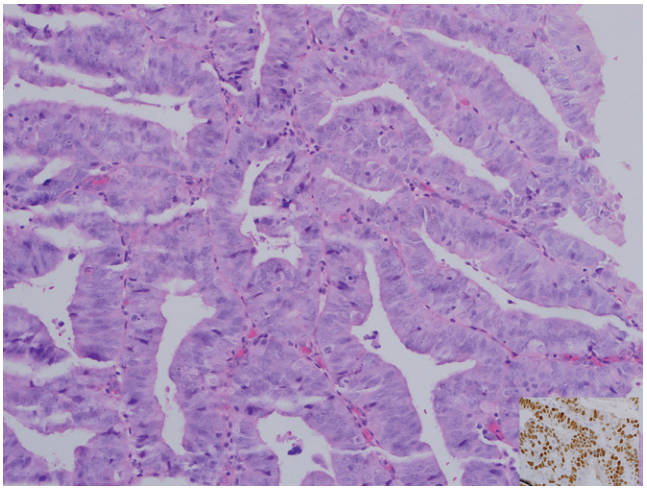


FIGURE 4

p53-Positive endometrioid adenocarcinoma. This population has moderate atypia, some loss of polarity, and some tubal-type differentiation.

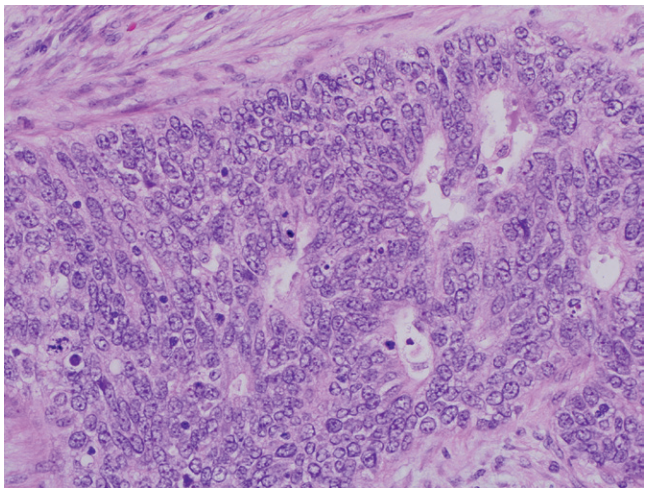


FIGURE 5

A biphasic tumor that ultimately would be classified as a serous carcinoma. The endometrioid component merges with a p53-positive serous component (see Figure 6).

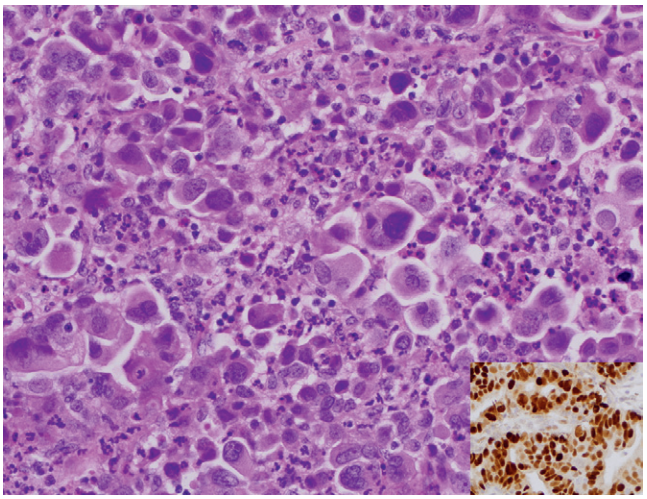


FIGURE 6

The endometrioid component (see Figure 5) merges with a p53-positive serous component *(shown here)*.

NEUROENDOCRINE DIFFERENTIATION IN ENDOMETRIAL CARCINOMA

Definition—A variant of endometrioid carcinoma with neuroendocrine features.

Clinical Features

Epidemiology

- A variant pattern seen in poorly differentiated carcinomas of the endometrium.
- The vast majority of patients are postmenopausal with a median age in the sixth to eighth decades.

Presentation

- Typically presents as stage III or IV (75%).
- May be a component of a diffusely undifferentiated carcinoma or part of a biphasic carcinoma that includes a conventional endometrioid component.

Prognosis and Treatment

- Prognosis is poor. Median survival was less than 1 year.
- Empiric therapy with neuroendocrine regimens is of unclear value, and the rationale for treating such tumors as neuroendocrine carcinomas is equally uncertain. In general, focal neuroendocrine differentiation does not justify treatment as such, whereas a tumor that is diffusely positive with multiple neuroendocrine markers might justify a neuroendocrine-specific regimen.

Pathology

Histology

- Can be both large and small cell types.
- Typically a diffuse proliferation of cells with a high nuclear-to-cytoplasmic (N/C) ratio and uniform nuclei, with variable nucleoli and stippled chromatin. Apoptosis is common. Vascular space invasion is the norm.
- The absence of gland formation in many; some may have tubular, cordlike, or sertoliform differentiation reminiscent of more well-defined neuroendocrine carcinomas.
- Geographic necrosis may be conspicuous.

Immunopathology (Including Immunohistochemistry)

- Neuron-specific enolase is often positive but not specific. Staining with chromogranin and synaptophysin is more reliable, but extent will vary greatly from case to case. Most cases do not exhibit diffuse staining with these markers.
- p53 and p16 are usually strong.

Preferred Diagnosis (When an Isolated Finding)

High-grade (grade 3) endometrial carcinoma with neuroendocrine differentiation.

Main Differential Diagnosis

- Grade 3 endometrioid adenocarcinoma—usually a lower N/C ratio, more homogeneous distribution of chromatin, and solid growth without neuroendocrine-like architecture.
- Undifferentiated carcinoma—this distinction may be a judgment call based on immunostains.
- Lymphoma—usually easily distinguished.
- Stromal sarcoma or sarcomas with sex cord–like differentiation.
- Cervical neuroendocrine carcinoma—p16 positive but p53 weak or heterogeneous.

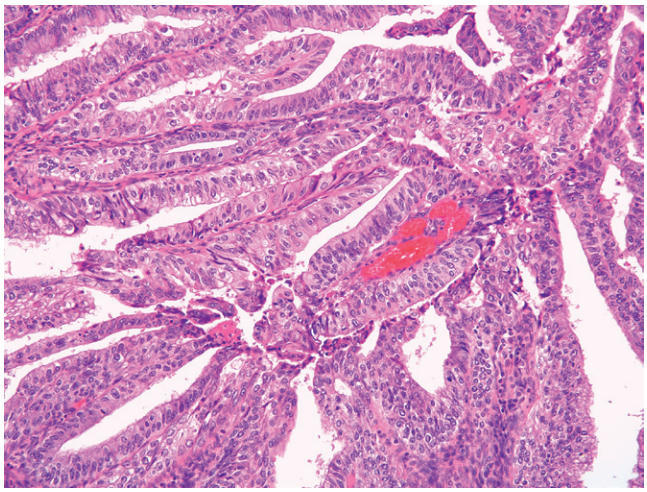


FIGURE 1

Neuroendocrine differentiation in carcinoma of the endometrium may coexist with conventional endometrioid histology as seen here.

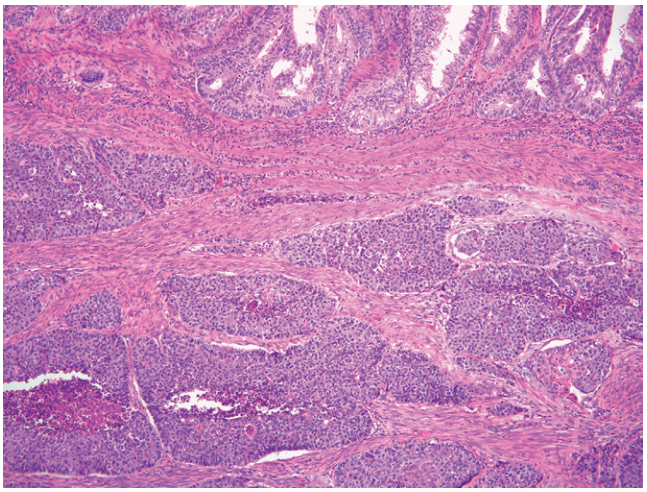


FIGURE 2

Neuroendocrine carcinoma of the endometrium. The endometrioid histology above is juxtaposed with undifferentiated carcinoma below. Note the necrosis.

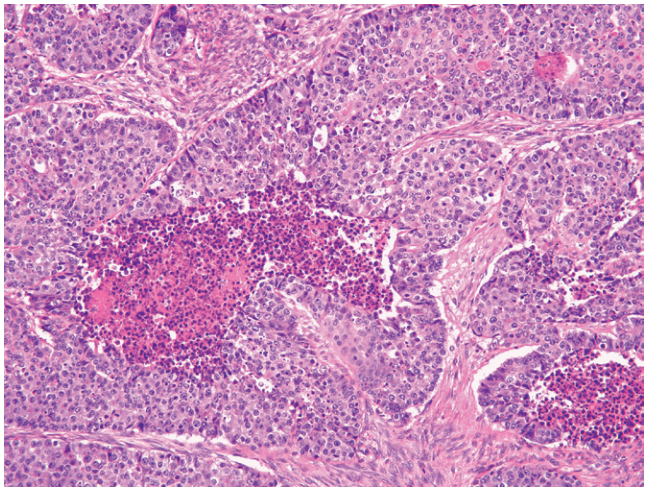


FIGURE 3

Neuroendocrine differentiation in endometrial carcinoma. Note the poorly differentiated albeit uniformly arranged cells.

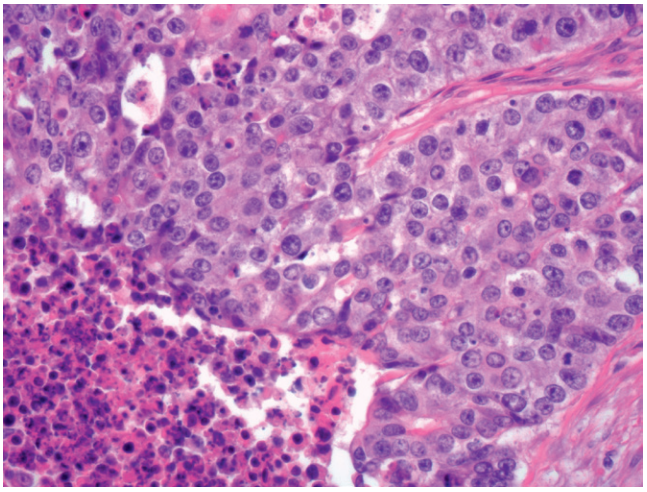


FIGURE 4

Neuroendocrine differentiation in carcinoma of the endometrium. At higher magnification the cells display uniform spacing, fine to coarse chromatin, and variable nucleoli.

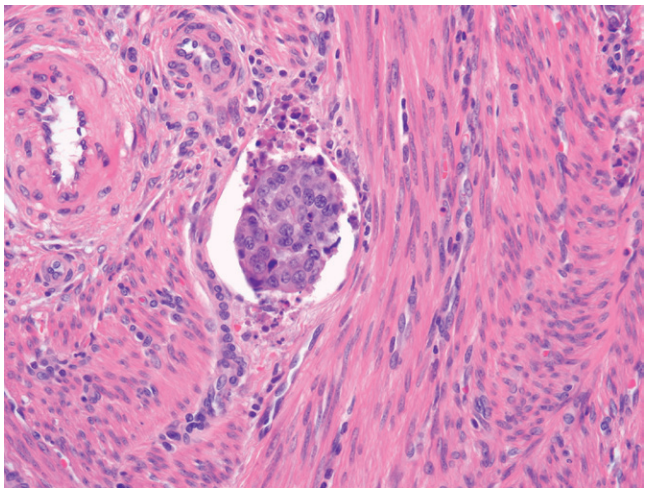


FIGURE 5

Neuroendocrine differentiation in carcinoma of the endometrium with vascular space involvement.

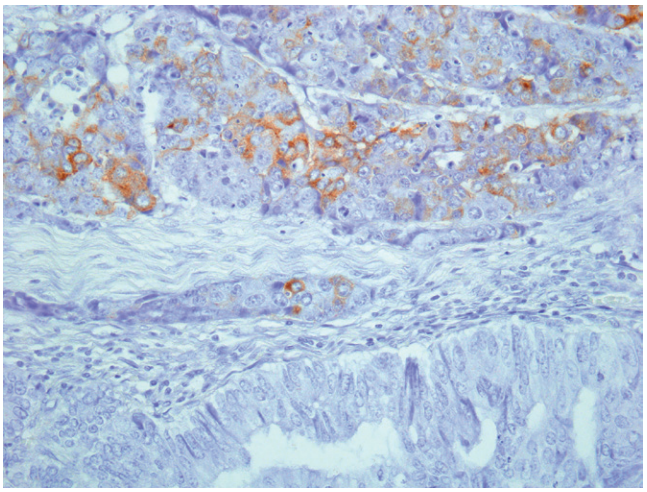


FIGURE 6

Neuroendocrine differentiation in carcinoma of the endometrium. The synaptophysin stain is positive.

UNDIFFERENTIATED CARCINOMA OF THE ENDOMETRIUM

Definition—Poorly differentiated carcinomas in which a line of differentiation cannot be determined.

Clinical Features

Epidemiology

- Pure undifferentiated carcinomas are rare.
- Patients may present at a wide range of ages, with a mean age of 63 years.

Presentation

- Abnormal vaginal bleeding.
- Diffuse lymphadenopathy may be present at the time of diagnosis, giving the false clinical impression of a hematologic neoplasm.

Prognosis and Treatment

- About 79% of stage I (up to 100% if tumor is in the inner half of the myometrium) and 33% stage II survive 5 years.
- Total abdominal hysterectomy with lymph node dissection followed by adjuvant chemotherapy or radiation is typically employed.

Pathology

Histology

- Undifferentiated carcinomas are typically composed of small- to medium-sized cells with vesicular nuclei and prominent nucleoli.
- The tumor cells may appear discohesive, mimicking lymphoma.
- Mitotic activity is markedly increased with many bizarre forms.
- Tumor-infiltrating lymphocytes may be prominent.
- Features of endometrioid (glands, squamous morules), serous, or clear cell (hyaline stroma, hobnailing) differentiation should be absent, but rare foci of glandular differentiation are not uncommon.

Immunopathology (Including Immunohistochemistry)

- Keratin immunostaining may be focally positive (AE1/AE3, CK18).
- EMA may be focally positive.
- Markers of other lines of differentiation (CD45, MyoD1, SMA, Desmin) are negative NSE or synaptophysin are found in 10% to 30% but do not correlate with prognosis.
- ER and PR are typically negative.

Main Differential Diagnosis

- The International Federation of Gynecology and Obstetrics (FIGO) grade III endometrioid adenocarcinoma.
- Serous adenocarcinoma (solid variant)—these tumors typically demonstrate marked nuclear atypia.
- Poorly differentiated stromal sarcoma—these may be difficult to distinguish but should demonstrate a reticulin pattern of a mesenchymal tumor.
- Lymphoma—distinguished principally by immunohistochemistry.
- Neuroendocrine carcinoma—neuroendocrine differentiation (positive for chromogranin, synaptophysin, and NSE).
- Rhabdomyosarcoma—skeletal muscle differentiation.
- Leiomyosarcoma—smooth muscle differentiation.

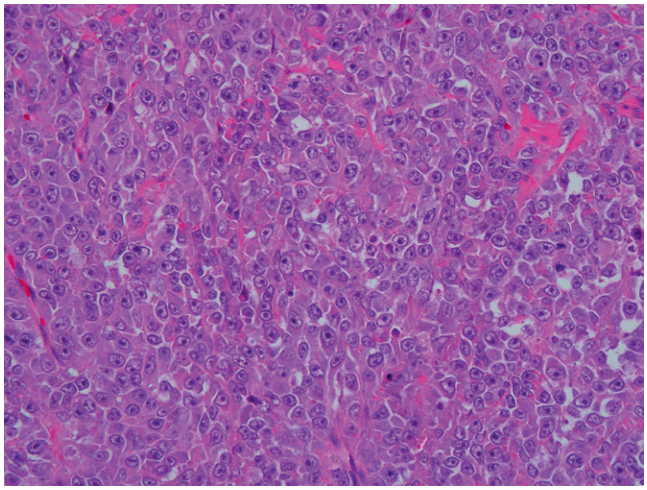


FIGURE 1

Undifferentiated carcinoma. Pleomorphic cells with prominent nucleoli.

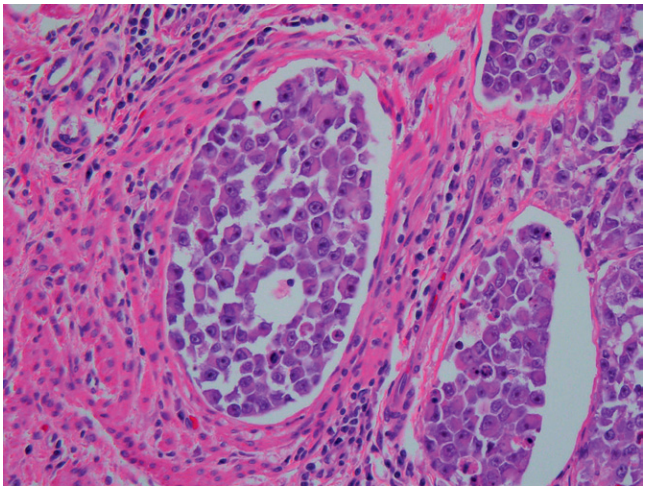


FIGURE 2

Undifferentiated carcinoma. Discohesive, plasmacytoid cells present within the lymphatics.

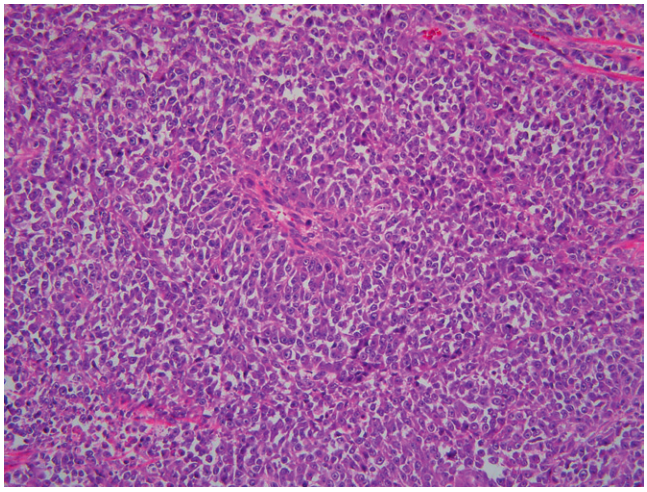


FIGURE 3

Undifferentiated carcinoma. Sheets of discohesive cells. Note the lack of architectural differentiation.

CLEAR-CELL CARCINOMA

Definition—A high-grade, malignant neoplasm of the endometrium.

Clinical Features

Epidemiology

- Clear-cell carcinoma of the endometrium is a rare malignancy comprising less than 1% of all endometrial cancers.

Presentation

- Patients present with findings typical of endometrial carcinoma including bleeding, pain, and mass effect.
- Rarely patients may be asymptomatic.

Prognosis and Treatment

- Although classified as a high-grade carcinoma, 5-year progression-free and overall survival (OS) are 61% and 78%, respectively, and OS is 94% and 88% for stage I and II, respectively.
- Surgical staging is considered first-line therapy with chemotherapy and radiation as an option for high-stage cases.

Pathology

Histology

- Large, polyhedral cells with distinct cell borders compose most tumors.
- Growth patterns range from small tubular glands to papillae to solid growth.
- In the glandular and papillary patterns these structures are lined by a single row of pleomorphic cells with distinct cell borders and varying levels of clear, vacuolated cytoplasm.
- Stromal hyalinization often accompanies the malignant epithelium and can be a helpful diagnostic clue.
- The presence of diffuse atypia and mitotic activity can help to differentiate clear-cell carcinoma from Arias-Stella effect (ASE).

Immunopathology (Including Immunohistochemistry)

- Immunostaining for p53 typically shows an increased level of staining compared with low-grade endometrioid adenocarcinoma and a lower level of staining than serous carcinoma.
- Staining for hepatocyte nuclear factor (HNF-1beta) stains clear-cell neoplasms, but overlap can be seen in ASE and some endometrioid carcinomas.
- Napsin A is a sensitive marker (and should usually be positive) and AMACR a relatively specific marker for clear-cell carcinoma.

Main Differential Diagnosis

- Uterine serous carcinoma—typically more stratified, strongly p53 positive (or negative), and hyaline stromal changes are less conspicuous.
- ASE—can be particularly challenging in older women where the ASE is discrete (clonal-like).
- Endometrioid adenocarcinoma with secretory differentiation—less nuclear atypia with a lower nuclear-to-cytoplasmic (N/C) ratio and admixing of the vacuoles and nuclei with less hobnailing.
- Poorly differentiated endometrial carcinoma with clear-cell features—the predominant pattern is a stratified neoplastic epithelium with haphazardly arranged vacuoles. Staining for HNF1-beta may be positive but Napsin A and AMACR less so.

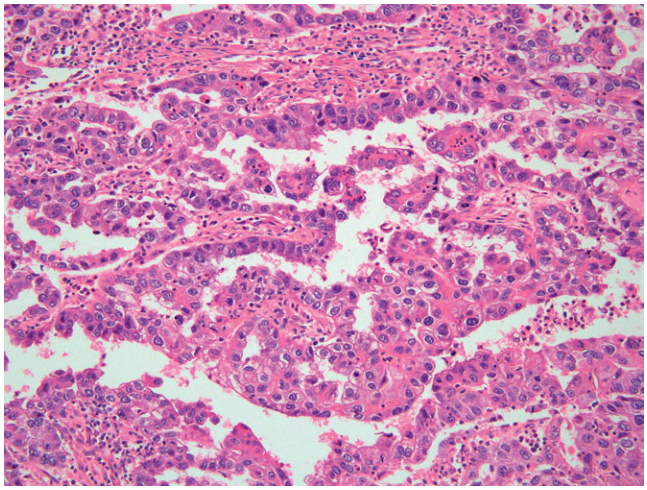


FIGURE 1

Clear-cell carcinoma. A single lining of pleomorphic epithelial cells. Note the focal cytoplasmic clearing in the middle aspect of the picture.

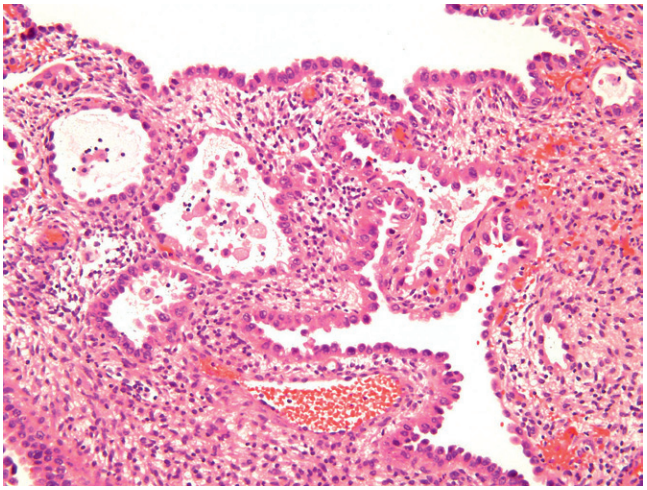


FIGURE 2

Clear-cell carcinoma. Glands with hobnail cells projecting into the lumen.

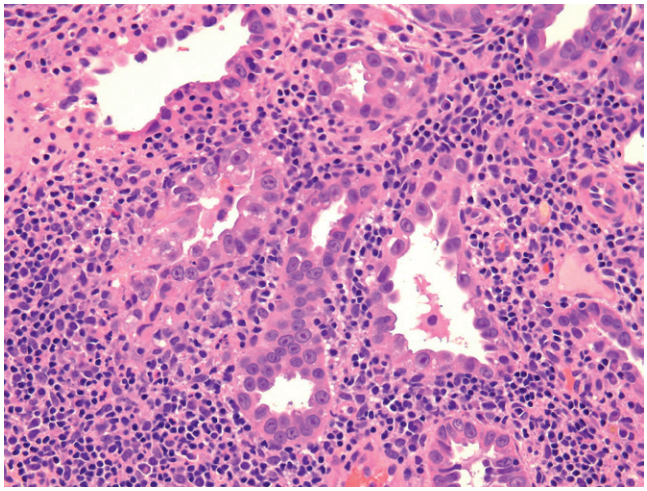


FIGURE 3

Clear-cell carcinoma. A single layer of markedly pleomorphic cells projecting into the glandular lumen.

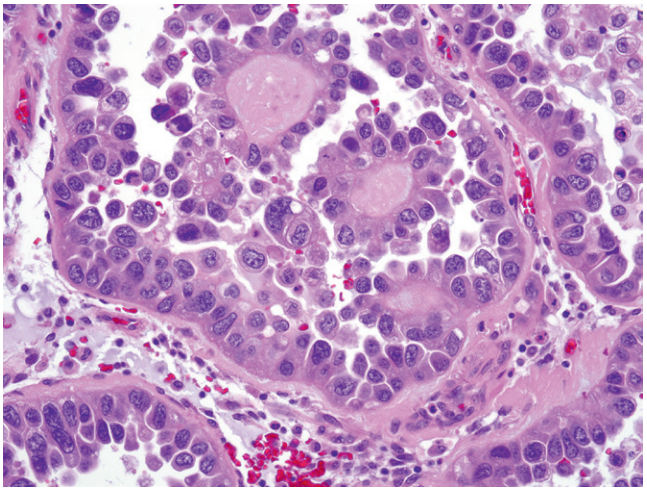


FIGURE 4

Clear-cell carcinoma. Small papillary cores with hyalinization and hobnail cells.

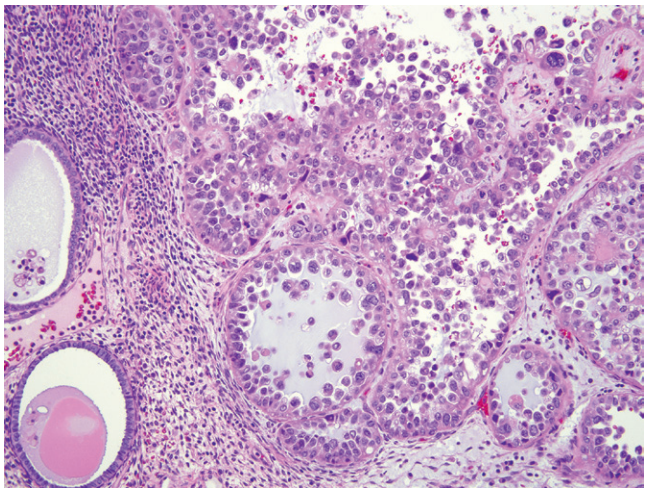


FIGURE 5

Clear-cell carcinoma. Pleomorphic, hobnail cells with focal cytoplasmic clearing. Uninvolved glands are on the left.

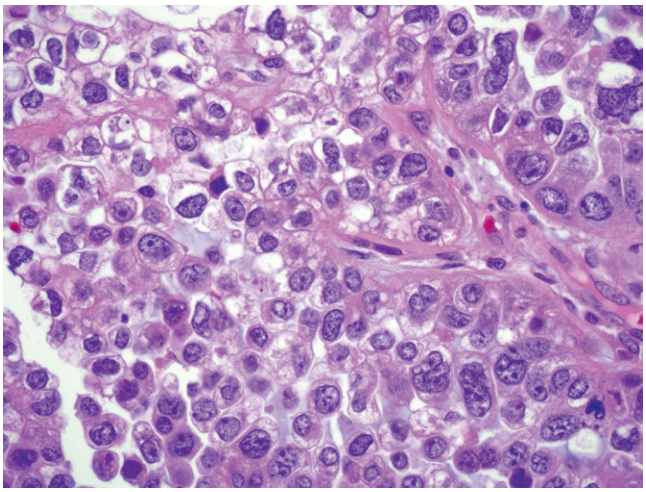


FIGURE 6

Clear-cell carcinoma. A solid sheet of pleomorphic cells with cytoplasmic clearing and distinct cell borders.

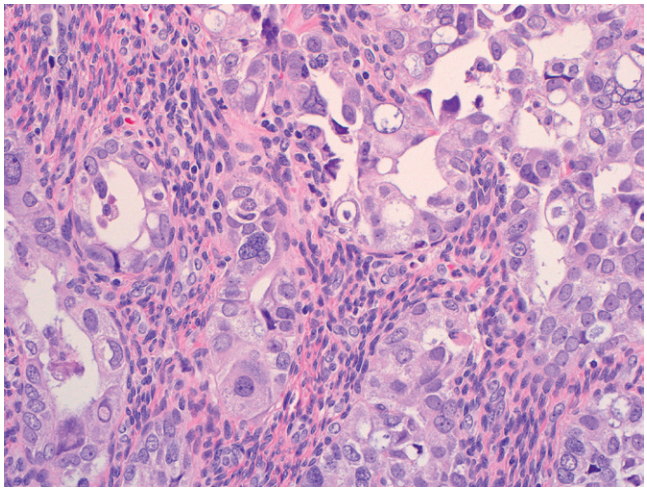


FIGURE 7

Clear-cell carcinoma. This tumor exhibits a more heterogeneous cell population.

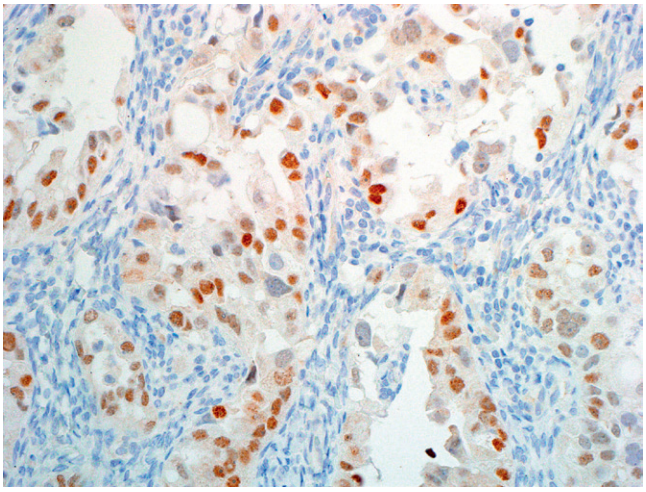


FIGURE 8

The field in Figure 7 following HNF-1beta immunostaining.

ENDOMETRIOID OR CLEAR-CELL CARCINOMA?

Definition—A problematic endometrioid carcinoma with some clear-cell features.

Clinical Features

Epidemiology

- Similar to other endometrioid carcinomas.

Presentation

- Patients present with findings typical of endometrial carcinoma including bleeding, pain, and mass effect.
- Rarely patients may be asymptomatic.

Prognosis and Treatment

- Approached as an endometrioid adenocarcinoma and managed based on stage and grade.
- Surgical staging is considered first-line therapy with chemotherapy and radiation as an option for high-stage cases.

Pathology

Histology

- There should be a recognizable endometrioid component.
- Clear cells show modest atypia and are arranged mostly in solid sheets or glands.
- In the glandular and papillary patterns, lining epithelium largely demonstrates monomorphic nuclei.
- Stromal hyalinization is absent or inconspicuous.

Immunopathology (Including Immunohistochemistry)

- Immunostaining for p53 should be heterogeneous.
- Staining for clear-cell carcinoma markers hepatocyte nuclear factor (HINF1-β) is positive.
- Napsin-A and AMACR will be contradictory.

Main Differential Diagnosis

- Uterine serous carcinoma—greater nuclear atypia and strongly p53 positive (or negative).
- Clear-cell carcinoma—greater atypia, stromal hyalinization, and hobnailing.

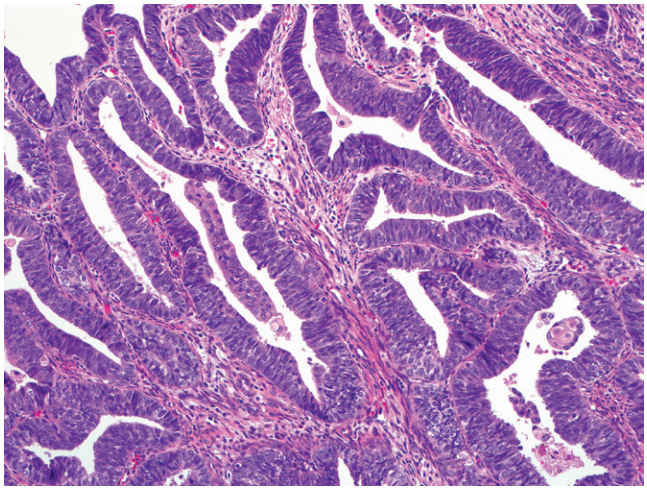


FIGURE 1

Endometrioid carcinoma with secretory clear-cell features. This focus contains typical endometrioid histology.

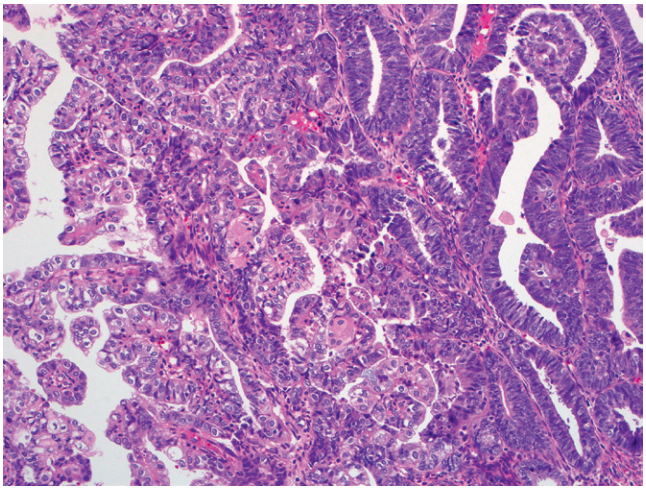


FIGURE 2

Endometrioid carcinoma with secretory clear-cell features. Transition from endometrioid to the secretory clear-cell pattern.

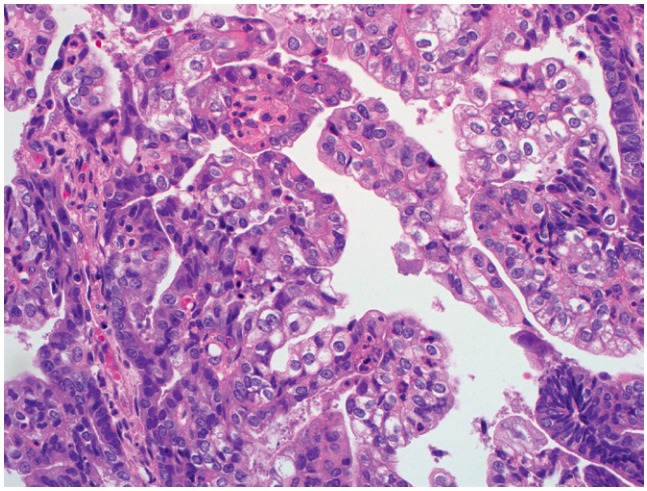


FIGURE 3

Endometrioid carcinoma with secretory clear-cell features. These areas show sheet-forming, glandlike, or ill-defined papillary architecture. Note the minimal nuclear atypia.

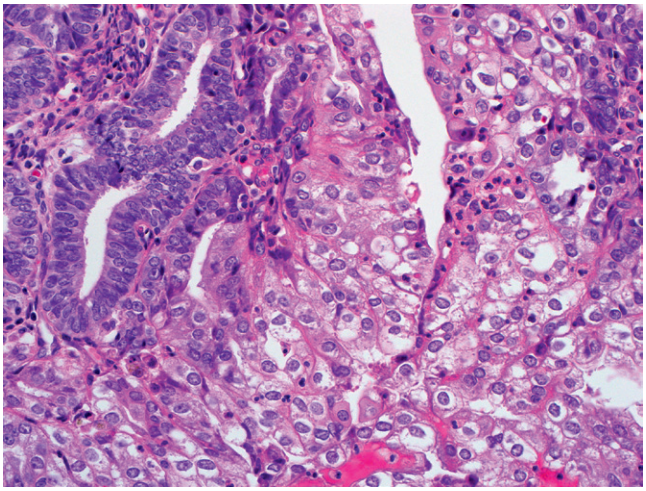


FIGURE 4

Endometrioid carcinoma with secretory clear-cell features. These areas show sheet-forming, glandlike, or ill-defined papillary architecture. Note the minimal nuclear atypia.

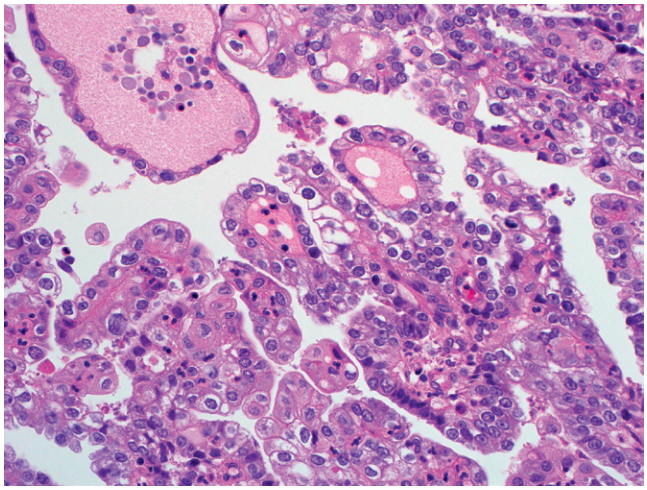


FIGURE 5

Endometrioid carcinoma with secretory clear-cell features. This one focus exhibits a few pseudopapillae. Note the absence of hyalinized stromal cores.

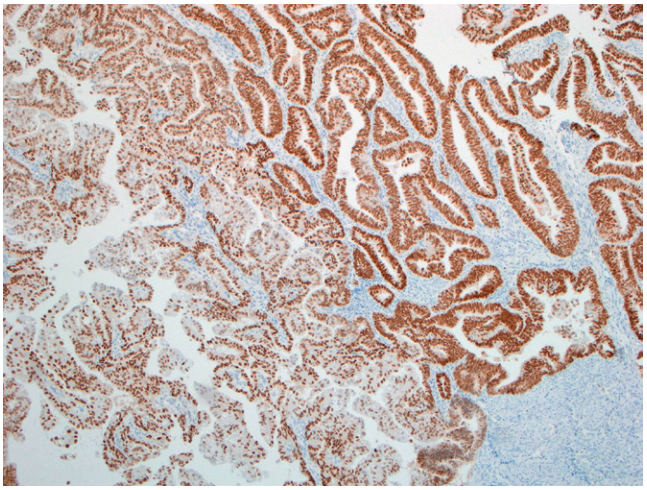


FIGURE 6

Endometrioid carcinoma with secretory clear-cell features. An HINF1 stain is positive but strongest in the endometrioid areas *(right),* diminishing somewhat in the secretory clear-cell region *(center).*

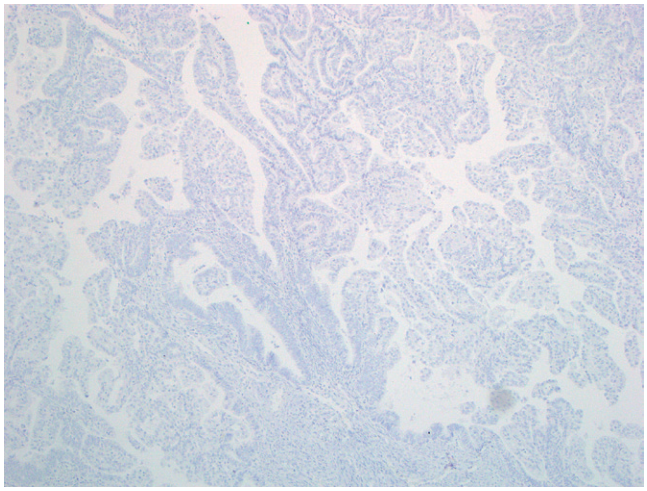


FIGURE 7

Napsin-A, a sensitive marker for clear-cell carcinoma, is negative.

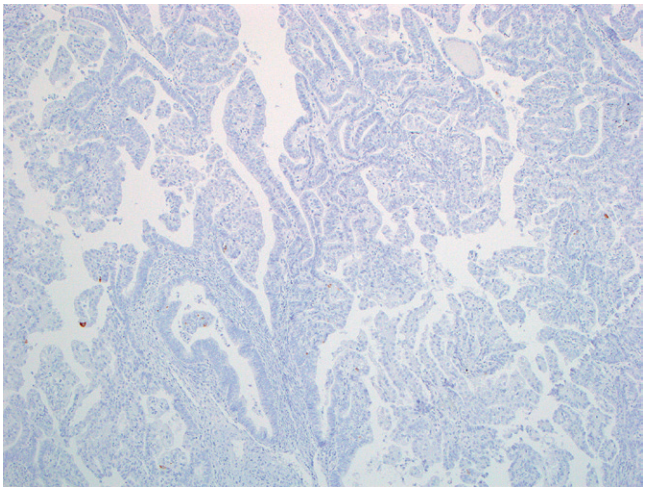


FIGURE 8

AMACR, a specific marker for clear-cell carcinoma, is also negative.

CARCINOSARCOMA

Definition—A highly malignant neoplasm composed of malignant glandular and stromal elements.

Clinical Features

Epidemiology

- Occurs almost exclusively in women over 60 years of age.
- An association with prior radiation has been described.
- Some studies show an increased frequency in African-American women.

Presentation

- Most cases present with postmenopausal bleeding.
- Occasional cases present with the striking finding of a vaginal mass, representing prolapsed uterine tumor.

Prognosis and Treatment

- Carcinosarcoma carries a dismal prognosis with a 5-year survival of around 30% to 40%.
- First-line treatment consists of a total abdominal hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and full surgical staging.
- Most patients will receive adjuvant chemotherapy and radiation therapy.

Pathology

Histology

- Malignant glandular and stromal elements with marked heterogeneity are present.
- The glandular component is often high grade and may display typical serous, endometrioid, or clear-cell patterns of growth. Uncommon patterns, such as neuroendocrine differentiation, primitive-appearing "secretory" changes, and bizarre squamous differentiation, should prompt a closer look for a malignant mesenchymal component.
- Poorly differentiated carcinoma with no discernible pattern of growth may be present.
- A common finding is that of solid carcinomatous growth with marked pleomorphism and necrosis.
- The sarcomatous component has typically been defined as homologous (stromal or smooth muscle) or heterologous (chondrosarcoma, rhabdomyosarcoma, osteosarcoma, or liposarcoma).
- The composition of the epithelial and stromal components is highly variable, and either may represent a focal finding.
- Poorly differentiated carcinomas with spindled areas or extensive desmoplasia may mimic carcinosarcoma, and in these cases the assessment of pattern variability coupled with immunostains for keratin may be helpful.
- Metastasis is typically composed of the malignant glandular component; however, either component of the primary tumor may be present.

Immunopathology (Including Immunohistochemistry)

- Pan-cytokeratin staining may be helpful in identifying the carcinomatous element in a tumor with sarcomatoid differentiation or extensive desmoplasia.
- Smooth muscle markers (SMA, desmin, h-caldesmon) may be helpful in identifying the mesenchymal component of some tumors.

Main Differential Diagnosis

- Sarcomatoid or spindled variants of carcinoma—this usually appears as a spindle cell component in an otherwise well-differentiated endometrioid adenocarcinoma.
- Extensive desmoplasia mimicking sarcoma.

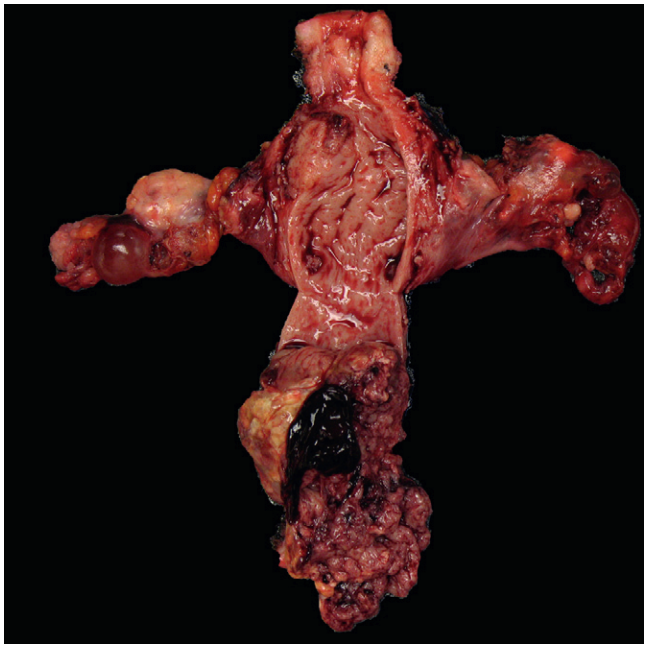


FIGURE 1

Carcinosarcoma. Gross example of carcinosarcoma presenting as a fungating, polypoid mass with associated hemorrhage.

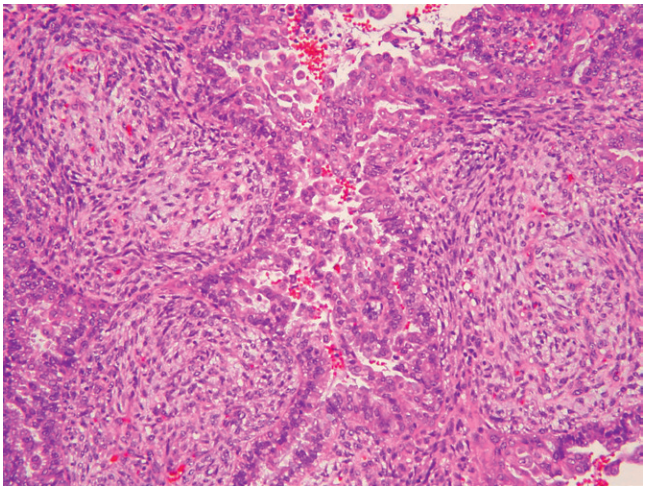


FIGURE 2

Carcinosarcoma. Typical arrangement of malignant glands and stroma. Note the faint basophilic hue to the stromal component.

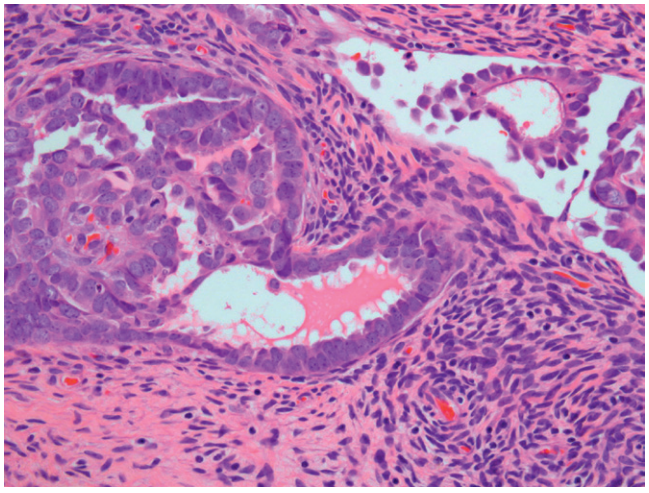


FIGURE 3

Carcinosarcoma. Malignant glandular component composed of serous adenocarcinoma.

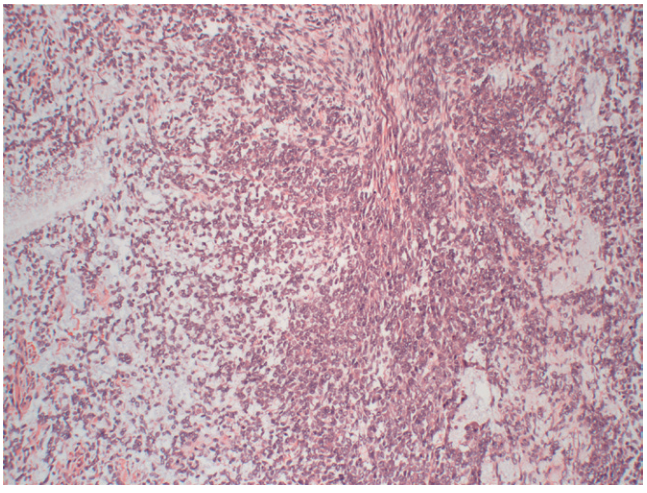


FIGURE 4

Carcinosarcoma. Primitive, high-grade carcinoma.

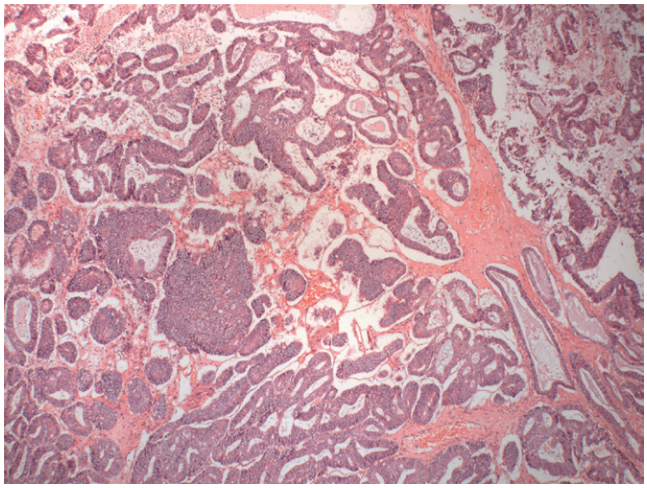


FIGURE 5

Carcinosarcoma. Endometrioid adenocarcinoma with focal solid growth (sarcomatous component is not pictured).

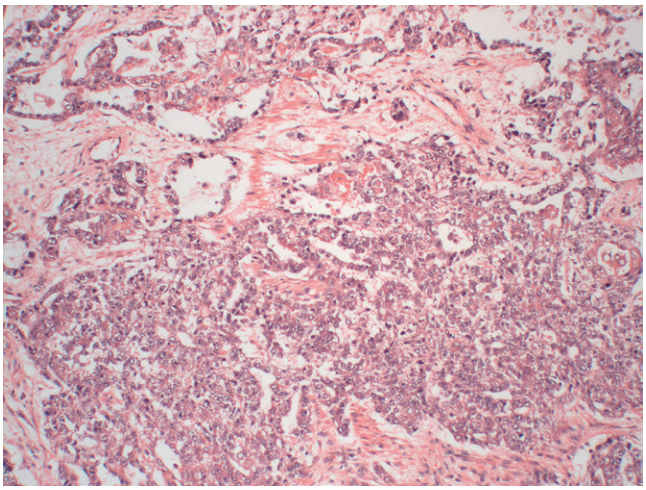


FIGURE 6

Carcinosarcoma. High-grade carcinoma with a primitive, "yolk sac–like" growth pattern.

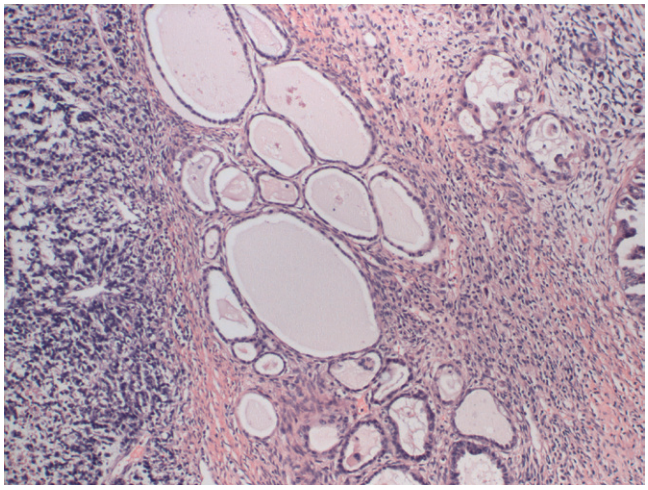


FIGURE 7

Carcinosarcoma. Atypical glands *(right)* with malignant stroma seen surrounding the glands on the right and filling the left side.

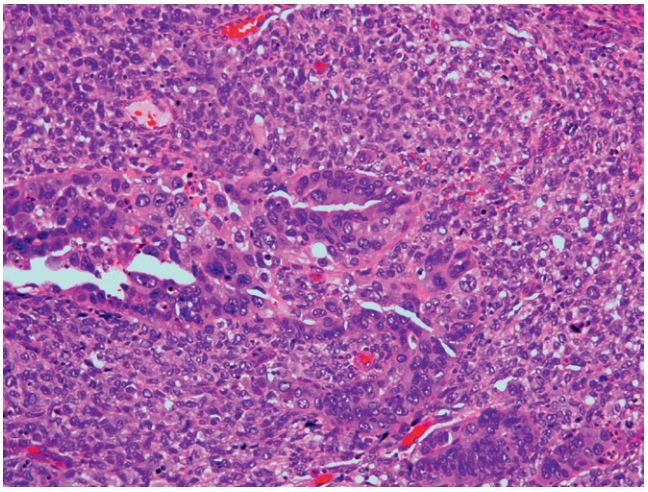


FIGURE 8

Carcinosarcoma. High-grade adenocarcinoma with marked nuclear pleomorphism and surrounding undifferentiated sarcoma.

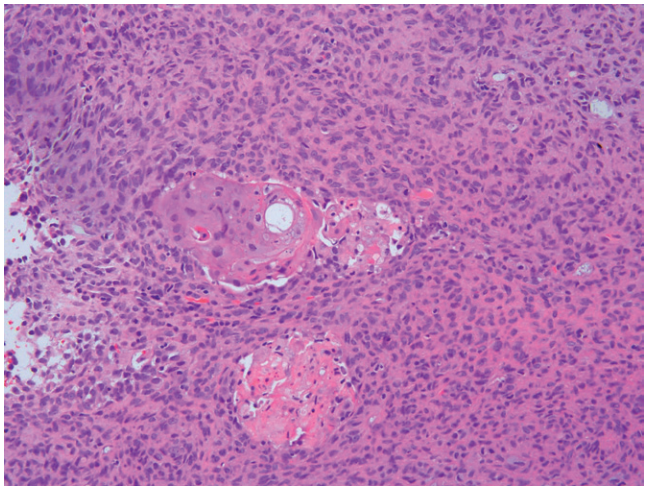


FIGURE 9

Carcinosarcoma. Sarcoma with focal glandular elements with abnormal keratinization.

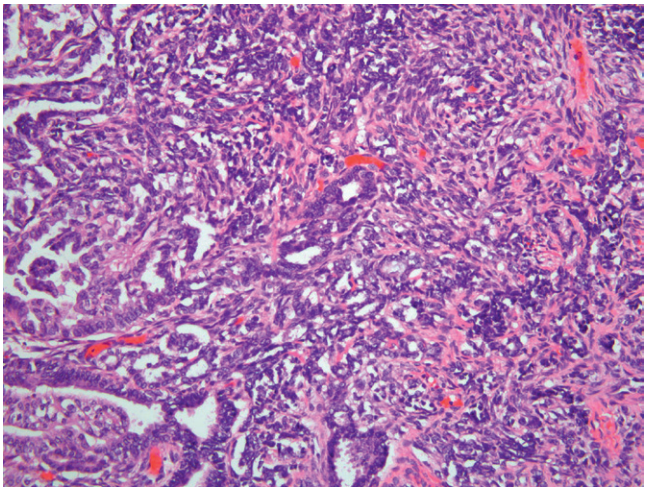


FIGURE 10

Carcinosarcoma. Malignant glands and stroma.

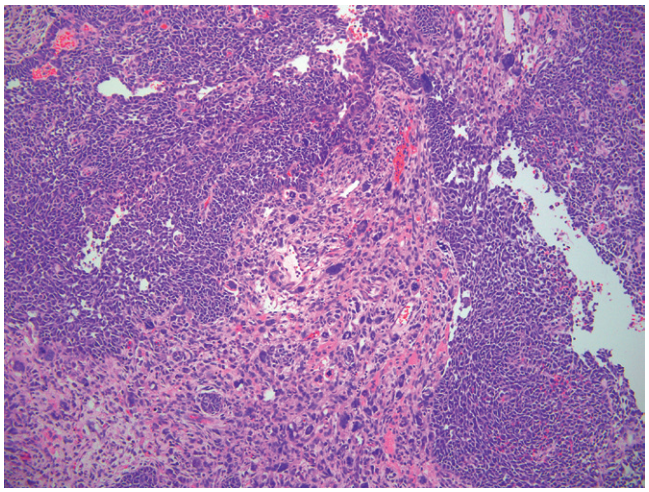


FIGURE 11

Carcinosarcoma. High-grade carcinoma with marked pleomorphism and sarcoma resembling endometrial stromal sarcoma.

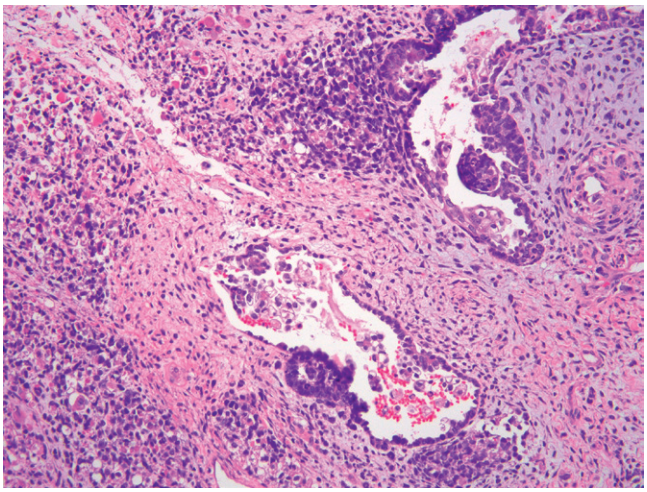


FIGURE 12

Carcinosarcoma. Malignant glands and stroma. A faint basophilic hue can be seen adjacent to one of the malignant glands.

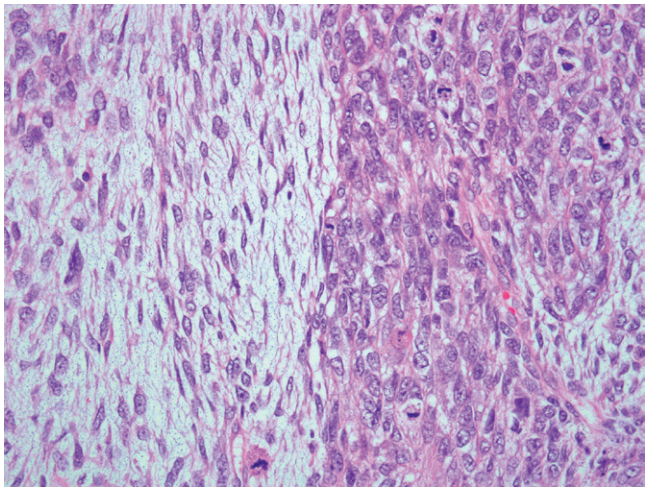


FIGURE 13

Carcinosarcoma. Sarcoma within a carcinosarcoma with a biphasic pattern of growth.

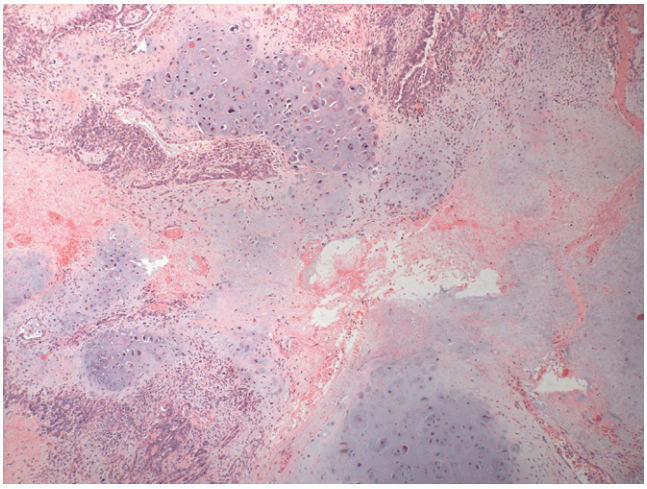


FIGURE 14

Carcinosarcoma. Heterologous cartilaginous differentiation.

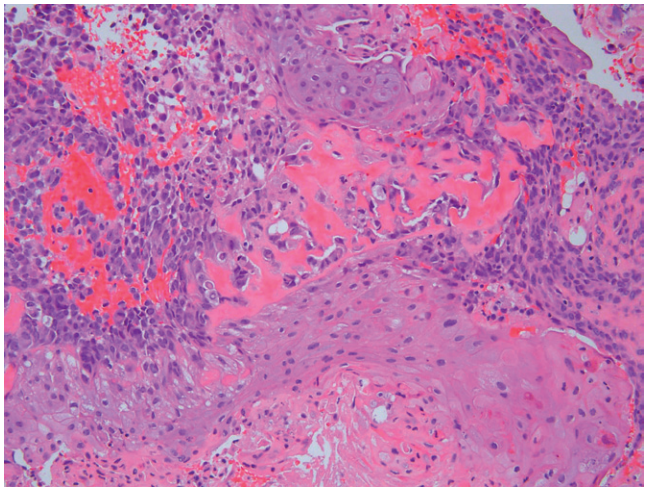


FIGURE 15

Carcinosarcoma. Heterologous osteoid formation *(center)* with adjacent keratinization.

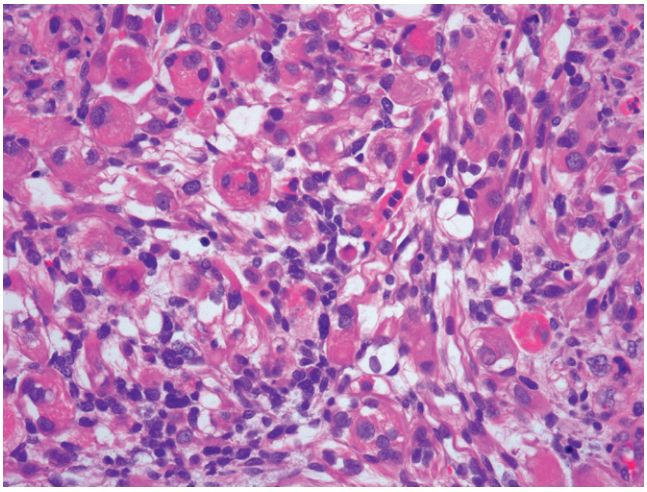


FIGURE 16

Carcinosarcoma. Malignant sarcoma with rhabdoid differentiation and marked pleomorphism.

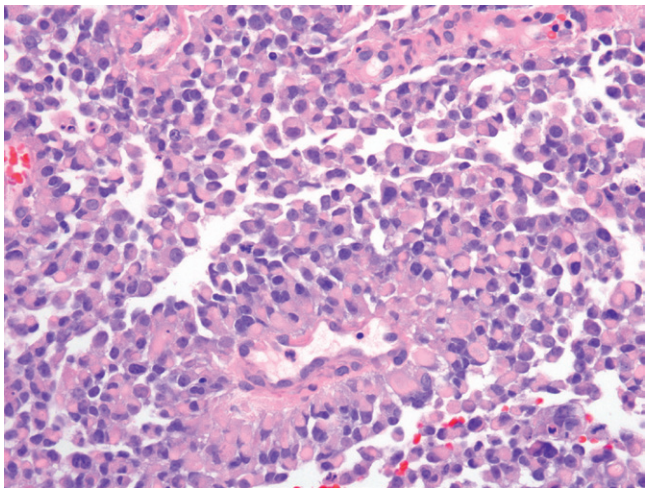


FIGURE 17
Carcinosarcoma. Rhabdoid differentiation.

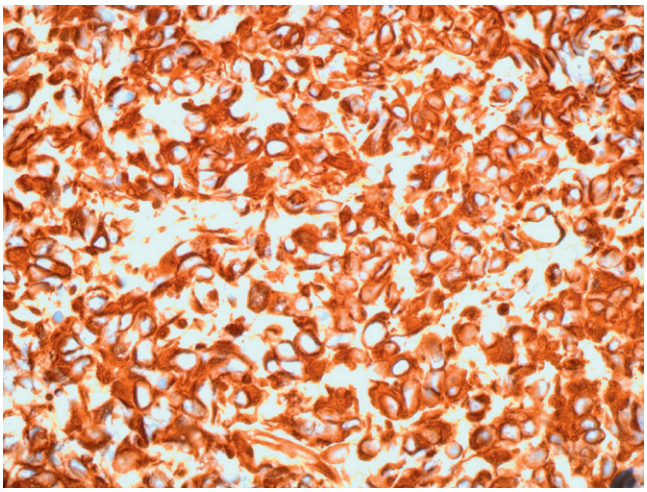


FIGURE 18
Carcinosarcoma. Rhabdoid cells staining positive for smooth muscle actin.

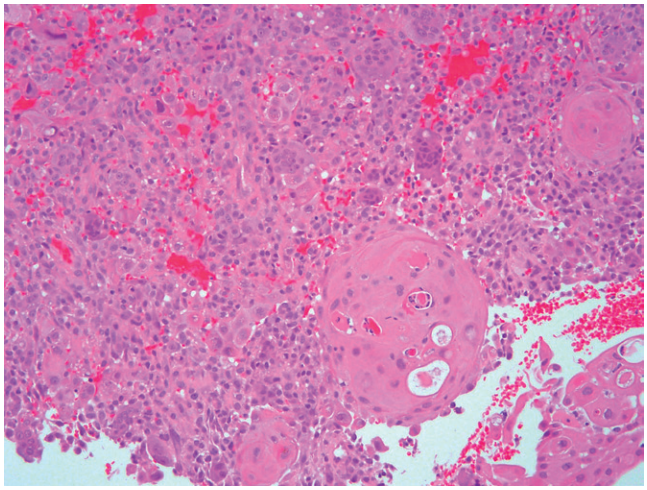


FIGURE 19
Carcinosarcoma. Syncytiotrophoblastic-like giant cells.

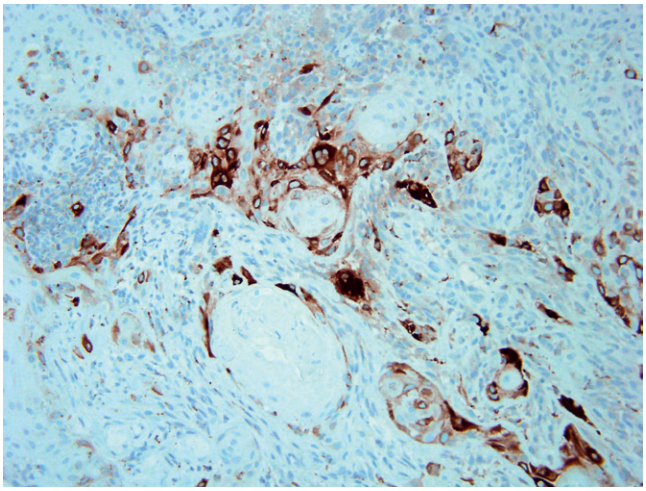


FIGURE 20
Carcinosarcoma. Syncytiotrophoblastic-like giant cells staining positive for human chorionic gonadotropin (HCG).

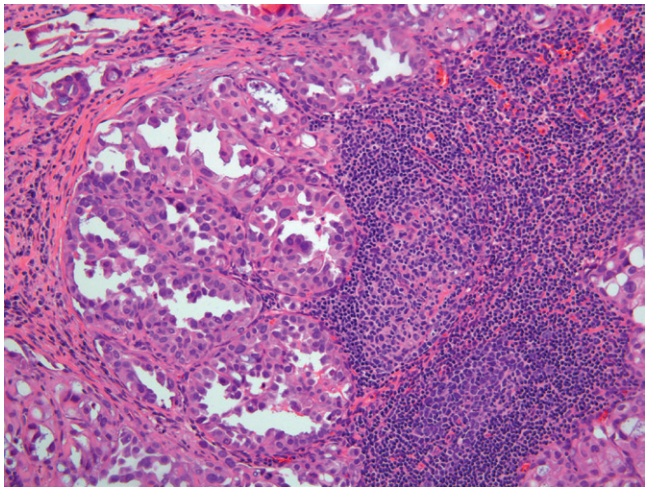


FIGURE 21
Carcinosarcoma. Lymph node metastasis composed of high-grade adenocarcinoma.

ADENOCARCINOMA WITH SPINDLE CELL FEATURES

Definition—A variant of endometrial carcinoma with pseudomesenchymal or spindle cell differentiation.

Clinical Features

Epidemiology

- Similar to that of conventional endometrioid adenocarcinoma.

Presentation

- Detected during histologic examination.

Prognosis and Treatment

- Outcome parallels that of conventional adenocarcinoma and distinct from that for carcinosarcoma.
- Management is based on stage and grade, similar to adenocarcinomas.

Pathology

Histology

- These tumors will typically (but not always) contain a component of well-differentiated adenocarcinoma, as opposed to carcinosarcomas, in which the glandular component is often poorly differentiated or demonstrates unusual patterns.
- Squamous differentiation may be present.
- A separate spindle cell component exhibits features not typical of sarcoma, including bland-appearing nuclei, an eosinophilic matrix, and eosinophilic cytoplasm.
- The spindle cells stream in an orderly fashion, often blending with the glandular or squamous component.
- The spindle cells are keratin positive.

Immunopathology (Including Immunohistochemistry)

- Spindle cells are positive for pan-cytokeratin and negative for desmin and SMA.

Main Differential Diagnosis

- Carcinosarcoma, which has an immunohistochemically defined stromal component.

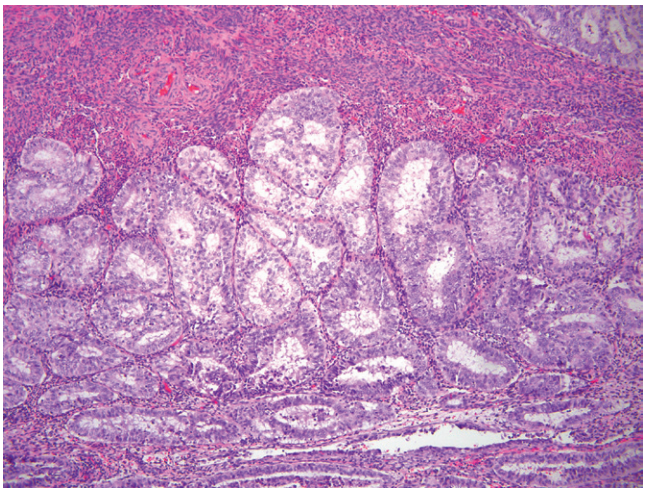


FIGURE 1

Endometrioid adenocarcinoma with spindle cell differentiation. The glandular component is distinctly bland and grade I when present.

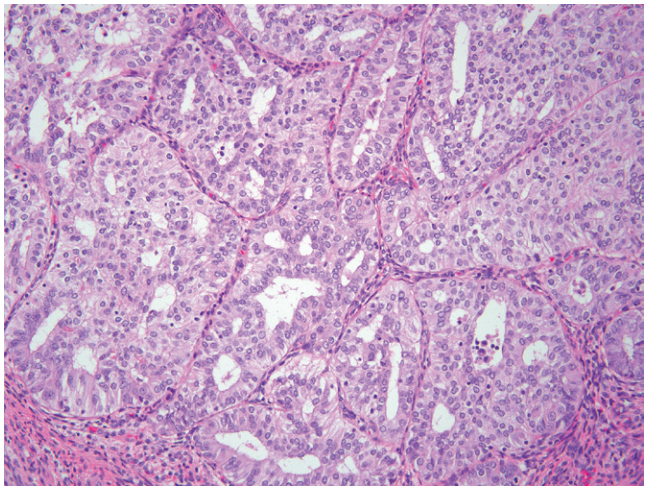


FIGURE 2

Endometrioid adenocarcinoma with spindle cell differentiation. The glandular component is distinctly bland and grade I when present.

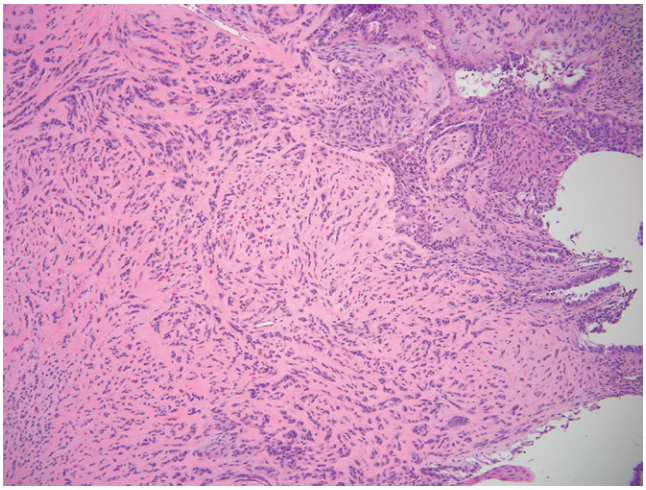


FIGURE 3

Endometrioid adenocarcinoma with spindle cell differentiation carcinosarcoma. At low magnification the spindle cell component demonstrates an orderly growth pattern, streaming into an eosinophilic matrix.

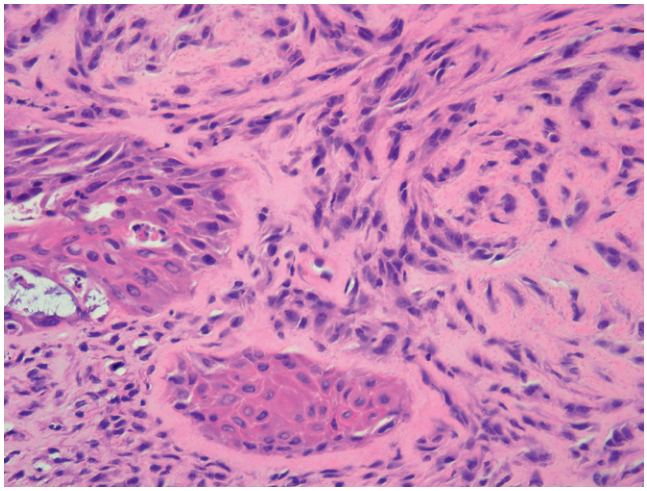


FIGURE 4

Endometrioid adenocarcinoma with spindle cell differentiation. At higher magnification the spindle cells are seen to stream from areas of squamous metaplasia.

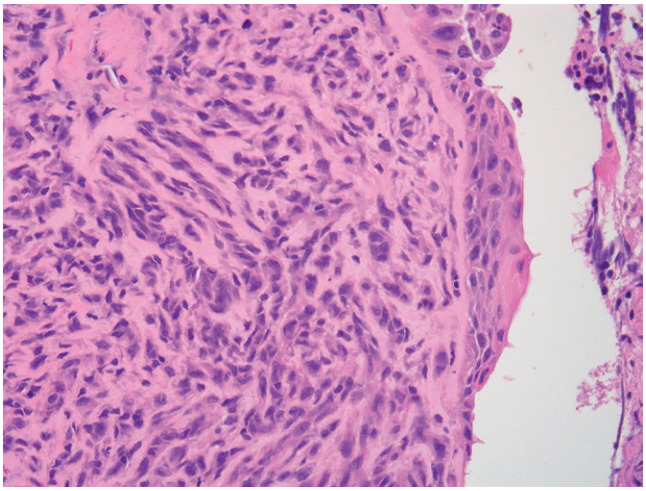


FIGURE 5

Endometrioid adenocarcinoma with spindle cell differentiation. Note the bland nuclei and conspicuous cytoplasm in the spindle cell component.

WILMS' TUMOR OF THE ENDOMETRIUM

Definition—A variant of carcinosarcoma recapitulating Wilms' tumor.

Clinical Features

Epidemiology

- Occurs over a wide age range from childhood to the eighth decade.
- Rare.
- Possibly arises from displaced metanephric rests.

Presentation

- Abnormal bleeding.
- Pelvic mass.
- Cervical polyp.

Prognosis and Treatment

- Numbers are small, but many have shown a favorable outcome and no recurrence.
- Managed by hysterectomy and salpingo-oophorectomy.
- Most patients will receive adjuvant chemotherapy and radiation therapy.

Pathology

Histology

- Classic triphasic pattern with epithelium, blastema, and stromal differentiation.
- Monotonous repetitive pattern is typical and distinguishes this tumor from a carcinosarcoma.
- Glomeruloid bodies.

Immunopathology (Including Immunohistochemistry)

- Neuron-specific enolase, CD99, CD56, WT-1 positive.

Main Differential Diagnosis

- Carcinosarcoma—should be more heterogeneous and lack the glomeruloid bodies. Uniform primitive tubules should be less conspicuous.
- Mesonephric carcinoma—may be a mixture of both spindle and epithelial cells, but the blastema and glomeruloid bodies should not be seen.
- Primitive neuroectodermal tumor—should be negative for WT-1 and lack glomeruloid bodies.

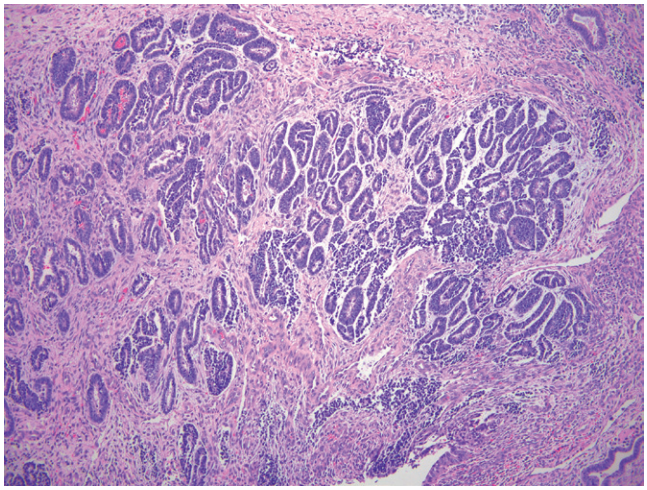


FIGURE 1

Extrarenal Wilms' tumor of the uterus. Note the uniform hyperchromatic glandlike structures.

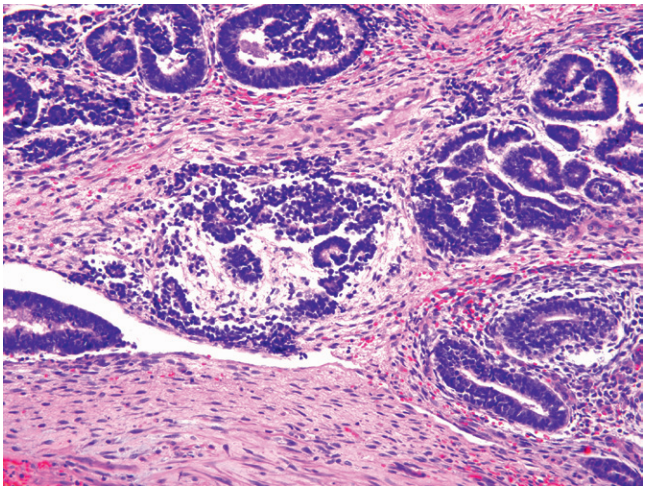


FIGURE 2

Extrarenal Wilms' tumor of the uterus. Glandlike structures are admixed with stroma.

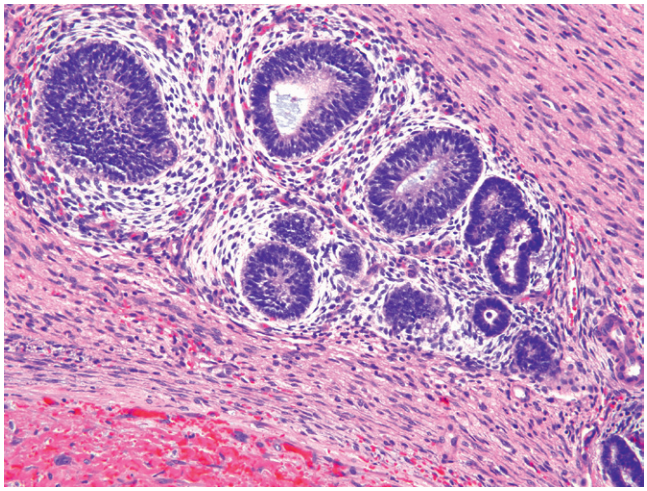


FIGURE 3

Extrarenal Wilms' tumor of the uterus. Spindled stromal envelops glands with focal eosinophilic rhabdoid cells.

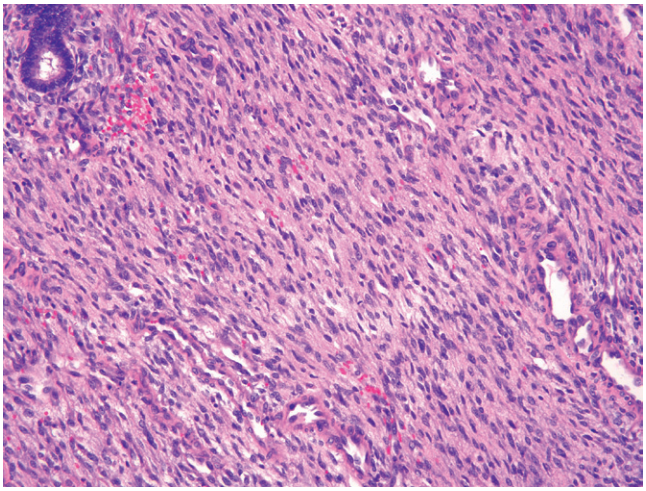


FIGURE 4

Extrarenal Wilms' tumor of the uterus. Another focus with a distinct mesenchymal appearance.

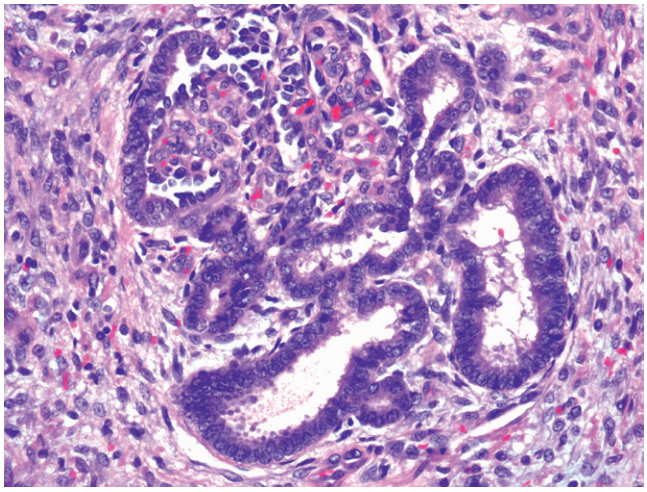


FIGURE 5

Extrarenal Wilms' tumor of the uterus. In this field there is a distinct glomeruloid structure.

ENDOMETRIAL STROMAL NODULE

Definition—A benign neoplasm composed of cells resembling normal endometrial stroma.

Clinical Features

Epidemiology

- Endometrial stromal nodules (ESNs) are uncommon neoplasms that occur at any age.
- Most often identified during the fifth and sixth decades of life.
- JAZF1/JJAZ1 gene fusion.

Presentation

- Patients are usually asymptomatic.
- ESN may be associated with abnormal uterine bleeding or mass effect, similar to the symptoms seen with leiomyomata.

Prognosis and Treatment

- ESN is a benign neoplasm; the prognosis is excellent.
- A stromal neoplasm suspected on biopsy or curettage should be excised to exclude the possibility of a low-grade endometrial stromal sarcoma.
- Conservative excision is curative.

Pathology

Histology

- Grossly ESN may be located intramurally, submucosally, or as an exophytic polypoid mass.
- The gross appearance is similar to that of a leiomyoma; however, ESNs are softer and do not bulge on cut section.
- At low power the hallmark feature of an ESN is the well-circumscribed border with adjacent myometrium.
- Foci of infiltrative fingerlike tumor projections of less than 0.3 cm are allowed in otherwise unremarkable ESN.
- At high power, ESN is composed of small spindled cells with scant cytoplasm that resemble normal proliferative-phase endometrial stroma.
- Small, uniformly sized arterioles are regularly interspersed throughout the tumor.
- Lymphatic or vascular invasion is absent.
- Scattered stromal foam cells may be present in varying amounts.
- Tumor size varies but is usually less than 10 cm (larger ESNs have been reported).

Immunopathology (Including Immunohistochemistry)

- Positive for CD10.
- Negative or weakly positive for SMA, desmin, and h-caldesmon.

Main Differential Diagnosis

- Cellular leiomyoma—larger caliber vessels, positive for SMA, desmin, caldesmon.
- Endometrial stromal sarcoma, low grade—infiltrative borders, vascular invasion.

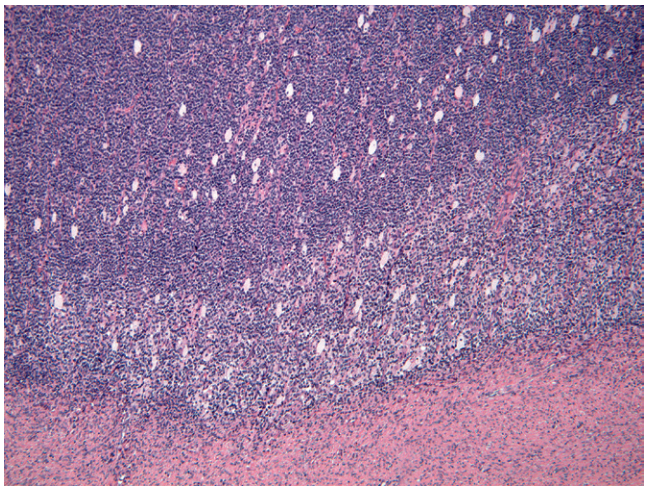


FIGURE 1

ESN. At low power the well-circumscribed border with adjacent myometrium is apparent. Note that slight irregularities are present.

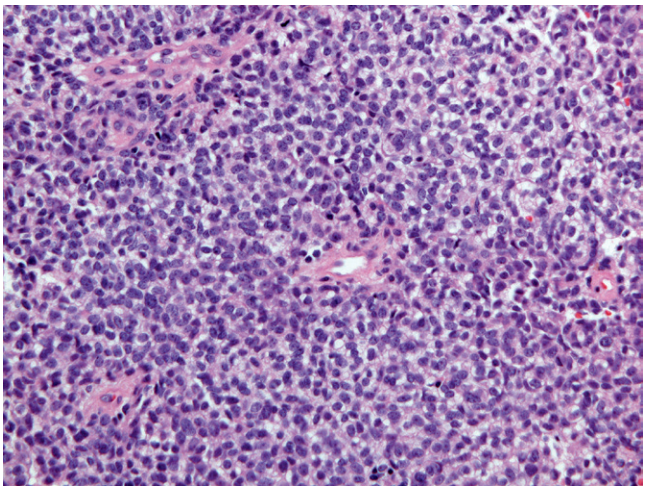


FIGURE 2

ESN. The neoplastic cells are small, with rounded nuclei and scant cytoplasm. Note the regularly spaced arterioles.

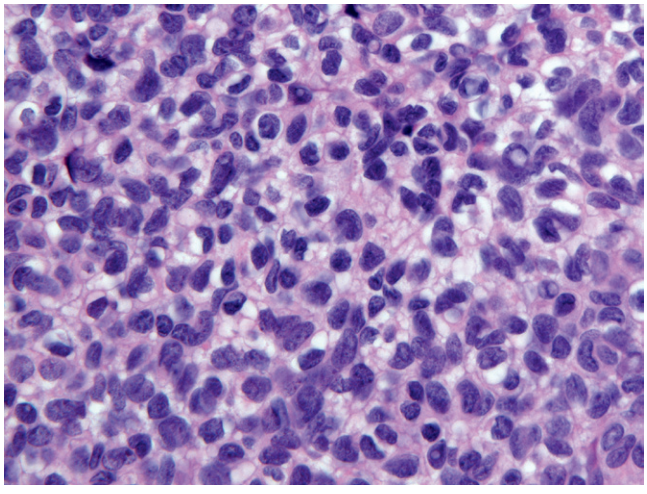


FIGURE 3

ESN. At high power the cells are small and bland.

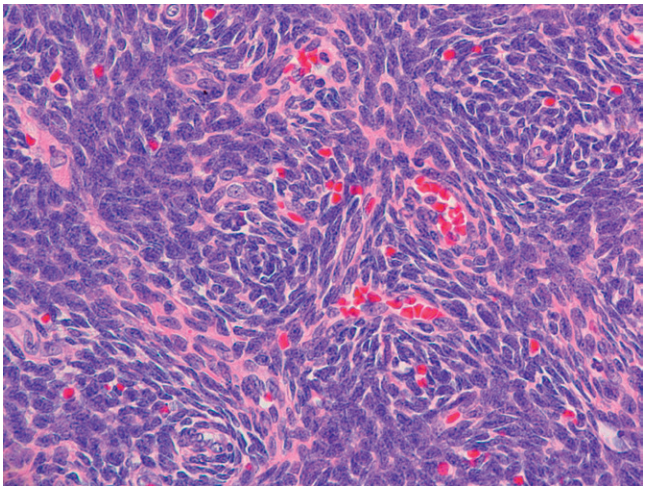


FIGURE 4

ESN. The spindled cells often whorl around the small vascular spaces.

STROMOMYOMA

Definition—A low-grade stromal tumor with smooth muscle differentiation.

Clinical Features

Epidemiology

- Same as endometrial stromal nodules (ESNs); are uncommon neoplasms that occur at any age.
- Most often identified during the fifth and sixth decades of life.

Presentation

- Patients are usually asymptomatic.
- Stromomyoma may be associated with abnormal uterine bleeding or mass effect, similar to the symptoms seen with leiomyomata.

Prognosis and Treatment

- Stromomyoma is a benign neoplasm if configured like a stromal nodule. This may require hysterectomy to confirm and exclude a low-grade stromal sarcoma.
- Conservative excision, if possible, is curative, provided that the uterus is monitored for regrowth.

Pathology

Histology

- Stromomyoma may be intramural, submucosal, or an exophytic polypoid mass.
- The gross appearance will vary from that of a leiomyoma to a softer neoplasm if predominantly stromal.
- At low magnification a stromomyoma will have a well-circumscribed border with adjacent myometrium if a nodule; careful scrutiny of borders will be important in assigning risk.
- Key features at low power include less nuclear dense areas with smooth muscle differentiation and fascicle formation intertwined with the stromal component.
- At high power, stromomyoma will display both stromal and smooth muscle differentiation.
- Lymphatic or vascular invasion is absent in nodules.
- Tumor size varies but is usually less than 10 cm (larger ESNs have been reported).

Immunopathology (Including Immunohistochemistry)

- Positive for CD10 in stromal areas and SMA, desmin, h-caldesmon in the smooth muscle foci.

Main Differential Diagnosis

- Cellular leiomyoma—will not display a stromal phenotype, but this may require immunostains to confirm.
- Endometrial stromal sarcoma, low grade with smooth muscle differentiation—this may require excision to exclude infiltrative borders or vascular space invasion.

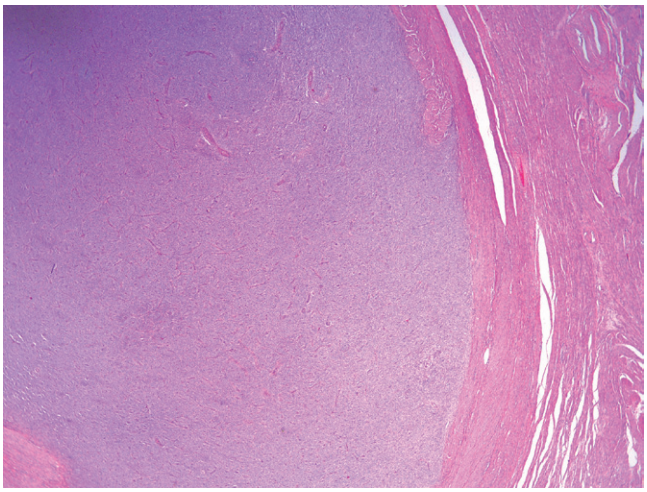


FIGURE 1

Stromomyoma. At low power there is a well-circumscribed border with adjacent myometrium.

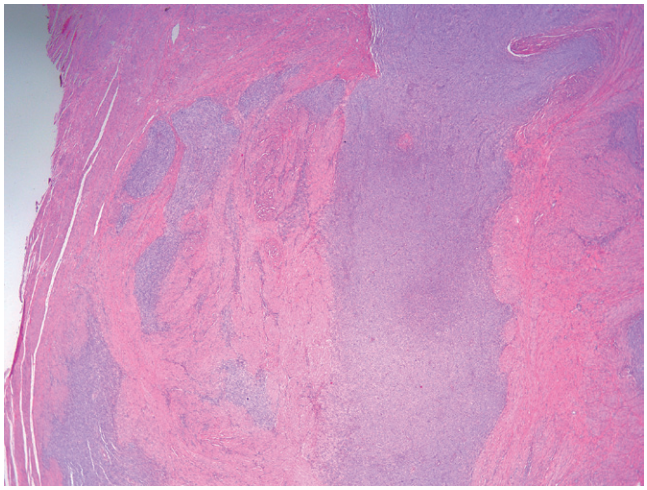


FIGURE 2

Stromomyoma. Note the admixed stromal and smooth muscle components in the center of the tumor. The periphery *(left)* is still circumscribed.

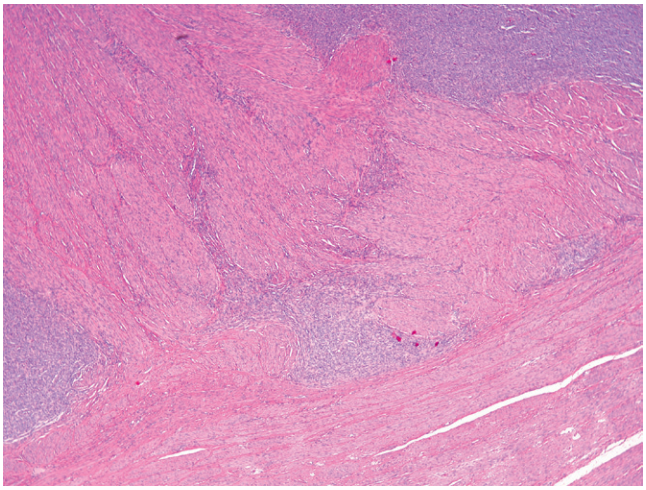


FIGURE 3

Stromomyoma. At higher power the juxtaposed stromal and smooth muscle elements can be appreciated. Again note the sharply demarcated border at the lower right, characteristic of a nodule.

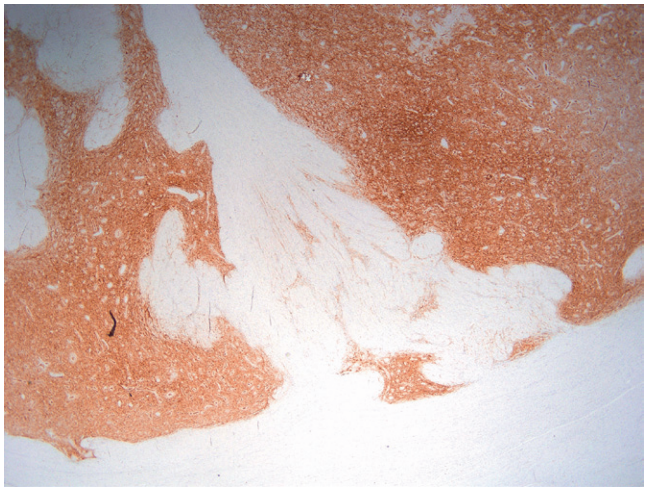


FIGURE 4

Stromomyoma. CD10 staining is strong in the stromal component.

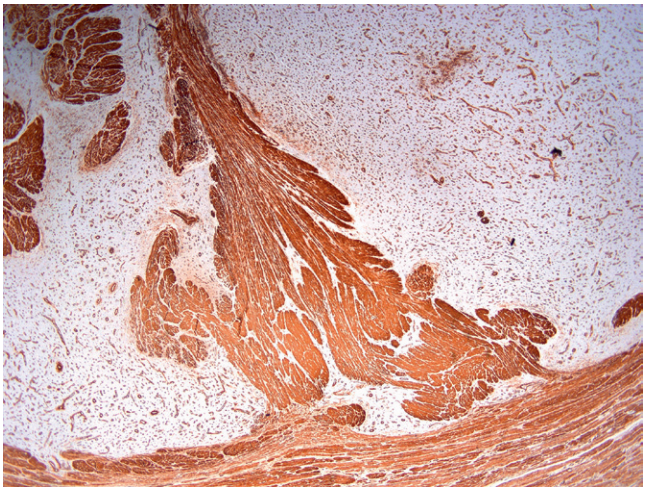


FIGURE 5

Stromomyoma. Desmin is strong in the areas of smooth muscle differentiation.

ENDOMETRIAL STROMATOSIS

Definition—An endometrial polyp, composed of benign smooth muscle and glands.

Clinical Features

Epidemiology

- Same as for adenomyosis, predominating in the fourth and fifth decades. However, the absence of glands is more likely to be seen postmenopause after glandular atrophy has taken place.

Presentation

- In premenopausal women, dysmenorrhea, pelvic discomfort, and abnormal bleeding.
- Postmenopause may be an incidental finding.

Prognosis and Treatment

- None required.

Pathology

Histology

- Stromal condensations in the endometrium.
- Stellate configuration is common.
- Somewhat vague interface between stroma and myometrium.
- Glands rare or nonexistent.

Immunopathology (Including Immunohistochemistry)

- CD10 positive but this entity is usually easily recognized on hematoxylin and eosin (H&E) stains.

Main Differential Diagnosis

- Low-grade endometrial stromal sarcoma (ESS)—this entity will typically display a more rounded, sharply demarcated border.

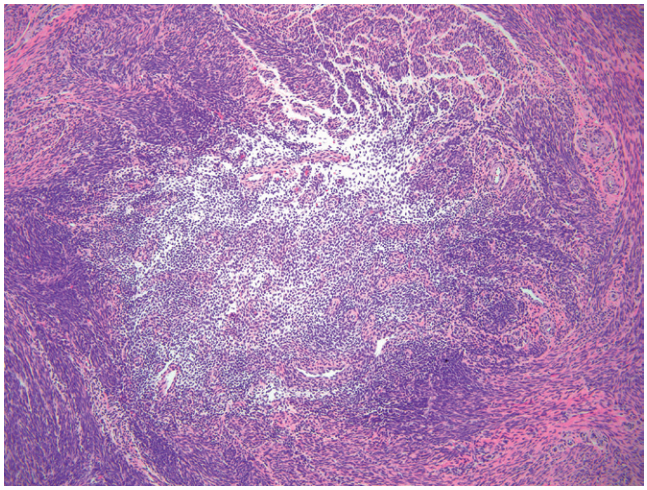


FIGURE 1

Endometrial stromatosis. Note the slightly stellate appearance relative to the surrounding myometrium and the vague stromal-myometrial interface.

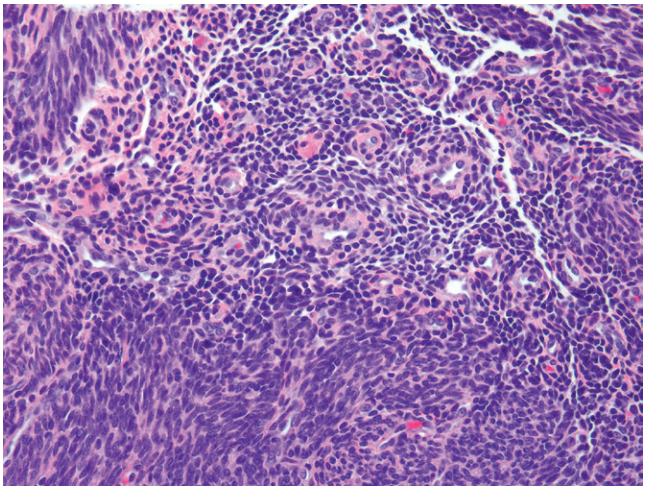


FIGURE 2

Endometrial stromatosis. At higher magnification the constituent cells are typical of benign endometrial stroma.

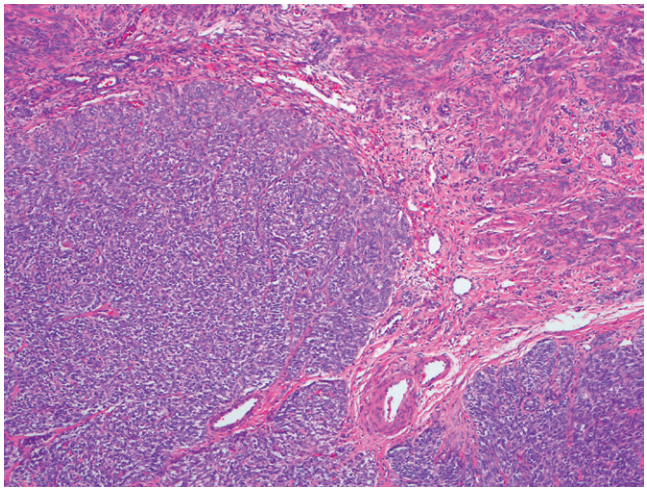


FIGURE 3

ESS. In contrast to stromatosis the neoplastic cells form a sharp interface with the surrounding myometrium.

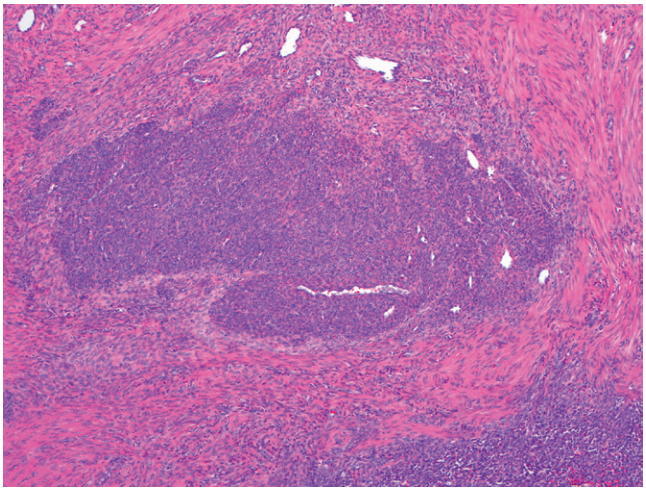


FIGURE 4

ESS. Note the rather sharp interface between tumor cells and myometrium; contrast to Figure 1.

LOW-GRADE ENDOMETRIAL STROMAL SARCOMA

Definition—A malignancy composed of cells resembling proliferative-phase endometrial stroma.

Clinical Features

Epidemiology

- Endometrial stromal sarcoma (ESS) is rare; it accounts for less than 0.5% of all uterine malignancies and only 10% to 15% of mesenchymal uterine malignancies.
- ESS tends to occur in younger women more than other mesenchymal uterine tumors and is typically seen in women in their 40s and 50s.
- The so-called low-grade endometrial stromal sarcomas (LGESSs) account for the majority of these tumors; high-grade and undifferentiated types are rare and are discussed separately.

Presentation

- Abnormal uterine bleeding is the most common presenting symptom.
- Patients may complain of pelvic pain or pressure.
- Up to one quarter of patients are asymptomatic.
- Endometrial sampling does not usually reveal the diagnosis.

Prognosis and Treatment

- If confined to the uterus, LGESS has an excellent prognosis (~90% 5-year survival).
- Up to one third of patients have extrauterine spread at the time of presentation.
- Standard treatment for LGESS is hysterectomy and bilateral salpingo-oophorectomy (with or without pelvic lymphadenectomy).
- Recurrence is common and seen in up to 25% of patients with stage I disease at the time of hysterectomy.
- Distant metastases usually occur late and most commonly involve the lungs.
- Treatment for advanced or metastatic disease often includes hormonal therapy as most LGESSs are strongly progestin receptor positive.
- Undifferentiated ESSs have a poor prognosis.

Pathology

Histology

- LGESS is characterized by a proliferation of cells that resemble nonneoplastic proliferative endometrial stroma.
- The tumor cells are spindled, with elongated round to oval nuclei and scant amounts of eosinophilic or amphophilic cytoplasm.
- At low power, LGESS is notable for its distinctive pattern of myometrial invasion, which is recognized by the characteristic "tongues" or "fingers" of tumor that dissect between the background smooth muscle bundles.
- Prominent (plugging) lymphovascular invasion is commonly noted.
- These growth and lymphovascular invasion patterns can impart a "wormlike" appearance grossly.
- At higher power, small round arterioles (analogous to the spiral arterioles) are interspersed within the tumor.
- Stromal hyalinization may occur and can be prominent.
- Divergent differentiation has been described and may consist of the following:
  1. Smooth muscle differentiation: Greater than 30% of the tumor should be composed of smooth muscle to qualify. The smooth muscle component may merge imperceptibly with the traditional ESS component, may have prominent central hyalinization in a so-called "starburst pattern," or may be present as irregular islands of differing morphology. Molecularly, these tumors are part of the ESS family of tumors and should be evaluated as such.
  2. Sex cord–like areas: Cords, tubules, and/or anastomosing trabeculae of cells resembling patterns seen in sex cord stromal tumors are present. These areas may be positive for inhibin. The presence of sex cord–like areas has no adverse prognostic implication.
  3. Endometrioid glands: Scattered endometrioid glands can be seen. Occasionally it may be difficult to

determine whether the glands are entrapped (as in adenomyosis) or truly part of the neoplastic process. The glands are most often well-formed endometrioid glands.

4. Fibrous or myxoid variants: Extensive hyalinization or myxoid change may be present, making the diagnosis of ESS challenging.

- Conventional LGESS (and variants) commonly exhibit a t(7;17) translocation involving the JAZF1 gene.

Immunopathology (Including Immunohistochemistry)

- Traditional LGESS is usually positive for CD10 and negative for SMA and desmin.
- Occasionally LGESS will show a mixture of CD10 and smooth muscle marker (SMA, desmin) positivity reflecting combined stromal and smooth muscle differentiation.
- h-Caldesmon is more specific for true smooth muscle and may be helpful when there is increased SMA or desmin; it should be negative in ESS.
- Leiomyosarcoma may display areas of CD10 positivity.

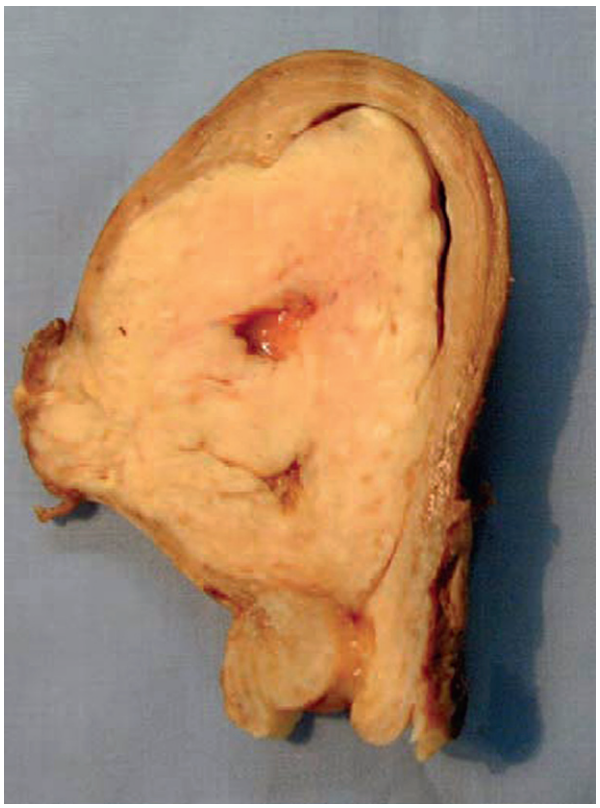


FIGURE 1

ESS. On sectioning, a somewhat irregular yellowish tumor mass distends the endometrial cavity. Note the solid appearance and the absence of any macroscopic features such as fascicle formation to suggest a smooth muscle tumor.

Main Differential Diagnosis

- Endometrial stromal nodule—this distinction may not be possible on curettage specimens if sufficient fragments of myometrium are not available to assess the border of the tumor and whether myometrial invasion is present.
- Leiomyoma—cellular leiomyomas may mimic ESS and can usually be distinguished by the different vascular pattern and special stains, if needed.
- Leiomyosarcoma—typically are not confused with ESS but may mimic higher-grade stromal sarcomas. The fascicular arrangement of mesenchymal cells is helpful as is special stains for desmin, SMA, and h-caldesmon.
- Carcinosarcoma—this entity can be easily confused with ESS in small samples.

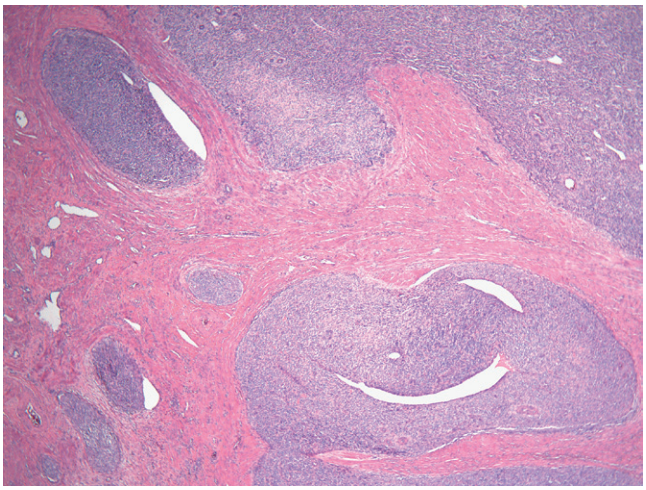


FIGURE 2

ESS. At low power the characteristic invasion pattern consisting of tongues and fingers of tumor pushing between smooth muscle bundles is apparent.

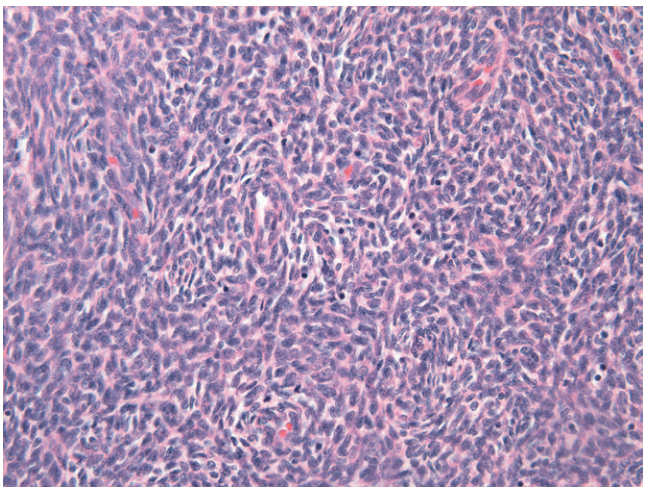


FIGURE 3

ESS. At high power LGESS is composed of small, spindled cells with elongated nuclei and scant cytoplasm. The tumor cells resemble proliferative stroma.

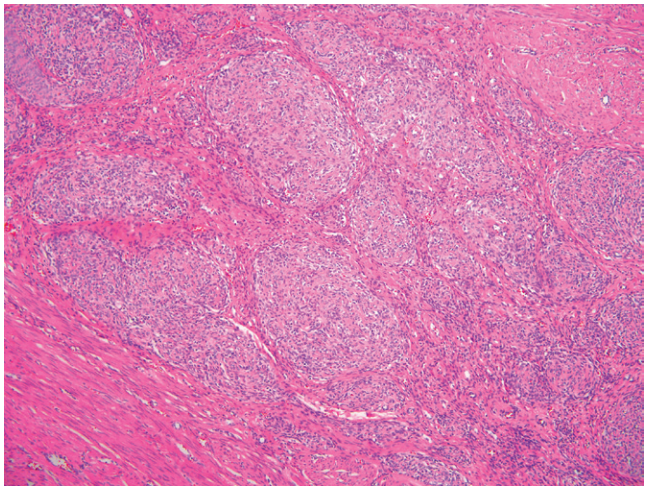


FIGURE 4

ESS. The fibrous variant of LGESS is present as multiple small nodules in this image. Note the resemblance to smooth muscle.

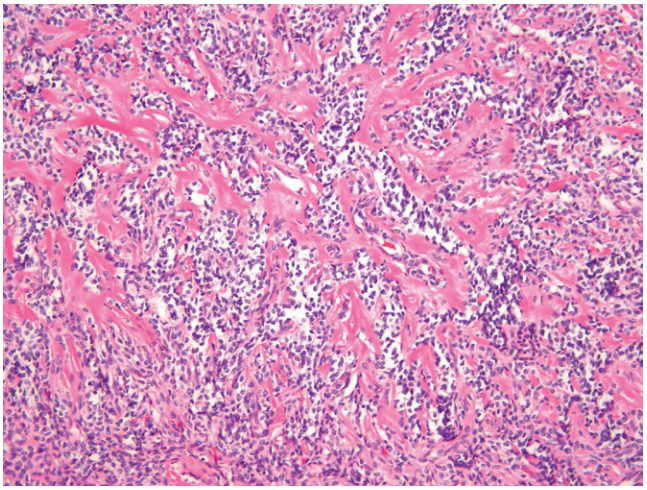


FIGURE 5

ESS. LGESS with extensive stromal hyalinization.

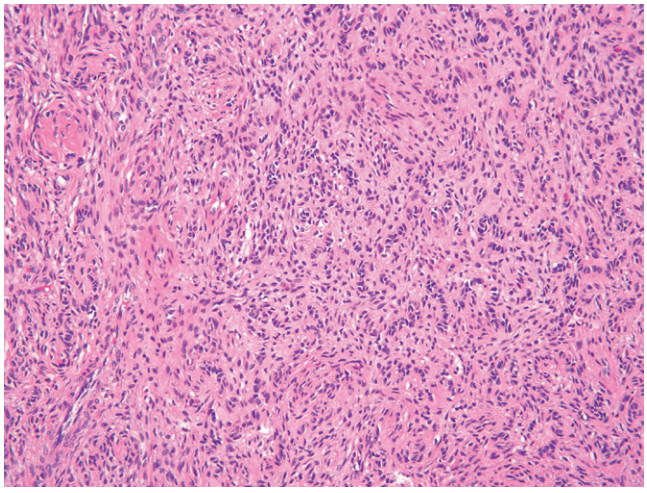


FIGURE 6

ESS. Cords of cells are prominent in this ESS with sex cord–like areas.

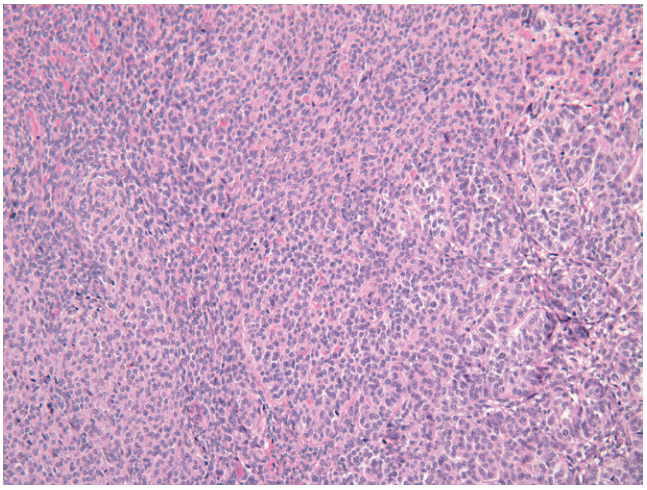


FIGURE 7

ESS. A subtle trabecular pattern *(right side of the image)* of sex cord–like growth is present in this ESS.

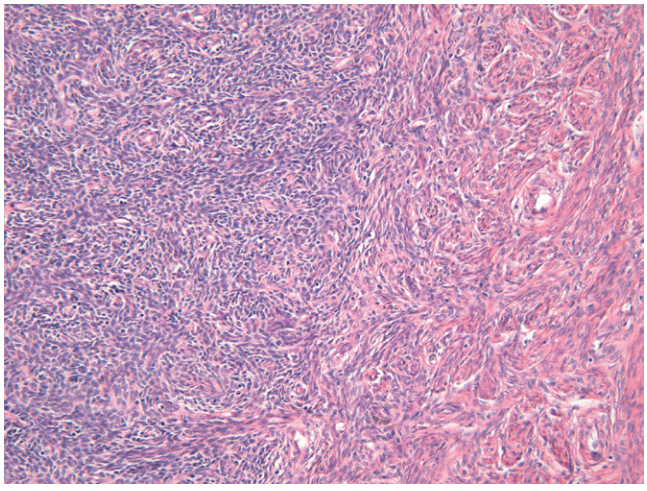


FIGURE 8

ESS. A typical appearance of LGESS *(left)* merges with an area of smooth muscle differentiation *(right)*.

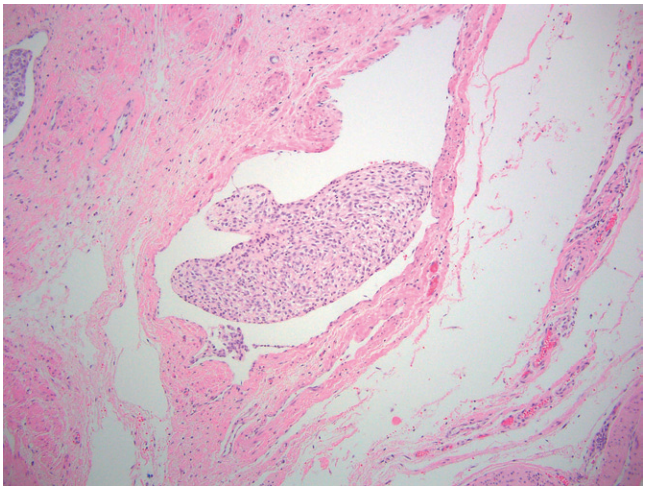


FIGURE 9

ESS. ESS commonly involves large vascular spaces in the myometrium and parametrium, as seen here.

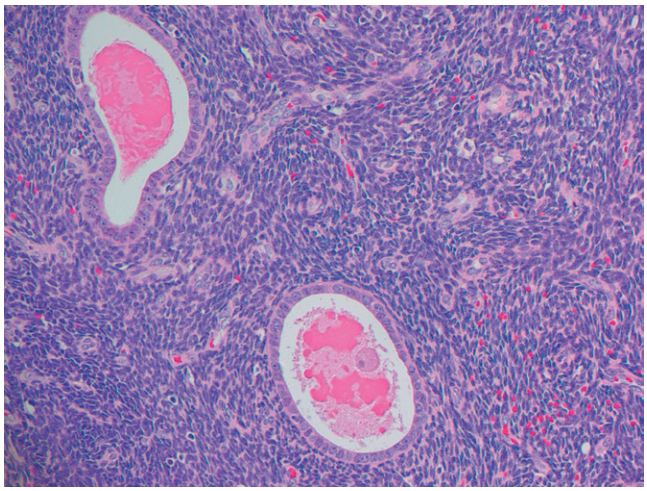


FIGURE 10

ESS. Scattered benign endometrioid glands are present in this metastatic focus.

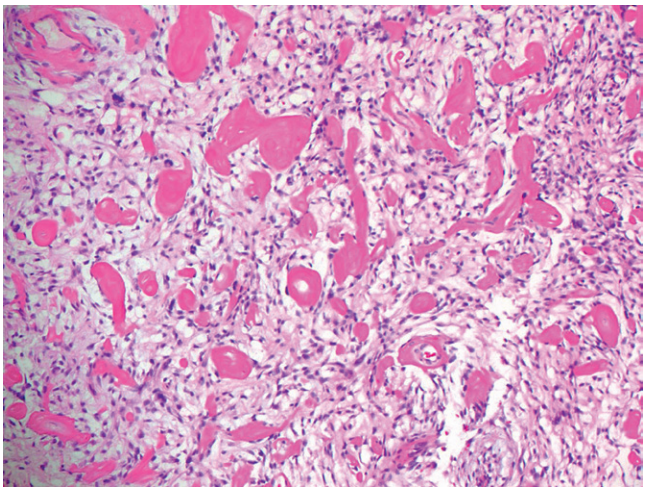


FIGURE 11

ESS. At low power this tumor is characterized by its prominent myxoid stroma rather than the more typical, densely cellular basophilic appearance of ESS. Note the presence of stromal collagen.

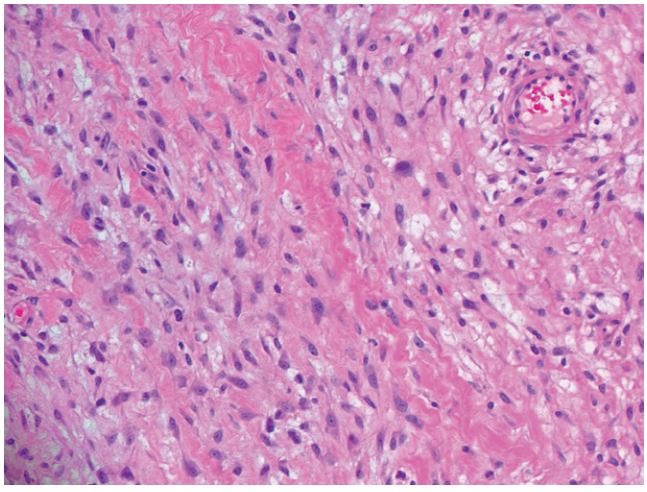


FIGURE 12

ESS. At high power this fibrous/myxoid example of ESS may be difficult to recognize. Note the round arteriole on the right.

UTERINE TUMOR RESEMBLING SEX CORD STROMAL TUMOR

Definition—A benign low-grade mesenchymal tumor of the uterus.

Clinical Features

Epidemiology

- Uterine tumor resembling sex cord tumor (UTRSCT) is rare; it accounts for less than 0.5% of all uterine malignancies and only 10% to 15% of mesenchymal uterine malignancies.
- Tumors are usually diagnosed in women in the fourth to sixth decades.
- These tumors in their pure form are held separate from low-grade endometrial stromal sarcomas (ESS) with sex cord—like areas. The latter have different biologic behavior.

Presentation

- Abnormal uterine bleeding is the most common presenting symptom.
- Patients may complain of pelvic pain or pressure.
- Up to a quarter of patients are asymptomatic.
- Endometrial sampling does not usually reveal the diagnosis.

Prognosis and Treatment

- UTRSCT is typically benign with survival approaching 100% and rare (5%) recurrences, so long as there is no evidence of coexisting stromal sarcoma. In the latter the recurrence risk is high and disease-free survival poor (~25%).
- Treated by excision.

Pathology

Histology

- UTRSCT is characterized by a repetitive pattern of cordlike or tubular growth.
- The tumor cells are bland appearing with noncomplex chromatin and round to oval features.

Immunopathology (Including Immunohistochemistry)

- Positive for inhibin and calretinin.
- Negative for CD10.

Main Differential Diagnosis

- ESS—may have sex cord–like areas, but such lesions are heterogeneous. UTRSCT will be uniformly sex cord like throughout. The presence of CD10 would support ESS.
- Mesonephric carcinoma—these tumors are usually seen in the cervix but can present with ill-defined tubules or other sex cord–like features, as well as spindled areas.

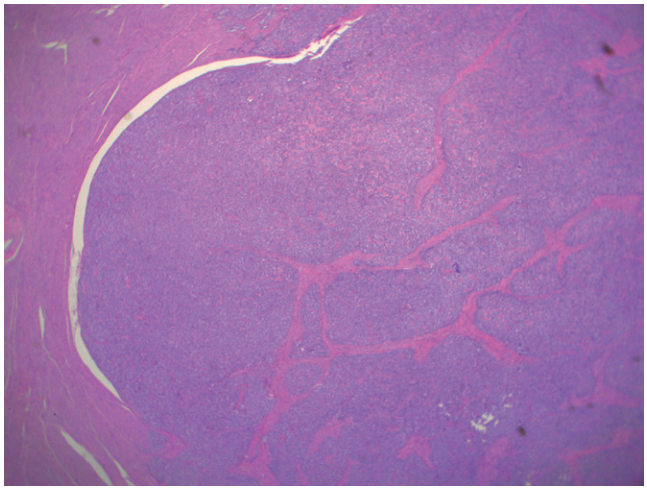


FIGURE 1

UTRSCT. The tumor is circumscribed at low magnification and resembles a stromal or smooth muscle neoplasm.

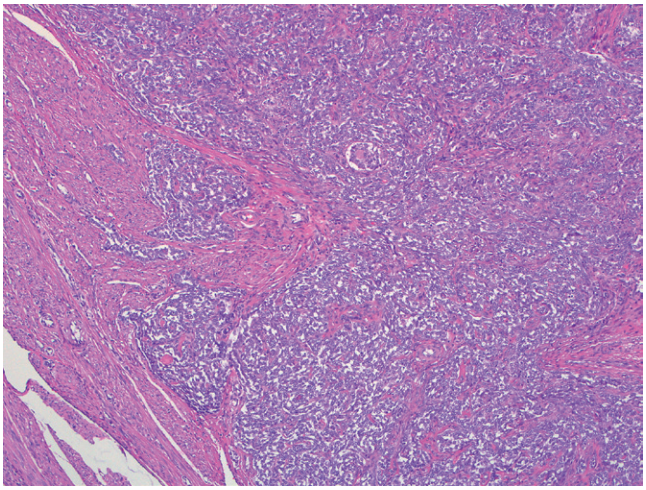


FIGURE 2

UTRSCT. At higher magnification a cordlike or ribbonlike pattern is seen, with vague acinar formation.

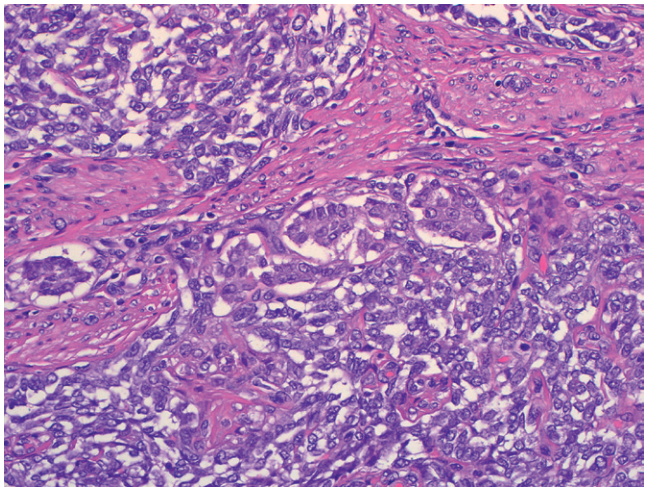


FIGURE 3

UTRSCT. At higher power a combination of some cordlike and acinar growth is seen.

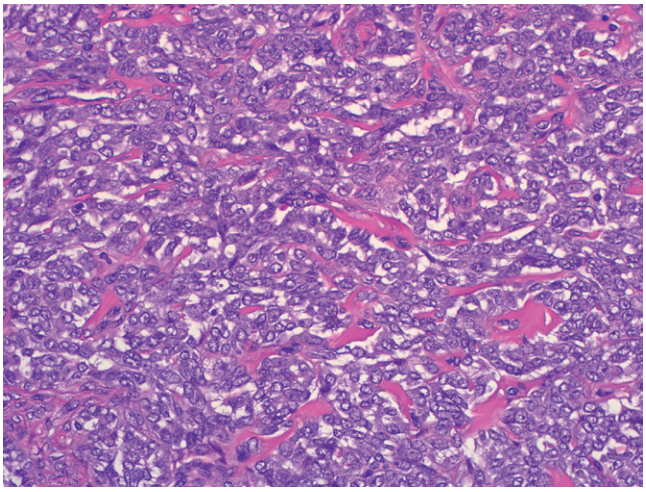


FIGURE 4

UTRSCT. This field appears vaguely ribbon like.

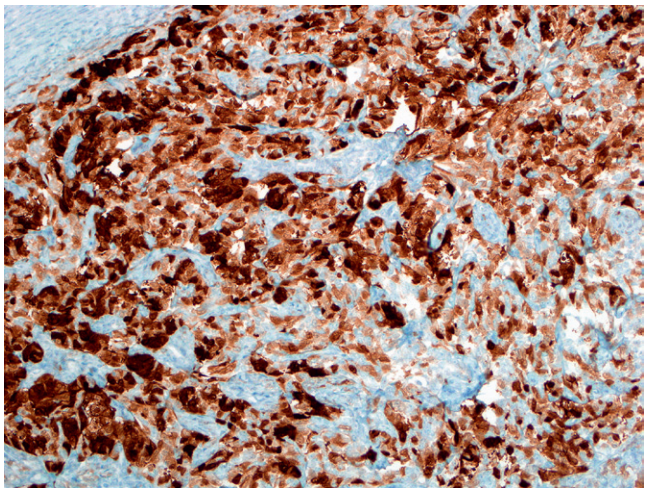


FIGURE 5

Stains for inhibin are strongly positive in UTRSCT.

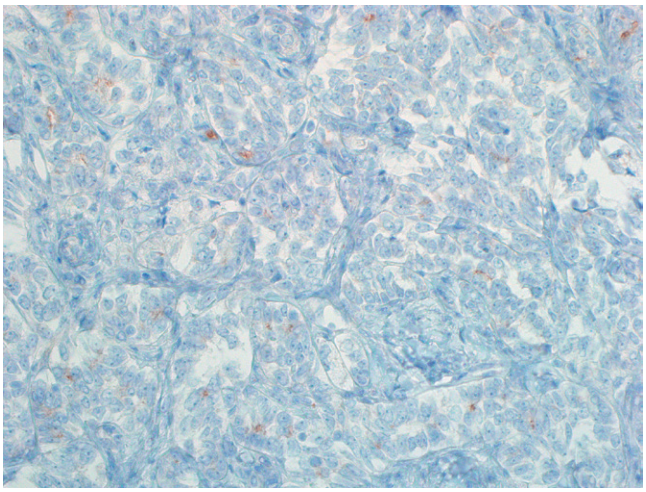


FIGURE 6

Typically UTRSCT is negative for CD10, as in this case.

HIGH-GRADE ENDOMETRIAL STROMAL SARCOMA

Definition—An intermediate to high-grade stromal sarcoma with a distinct molecular genotype.

Clinical Features

Epidemiology

- Overall endometrial stromal sarcoma (ESS) is rare; it accounts for less than 0.5% of all uterine malignancies and only 10% to 15% of mesenchymal uterine malignancies.
- This particular variant has a novel gene fusion between YWHAE and FAM22A/B harboring t(10 : 17)(q22;p13).
- Majority occur in the fifth and sixth decades, but can be seen at any decade in adulthood.

Presentation

- Abnormal uterine bleeding is the most commonly reported presenting symptom.
- Over 80% present as stage II or higher.
- Tumors range in size, with a mean diameter of around 8 cm.

Prognosis and Treatment

- In contrast to low-grade ESS, which commonly presents at stage I with an 80% or higher survival, most with this tumor either die of their disease or are alive with disease in recent studies.
- Standard treatment would be total hysterectomy and bilateral salpingo-oophorectomy with surgical staging. Most patients would also receive adjuvant chemotherapy and/or radiation therapy.
- Abdominal and pulmonary recurrences are common.

Pathology

Histology

- Tumors can be predominantly round or spindled cell or both.
- Extensive permeative growth in the myometrium.
- High mitotic index, exceeding 10/10 high-power fields.
- Invariable lymphovascular space invasion.

Immunopathology (Including Immunohistochemistry)

- CD10 negative except in spindle cell foci, when present.
- Typically strongly positive for cyclin D1 (>75% of cells).

Main Differential Diagnosis

- Low-grade ESS—significantly lower nuclear grade, positive for CD10, and typical stromal cell phenotype.
- Leiomyosarcoma—fascicle formation, desmin and caldesmon positive.
- Undifferentiated carcinoma—uniform population with prominent nucleoli.
- Undifferentiated uterine sarcomas—CD10 negative and cyclin D1 negative (also negative for the gene fusion).

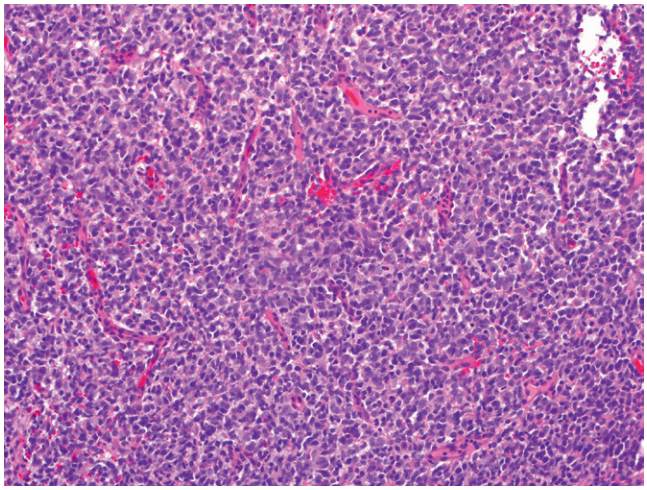


FIGURE 1

High-grade ESS. At low power the characteristic vascular pattern can be seen with a sea of round to slightly epithelioid cells lacking the more orderly elongated nuclei of lower-grade ESS.

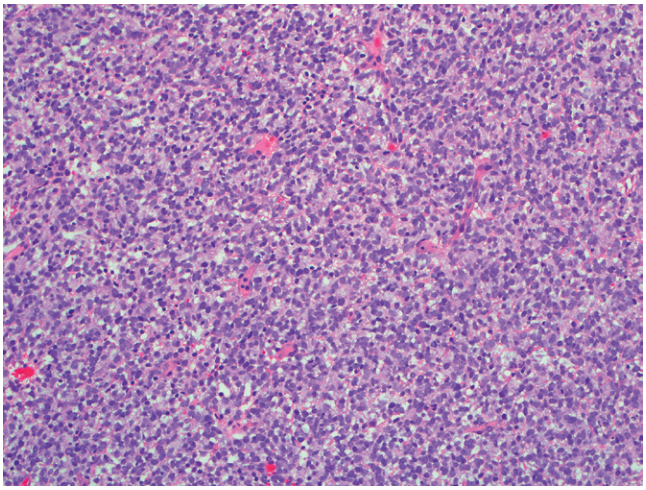


FIGURE 2

High-grade ESS.

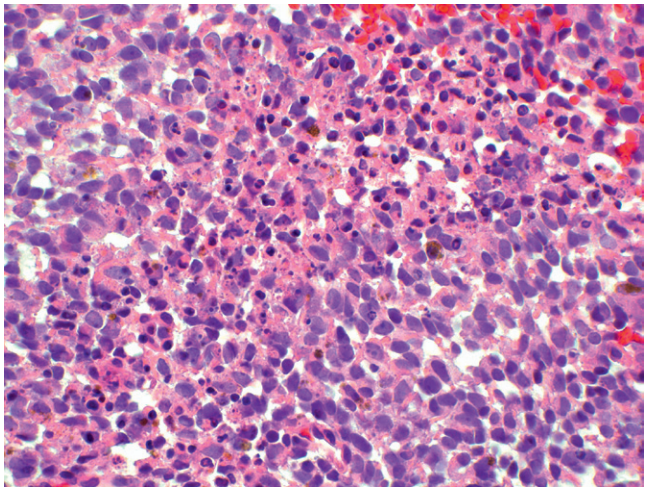


FIGURE 3

High-grade ESS. Image at higher magnification underscores the featureless arrangement of poorly differentiated stromal cells, with conspicuous mitoses, apoptosis, and focal necrosis.

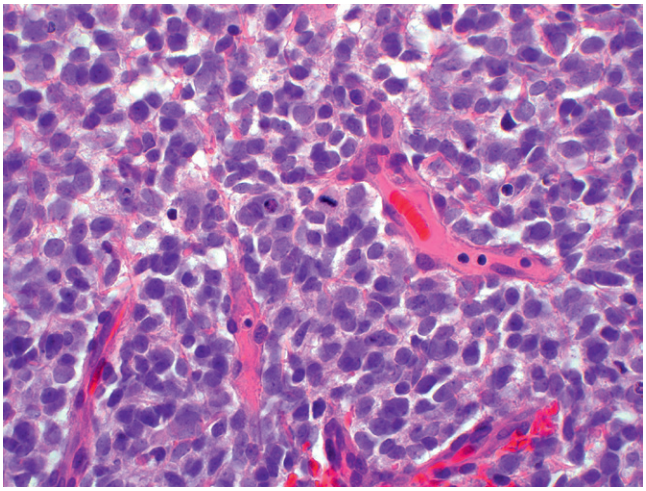


FIGURE 4

High-grade ESS. In this field a confluent array of cells with a high N/C ratio are punctuated by small vessels.

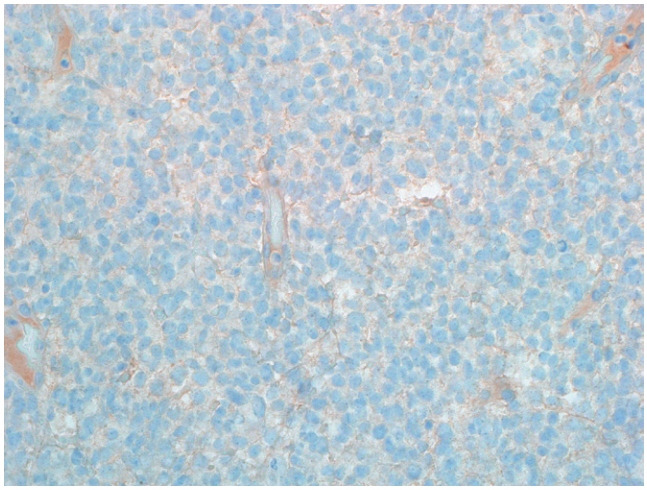


FIGURE 5

High-grade ESS. An area of predominantly round cells is CD10 negative.

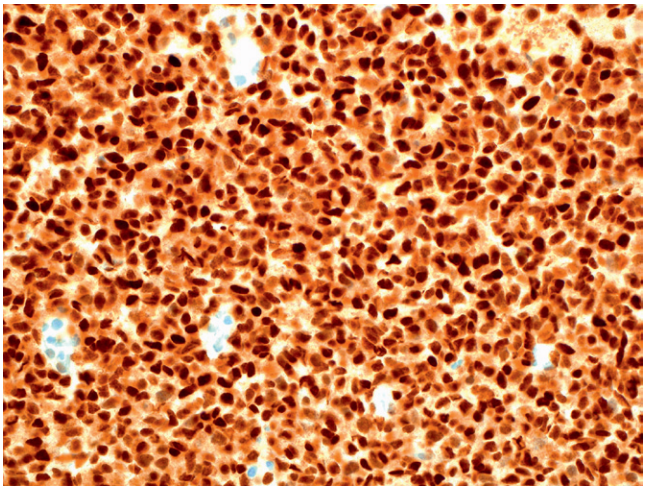


FIGURE 6

High-grade ESS. Strong staining for cyclin D1 is characteristic of these tumors, although confirmatory genetic testing (fluorescence in situ hybridization [FISH]) is needed to confirm.

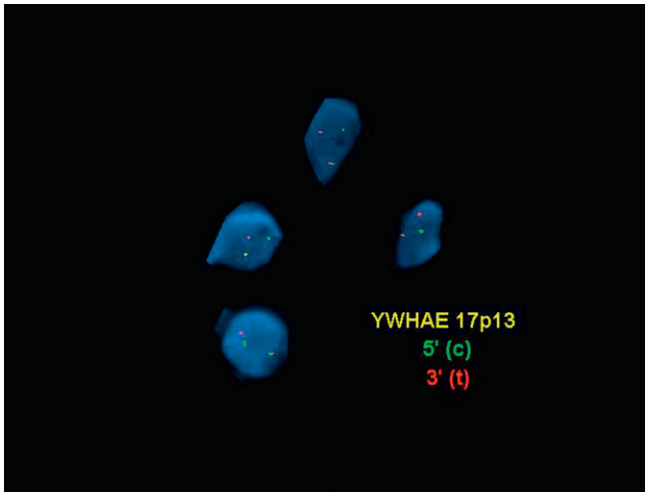


FIGURE 7

YWHAE-FAM22A/B fusion seen on FISH from tumor cells. The fusion is seen as a blend of green and red signals in each nucleus (yellow).

UNDIFFERENTIATED UTERINE SARCOMA

Definition—A mesenchymal tumor of the uterus without smooth muscle or endometrial stromal differentiation.

Clinical Features

Epidemiology

- Undifferentiated uterine sarcomas are rare and account for less than 0.5% of all uterine malignancies and only 10% to 15% of mesenchymal uterine malignancies.
- Mostly occur in the fifth and sixth decades, but can be seen at any decade in adulthood.

Presentation

- Abnormal uterine bleeding is the most commonly reported presenting symptom.
- Over 60% present as stage III or higher.

Prognosis and Treatment

- Survival is poor irrespective of stage in most cases.
- Standard treatment would be total hysterectomy and bilateral salpingo-oophorectomy with surgical staging. Most patients would also receive adjuvant chemotherapy and/or radiation therapy.
- Over 60% will respond to chemotherapy, either gemcitabine/docetaxel or doxorubicin.
- Responses are usually short lived, with mean progression-free and overall survival of less than a year. Survival is improved (1-year survival of 80%) if there is no measurable disease following surgery and prior to chemotherapy.
- Residual disease and vascular invasion worsen the outcome expectations. Low-stage tumors without vascular invasion have up to an 83% 5-year survival in some studies in contrast to 17% when vascular invasion is present.
- A subset of tumors has been described with more uniform nuclear morphology and a somewhat more favorable prognosis. Authors have suggested that these tumors may be more like the traditionally designated high-grade endometrial stromal sarcoma (ESS). In retrospect at least some of these tumors are probably within the currently resurrected and genetically classified high-grade ESS group.

Pathology

Histology

- Tumor cells are typically highly pleomorphic.
- Extensive permeative growth in the myometrium but lacking the more sinuous wormlike invasion seen in recognizable ESSs.
- High mitotic index, often exceeding 50/10 high-power fields.
- Occasionally a lower-grade component will be seen, suggesting that the tumor is a de-differentiated ESS.

Immunopathology (Including Immunohistochemistry)

- CD10 variable and not helpful in separation from other tumors.
- Cyclin D1 should be weak or negative to exclude high-grade ESS.
- Smooth muscle markers (desmin and h-caldesmon) will be helpful in ruling out a poorly differentiated leiomyosarcoma, as will the lack of fascicle development.

Main Differential Diagnosis

- Low-grade ESS—significantly lower nuclear grade, positive for CD10, and typical stromal cell phenotype.
- Leiomyosarcoma—fascicle formation, desmin and caldesmon positive.
- Undifferentiated carcinoma—uniform population with prominent nucleoli and the absence of mesenchymal markers.
- High-grade stromal sarcoma—CD10 negative and cyclin D1 positive (also positive for the YWHAE-FAM22A/B gene fusion).

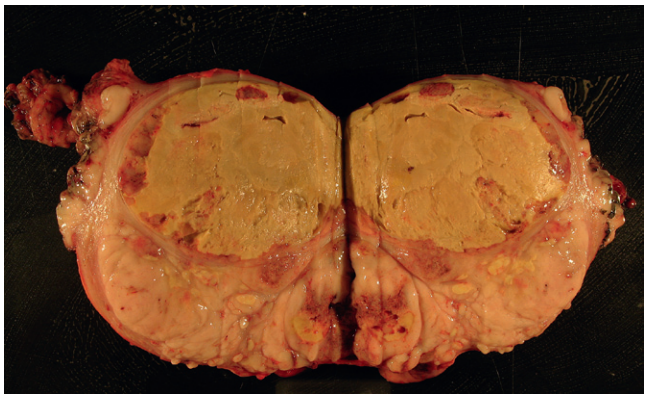


FIGURE 1

Undifferentiated uterine sarcoma. This gross photograph of the uterus shows a myometrium distended by multiple yellow nodules of necrotic tumor.

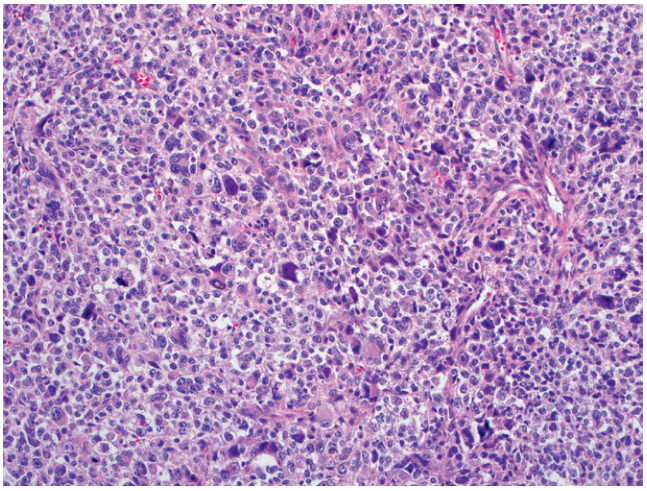


FIGURE 2

Undifferentiated uterine sarcoma. The cells lie in a featureless landscape; too pleomorphic for stromal sarcoma and without the fascicles that typify leiomyosarcoma.

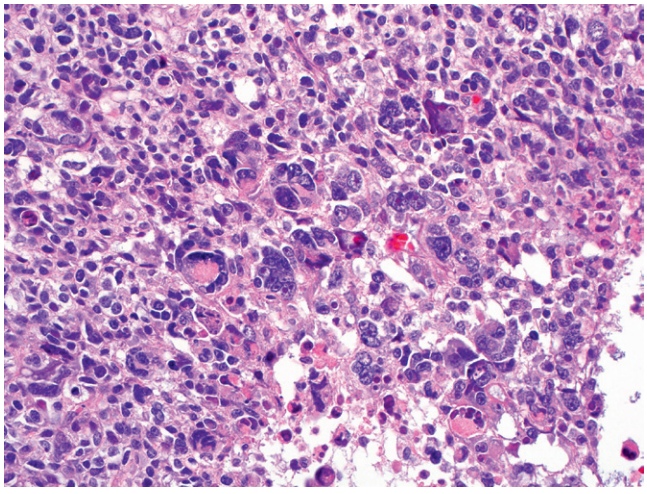


FIGURE 3

Undifferentiated uterine sarcoma. Note the tumor giant cells.

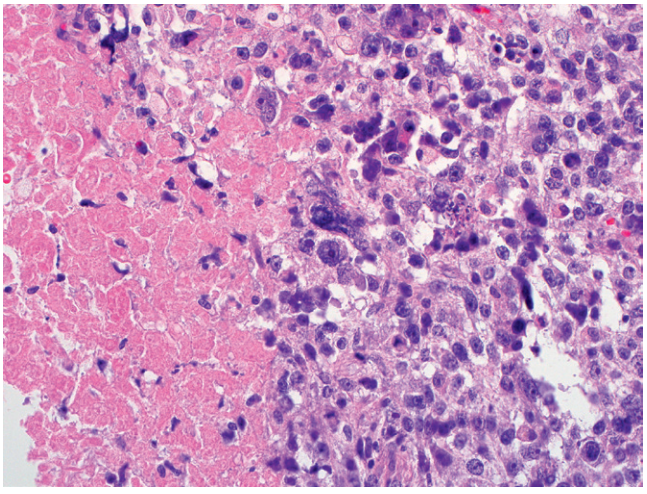


FIGURE 4

Undifferentiated uterine sarcoma showing necrosis.

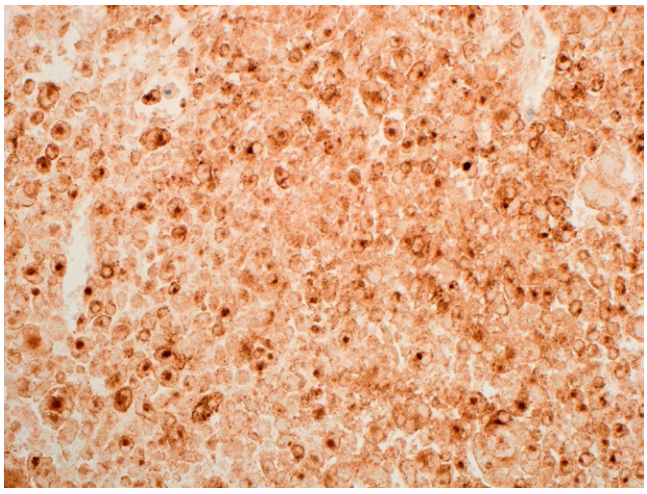


FIGURE 5

Positive staining for IFITM1 in this tumor raises the possibility of a stromal origin; however, these tumors are best approached as undifferentiated sarcomas.

ADENOSARCOMA OF THE ENDOMETRIUM

Brooke E. Howitt, MD

Definition—A low-grade stromal malignancy of the uterus with preservation of the normal resident endometrial epithelium.

Clinical Features

Epidemiology

- Most cases occur in postmenopausal women in their 60s, but a wide age range has been reported (teenagers to centenarians).
- Tamoxifen therapy for breast cancer, as well as prolonged hyperestroginism (either exogenous or endogenous), has been linked to endometrial malignancy, including adenosarcoma.

Presentation

- Presenting symptoms are nonspecific and may include vaginal bleeding, pelvic mass, and tissue protruding through the cervical os.
- Recurrent endometrial polyps may be in the patient's medical history.

Prognosis and Treatment

- Hysterectomy with surgical staging is the treatment of choice.
- Oophorectomy is usually recommended, but the necessity of this procedure is not clear, particularly in the setting of noninvasive tumors.
- Prognosis is better than that of other uterine mesenchymal malignancies, but up to one third of patients will experience a recurrence.

Pathology

Histology

- Grossly, the tumor is bulky, and the soft exophytic mass fills the endometrial cavity.
- The histology is characterized by a biphasic tumor composed of malignant stroma and benign endometrial glands.
- At low power the endometrial glands may be dilated, have a leaflike (phyllodes-like) architectural pattern, or may be present as slitlike spaces.
- Also notable at low power is stromal condensation (cuffing) around the glandular elements.
- At higher power the epithelial elements are benign and may appear cuboidal, endometrial, or even metaplastic (such as tubal or mucinous).
- The stromal element is most often homologous, with a fibrous or endometrial stromal appearance.
- Less commonly, heterologous elements such as rhabdomyosarcoma are identified.
- Nuclear atypia in the stromal component is variable and ranges from mild to marked.
- Mitotic activity is present in the stromal element and must be greater than 2/10 high-power field.
- Stromal overgrowth at the time of initial resection is thought to indicate poor prognosis and higher risk of recurrence.

Immunopathology (Including Immunohistochemistry)

- Epithelial elements: keratin positive.
- Stromal/mesenchymal elements: CD10 or CD34 may be positive.
- Epithelial and stromal elements: variable ER and PR expression.

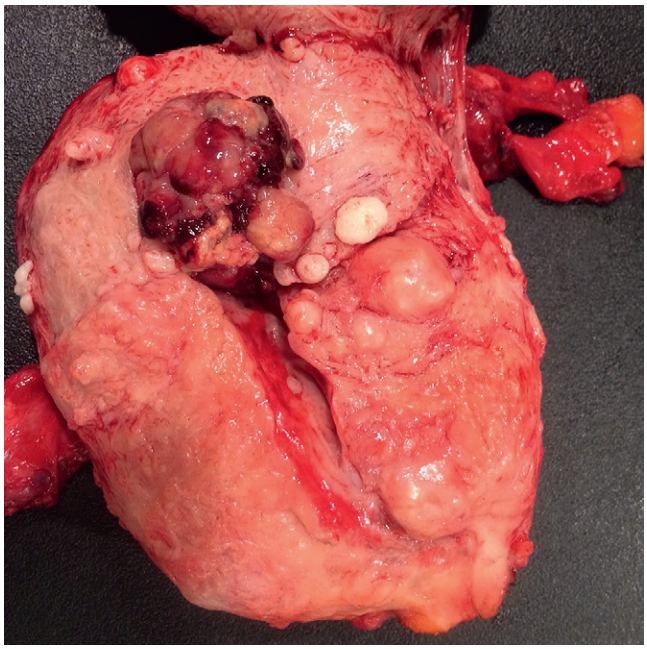


FIGURE 1

Adenosarcoma of the uterus presenting as an irregular, partially gelatinous, and hemorrhagic polypoid mass confined to the lumen in the opened uterus. Several intramural leiomyomata can be seen for comparison in the sectioned myometrium.

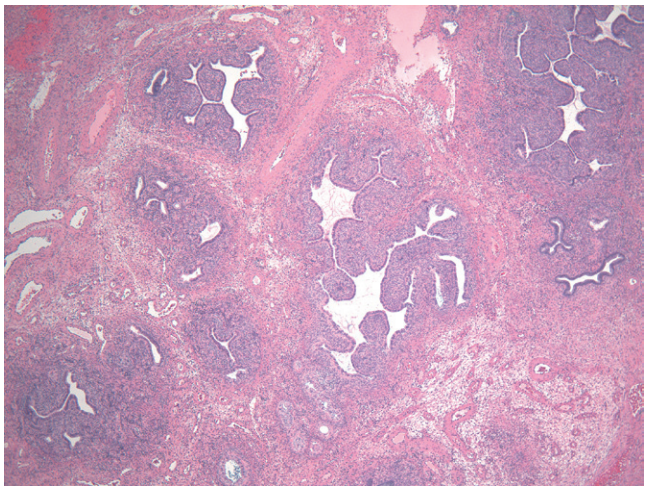


FIGURE 2

Adenosarcoma. Low-power view of cellular, stromal cuffing surrounding "leaf-like" glandular spaces.

Main Differential Diagnosis

- Endometrial stromal sarcoma—this tumor does not have the organized epithelial component, but in a small sample the distinction may be difficult.
- Uterine adenofibroma—this diagnosis is becoming obsolete as the existence of adenofibromas is called into question. "Borderline" adenosarcomas are typically classified as atypical endometrial polyps and, in contrast to adenosarcomas, should lack stromal atypia in the form of high cellularity, increased mitoses, and nuclear pleomorphism with overlap.
- Carcinosarcoma—look for neoplastic epithelium. However, there are carcinosarcomas that are distinctly "adenosarcoma like."

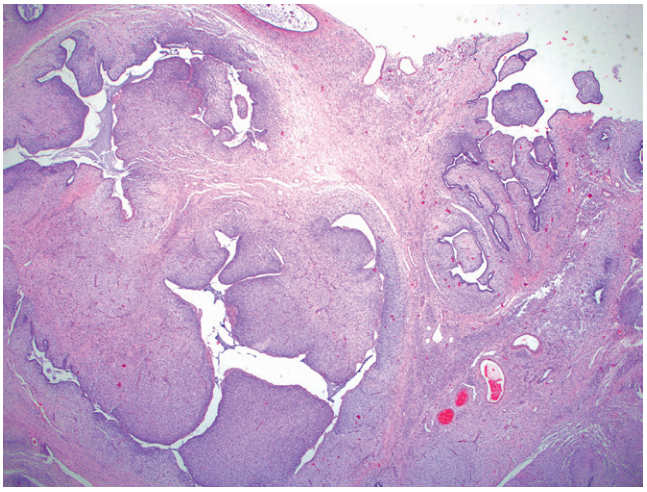


FIGURE 3

Adenosarcoma. Low-power view of cellular, stromal cuffing surrounding "leaf-like" glandular spaces.

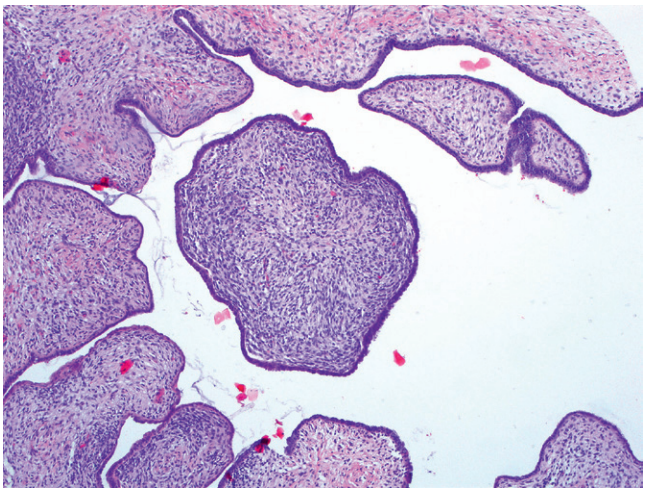


FIGURE 4

Adenosarcoma. Leaflike architecture with hypercellular stroma. Note that it may not be highly cellular, but there is a clear increase in stromal density under the surface epithelium. Note the benign glandular epithelium.

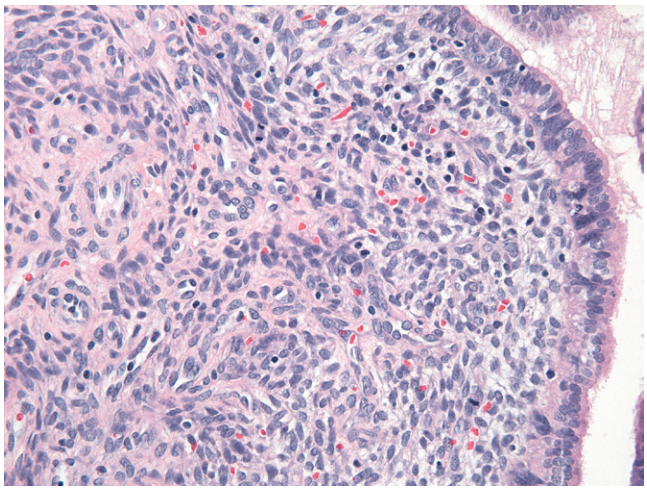


FIGURE 5

Adenosarcoma. Variably dense but consistently atypical subepithelial stromal cells with mitoses.

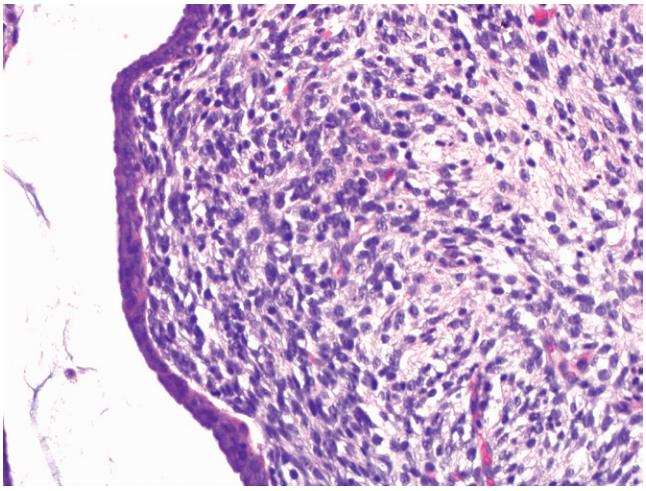


FIGURE 6

Adenosarcoma. In this focus the subepithelial cells are particularly hyperchromatic.

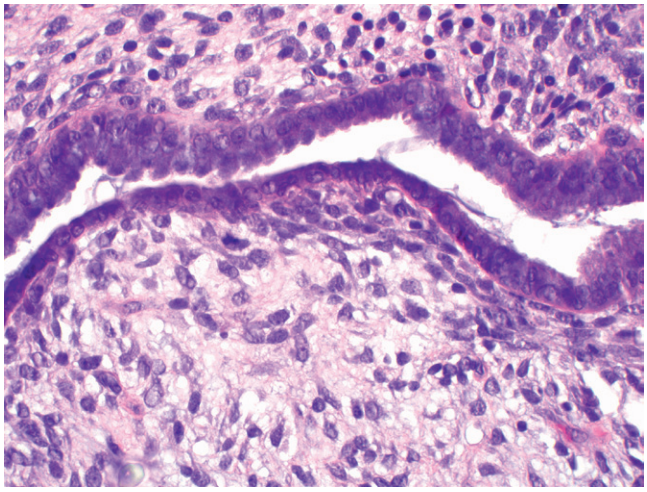


FIGURE 7

Adenosarcoma. Another focus with subepithelial stromal condensation.

ATYPICAL ENDOMETRIAL POLYP

■ **Brooke E. Howitt, MD**

Definition—An endometrial polyp with features suggestive, but not diagnostic, of an müllerian adenosarcoma.

Clinical Features

Epidemiology

- Wide age range.
- Typically fourth to sixth decades.

Presentation

- Abnormal vaginal bleeding.
- Can be asymptomatic, with a polyp identified on ultrasound or during exam.

Prognosis and Treatment

- Atypical polyps are presumably benign and so have an excellent prognosis.
- Excision of the polyp or mass is required for diagnosis and is also the treatment of choice; additional therapy is not warranted, but monitoring of the endometrium for regrowth is advised.

Pathology

Histology

- Adenosarcoma-like endometrial 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.
- High-power examination reveals a notable lack of significant cytologic atypia.
- Mitotic activity is often very low, but may be elevated when the stromal cells are morphologically similar to proliferative-type endometrial stroma.
- Periglandular stromal condensation (cuffing) may be present but is typically ill-defined and not a prominent feature.
- Typically the atypical or unusual histologic features are seen in only a portion of the polyp.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Endometrial polyp—typical polyps present no problem given the lack of stromal hypercellularity.
- Low-grade endometrial adenosarcoma—these should have conspicuous nuclear atypia in the periglandular stroma, coupled with mitotic activity.
- Adenomyoma—the key to this diagnosis is the presence of smooth muscle fascicles between the irregularly shaped glands.
- Atypical polypoid adenomyoma—this is a tumor with both smooth muscle differentiation and an atypical glandular proliferation with squamous metaplasia.

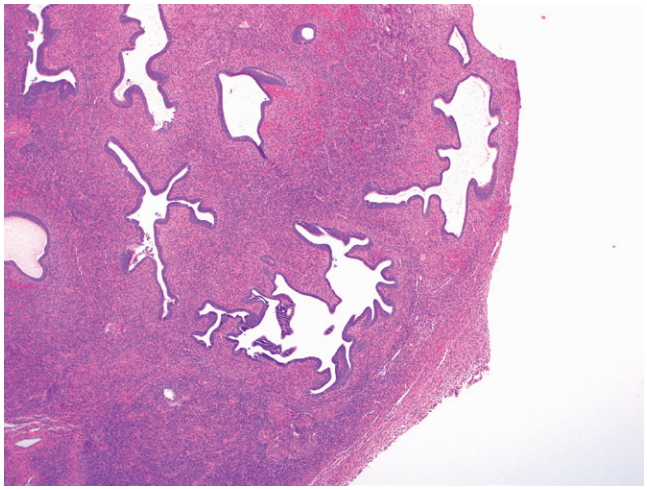


FIGURE 1

Atypical endometrial polyps. Low-power examination shows various degrees of branching or phyllodiform architecture.

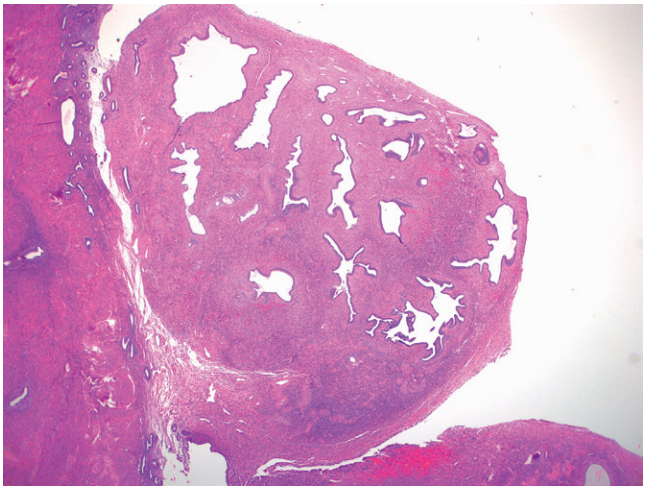


FIGURE 2

Atypical endometrial polyps. Low-power examination shows various degrees of branching or phyllodiform architecture.

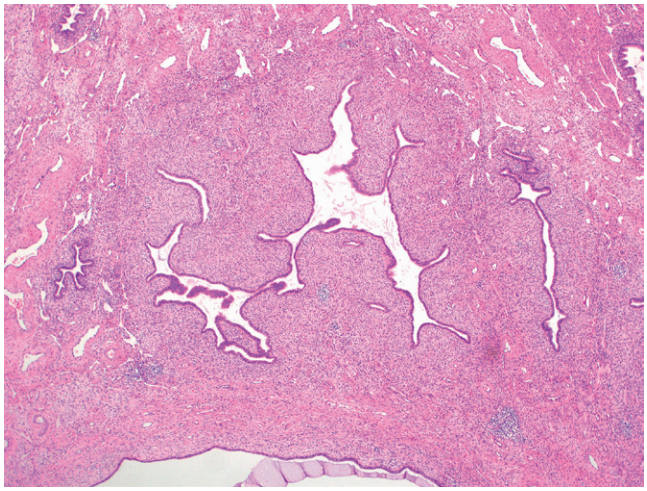


FIGURE 3

Atypical endometrial polyps. Low-power examination shows various degrees of branching or phyllodiform architecture but a lack of prominent periglandular cuffing.

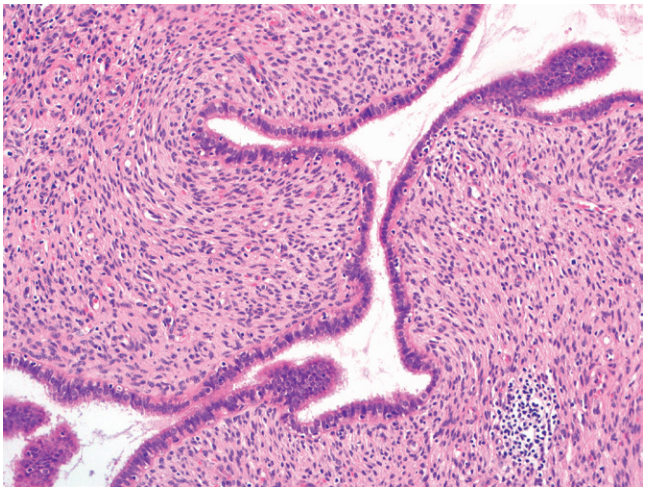


FIGURE 4

Atypical endometrial polyps. At higher magnification the stromal cells are uniform, and there is minimal nuclear enlargement or crowding.

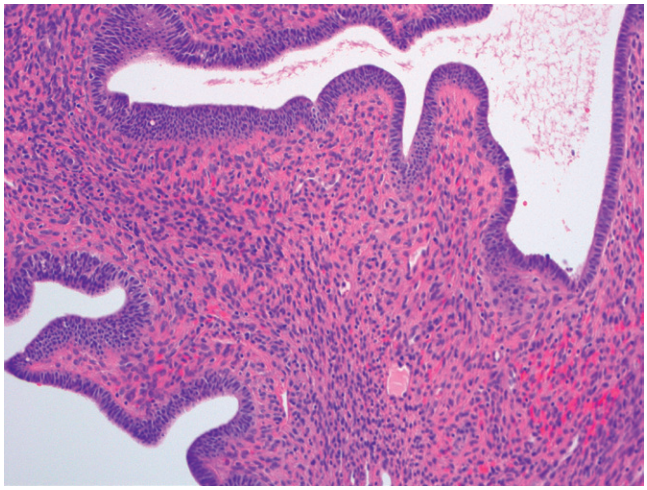


FIGURE 5

Atypical endometrial polyps. At higher magnification the stromal cells are uniform, and there is minimal nuclear enlargement or crowding.

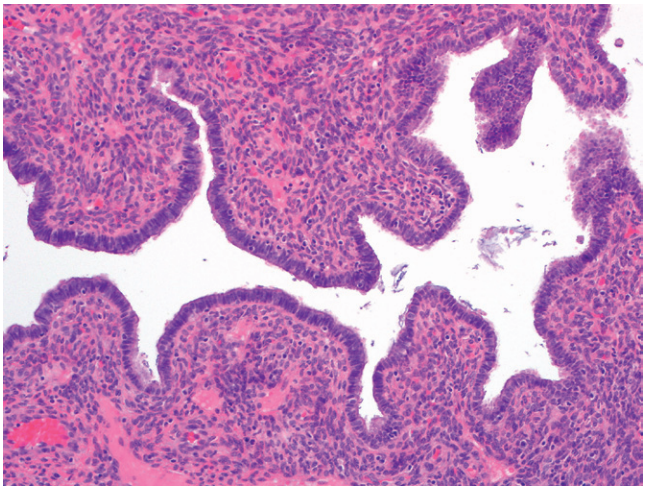


FIGURE 6

Atypical endometrial polyps. At higher magnification the stromal cells are uniform, and there is minimal nuclear enlargement or crowding.

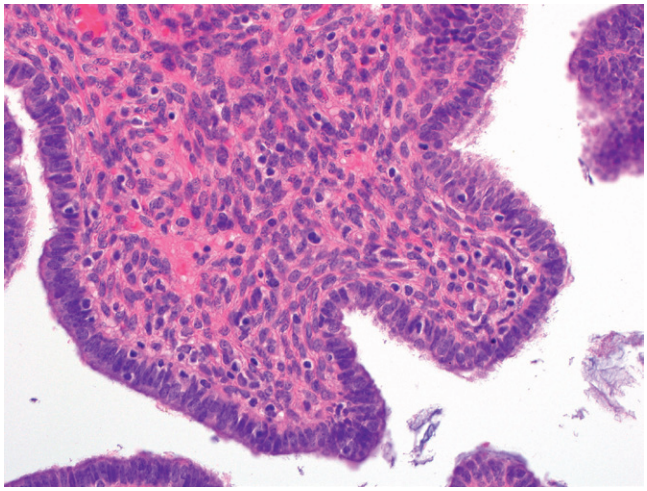


FIGURE 7

Atypical endometrial polyps. Higher magnification confirms a lack of stromal cell atypia.

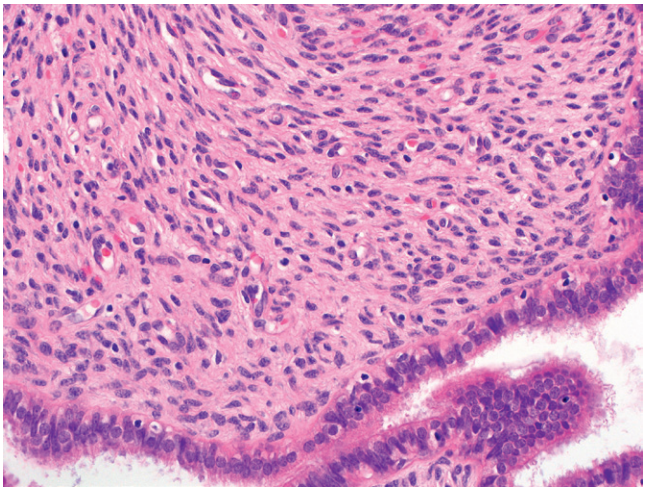


FIGURE 8

Atypical endometrial polyps. Higher magnification confirms a lack of stromal cell atypia.

ADENOMATOID TUMOR

Definition—A benign tumor composed of smooth muscle and mesothelium that is most common in the outer myometrium and fallopian tube.

Clinical Features

Epidemiology

- Uncommon but not rare.
- Reproductive-age to perimenopausal women.

Presentation

- Most often incidental and less than 2 cm in size.
- May be associated with symptomatic leiomyomata.

Prognosis and Treatment

- Prognosis is excellent; this is a benign tumor.
- Excision is adequate treatment.

Pathology

Histology

- On gross examination, tumors are rubbery and white to gray, and lack prominent bulging on cut section.
- The border with myometrium is less defined than that seen with leiomyomata.
- At low power, fascicles of brightly eosinophilic smooth muscle cells with bland, elongated nuclei are apparent.
- The mesothelial component is interspersed between bundles of smooth muscle and can vary from inconspicuous to prominent.
- Mesothelial cells are usually arranged in small glandlike spaces with frequent "chaining," although other patterns have been described, including sheets and densely glandular appearing proliferation.
- Mesothelial cells are epithelioid and cuboidal to squamoid, with bland nuclei.
- Signet-ring–like cells and pseudolipoblasts are almost always seen.
- An infiltrative growth pattern, with tumor cells involving adjacent myometrium, is not uncommon; extension beyond the uterus is rare.
- Marked nuclear atypia, tumor necrosis, and atypical mitotic figures are absent.

Immunopathology (Including Immunohistochemistry)

- Positive for smooth muscle components: desmin, smooth muscle actin, and CD34.
- Positive for mesothelial components: calretinin (nuclear) and pankeratins.

Main Differential Diagnosis

- Lipoleiomyoma—the key here is to pay close attention to the spaces and whether they are adipose tissue or mesothelial lined.
- Carcinomas, particularly signet-ring cell tumors—the mesothelial-lined spaces may be less conspicuous, and the mesothelial cells may take on a "signet ring" appearance, which can be misleading.

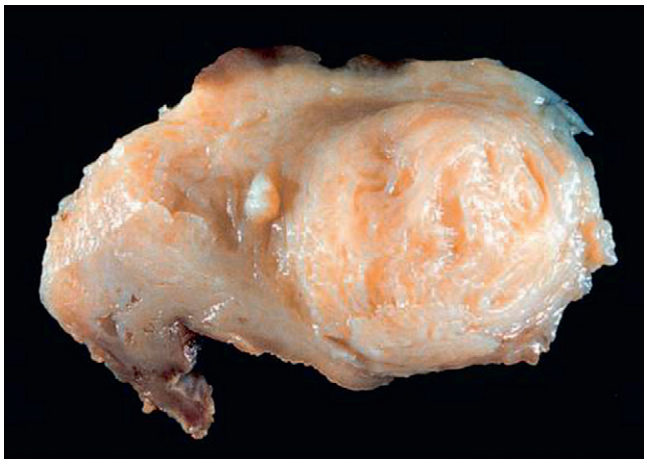


FIGURE 1

Adenomatoid tumor. This myometrial tumor resembles a leiomyoma. If the mesothelial lined spaces are prominent, the lesion may take on a spongy consistency.

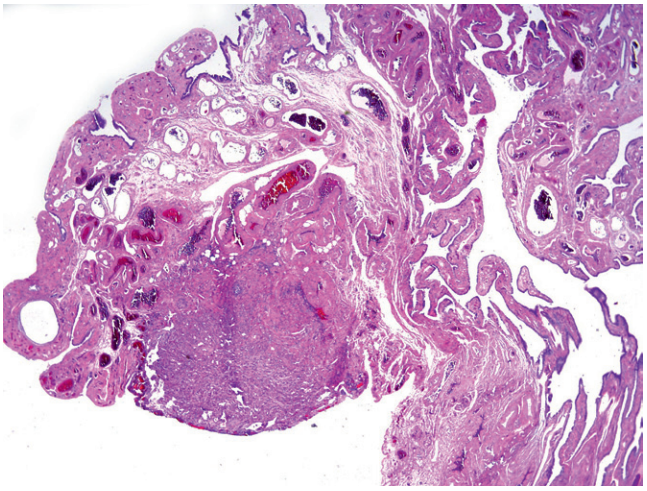


FIGURE 2

Adenomatoid tumor. A small tubal tumor within the fimbria.

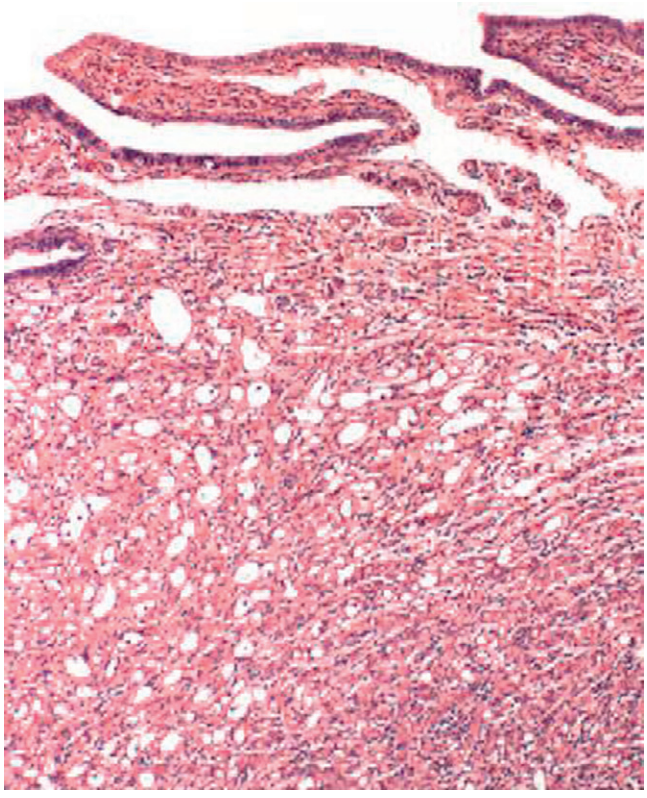


FIGURE 3

Adenomatoid tumor. This is a common appearance at low magnification, with numerous small spaces creating a honeycomb pattern.

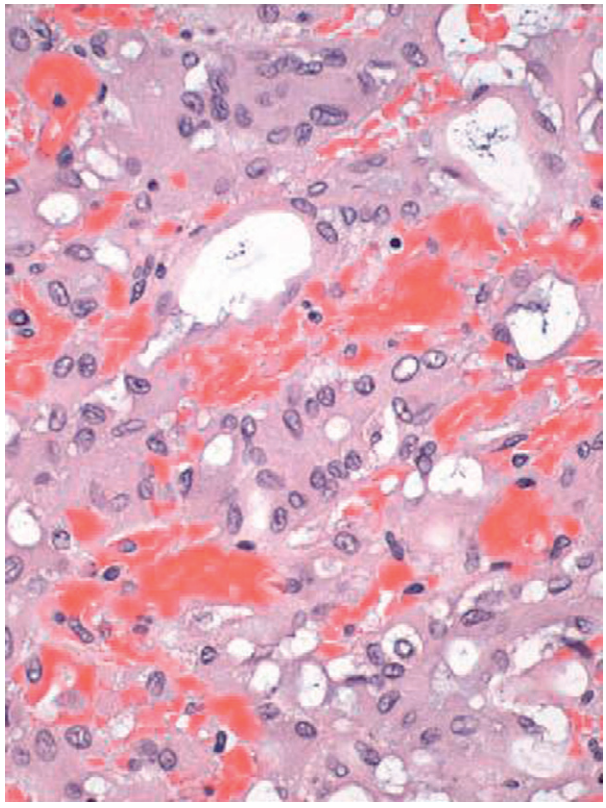


FIGURE 4

Adenomatoid tumor. In this variant the mesothelial cells are plump and glandlike, and may be confused with malignancy.

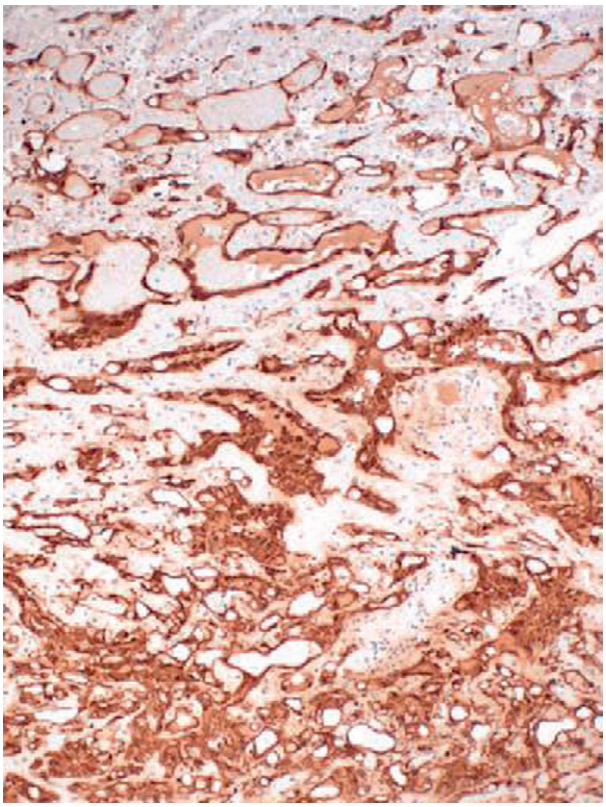


FIGURE 5

Calretinin staining is strong in these lesions and will distinguish them from adenocarcinomas.

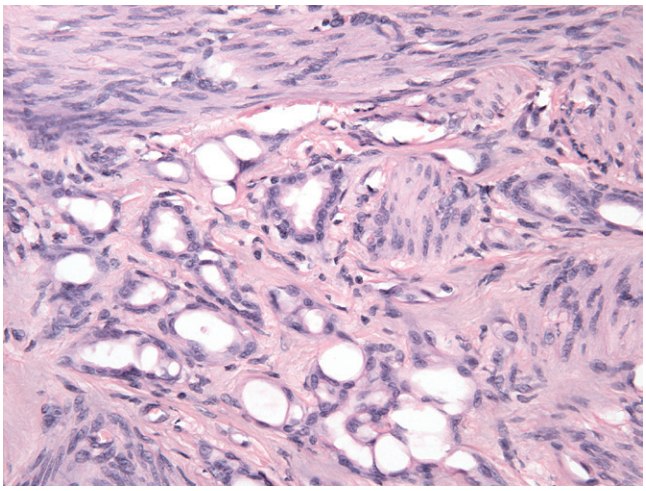


FIGURE 6

At high magnification note the variably sized spaces. When small, they may mimic signet-ring tumor cells.

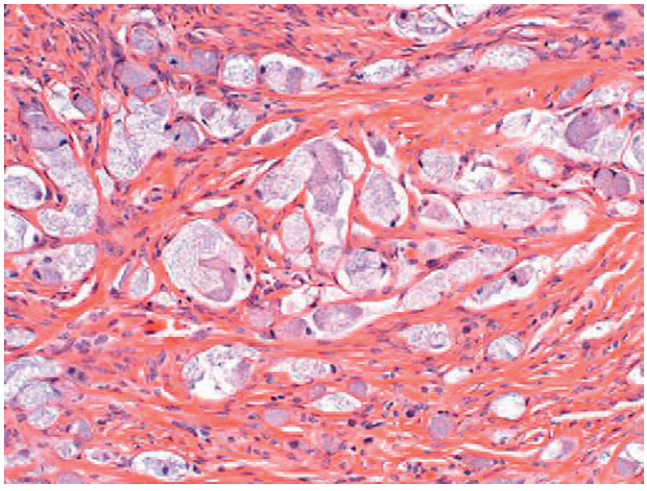


FIGURE 7

A signet-ring cell adenocarcinoma for comparison.

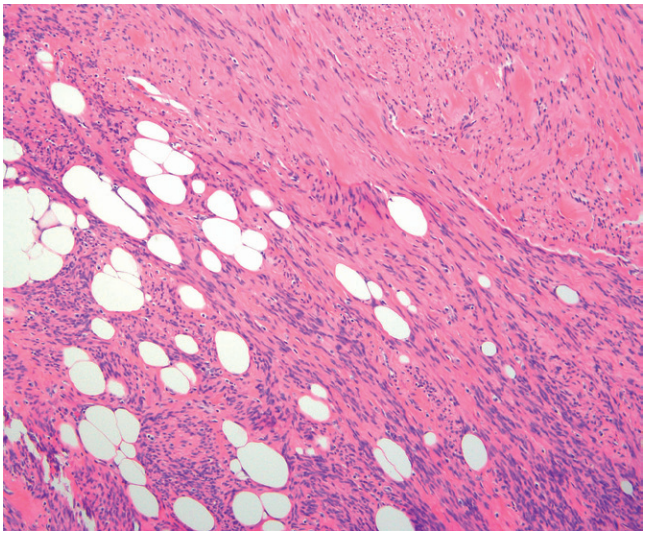


FIGURE 8

A lipoleiomyoma may mimic an adenomatoid tumor, both on gross exam and at low-power magnification.

LIPOLEIOMYOMA

Definition—A benign tumor of the uterus composed of both smooth muscle and adipose cells.

Clinical Features

Epidemiology

- Rare.
- Postmenopausal women.
- t(12;14) a common chromosomal rearrangement similar to other leiomyomas.

Presentation

- Abnormal vaginal bleeding.
- Pelvic pressure or pain.

Prognosis and Treatment

- Excellent; these are benign tumors.

Pathology

Histology

- Grossly a yellow (even bright yellow) appearance may be noted.
- Histologically these tumors are characterized by an admixture of smooth muscle cells and adipose cells.
- The bland, brightly eosinophilic smooth muscle cells are arranged in the usual bundles and fascicles of a leiomyoma.
- Adipocytes are interspersed within the bundles of smooth muscle singly and in groups.
- Rarely the adipocytic component may constitute the majority of tumor cells.

Immunopathology (Including Immunohistochemistry)

- Noncontributory. However, HMGI-C is aberrantly expressed in this tumor.
- Cytogenetic and molecular data suggest that these tumors represent a distinct variant and are not simply a degenerative phenomenon, as was traditionally presumed.

Main Differential Diagnosis

- Lipoma (when adipocytes predominate).

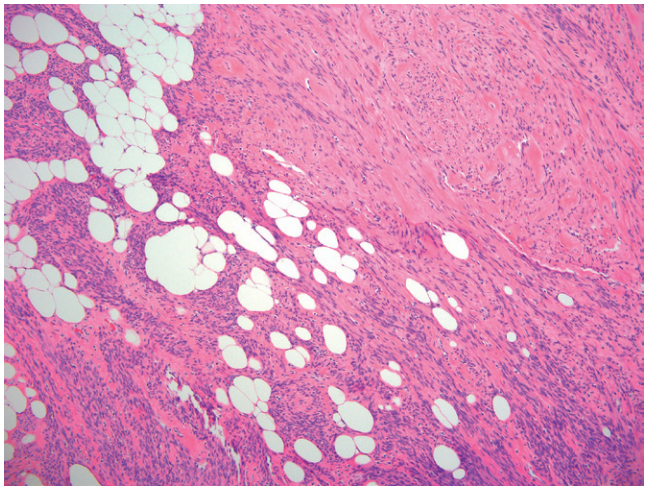


FIGURE 1

Lipoleiomyoma. Fascicles of smooth muscle with interspersed mature adipose tissue.

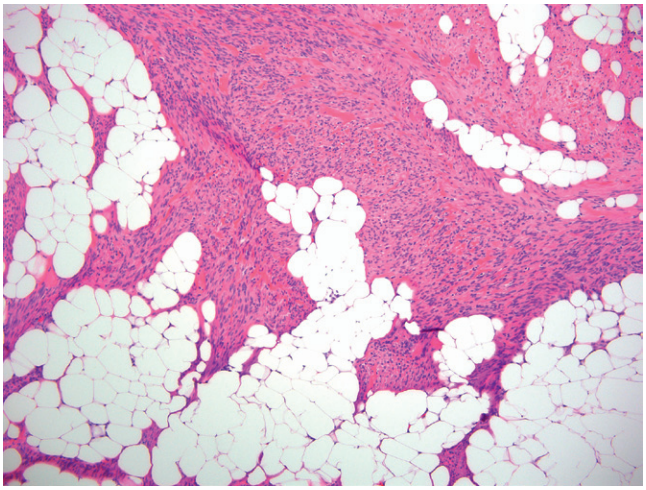


FIGURE 2

Lipoleiomyoma. Fascicles of smooth muscle with interspersed mature adipose tissue.

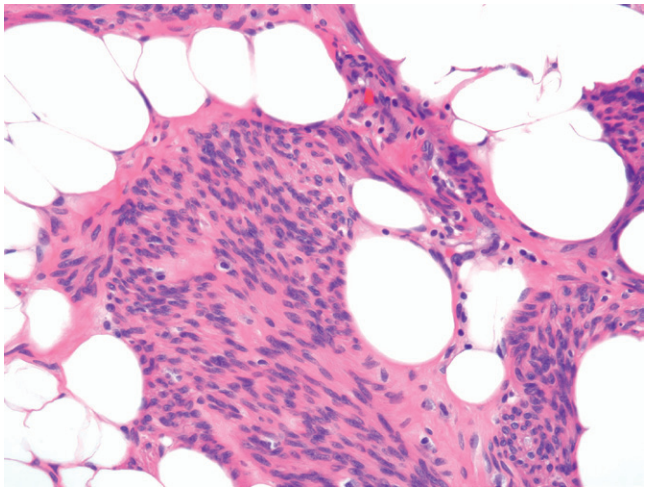


FIGURE 3

Lipoleiomyoma. Fat cells with spindled smooth muscle cells.

CELLULAR LEIOMYOMA

Definition

- A smooth muscle tumor with conspicuous increased cellularity.

Clinical Features

Epidemiology

- The same as for usual leiomyoma.

Presentation

- The same as for usual leiomyoma.
- On gross exam these tumors tend to be softer and "fleshier" than usual leiomyomas, with a slightly more gray or pink color.

Prognosis and Treatment

- Generally excellent; these are benign tumors. However, the cellular leiomyoma phenotype with loss of 1p has been described in some reports as behaving more aggressively.

Pathology

Histology

- At low power, cellular leiomyomas are notable for increased cellularity.
- The degree of increased cellularity required for a designation of "cellular leiomyoma" is debatable, and strict criteria are not available, although there is a suggestion that these more cellular tumors have a distinct molecular signature.
- The tumor cells themselves are bland, with minimal amounts of eosinophilic cytoplasm, and are arranged (at least focally) in the usual fascicles and bundles of leiomyomata.
- Highly cellular leiomyomas, in particular, may have an irregular border with surrounding myometrium, which can be mistaken for the infiltrative borders of more worrisome lesions.
- Interspersed large thick-walled blood vessels are present.
- Characteristic cleftlike spaces between the tumor and surrounding myometrium.
- Nuclear atypia and tumor necrosis are absent.
- Cellular leiomyomas are often also mitotically active (see Mitotically Active Leiomyoma).

Immunopathology (Including Immunohistochemistry)

- Positive for desmin (strong positive) and h-caldesmon.
- Negative for CD10 (in most cases).
- Overall the use of immunohistochemistry to distinguish cellular leiomyoma from endometrial stromal sarcoma is not advisable as the profiles share significant overlap.

Main Differential Diagnosis

- Leiomyosarcoma—the keys to a diagnosis of leiomyosarcoma are atypia, increased mitotic activity, and tumor necrosis. Cellular leiomyomas exhibit increased nuclear density and may exhibit an increase in mitotic index but should contain neither atypia nor necrosis.
- Low-grade endometrial stromal sarcoma—careful scrutiny of a cellular leiomyoma will reveal the fasciculated pattern of a smooth muscle tumor. Moreover, the fine vascular pattern of an endometrial stromal tumor should not be present and thick-walled blood vessels should be seen. In difficult cases, smooth muscle (desmin, h-caldesmon, increased) and stromal (CD10, decreased relative to endometrial stromal sarcoma) staining should make the distinction.

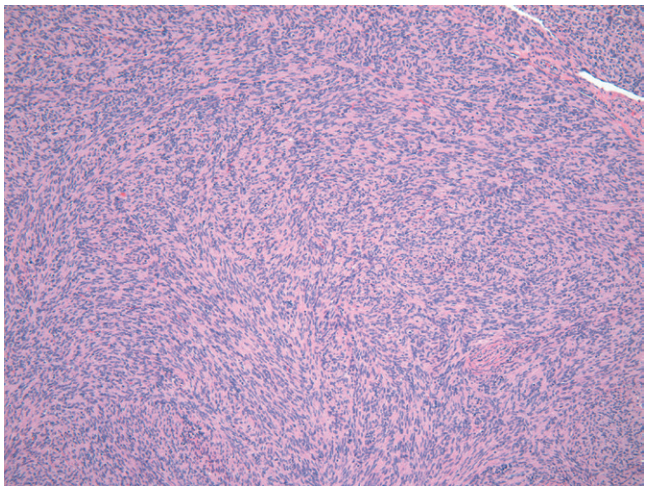


FIGURE 1

Cellular leiomyoma. Increased cellularity and nuclear density evident at low power.

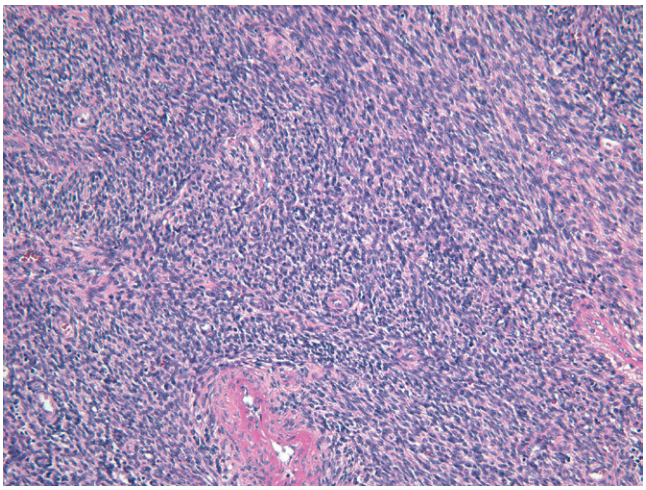


FIGURE 2

Cellular leiomyoma. A highly cellular variant, with numerous overlapping nuclei.

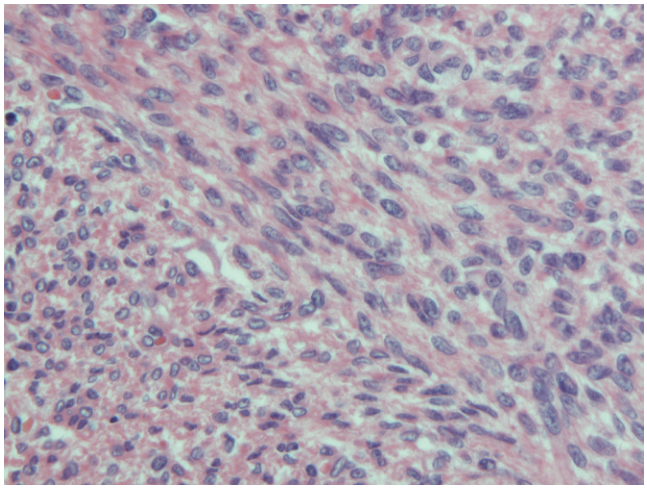


FIGURE 3

Cellular leiomyoma. High-power view displaying bland smooth muscle cells with cigar-shaped nuclei.

HYDROPIC LEIOMYOMA

Definition—Uterine smooth muscle tumor with prominent degenerative changes.

Clinical Features

Epidemiology

- Same as for leiomyoma.
- Degenerative change within leiomyomata is extremely common.

Presentation

- Same as for leiomyoma.
- Some believe that a component of the pain associated with leiomyomata is due to degeneration.

Prognosis and Treatment

- Excellent; these are benign tumors.

Pathology

Histology

- The gross appearance of degenerative change is variable; in some instances it may appear as a round, white area in the center of a leiomyoma.
- In other cases the mass may be diffusely yellow and gelatinous, or extensively calcified.
- Occasionally the tumoral mass may be extensively replaced by cystic structures filled with serous fluid.
- Hemorrhage may also be seen, resulting in a pink or even red appearance (carneous).
- Histologically the areas of necrosis have a characteristic interface (transition zone) between viable and nonviable tissues.
- The interface is composed of fibroblasts, viable and nonviable smooth muscle cells, and inflammation, similar to granulation tissue.
- The interface or transition zone should be relatively uniform (although not easily demarcated) around the area of necrosis, and at least several cells thick.
- Within the necrotic tissue, cells should not have prominent or well-defined cell outlines (ghost cells).
- Other patterns of degeneration are characterized by prominent edema and accumulation of fluid ("hydropic" change).
- The hydropic areas generally lack cellular debris within the areas of fluid accumulation.
- In any pattern of degeneration the border with background myometrium should be sharp; infiltration of the surrounding smooth muscle should not be present.

Immunopathology (Including Immunohistochemistry)

- Positive for smooth muscle actin and desmin.

Main Differential Diagnosis

- Myxoid leiomyosarcoma. Look for increased mitotic activity, atypia, necrosis, and infiltration of the adjacent myometrium.

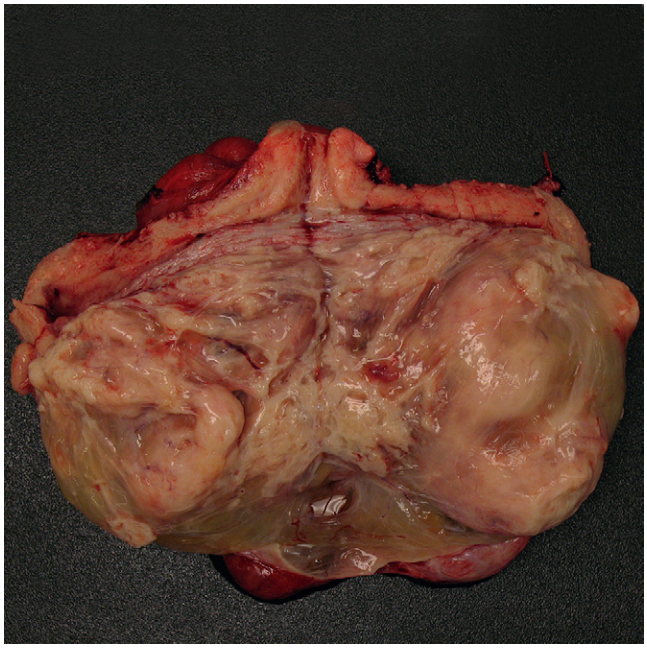


FIGURE 1

Hydropic leiomyoma. Gross specimen with cystic degeneration.

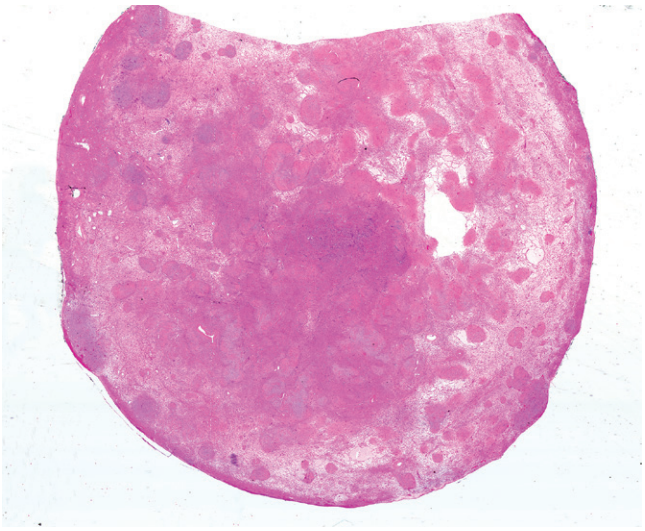


FIGURE 2

Hydropic leiomyoma. Low-power view showing alternating areas of hypercellularity and hypocellularity within a well-circumscribed mass.

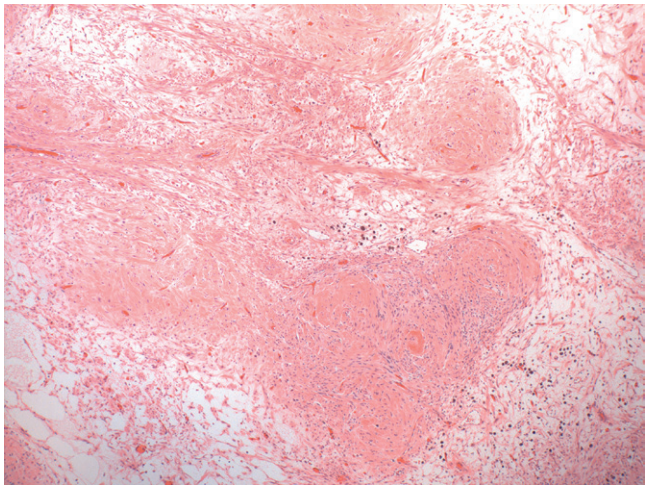


FIGURE 3

Hydropic leiomyoma. Bundles of bland smooth muscle with areas of edema.

MITOTICALLY ACTIVE LEIOMYOMA

Definition—A morphologic variant of uterine leiomyoma.

Clinical Features

Epidemiology

- Mitotic activity within normal and leiomyomatous smooth muscle cells is a well-established phenomenon.
- Exogenous progesterones increase the observed mitotic rate in leiomyomata.

Presentation

- Same as for usual leiomyoma.

Prognosis and Treatment

- Excellent; these are benign tumors.

Pathology

Histology

- Overall these tumors are histologically identical to other leiomyomata and are composed of fascicles and bundles of smooth muscle cells with brightly eosinophilic cytoplasm and bland, blunt-ended nuclei.
- Significant mitotic activity is present (up to 15/10 high-power fields), but atypical mitotic figures should not be present.
- Mitotic activity should always be assessed in the most mitotically active area, and at least 30 high-power fields should be examined.
- Mitotically active tumors are often cellular or highly cellular; it is critical to ensure that nuclear atypia and tumor necrosis are absent in these lesions.

Immunopathology (Including Immunohistochemistry)

- The proliferation marker Ki-67 may be useful in some cases to exclude overinterpretation of pyknotic nuclei as mitotic figures.

Main Differential Diagnosis

- Smooth muscle tumor of uncertain malignant potential—these will be considered when there is atypia and moderately increased mitotic activity (5 to 10 mitoses per 10 HPF).
- Leiomyosarcoma—atypia and mitoses exceeding 10 per 10 HPF or the presence of tumor necrosis.

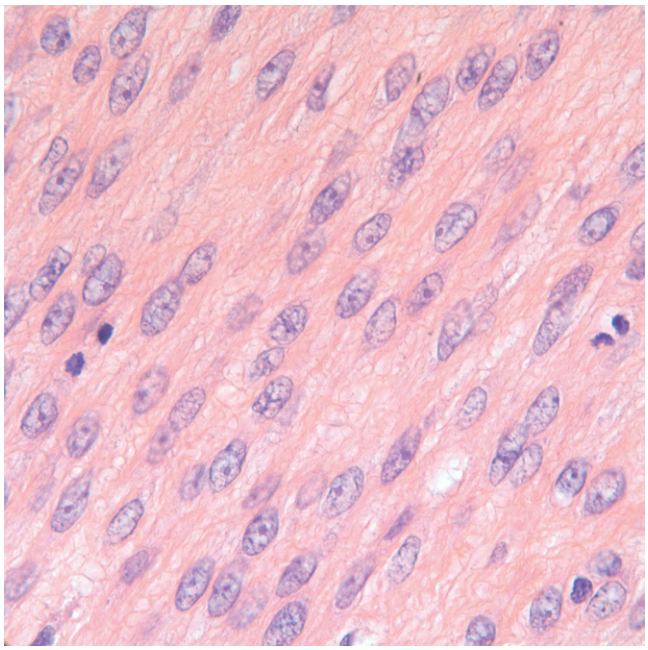


FIGURE 1

Mitotically active leiomyoma. A typical leiomyoma with two mitotic figures (anaphase).

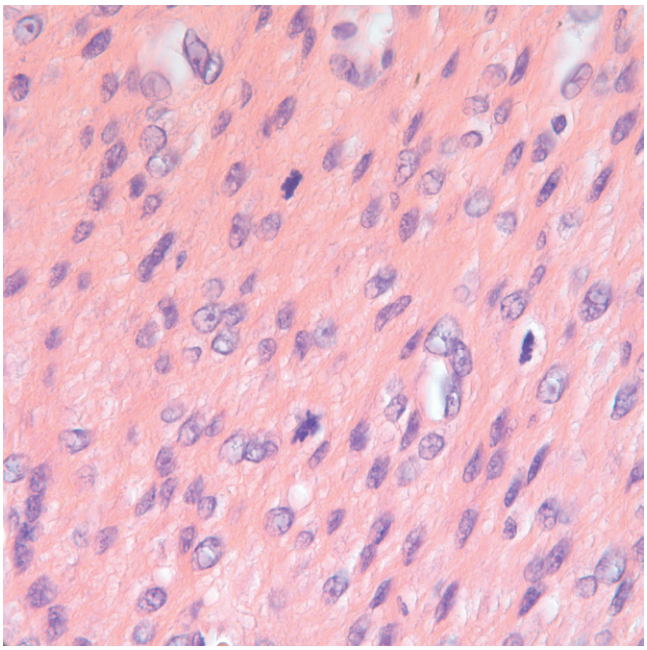


FIGURE 2

Mitotically active leiomyoma. Three mitotic figures admixed with bland smooth muscle cells.

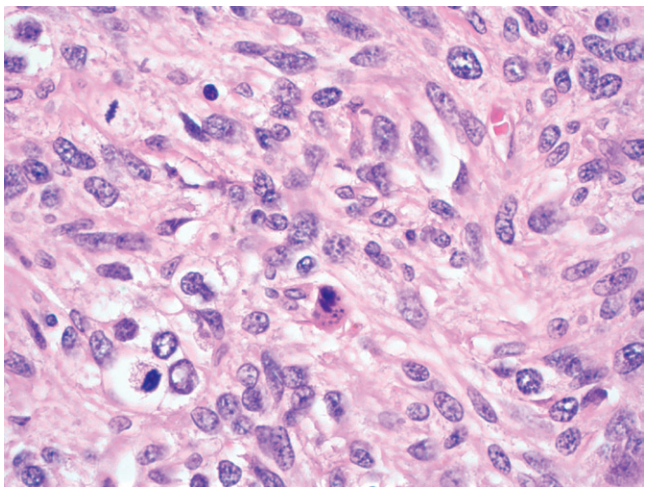


FIGURE 3

Mitotically active leiomyoma. An atypical leiomyoma with one mitotic figure (*upper left,* metaphase) and one pseudomitosis noted by its bright pink, well-defined cytoplasm *(center)*.

ATYPICAL LEIOMYOMA (LEIOMYOMA WITH BIZARRE NUCLEI)

Definition—A benign smooth muscle tumor with prominent nuclear atypia.

Clinical Features

Epidemiology

- Uncommon.
- Identified in the same patient population as typical leiomyomata.

Presentation

- The same as for usual leiomyoma.

Prognosis and Treatment

- Complete excision is recommended, with periodic monitoring if only a myomectomy has been performed.
- Rarely, recurrent atypical leiomyomata and association with leiomyosarcoma have been reported.
- Risk of recurrence or malignant behavior is very low (under 5%).

Pathology

Histology

- This diagnosis is restricted to tumors that exhibit atypia discernible at low power.
- The striking atypia is appreciated at low power and often brings to mind the possibility of leiomyosarcoma.
- Nuclear atypia may consist of enlargement, hyperchromasia, multinucleated cells or multilobated nuclei, prominent nucleoli, or any combination of them.
- Cytoplasmic atypia may also be demonstrated and may consist of abundant eosinophilic cytoplasm, with or without cytoplasmic whorling.
- Tumor "giant" cells may be seen.
- The markedly atypical cells may be very focal or may be diffusely present throughout the tumor.
- By definition, geographic tumor necrosis and increased mitotic activity (>10/10 high-power fields) are absent.

Immunopathology (Including Immunohistochemistry)

- Positive for p53, desmin, and smooth muscle actin.
- A Ki-67 proliferation index is low.

Main Differential Diagnosis

- Smooth muscle tumor of uncertain malignant potential (STUMP)—this might be considered if mitoses approach 10/10 HPF or if infiltrative borders are present.
- Leiomyosarcoma—considered if there is tumor necrosis.

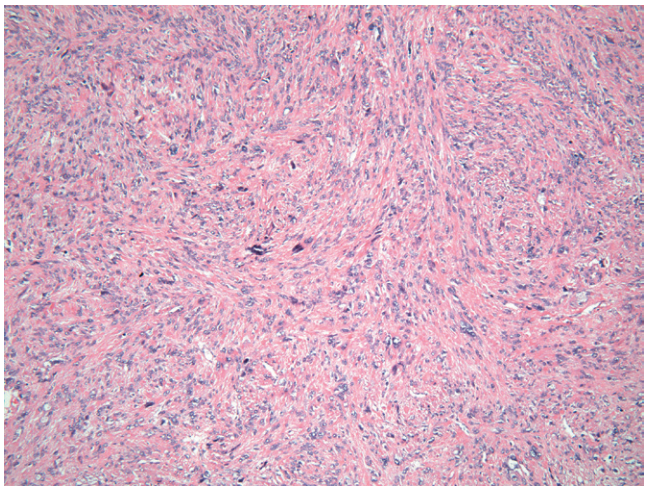


FIGURE 1

Atypical leiomyoma. Atypical nuclear features evident at low magnification.

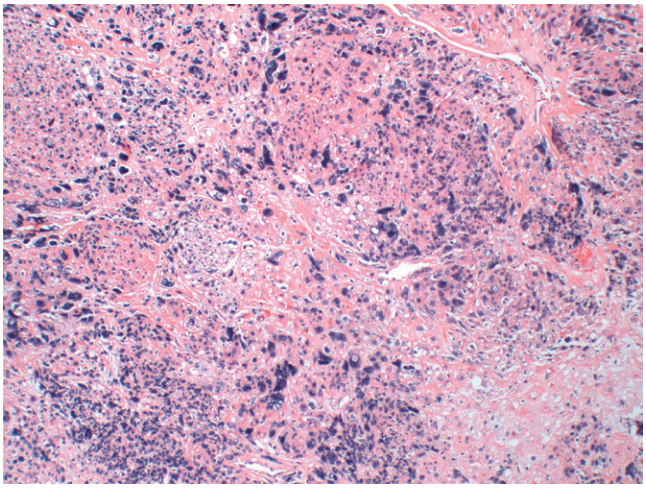


FIGURE 2

Atypical leiomyoma. 10× view (definition of low power according to the Bell criteria) of diffuse nuclear atypia.

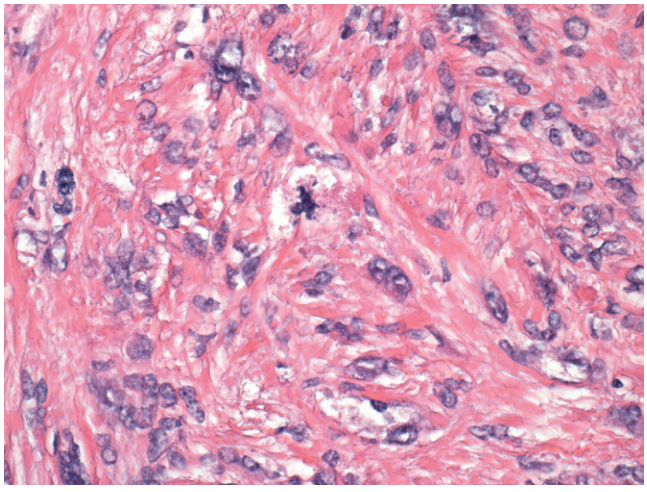


FIGURE 3

Atypical leiomyoma. Pseudomitosis within an atypical leiomyoma. Note the vacuolization and the eosinophilic, cytoplasmic clumping.

LEIOMYOMATOSIS

Definition—Uterine smooth muscle tumor composed of multiple repetitive fascicles of smooth muscle diffusely involving the myometrium without a definable border.

Clinical Features

Epidemiology

- Same as for leiomyoma, but extremely rare.

Presentation

- Same as for leiomyoma, dysmenorrhea, bleeding, pelvic pressure, discomfort, and infertility.
- Uterus is diffusely enlarged due to the absence of a discrete intramural nodule.

Prognosis and Treatment

- Excellent; these are benign tumors, but hysterectomy is the only effective approach given the diffuse nature of the process.

Pathology

Gross and Microscopic

- The gross appearance is that of a diffusely expanded myometrium with confluent variably defined nodules of variable size, ranging from a few millimeters to several centimeters.
- Isolated infarcts may be seen.
- On microscopy the nodules may blend but overall display the histology of typical leiomyomas.

Immunopathology (Including Immunohistochemistry)

- Not usually necessary; positive for smooth muscle markers.

Main Differential Diagnosis

- Leiomyosarcoma—this may be considered on gross exam given the unexpected diffuse appearance and presence of infarcts; however, this can be readily excluded on histologic examination.
- Hydropic leiomyoma—this entity will display small confluent nodules similar to leiomyomatosis, but this process is within a discrete mass.

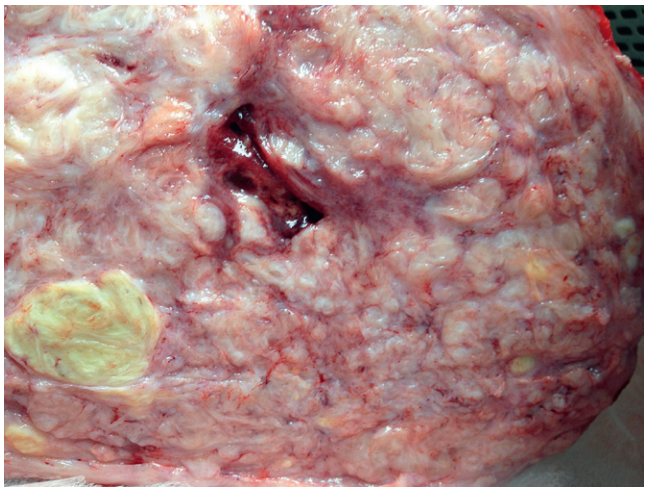


FIGURE 1

Leiomyomatosis. This gravid uterus contains confluent firm white nodules of variable size. Note the small yellow infarct on the left.

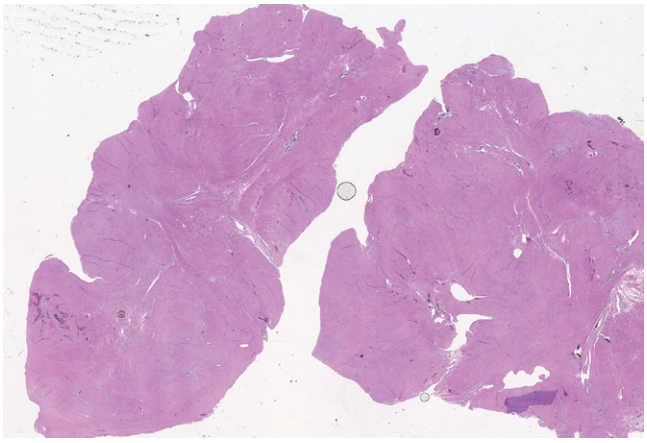


FIGURE 2

Leiomyomatosis. At low magnification partially defined nodules of smooth muscle merge.

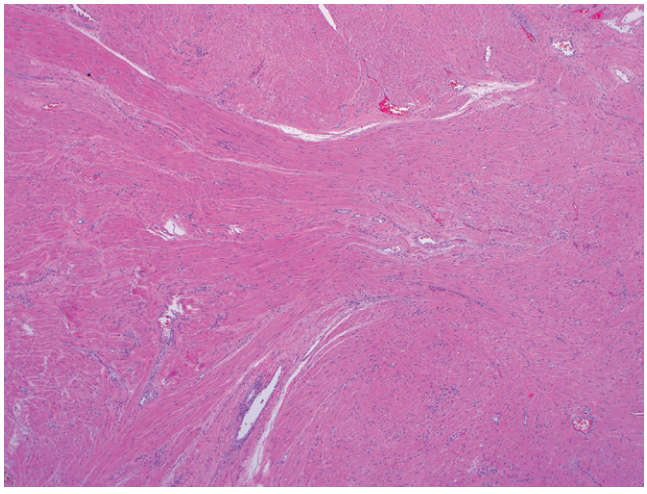


FIGURE 3

Leiomyomatosis. At medium power the cleavage planes formed by the perimeter of the myomas can be appreciated.

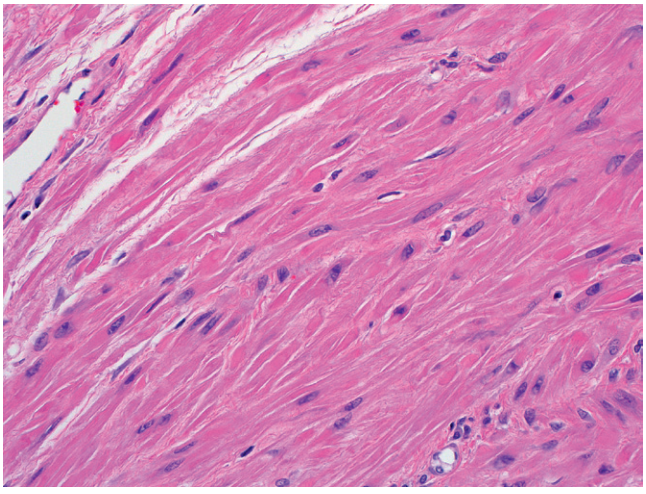


FIGURE 4

Leiomyomatosis. At higher magnification the nodules are clearly benign.

INTRAVENOUS LEIOMYOMA

Bradley J. Quade, MD, PhD

Definition—An unusual smooth muscle tumor of the uterus with a predilection for vascular involvement.

Clinical Features

Epidemiology

- Rare.
- Same patient population as for usual leiomyoma.

Presentation

- Same as for usual leiomyoma.
- May present with dyspnea, syncope, abnormal electrocardiograms, or other findings of hemodynamic compromise when the lesion fills the vena cava.

Prognosis and Treatment

- Long-term studies of this phenomenon have not been done, but they seem to be entirely benign; no particular additional treatment is warranted.
- Removal of lesions filling the vena cava relieves symptoms of hemodynamic compromise.
- Some suspect that these lesions may be the origin of the so-called benign metastasizing leiomyomas and/or intravenous leiomyomatosis.

Pathology

Histology

- The gross appearance is the same as for usual leiomyoma, with bulging white to gray cut surfaces.
- At low power the tumor is composed of bundles and fascicles of brightly eosinophilic spindle cells with bland, blunt-ended nuclei.
- Either focally or multifocally, the bland smooth muscle cells can be seen within, filling, and distending venous spaces.
- Venous space involvement is limited to the tumor itself.
- Other worrisome features such as increased mitoses, necrosis, and nuclear atypia are absent.

Immunopathology (Including Immunohistochemistry)

- Positive for smooth muscle actin and desmin.
- Often aberrantly expresses HMGA2 due to the effect of a chromosomal translocation, t(12;14).

Main Differential Diagnosis

- Endometrial stromal sarcoma.
- Leiomyosarcoma.

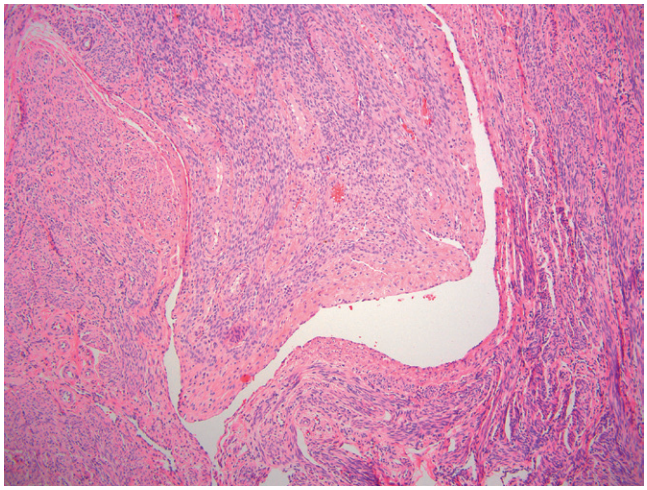


FIGURE 1

Intravascular leiomyoma. A cleftlike vascular space filled with fascicles of smooth muscle.

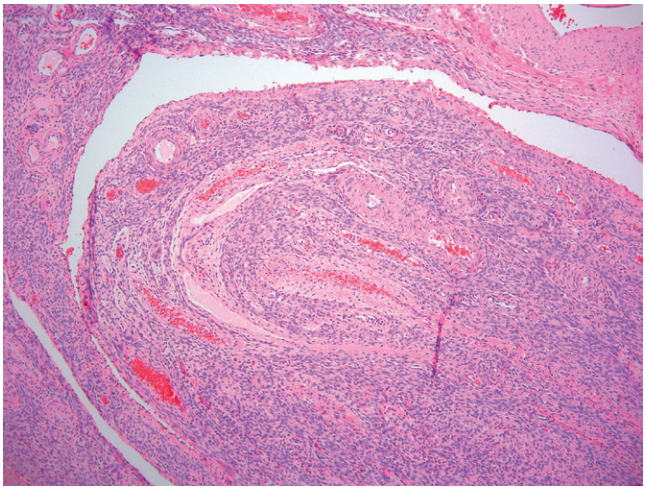


FIGURE 2

Intravascular leiomyoma. Smooth muscle bundles seen bulging into a dilated vascular space.

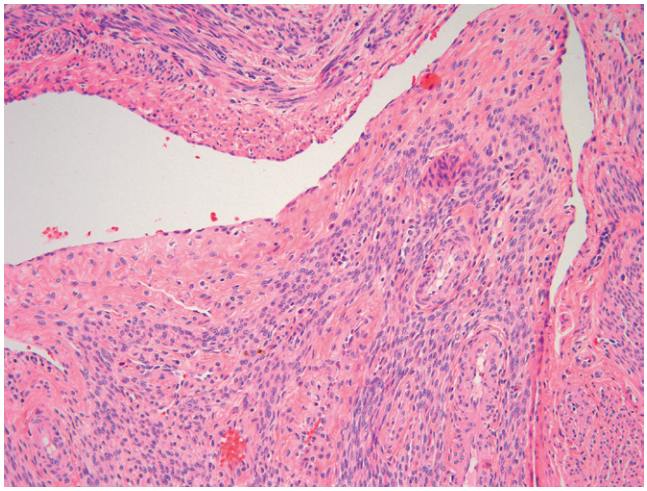


FIGURE 3

Intravascular leiomyoma. A single layer of flat endothelial cells can be seen lining the smooth muscle tumor.

INTRAVENOUS LEIOMYOMATOSIS

Bradley J. Quade, MD, PhD

Definition—A variant of leiomyoma in which the tumor is located entirely within vein(s) of the uterus, pelvis, or even the vena cava.

Clinical Features

Epidemiology

- Rare.
- Same patient population as typical uterine leiomyoma.

Presentation

- Same as for usual leiomyoma.

Prognosis and Treatment

- These tumors are at risk for either regional vascular spread or spread to the lung.
- Patients must be monitored accordingly.
- Spread may necessitate further surgery.

Pathology

Histology

- On gross exam the tumor may present as multiple wormlike structures coursing through the myometrium or out of the uterine veins.
- At low power the tumor is composed of bundles and fascicles of brightly eosinophilic spindle cells with bland, blunt-ended nuclei coursing through vascular channels.
- There often is a prominent collagenized component with small vessels.
- Venous space involvement is limited to the tumor itself.
- Other worrisome features (increased mitoses, necrosis, nuclear atypia) are absent.
- The tumor may be found in association with adenomyosis in some cases.

Immunopathology (Including Immunohistochemistry)

- Positive for smooth muscle actin and desmin.

Main Differential Diagnosis

- Vascular leiomyoma—typically a myometrial tumor with focal vascular involvement.
- Myxoid variant of endometrial stromal sarcoma (ESS)—usually more typical ESS is present; positive for CD10 and negative or weak for desmin.

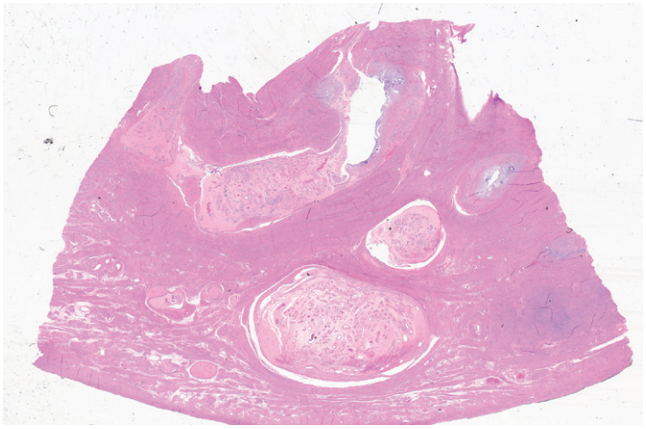


FIGURE 1

Intravenous leiomyomatosis. Note the multiple distended vascular spaces with tumor.

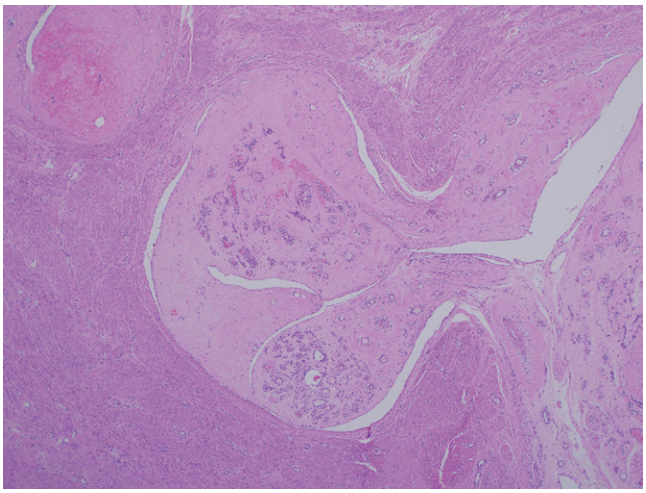


FIGURE 2

Intravenous leiomyomatosis. Tumor permeates vascular spaces. Note the prominent collagenized appearance with small vessels in the tumor.

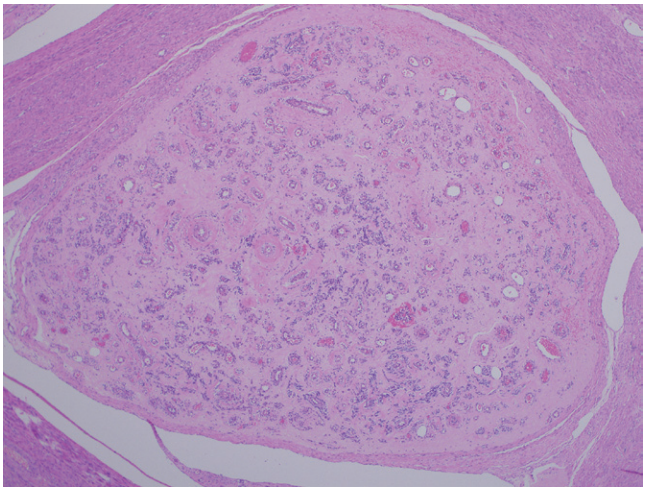


FIGURE 3

Intravenous leiomyomatosis. Here the multiple small vessels are prominent, some with thick walls.

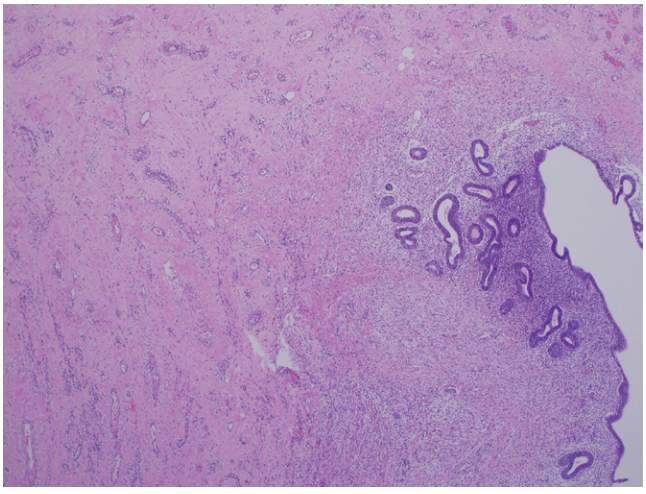


FIGURE 4

In this case of intravenous leiomyomatosis the tumor is closely associated with adenomyosis.

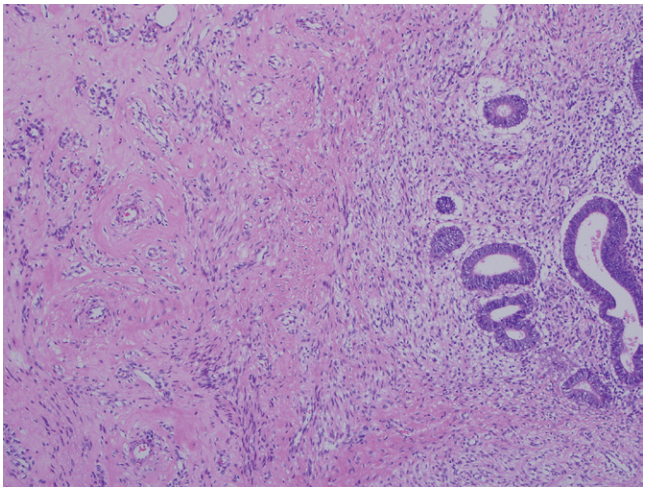


FIGURE 5

Higher magnification illustrates the relationship of the smooth muscle and endometrial tissue in a case of intravenous leiomyomatosis with an adenomyotic focus.

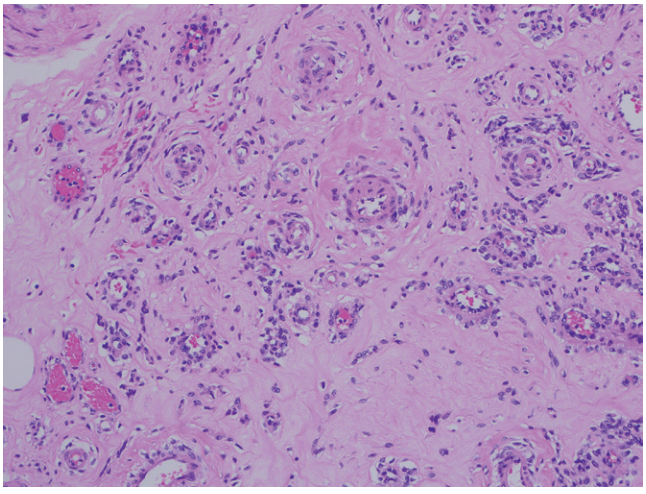


FIGURE 6

Higher magnification of small vessels and capillaries.

MORCELLATION-RELATED DISSEMINATION OF SMOOTH MUSCLE NEOPLASIA

Bradley J. Quade, MD, PhD

Definition—A specific syndrome caused by the iatrogenic dissemination of a morcellated smooth muscle tumor, which is distinct from spontaneous disseminated peritoneal leiomyomatosis.

Clinical Features

Epidemiology

- Power morcellation has been a commonly used technique for removing intraabdominal smooth muscle tumors and may disseminate both normal and tumor tissues in the peritoneal cavity.
- Unexpected leiomyosarcoma occurs in approximately 1 to 2 per 1000 routine hysterectomies for presumed benign leiomyomata.
- Malignancies can be detected in as high as 1:350 morcellation procedures for presumed symptomatic leiomyomata.

Presentation

- Recurrent neoplasms following morcellation are typically seen as multiple tumor nodules or plaques on peritoneal surfaces.
- In comparison to the typical case of sporadic disseminated peritoneal leiomyomatosis, morcellation-associated cases tend to have fewer and larger peritoneal or omental tumors.

Prognosis and Treatment

- Morcellation is associated with a higher frequency of abdominal-pelvic recurrence relative to conventional hysterectomy, for both benign and malignant soft tissue tumors.
- Morcellation is associated with a significantly shorter median recurrence-free survival (10 vs. 40 months for conventional hysterectomy) in cases of leiomyosarcoma.

Pathology

Histology

- Implantation of normal endometrium and other mesenchymal tumors also have been observed.
- The characteristic histologic features of benign and malignant smooth muscle tumors will be seen.
- However, given the random nature of the fragmentation at the time of morcellation, the deposits may be irregular.
- Evaluation of the interface between tumor and normal tissues may be limited, as is the assessment of tumor size.
- A high proliferative rate or infiltration into adjacent normal tissues at site(s) of dissemination may herald an aggressive clinical course.

Immunopathology (Including Immunohistochemistry)

- Usually noncontributory unless the histology of the tumor is unclear.

Main Differential Diagnosis

- Disseminated peritoneal leiomyomatosis—may have a similar distribution, but without a history of power morcellation, and sporadic disseminated peritoneal leiomyomatosis typically presents with higher numbers of smaller tumorlets.

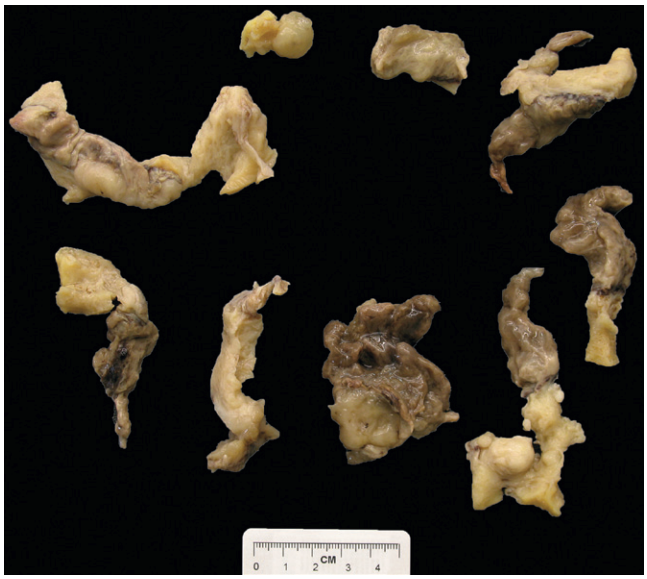


FIGURE 1

Typical morcellation specimen with irregular fragments of smooth muscle tumor.

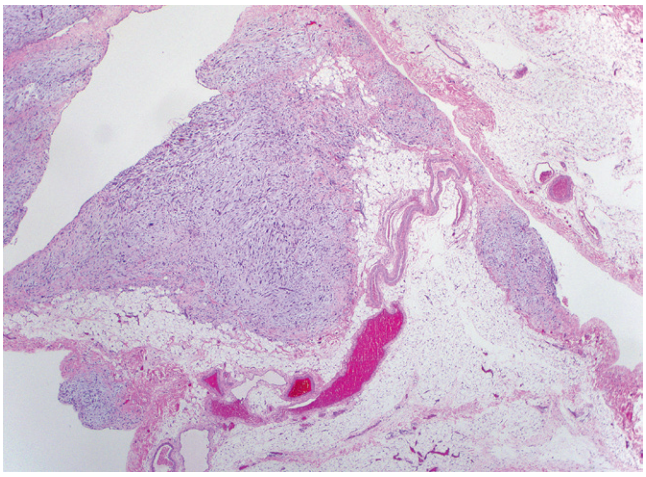


FIGURE 2

Recurrent leiomyosarcoma post morcellation. Note the irregular size and shape of the tumor on histology, corresponding to a variable clinical presentation.

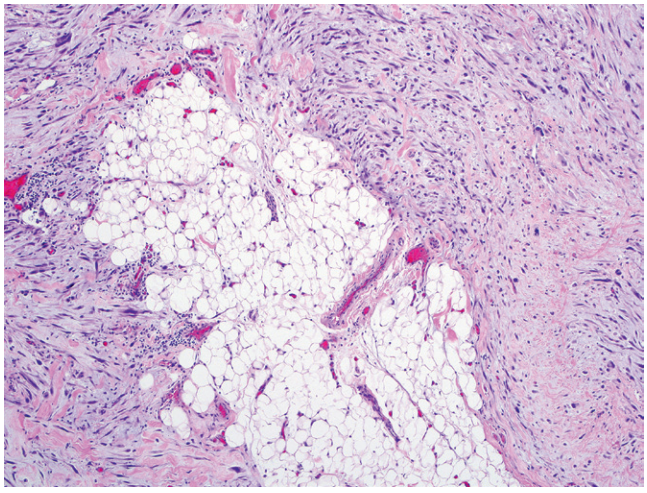


FIGURE 3

Recurrent leiomyosarcoma post morcellation. At higher magnification obvious infiltration of adipose tissue can be appreciated.

DISSEMINATED PERITONEAL LEIOMYOMATOSIS

Bradley J. Quade, MD, PhD

Definition—An uncommon disorder marked by the presence of multiple smooth muscle tumors that are scattered throughout the peritoneum and omentum.

Clinical Features

Epidemiology

- Disseminated peritoneal leiomyomatosis (DPL) is a rare disorder.
- It is most commonly seen in reproductive-age women; however, cases have been identified after menopause.

Presentation

- Patients may be asymptomatic or may present with symptoms of mass effect.

Prognosis and Treatment

- Overall, DPL has a benign (and sometimes protracted) clinical course.
- Surgical intervention may be warranted in severe or symptomatic cases.
- Several reports suggest that aggressive surgical intervention may be detrimental as it can be associated with increased morbidity.

Pathology

Histology

- The tumorlets of DPL may range from 1 to 2.5 cm and may be limited to a few nodules or present as hundreds of nodules.
- Histologically each nodule should represent a discreet leiomyoma.
- The leiomyomas should not display any atypia, significant mitotic activity, or necrosis, in keeping with their uterine counterparts.
- Malignant transformation has been known to occur and is marked by the same features that are diagnostic of leiomyosarcoma in the uterus. The presence of necrosis, atypia, and increased mitotic activity should be readily apparent.

Immunopathology (Including Immunohistochemistry)

- The individual tumorlets will stain positive for SMA and desmin, analogous to their uterine counterparts.

Main Differential Diagnosis

- Metastatic leiomyosarcoma.
- Metastatic carcinoma (clinically and grossly).
- Seeding of the abdominal cavity following morcellation procedures.

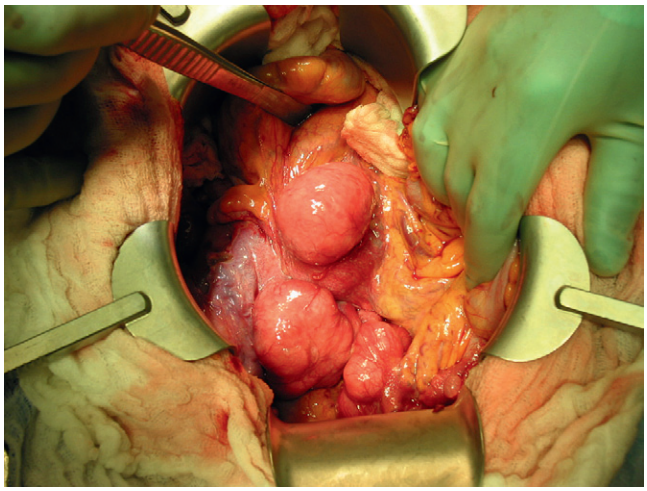


FIGURE 1

DPL. Numerous smooth muscle tumors can be seen growing within the abdominal cavity.

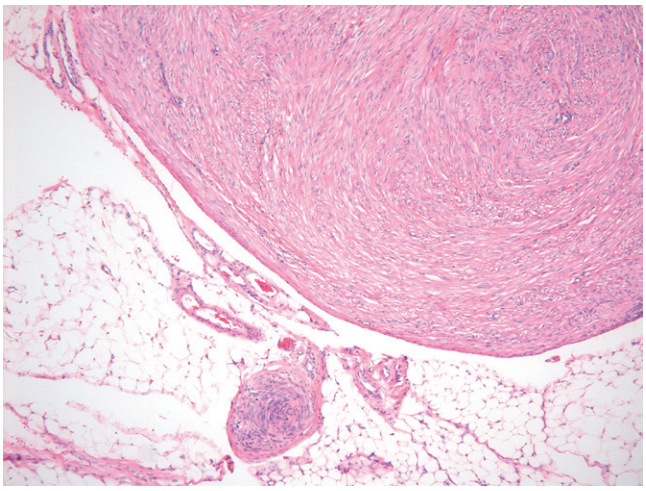


FIGURE 2

DPL. Two leiomyomas within the omentum.

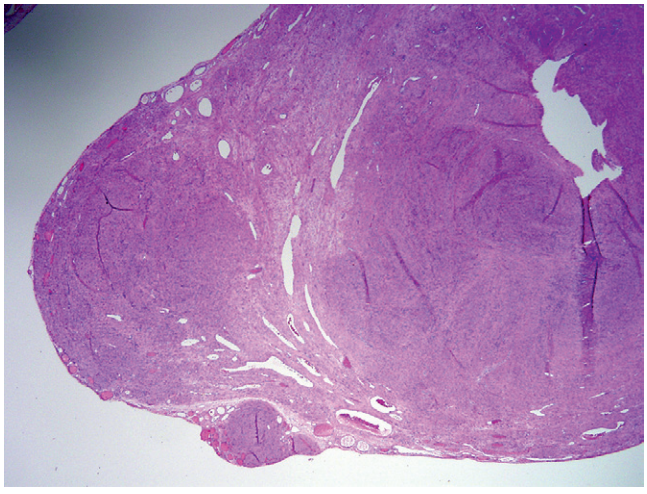


FIGURE 3

DPL. Low-power view of three discrete leiomyomas within the abdominal cavity.

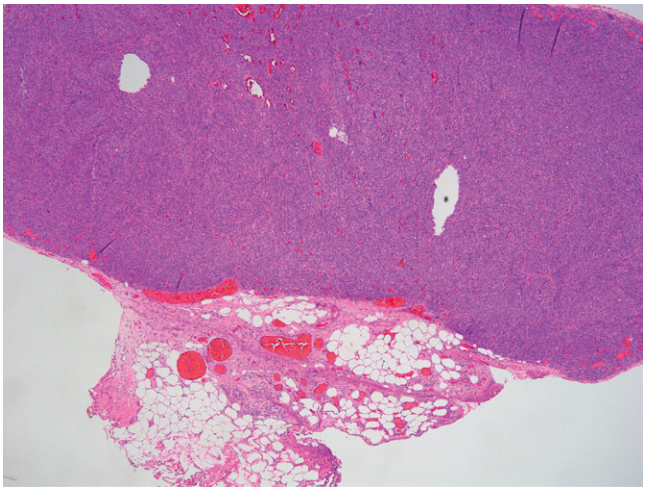


FIGURE 4

DPL. Mesentery with a cellular leiomyoma.

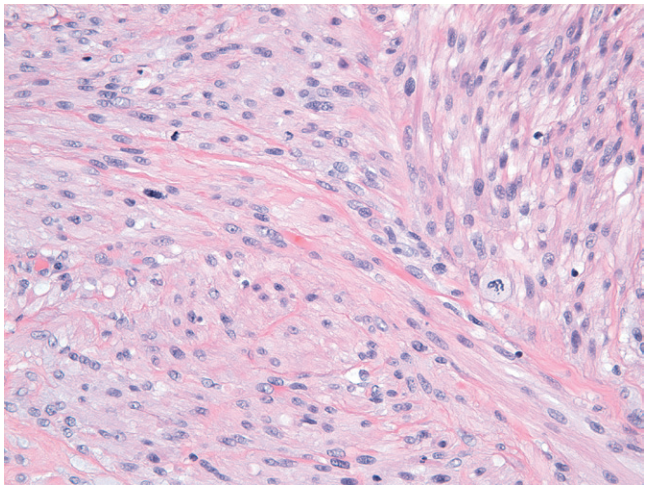


FIGURE 5

DPL. Malignant transformation may occur. Note the increased mitotic activity and subtle nuclear pleomorphism.

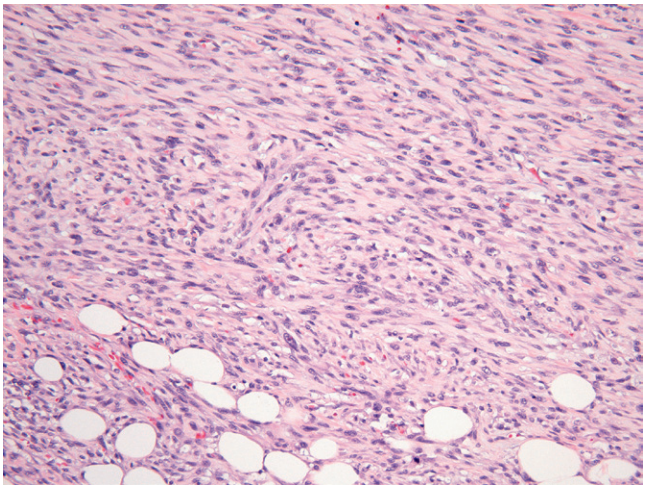


FIGURE 6

DPL. The tumor pictured in Figure 5, infiltrating omental fat.

PATHOLOGY FOLLOWING UTERINE ARTERY EMBOLIZATION

■ **Bradley J. Quade, MD, PhD**

Definition—Changes in the myometrium following an embolization procedure for a presumed leiomyoma using synthetic material.

Clinical Features

Epidemiology

- Uterine embolization procedures are performed about 25,000 times per year in the United States.

Presentation

- The procedure is performed by introducing a catheter into the uterine artery and injecting synthetic material (often polyvinyl alcohol or tris-acryl gelatin microspheres).
- Continued growth or postprocedure pain may result in subsequent hysterectomy and examination of these embolized tumors by pathologists.

Prognosis and Treatment

- In rare cases leiomyosarcomas have been embolized, resulting in slightly delayed diagnosis and treatment.

Pathology

Histology

- On gross examination, ischemic necrosis with or without calcification is present, usually as circumscribed soft yellow change of the myometrial mass.
- Spheres of foreign material can be seen grossly, filling and distending vessels within and adjacent to the ischemic tumor mass.
- At low power, homogenous acellular bluish-purple to pink material is apparent within vascular spaces and sometimes associated with foreign body giant cell reaction around the microsphere.
- Bland ischemic necrosis is often prominent; mitotic activity may be present, particularly immediately adjacent to the zone of necrosis.
- Ischemic necrosis is characterized by pink necrotic debris without prominent cell borders (ghost cells) and with a transition zone (similar to granulation tissue) from viable to nonviable areas.
- Tumor necrosis, atypical mitotic figures, and significant mitotic activity are not present.

Immunopathology (Including Immunohistochemistry)

- Positive for smooth muscle actin and desmin.

Main Differential Diagnosis

- Leiomyosarcoma, if ischemic necrosis is misclassified as tumor necrosis.

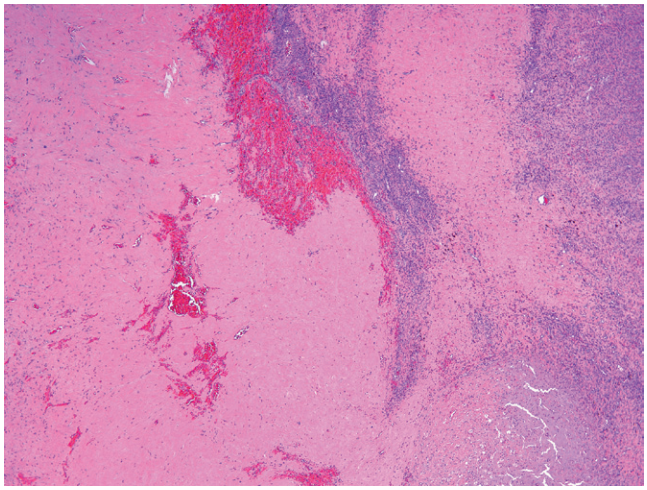


FIGURE 1

Leiomyoma embolization artifact. An abrupt transition to ischemic necrosis with hemorrhage.

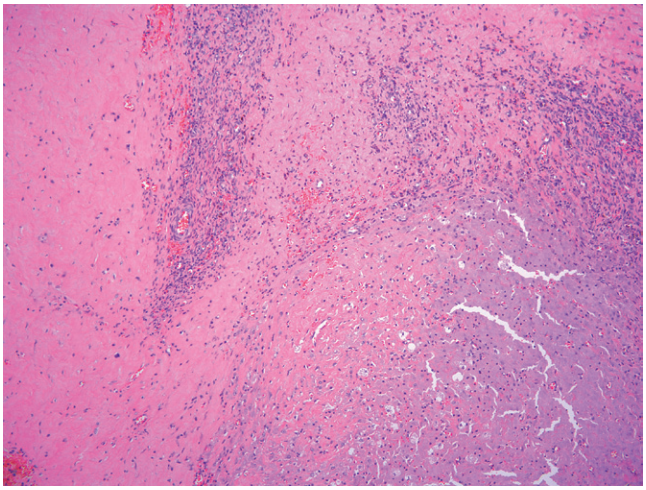


FIGURE 2

Leiomyoma embolization artifact. Ischemic necrosis.

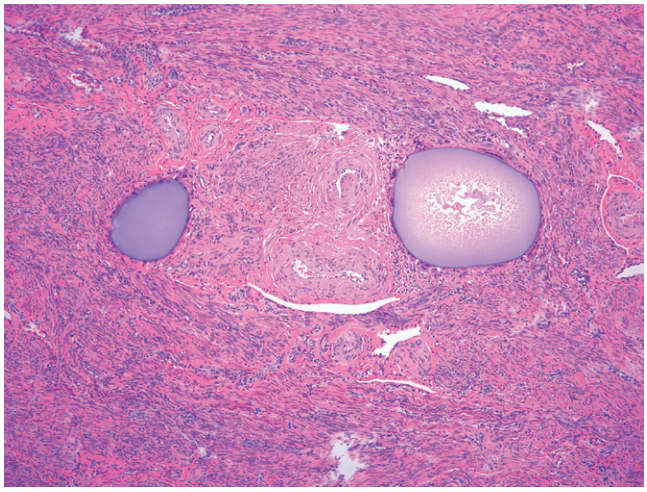


FIGURE 3

Leiomyoma embolization artifact. Blue to pink embolization material is seen within the vascular spaces in the adjacent myometrium.

HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CARCINOMA SYNDROME

PITFALL

Definition—A unique variant of uterine smooth muscle tumor associated with a genetically transmitted increased risk of renal cell carcinoma (RCC) (loss of heterozygosity [LOH] at 1q43).

Clinical Features

Epidemiology

- The underlying defect is a germ-line heterozygous loss of function mutation in the fumarate hydratase gene with LOH at 1q43. Cases can be both germ-line and sporadic.
- Patients typically (77%) present with leiomyomas, often at a young age.
- The associated RCC is aggressive and often presents at a late stage.

Presentation

- Typically younger age of onset and with multiple leiomyomata up to 8 cm.

Prognosis and Treatment

- The leiomyoma carries no risk to the patient other than signifying an increased risk of RCC.
- Identification of subjects at risk for RCC may reduce mortality by earlier detection.

Pathology

Histology

- Three characteristic low-power features include increased cellularity, multinucleation, and increased atypia.
- The hallmark feature is a large orangeophilic nucleolus with a perinuclear halo.
- Modest (up to 3 per 10 HPF) increase in mitotic index.
- Features of sarcoma (high mitotic index, tumor necrosis) are not present.

Immunopathology (Including Immunohistochemistry)

- Same as any conventional leiomyoma.

Main Differential Diagnosis

- Cellular leiomyoma—the prominent nucleolar features exclude this tumor.
- Leiomyosarcoma—contains both necrosis and high mitotic index as well as prominent atypia.

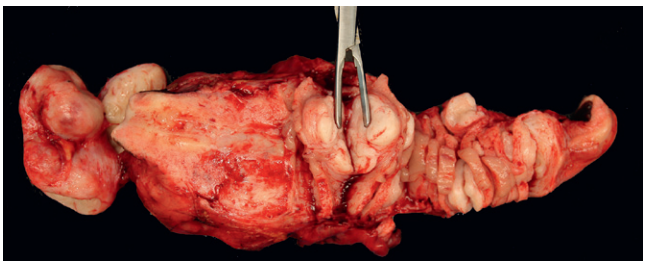


FIGURE 1

Suspected hereditary leiomyomatosis and renal cell carcinoma (HLRCC). Multiple leiomyomata in the uterus of a young woman whose tumor contained the characteristic histologic features associated with fumarate hydratase deficiency.

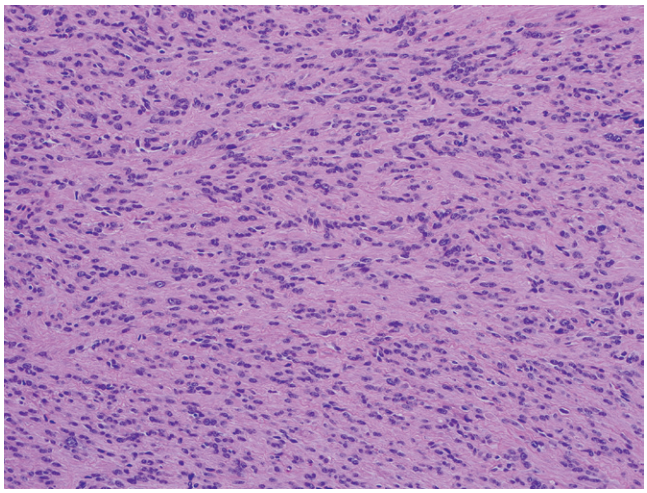


FIGURE 2

Leiomyoma in a case of documented HLRCC. Note the modest increase in cellularity. Some nuclear variation is visible at this power.

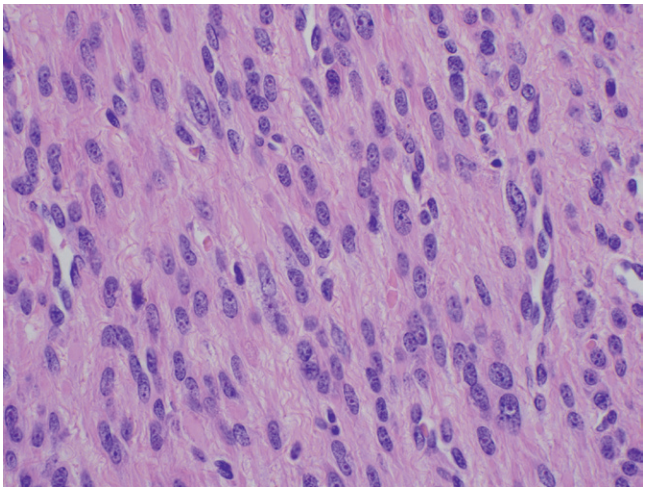


FIGURE 3

Leiomyoma in a documented case of HLRCC. The atypia is more conspicuous at this magnification.

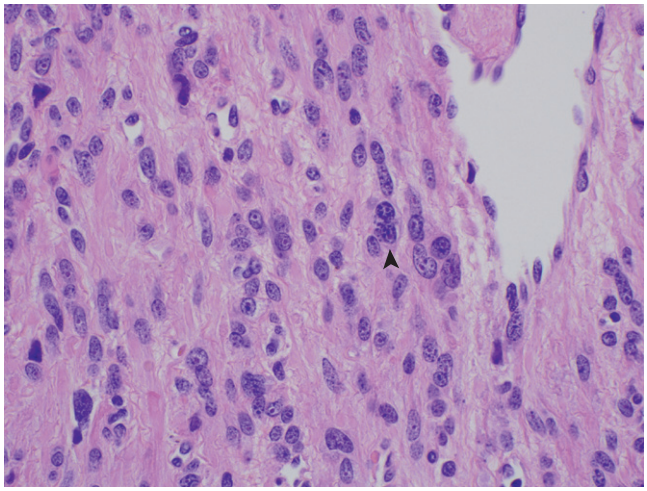


FIGURE 4

HLRCC. Nuclear overlap suggesting multinucleation *(arrow)*.

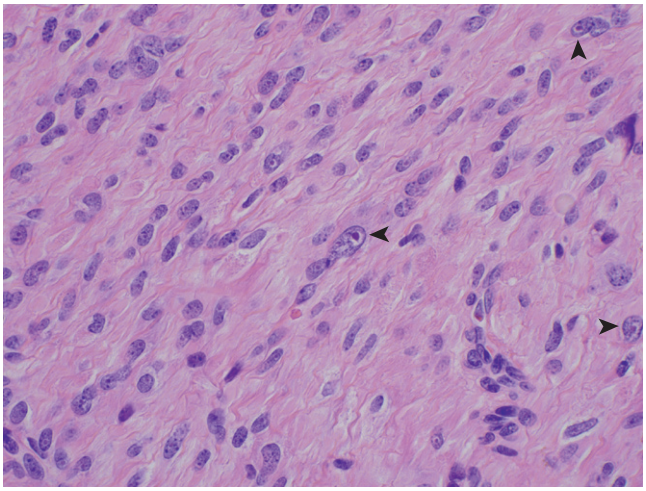


FIGURE 5

HLRCC. This field contains several prominent orangeophilic nuclei *(arrows)*.

LEIOMYOSARCOMA

Definition—A malignant tumor of smooth muscle originating in the myometrium.

Clinical Features

Epidemiology

- Rare (estimated incidence of 0.64 per 100,000 women).
- Account for 1% of all uterine malignancies and more than 25% of uterine mesenchymal malignancies.
- Mostly occurs in postmenopausal women.

Presentation

- Most cases of leiomyosarcoma are discovered following a procedure for symptomatic leiomyoma.
- Less often, postmenopausal patients present with a rapidly enlarging uterine mass.

Prognosis and Treatment

- The mainstay of primary treatment includes hysterectomy and resection of extrauterine disease. Adjuvant chemotherapy is of unclear benefit at this time.
- Aggressive behavior, with frequent aggressive local growth, recurrence, and distant metastases (lung, liver).
- The 5-year survival rate has been reported between 15% and 25%.
- A new disease pattern is being encountered following morcellation for what was assumed to be a benign leiomyoma. Morcellation can result in dissemination of the tumor within the peritoneal cavity with an anticipated poor outcome.

Pathology

Histology

- Grossly, leiomyosarcomas are often seen as a solitary or dominant mass (usually at least 10 cm) with grossly evident infiltration of the myometrium, and a soft, tan cut surface (fish flesh).
- On cut section the tumor does not bulge and often has a gray or variegated appearance.
- The three basic histologic components of leiomyosarcoma are atypia, increased numbers of mitoses, and tumor necrosis (not ischemic necrosis). Tumor cell necrosis is abrupt, with irregular borders and abundant "ghost nuclei" present within the zone of necrosis. As opposed to ischemic necrosis, a reactive rim of myofibroblasts is not present (although this distinction is sometimes difficult).
- If all three features are present, the diagnosis is straightforward, but this is often not the case.
- In the presence of true, multifocal, tumor necrosis, a high mitotic rate and nuclear atypia are not required.
- Evaluation of tumor necrosis is both the most critical and the most controversial aspect of smooth muscle neoplasms.
- If tumor necrosis is absent, then marked diffuse nuclear atypia and a mitotic rate greater than 10/10 high-power fields must be present.
- Mitotic activity should be assessed in more than one area; usually at least three sets of 10 high-power fields should be counted (be sure to exclude pyknotic cells).
- Atypical mitotic figures (multipolar mitoses, lagging chromosomes, and extreme aneuploidy) are often seen.
- Nuclear atypia is usually identifiable at low power and is characterized by any nuclear enlargement and irregularity, hyperchromasia, clumped chromatin, prominent nucleoli, and multilobation, often in combination.
- Other helpful features include increased cellularity or marked hypercellularity and infiltration into the surrounding myometrium.

Immunopathology (Including Immunohistochemistry)

- Positive for desmin and smooth muscle actin.
- Negative for S100.

Main Differential Diagnosis

- Smooth muscle tumor of uncertain malignant potential (see chapter on STUMP).
- Endometrial stromal sarcoma (on small samples). See chapter on ESS.

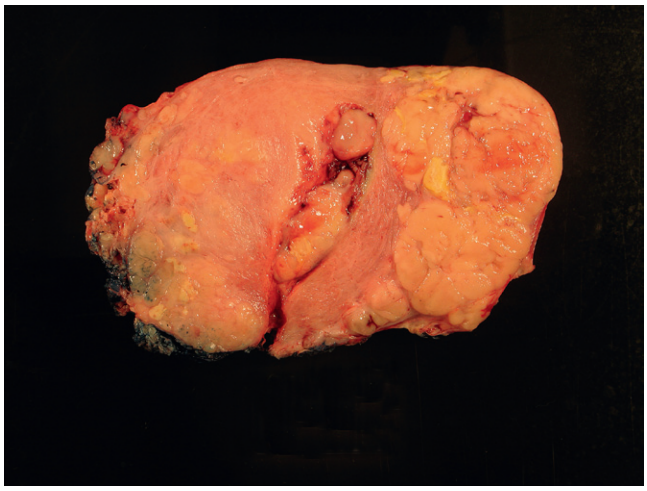


FIGURE 1

Leiomyosarcoma. Gross image of an irregular tumor with a tan-brown, fleshy cut surface. Note how the tumor does not bulge as seen in a typical leiomyoma.

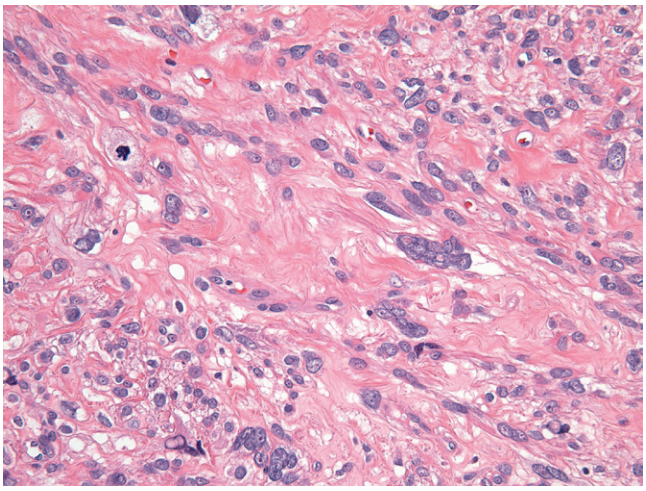


FIGURE 2

Leiomyosarcoma. Nuclear atypia.

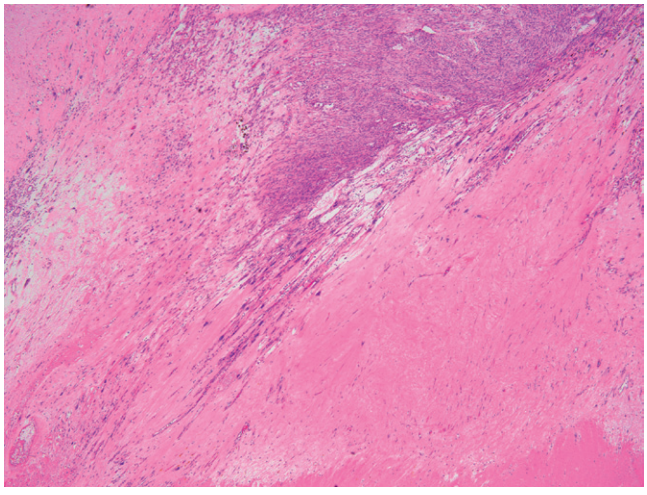


FIGURE 3

Leiomyosarcoma. Low-power view of an area of geographic necrosis. Note the abrupt transition between viable and necrotic areas.

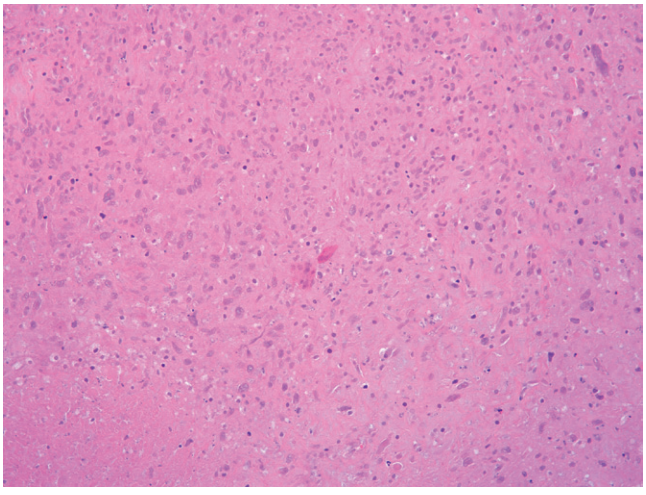


FIGURE 4

Leiomyosarcoma. Tumor cell (ghost cells) within an area of coagulative tumor necrosis.

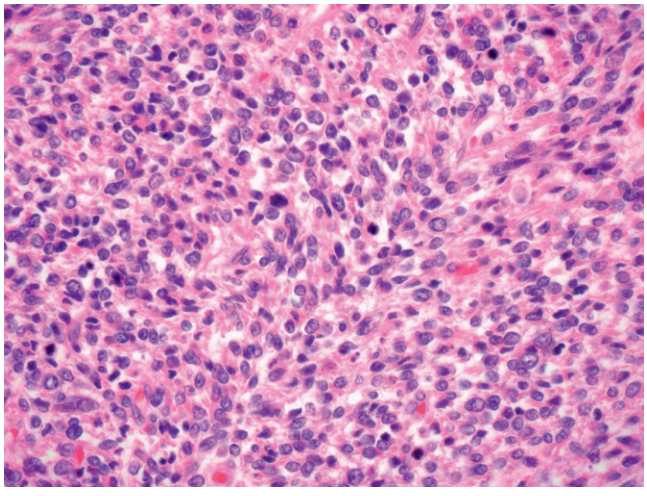


FIGURE 5

Leiomyosarcoma. A cellular area with nuclear atypia and numerous mitotic figures.

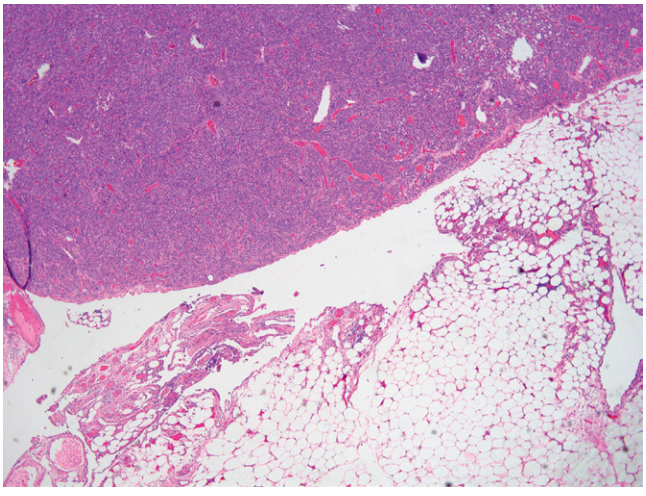


FIGURE 6

Leiomyosarcoma. A nodule of leiomyosarcoma, metastatic to the omentum.

MYXOID LEIOMYOSARCOMA

Definition—An aggressive histologic variant of uterine leiomyosarcoma.

Clinical Features

Epidemiology

- Rare, even among uterine leiomyosarcomas.

Presentation

- Similar to usual leiomyosarcoma.

Prognosis and Treatment

- Prognosis is poor, and overall survival seems to be lower than in usual leiomyosarcoma.

Pathology

Histology

- The gross appearance is usually characterized by a large mass with a soft, gelatinous cut surface.
- At low power these tumors often appear relatively hypocellular due to the accumulation of blue intracellular myxoid material.
- Criteria for a diagnosis of malignancy in myxoid smooth muscle lesions (leiomyosarcoma) include at least one of the following features:
- Mitoses greater than 2/10 high-power fields.
  - Significant cytologic atypia (e.g., nuclear irregularity and hyperchromasia).
  - True tumor cell necrosis.
  - Destructive infiltration into the surrounding myometrium.
- The presence of vascular involvement may be helpful, but it is not diagnostic of malignancy and must be distinguished from myxoid intravascular leiomyomatosis.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Other, less aggressive, myxoid smooth muscle neoplasms of the uterus.

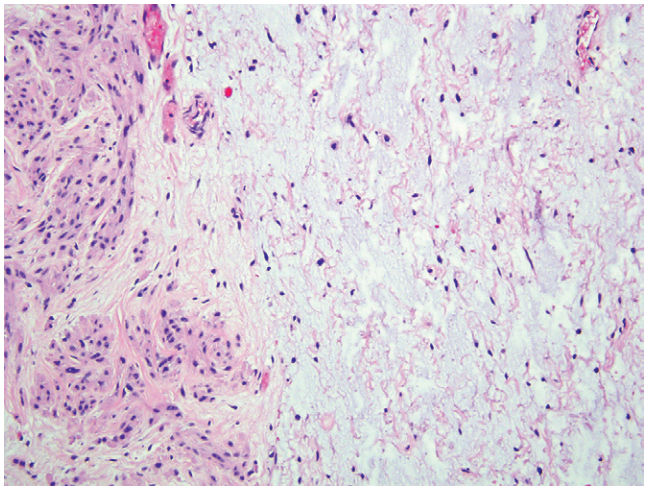


FIGURE 1

Myxoid leiomyosarcoma. A myxoid neoplasm is seen adjacent to bundles of smooth muscle.

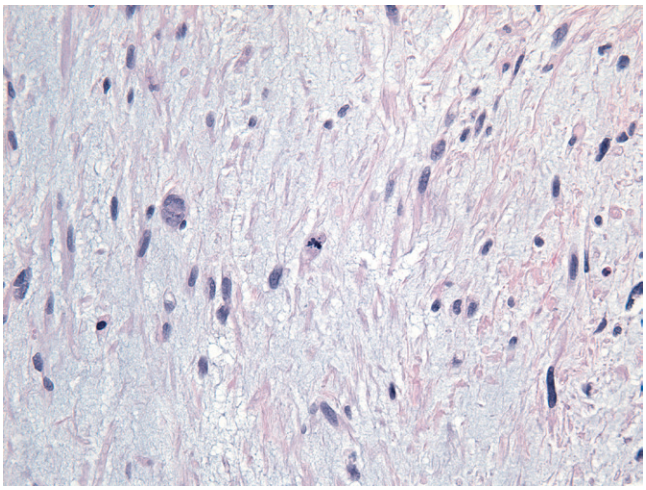


FIGURE 2

Myxoid leiomyosarcoma. A mitotic figure. Note the cigar-shaped smooth muscle cells that are present within the myxoid stroma.

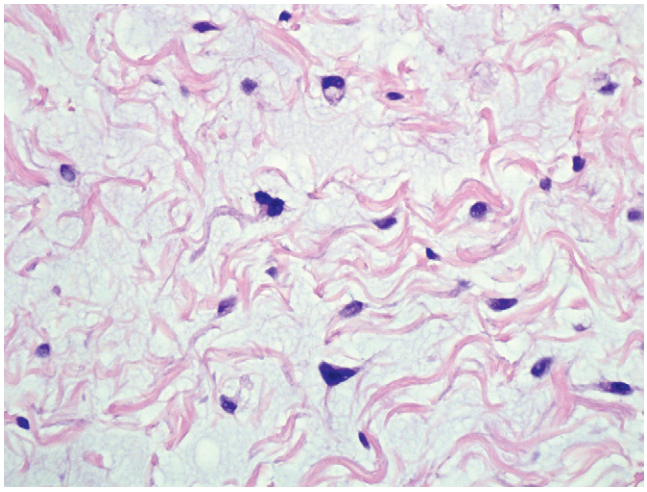


FIGURE 3

Myxoid leiomyosarcoma. Nuclear pleomorphism may be present but is usually mild.

EPITHELIOID LEIOMYOSARCOMA

Definition—A distinctive histopathologic variant of uterine leiomyosarcoma.

Clinical Features

Epidemiology

- Rare.

Presentation

- Similar to usual leiomyosarcoma with nonspecific symptoms including vaginal bleeding, pelvic pressure, and pain.

Prognosis and Treatment

- This variant appears to have a lower overall survival than usual leiomyosarcoma.

Pathology

Histology

- The defining feature of this variant is the presence of nonspindled, round, epithelioid cells.
- The cells have abundant brightly eosinophilic cytoplasm and often appear slightly discohesive.
- Criteria for a diagnosis of leiomyosarcoma are slightly altered if an epithelioid phenotype is present: either true tumor necrosis *or* mitotic count greater than 5/10 high-power fields is sufficient.
- Nuclear atypia, vascular invasion, and large tumor size are also indicative of aggressive behavior but are not sufficient for diagnosis.
- The epithelioid component may be focal or diffuse.

Immunopathology (Including Immunohistochemistry)

- Less positivity for desmin and smooth muscle actin compared with usual leiomyosarcoma.
- Cytokeratin stains will be negative.

Main Differential Diagnosis

- Epithelioid smooth muscle tumor of uncertain malignant potential.
- Undifferentiated carcinoma. Smooth muscle markers will be negative.

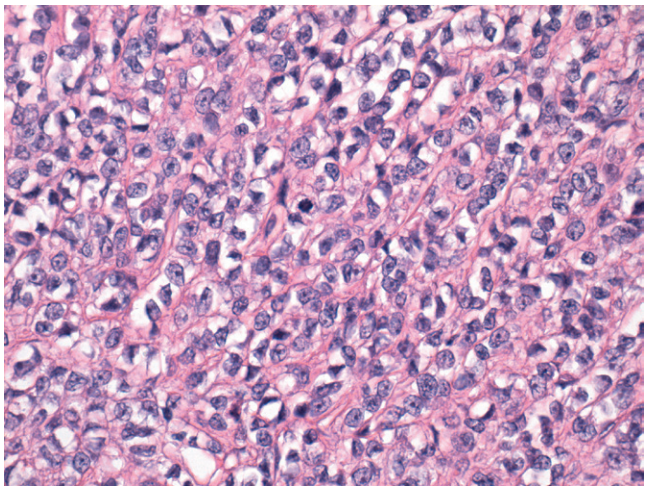


FIGURE 1

Epithelioid leiomyosarcoma. Smooth muscle cells with abundant clear cytoplasm arranged in cords.

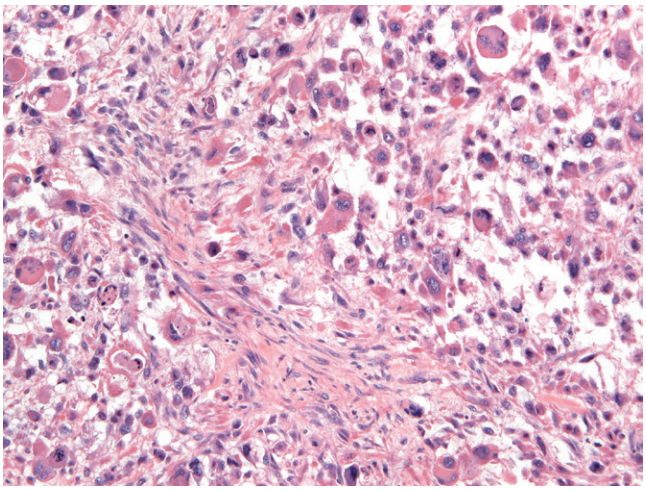


FIGURE 2

Epithelioid leiomyosarcoma. Epithelioid cells with abundant, eosinophilic cytoplasm and distinct cell borders. These cells can appear similar to those seen in poorly differentiated carcinoma.

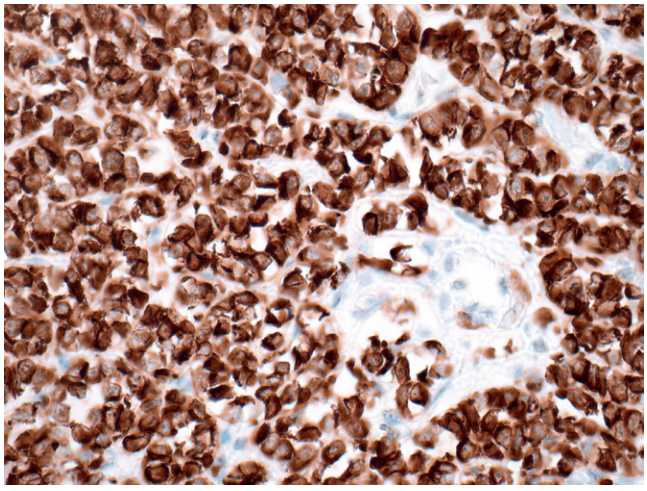


FIGURE 3

Epithelioid leiomyosarcoma. Immunohistochemical stain for desmin showing strong cytoplasmic positivity.

PEComa

Definition—A tumor composed of a morphologically and immunohistochemically distinct cell type with features of smooth muscle and melanocytic differentiation.

Clinical Features

Epidemiology

- Very rare; a somewhat controversial diagnosis at this site (uterus).
- Cases have been reported in a wide age range (40s to 80s).

Presentation

- Presumably similar to leiomyomata, although the number of reported cases is very small.

Prognosis and Treatment

- Prognosis is difficult to estimate due to the small number of cases, although some histologic features are associated with aggressive behavior.
- Hysterectomy is the treatment of choice.

Pathology

Histology

- The overriding histologic feature that should prompt the pathologist to consider this diagnosis is the presence of epithelioid cytomorphology.
- In particular the epithelioid cells tend to have abundant clear to eosinophilic (and sometimes granular) cytoplasm with a centrally placed nucleus.
- In some areas these cells can be seen in a distinctly perivascular distribution and located just under the endothelial layer.
- A commonly identified invasive growth pattern is similar to that seen in an endometrial stromal sarcoma, with fingers and tongues of tumor cells permeating the myometrium.
- Important histologic features that apparently portend a worse prognosis include large size (greater than 5 cm), an infiltrative growth pattern, high nuclear grade, the presence of true tumor necrosis, and identifiable mitotic activity (>1/50 high-power fields).
- As this entity is controversial in the uterus, strict application of histologic and immunophenotypic criteria should be used before rendering this diagnosis.

Immunopathology (Including Immunohistochemistry)

- Positive for muscle markers: desmin, smooth muscle actin, and calponin.
- Positive for melanocytic markers: HMB45, Melan-A, and MiTF.

Main Differential Diagnosis

- Epithelioid leiomyoma.
- Epithelioid leiomyosarcoma.
- Endometrial stromal sarcoma with focal clear-cell features. All of these entities are best excluded by the absence of melanocytic markers.

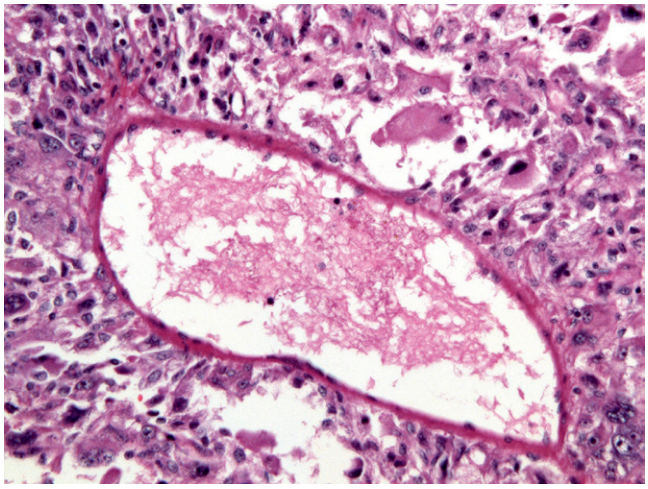


FIGURE 1

Uterine PEComa. Cells can be seen in a perivascular distribution, directly under the endothelial surface.

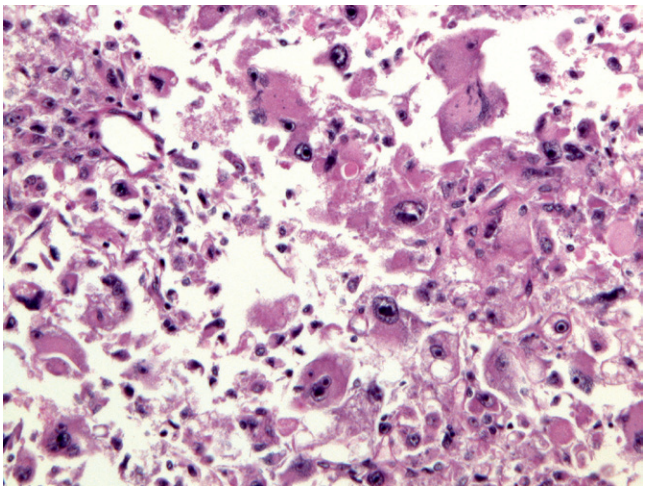


FIGURE 2

Uterine PEComa. Epithelioid cells with atypical nuclei and clear cytoplasm.

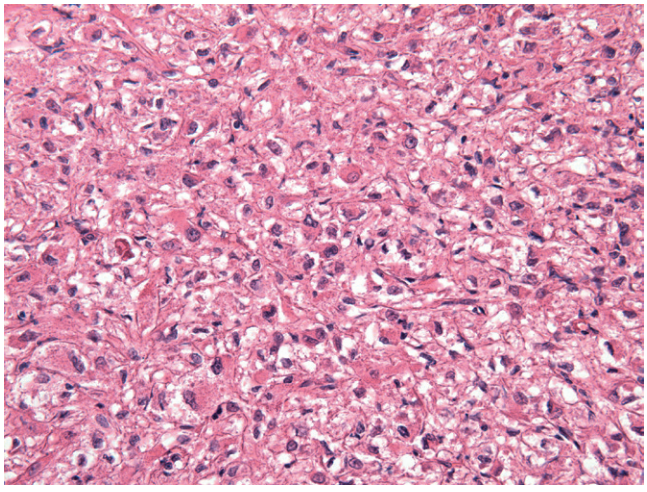


FIGURE 3

Uterine PEComa. Alternatively eosinophilic cells may predominate.

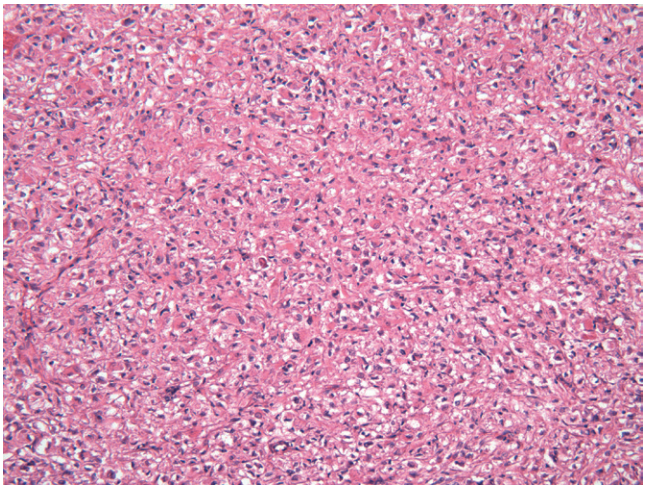


FIGURE 4

Uterine PEComa. In some cases a vague, nested pattern may be present.

REPRODUCTIVE TRACT LYMPHOMA

■ **Emily E.K. Meserve, MD, MPH**

DEFINITION—A malignant lymphoid process involving the reproductive tract.

CLINICAL FEATURES

EPIDEMIOLOGY

- Reproductive tract lymphoma is exceedingly rare but about two thirds will be primary tumors.
- In about one third of cases the tumor will be a manifestation of a systemic lymphoma.

PRESENTATION

- Patients may present with abnormal uterine bleeding. About two thirds involve the adnexae, followed by the uterus and cervix.

PROGNOSIS AND TREATMENT

- Uterine or adnexal involvement by lymphoma typically represents advanced stage disease and has a dismal prognosis.
- Chemotherapy specific to the type of lymphoma present is the treatment of choice.

PATHOLOGY

HISTOLOGY

- An infiltrate of monomorphic lymphocytes is invariably present.
- Loss of normal architecture and glands (effacement) may occur.
- In small biopsy specimens of the endometrium the fragments may resemble those seen in submucosal leiomyomas (aglandular functionalis); however, the stroma will appear hypercellular.
- The most common cell types are diffuse large B-cell lymphoma, follicular lymphoma, and Burkitt lymphoma.

IMMUNOPATHOLOGY (INCLUDING IMMUNOHISTOCHEMISTRY)

- Immunostains for lymphoid differentiation (CD45) and B and T cell markers are helpful for the classification of lymphoid neoplasms.

MAIN DIFFERENTIAL DIAGNOSIS

- Marked chronic inflammation (cervicitis, endometritis, salpingitis)—there will be a mixed infiltrate.

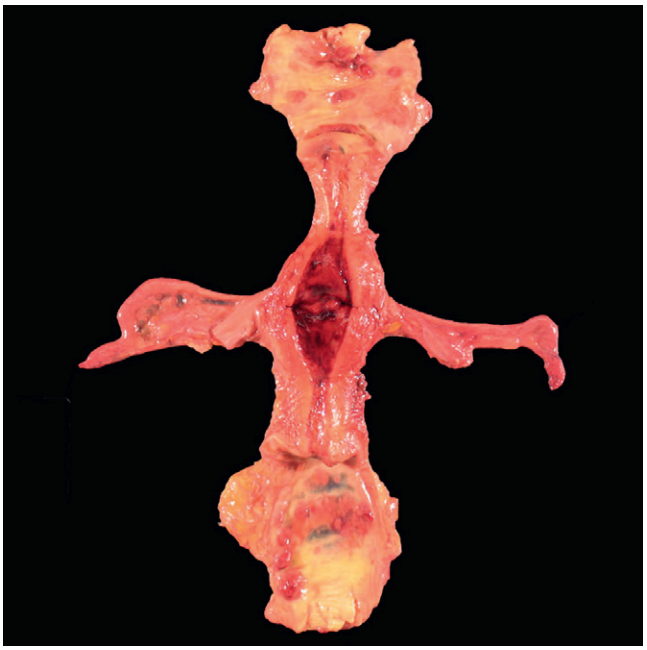


FIGURE 1
Vaginal lymphoma, seen as multiple small submucosal nodules *(top)*.

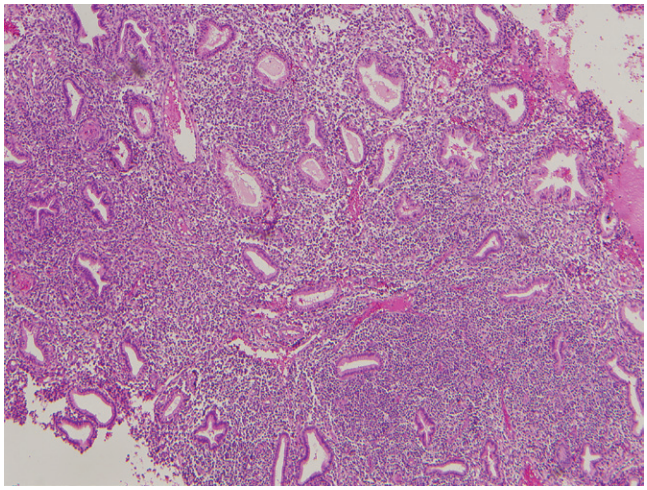


FIGURE 2
Diffuse large B cell lymphoma of the endometrium.

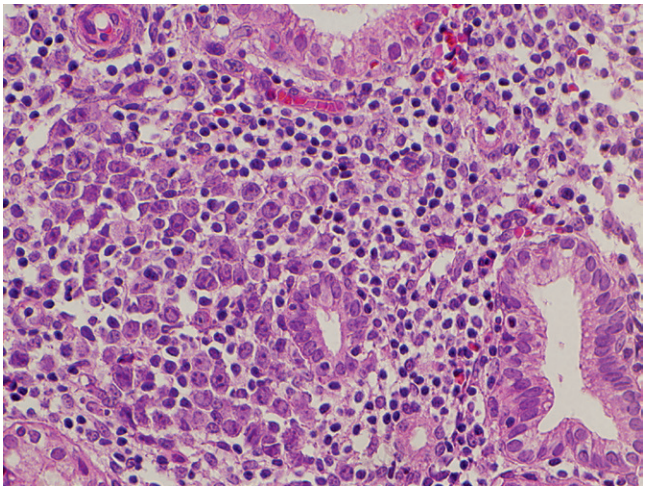


FIGURE 3
Diffuse large B cell lymphoma of the endometrium.

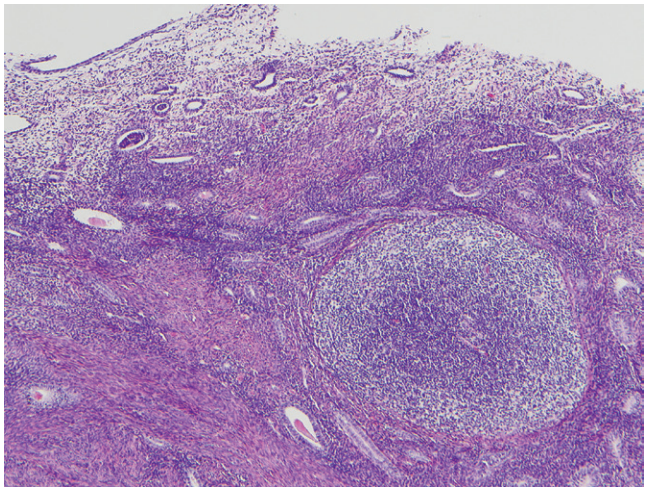


FIGURE 4
Non-Hodgkin's lymphoma involving the endometrium.

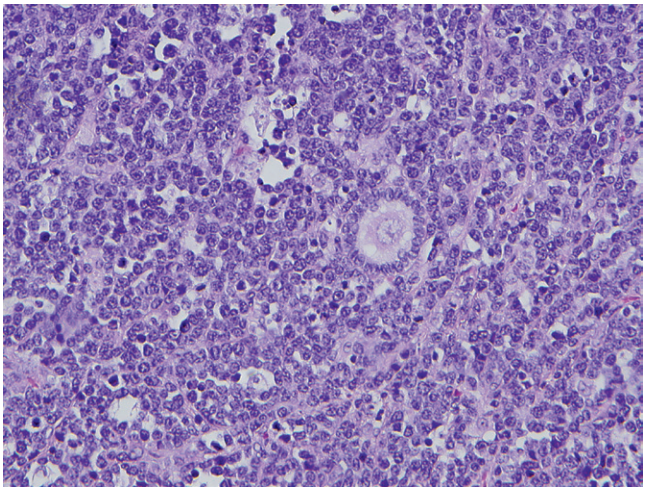


FIGURE 5
Burkitt lymphoma of the ovary. Note the residual oocyte *(center).*

SECTION 4

Fallopian Tube

ADRENAL REST

Definition—A developmental rest of adrenal tissue in the adnexal soft tissue.

Clinical Features

Epidemiology

- Can be seen at all ages and in up to one fourth of fallopian tubes examined. Presumably adrenal rests are misplaced deposits of adrenal tissue.

Presentation

- This is an incidental finding seen in surgical specimens. The most common location is the paratubal or paraovarian soft tissue.

Prognosis and Treatment

- None.

Pathology

Histology

- The appearance is identical to adrenal tissue, consisting of polyhedral cortical cells. Some smaller cells similar to those seen on the surface may also be present. The cells are within a well-defined delicate vascular network. The rest is composed of cortex only; no medullary cells are present.

Immunopathology (Including Immunohistochemistry)

- Noncontributory, although will be negative for inhibin or calretinin (excluding hilar cells).

Main Differential Diagnosis

- Macrophages or histiocytes—typically will manifest with finely granular cytoplasm and pigment deposition.
- Hilar cells—typically found in the ovarian hilus, but might be seen in the adnexae where they will mimic adrenal rest. Will be inhibin or calretinin positive.

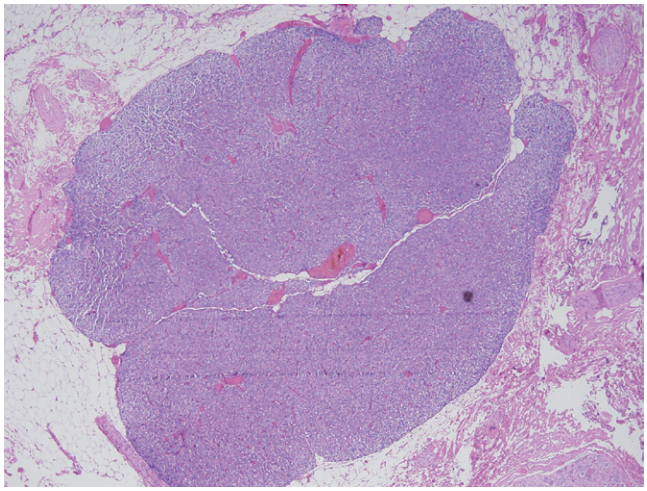


FIGURE 1

Low magnification of an adrenal rest, seen as a lobular, well-circumscribed mass.

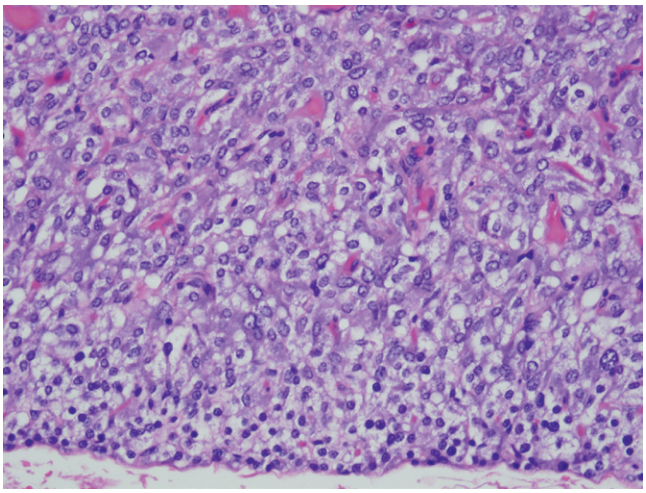


FIGURE 2

Adrenal rest at higher magnification; note the smaller cells at the periphery, similar to those seen in the peripheral cortex of the normal adrenal gland.

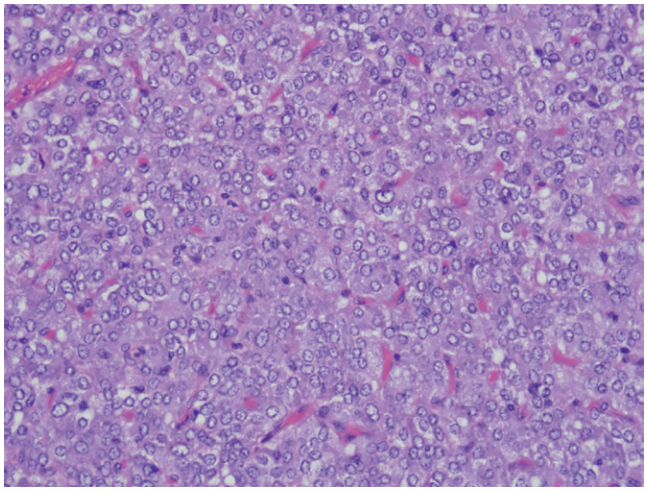


FIGURE 3

Uniform cortical cells with open nuclei. Note the regular vascular network.

PSEUDOXANTHOMATOUS SALPINGIOSIS

Definition—Accumulation of histiocytic cells within the fallopian tube in association with pelvic endometriosis.

Clinical Features

Epidemiology

- Pseudoxanthomatous salpingiosis is an uncommon entity that may be found in association with endometriosis.

Presentation

- Usually found incidentally at the time of histologic examination of the fallopian tube. Patients may present with clinical symptoms or signs of endometriosis and/or endometrioma formation.

Prognosis and Treatment

- Pseudoxanthomatous salpingiosis is benign, and treatment of the underlying cause (endometriosis) may be necessary for symptomatic relief. There is an increased risk for infertility and ectopic pregnancy in patients with this process.

Pathology

Histology

- Histiocytes with foamy cytoplasm can be seen within the tubal plica. Evidence of hemorrhage may be seen within the histiocytes and the stroma. A conspicuous lack of other acute and chronic inflammatory cells should be present (hence the alternate name salpingiosis).

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Xanthogranulomatous salpingitis—this entity has considerable inflammation and fibroblast proliferation.
- Chronic salpingitis—may overlap with xanthogranulomatous salpingitis.

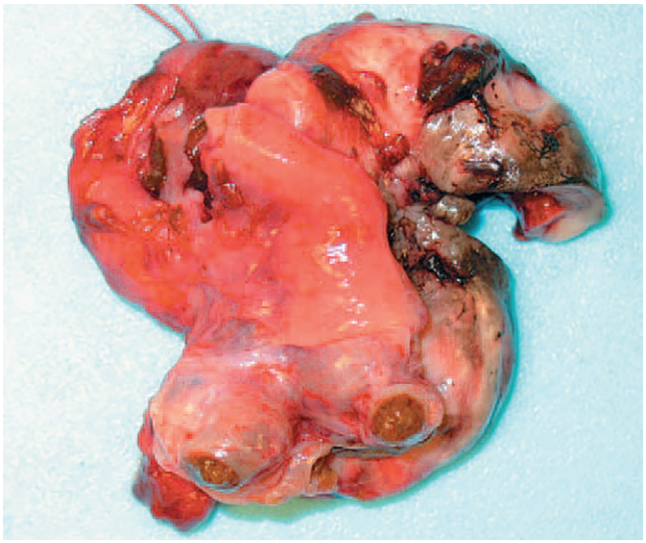


FIGURE 1

Sectioned tubes *(near bottom of picture)* display a golden-brown appearance to the endosalpinx.

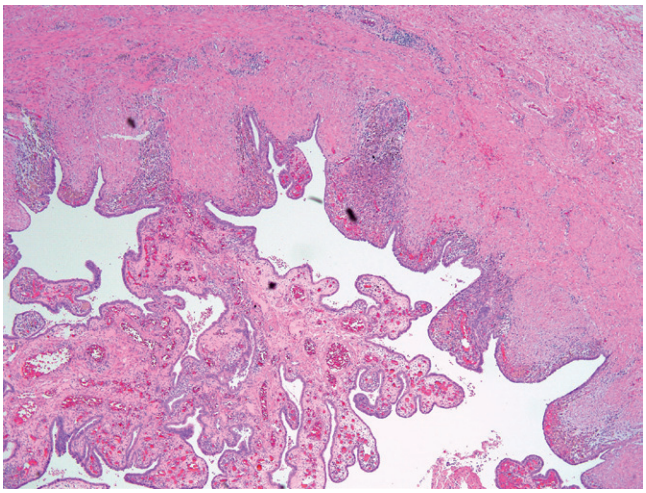


FIGURE 2

Low magnification of tubal lumen shows blunt plica with increased stromal cellularity.

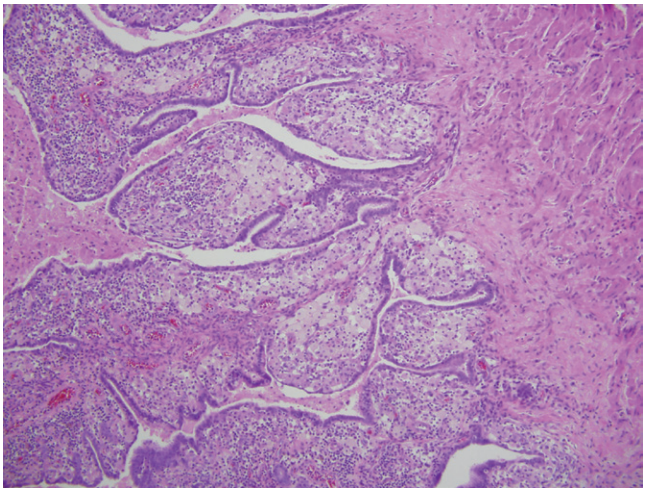


FIGURE 3

Low magnification of mucosa showing prominent macrophages and xanthoma cells.

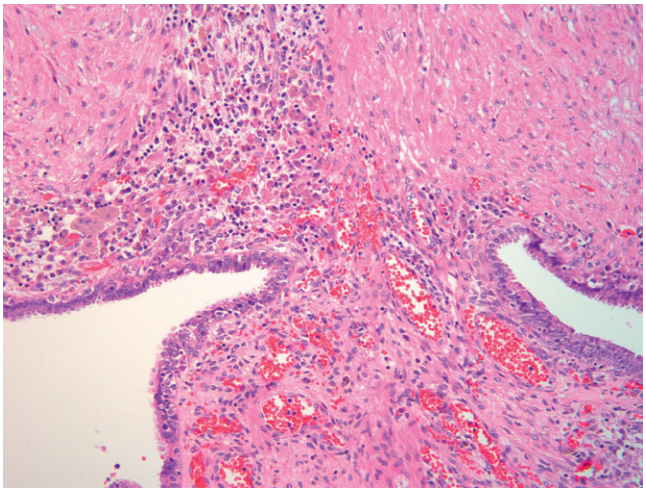


FIGURE 4

A plica with old hemorrhage but few inflammatory cells.

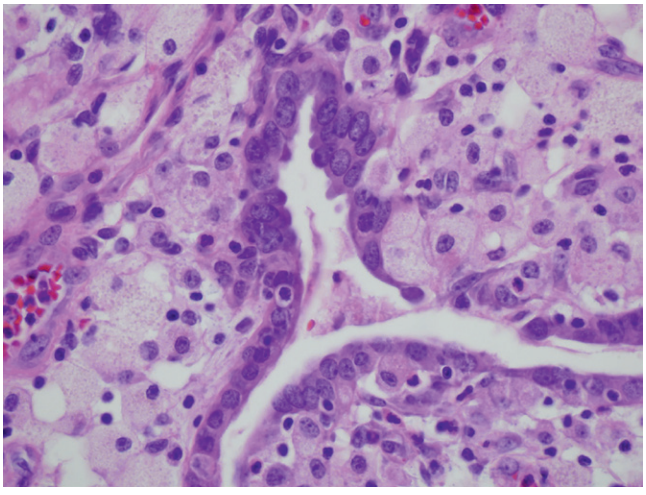


FIGURE 5

Higher magnification shows xanthoma cells in the lamina propria.

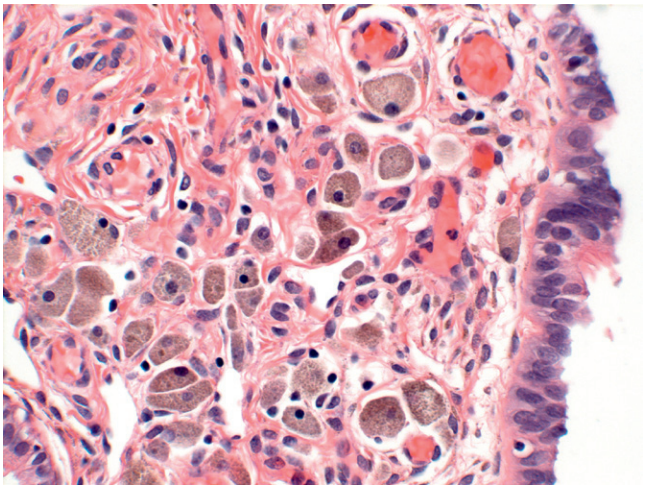


FIGURE 6

These macrophages are heavily pigmented.

XANTHOGRANULOMATOUS SALPINGITIS

Definition—An admixture of inflammatory cells and histiocytes within the fallopian tube.

Clinical Features

Epidemiology

- Xanthogranulomatous salpingitis is an uncommon entity. It is most commonly seen in association with pelvic inflammatory disease, extensive endometriosis, and intrauterine contraceptive devices. Infection with one of a variety of coliform bacteria likely plays a role in some cases. Rare cases have been associated with contrast agents.

Presentation

- Patients present with signs and symptoms of pelvic inflammatory disease including pelvic pain, abnormal bleeding, and fever. The presence of xanthogranulomatous salpingitis is typically identified at the time of histologic examination of the tube in these cases.

Prognosis and Treatment

- Xanthogranulomatous salpingitis is benign; however, treatment of the underlying cause is required (antibiotics and surgery).

Pathology

Histology

- Xanthogranulomatous salpingitis displays a prominent acute and chronic inflammatory infiltrate with admixed foamy histiocytes. The presence of the acute and chronic inflammatory infiltrate differentiates this from pseudoxanthomatous salpingitis.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Pseudoxanthomatous salpingitis—typically characterized by xanthoma cells and pigment in the lamina propria with preservation of architecture, but without the prominent inflammatory component.
- Granulomatous salpingitis—well-developed granulomas are present.

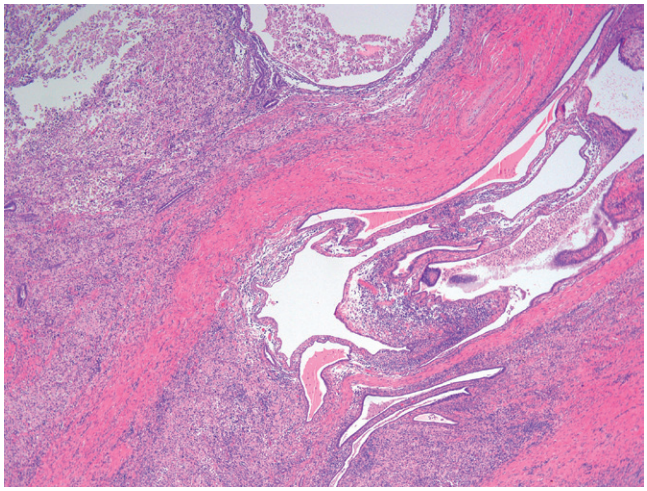


FIGURE 1

Xanthogranulomatous salpingitis. At low magnification the tubal architecture is distorted by the prominent inflammatory process.

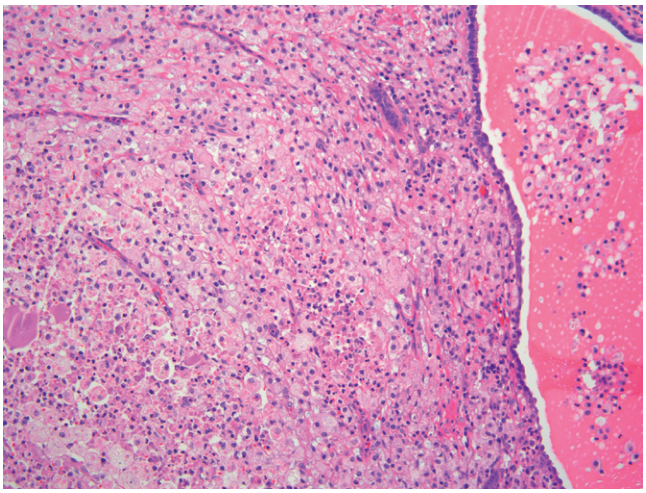


FIGURE 2

Xanthogranulomatous salpingitis. A prominent inflammatory infiltrate with foamy histiocytes. This distinguishes this entity from pseudoxanthomatous salpingitis, which typically does not cause marked distortion of plical architecture.

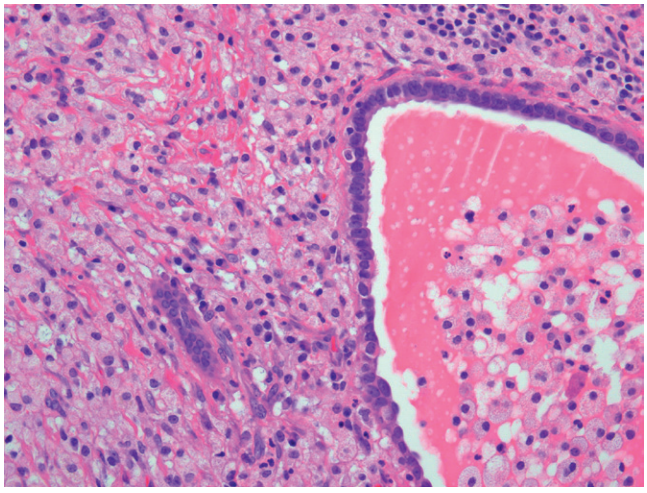


FIGURE 3

High magnification shows numerous foamy histiocytes.

FOLLICULAR SALPINGITIS

Definition—The chronic phase of pelvic inflammatory disease.

Clinical Features

Epidemiology

- Follicular salpingitis is the chronic phase of pelvic inflammatory disease, which is common in the United States (as well as the remainder of the world). The majority of cases happen in young adults and are related to sexual activity. The majority of the remaining cases are secondary to instrumentation or intrauterine device use.

Presentation

- Patients may be asymptomatic, and the follicular salpingitis may be discovered after it has resolved (as hydrosalpinx or chronic follicular salpingitis).

Prognosis and Treatment

- As a result of scarring after resolution, fertility may be greatly diminished or lost. With repeated bouts of salpingitis the risk of infertility climbs over 50%. There is a greatly increased risk of ectopic (tubal) pregnancy following cases of pelvic inflammatory disease. About one half of ectopic pregnancies are related to chronic salpingitis and the presence of pre-existing inflammation increases the risk of ectopic to greater than 7 fold that of the general population. Antibiotic therapy with multiagent drugs is the typical first-line treatment choice; however, severe or refractory cases (including tubo-ovarian abscess formation) may require surgery.

Pathology

Histology

- During the chronic phase of pelvic inflammatory disease (follicular salpingitis), the inflammatory infiltrate within the tubal lamina propria is comprised of lymphocytes and plasma cells. As the lesion progresses, the plica becomes scarred and fused and the inflammatory infiltrate decreases. In resolved lesions the inflammatory infiltrate is sparse and the lamina propria is fibrotic; eventual hydrosalpinx (tubal dilation) may occur.

Diagnostic terminology—Chronic follicular salpingitis (e.g., with or without hydrosalpinx, adhesions).

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Acute salpingitis—typically will exhibit intraluminal acute inflammatory exudate and neutrophils.
- Salpingitis isthmica nodosum—this entity is not associated with inflammation, and the "follicles" are separated by the smooth muscle of the tubal wall.

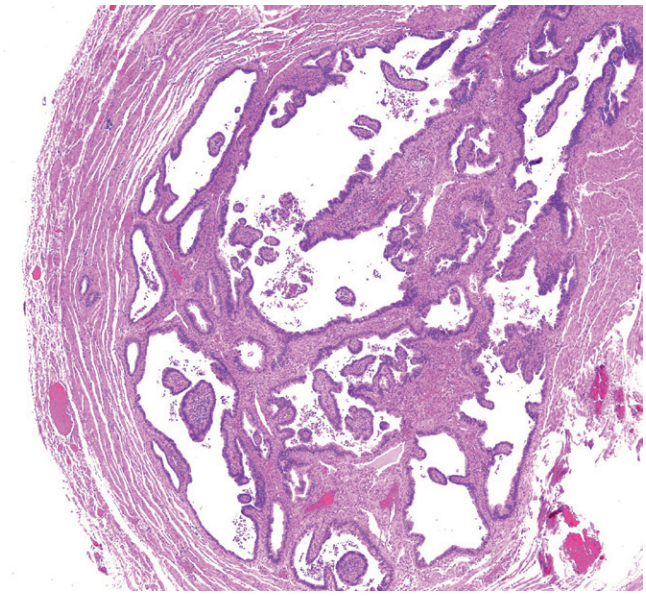


FIGURE 1

Chronic follicular salpingitis. Note the prominent fusion of the plicae imparting a follicle-like appearance.

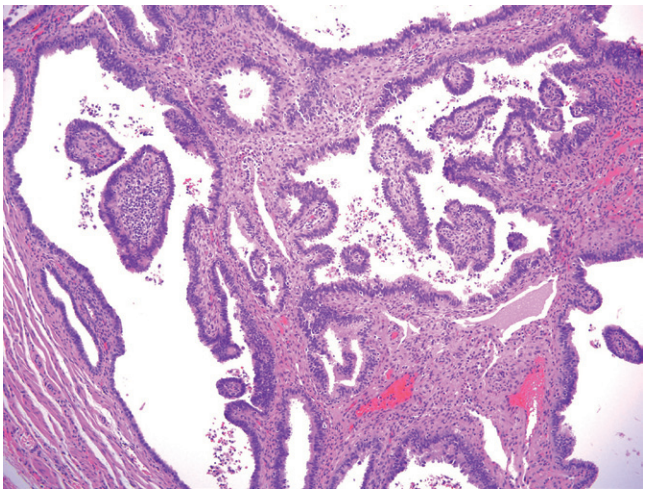


FIGURE 2

Chronic follicular salpingitis. Entrapment of epithelium within adhered plicae is characteristic of this disorder and cannot be produced by tangential sectioning.

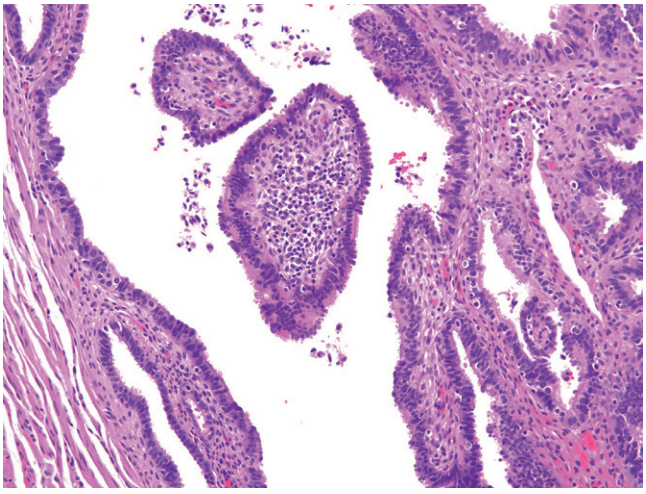


FIGURE 3

Chronic follicular salpingitis. There is virtually always a lymphoid infiltrate with plasma cells.

SALPINGITIS ISTHMICA NODOSUM

Definition—A proliferation of smooth muscle with accompanying epithelium in the fallopian tube, analogous to adenomyosis/adenomyoma seen within the uterus.

Clinical Features

Epidemiology

- Salpingitis isthmica nodosum (SIN) is a relatively common phenomenon seen in up to 11% of thoroughly examined fallopian tubes.

Presentation

- SIN can be grossly identified as a beadlike nodule within the tube, usually in the more proximal aspects. The patient may present clinically with infertility or ectopic pregnancy, both of which are heavily associated with SIN.

Prognosis and Treatment

- SIN is benign. Because of the proximal location within the tube, surgical repair is rarely considered. If the patient elects to have in vitro fertilization (IVF), the tubes may be removed to lower the risk of tubal pregnancy.

Pathology

Histology

- A nodule is typically present within the fallopian tube. Within this nodule there is a proliferation of smooth muscle with multiple, discrete tubal lumina. Inflammation is typically sparse, and reactive fibrosis, as seen in follicular salpingitis, is absent.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Follicular salpingitis—this is characterized by fusion of the plica, which will be suspended in the lumen and not ensconced in the wall of the tube, as seen in SIN.
- Sectioning of the fallopian tube in the cornu—this may be difficult to distinguish from SIN, but some endometrial stroma should be seen.

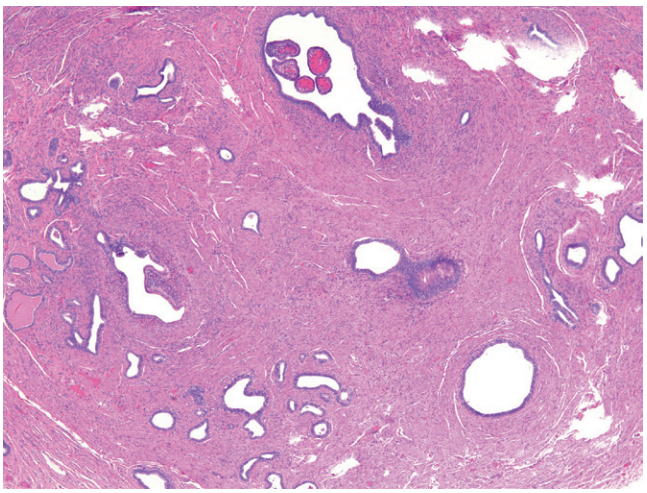


FIGURE 1

SIN. Giving the impression of tubal "adenomyosis," the epithelium is arranged in glandlike structures spaced between smooth muscle of the tubal wall.

GRANULOMATOUS SALPINGITIS

Definition—Granulomatous inflammation of the fallopian tube.

Clinical Features

Epidemiology

- Granulomatous salpingitis is uncommon. The granulomatous inflammation may be secondary to infectious causes (*Mycobacterium tuberculosis*, actinomyces, and parasitic infections) or noninfectious causes (sarcoid, Crohn's disease, or foreign-body giant cell reaction).

Presentation

- Patients may be asymptomatic or may present with symptoms of the underlying condition responsible for the inflammation.

Prognosis and Treatment

- Granulomatous salpingitis in isolation is a benign process; however, the underlying cause should be sought out and treated.

Pathology

Histology

- Granuloma formation is the hallmark of granulomatous salpingitis. The accompanying giant cells are frequently large, with abundant eosinophilic cytoplasm and numerous nuclei. Variable amounts of acute and chronic inflammation may be present. In cases secondary to foreign material, polarizable debris may be identified.

Diagnostic Terminology

- Granulomatous salpingitis. Note: Granulomatous salpingitis is not specific. Infectious etiology (e.g., tuberculosis [TB]) or other inflammatory etiologies should be excluded as clinically appropriate.

Immunopathology (Including Immunohistochemistry)

- In cases of infectious granulomatous salpingitis special stains for fungus (Grocott's methenamine silver [GMS]) and mycobacterium (acid-fast stains) may be helpful in identifying organisms; however, molecular methods, such as polymerase chain reaction (PCR) in the case of TB, are more sensitive.

Main Differential Diagnosis

- Crohn's disease, sarcoid, other nontuberculous infections, and foreign material can all produce granulomas and should be excluded, as appropriate to the clinical setting.

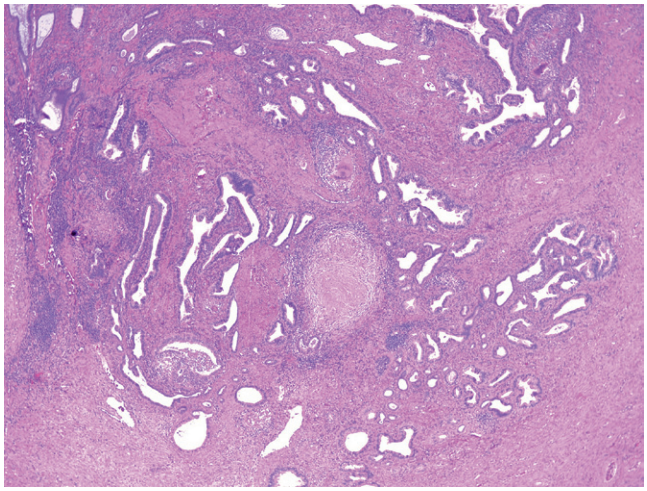


FIGURE 1

Granulomatous salpingitis. At low power note the prominent follicular salpingitis pattern with fused plicae.

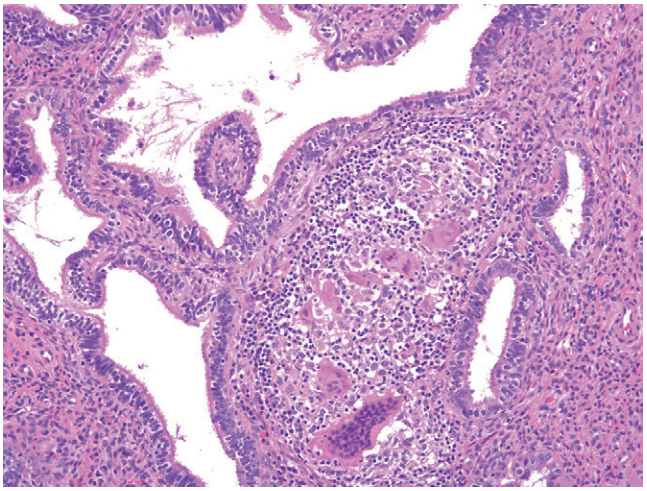


FIGURE 2

Granulomatous salpingitis. At higher magnification a granuloma is seen in the center just beneath the epithelium.

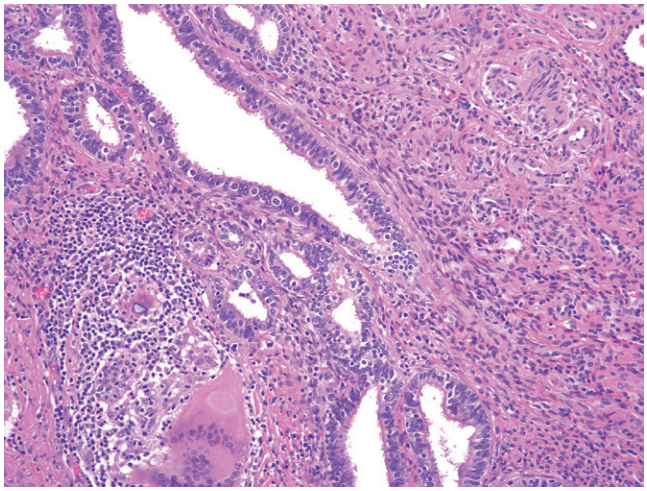


FIGURE 3

Granulomatous salpingitis. At higher magnification a granuloma with prominent giant cells is seen.

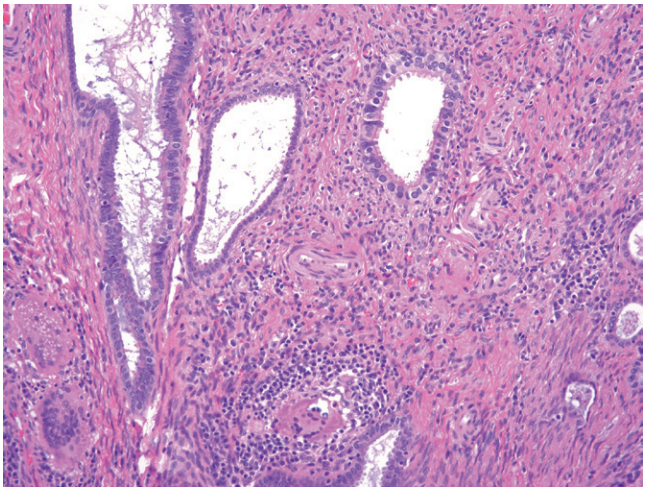


FIGURE 4

Granulomatous salpingitis. There is a variable lymphoplasmacytic infiltrate.

TORSION OF THE TUBE AND OVARY

Definition—Mechanical interruption of the adnexal arterial and/or venous blood flow by mechanical factors.

Clinical Features

Epidemiology

- Rare (reported in as few as 1 in every 1.5 million women), can occur at any age but usually in reproductive-age women.
- Most commonly seen with pregnancy, hydrosalpinx, ovarian cysts, tubal ligation, and benign tumors.
- Uncommonly associated with malignancies.
- Caused by rotation on the vascular pedicle. Fallopian tube and ovary can torse together or individually via rotation of the mesosalpinx and mesovarium, respectively.

Presentation

- Abdominal pain, nausea, and vomiting.
- Fever can occur if the torsion results in tissue necrosis.
- Ultrasound and Doppler evidence of a uniformly expanded ovary with decreased blood flow.

Prognosis and Treatment

- Immediate management entails untwisting the adnexa.
- Recurrence rates are high with mechanical relief alone, and fixation of the ovary (oophoropexy) is often required.
- Salpingo-oophorectomy may be required if the torsion has resulted in extensive loss of tissue viability.

Pathology

Histology

- Early on, torsion manifests as marked vascular congestion followed by early hemorrhagic necrosis in the form of interstitial hemorrhage.
- Prolonged torsion leads to devitalized tissue and variable inflammatory response.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Massive ovarian edema—this is not characterized by hemorrhagic necrosis.
- Excluding malignancy—this diagnostic dilemma occurs when there is an obvious tumor that has undergone necrosis due to torsion. In such instances the pathologist must carefully examine the devitalized tissue for clues that might indicate malignancy, focusing on the most well-preserved portion of the tumor and taking into account cell density, uniformity, or lack of in nuclear size and overall architecture.

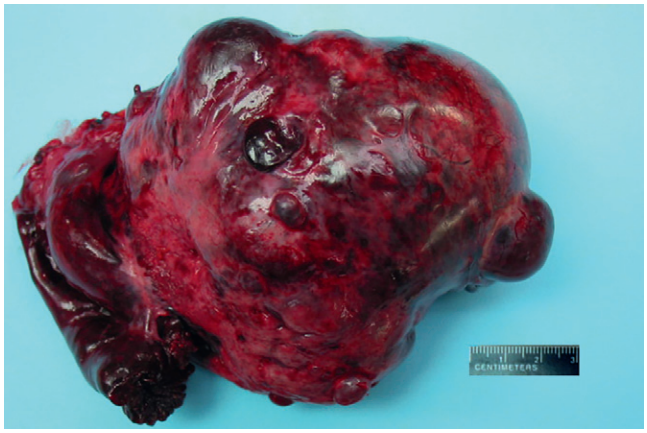


FIGURE 1

Adnexal torsion. In this case the tube and ovary are a single ischemic and hemorrhagic mass.

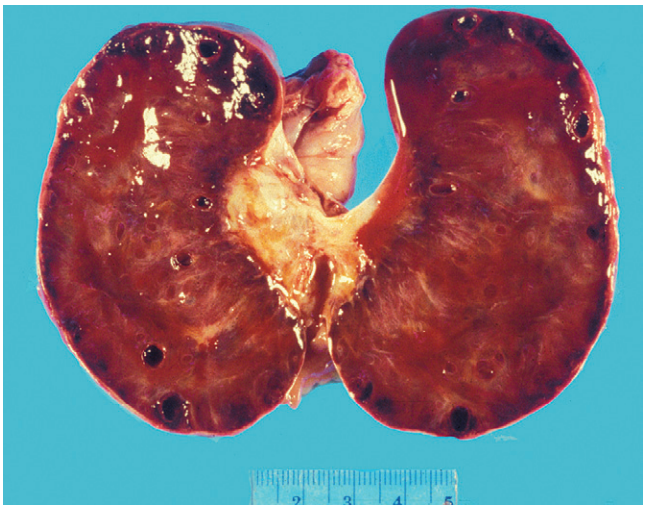


FIGURE 2

Ovarian torsion. The ovary is diffusely hemorrhagic and uniformly expanded.

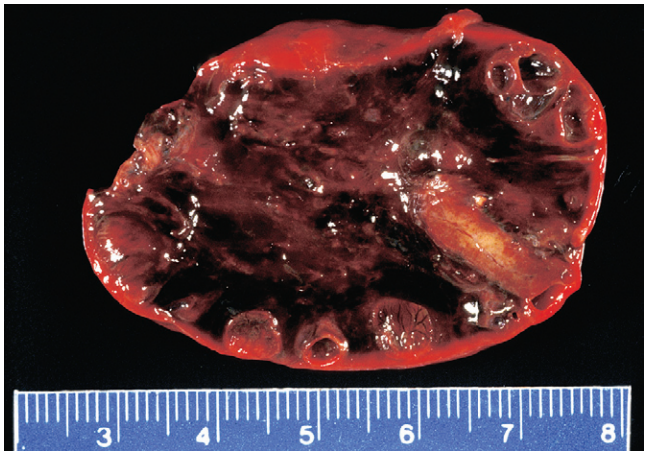


FIGURE 3

Ovarian torsion during pregnancy. The follicles are pushed to the periphery by the interstitial hemorrhage.

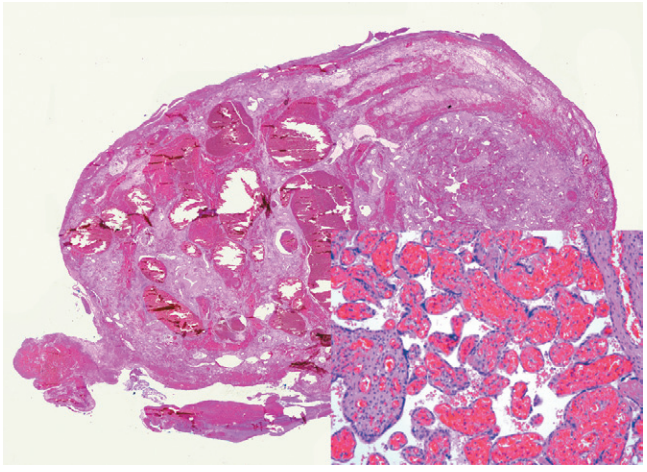


FIGURE 4

Low-power photomicrograph of a torsed fallopian tube. The lumen is designated by the dotted circle, with marked congestion of adnexal vessels on the left. The inset shows interstitial hemorrhage in the plicae.

TUBAL ARIAS-STELLA EFFECT

PITFALL

Definition—Hormonally induced changes that occur within the epithelium of the gynecologic tract (typically secondary to pregnancy).

Clinical Features

Epidemiology

- Arias-Stella effect is most commonly seen in the background of pregnancy; however, it can be seen in any case of hormonal alteration (whether exogenous or endogenous).

Presentation

- Arias-Stella effect is typically an incidental finding on microscopic examination of the fallopian tube removed for other reasons.

Prognosis and Treatment

- Arias-Stella effect associated with pregnancy or exogenous hormone effect is benign, and no further treatment is warranted.

Pathology

Histology

- Arias-Stella effect of the fallopian tube is similar to that seen elsewhere in the gynecologic tract. It can be discrete or more generalized as a form of hypersecretory change. Variable cellular and nuclear enlargement may be seen. The affected cells typically have abundant eosinophilic cytoplasm. Despite the large nuclei and cells, the nuclear-to-cytoplasmic (NC) ratio will usually remain low (as opposed to a high NC ratio as seen in serous tubal intraepithelial neoplasia). Mitotic activity should be absent; however, very rare mitoses have been described in association with Arias-Stella effect in other sites.

Immunopathology (Including Immunohistochemistry)

This is a good example of where immunostaining can be helpful in excluding a serous tubal intraepithelial carcinoma (STIC), although the suspicion would be very low in a central section of a tube from a reproductive-age woman. Arias-Stella effect is negative (i.e., weakly staining) for p53. This is a key piece of confirming evidence. Arias-Stella effect should also have a low proliferative index (under 50%) by Ki-67 immunohistochemistry.

Main Differential Diagnosis

- Serous tubal intraepithelial neoplasia: This is vanishingly rare in the fallopian tubes of women who are pregnant. It can be excluded by the aforesaid approach.

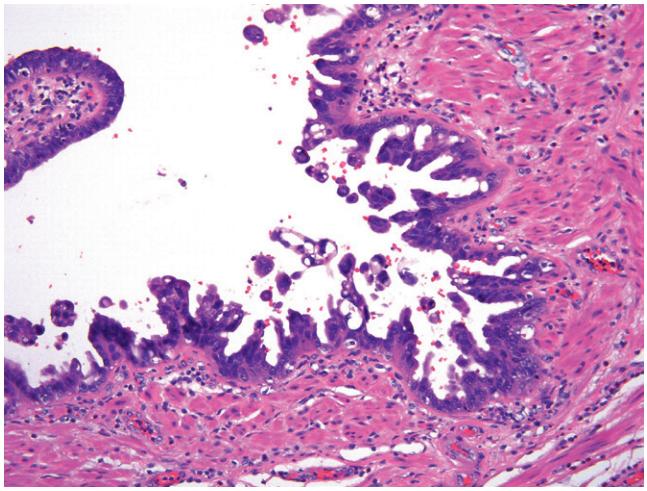


FIGURE 1

Arias-Stella effect in the fallopian tube. Note the exfoliative nature of the process at low magnification.

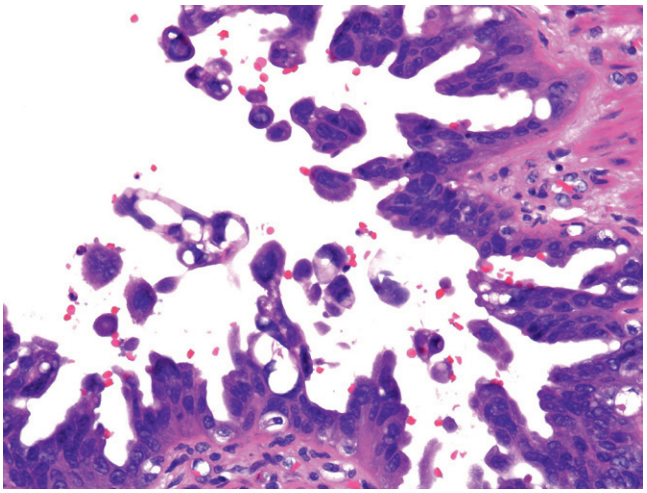


FIGURE 2

Arias-Stella effect in the fallopian tube. At higher power the vacuolated cells and enlarged nuclei are present.

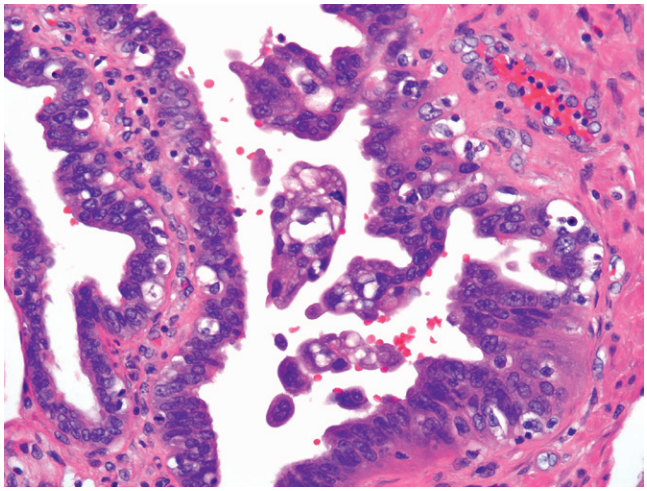


FIGURE 3

Arias-Stella effect. Another field showing mild nuclear enlargement.

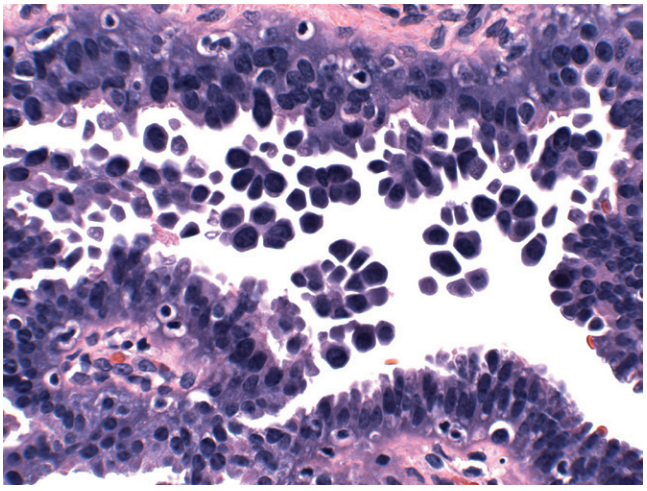


FIGURE 4

Hypersecretory changes in the fallopian tube of a pregnant woman.

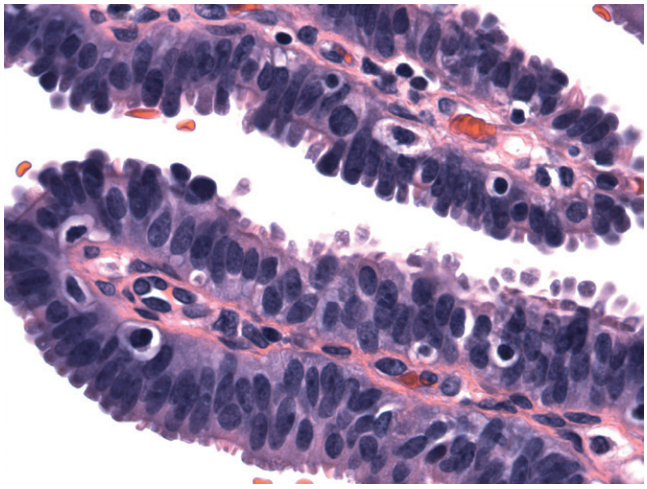


FIGURE 5

Hypersecretory change at higher power. Note the prominent admixture of ciliated and secretory type cells, many with extruded nuclei at the luminal border.

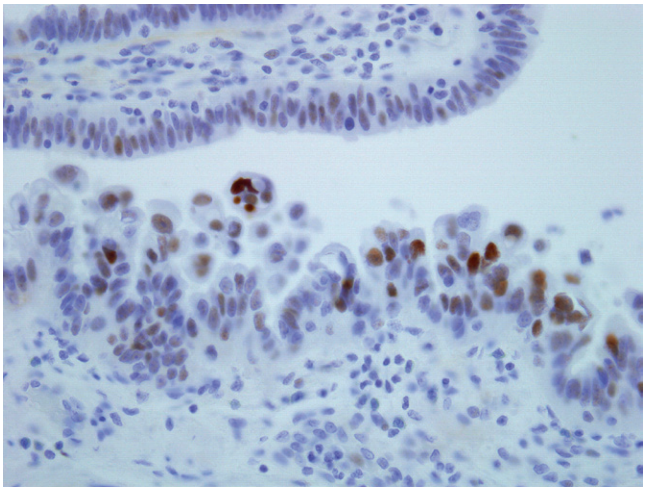


FIGURE 6

Arias-Stella effect stained for p53, showing scattered weak to moderate staining.

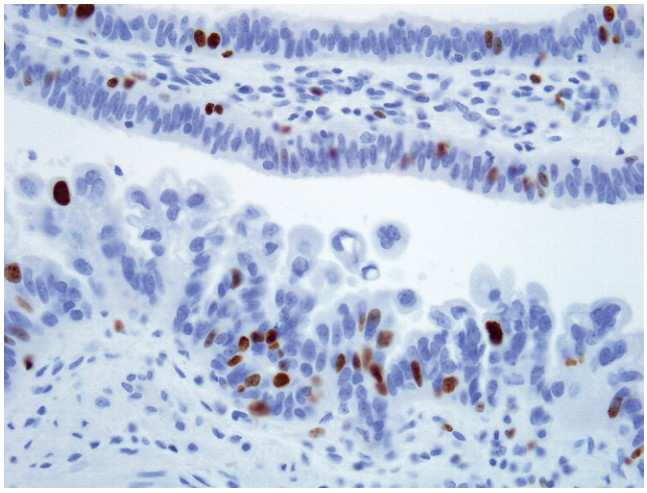


FIGURE 7

Arias-Stella effect, showing a low MIB1 index.

ADENOFIBROMA

Definition—A benign neoplasm of the distal tube.

Clinical Features

Epidemiology

- Adenofibromas are thought to be relatively common entities within the fallopian tube and are found predominantly within the fimbriated end of the tube.

Presentation

- Tubal adenofibromas are typically found incidentally at the time of histologic examination for other causes. There are essentially two forms. One is a conspicuous lesion seen on gross exam, and the other is a microscopic lesion that cannot be seen with the naked eye.

Prognosis and Treatment

- The prognosis of these tumors is uneventful when not complicated by any other form of neoplasia. Adenofibromas themselves are benign and carry no risk of subsequent malignancy. Occasional malignancies are found in association with an adenofibroma, the best examples being ovarian adenocarcinomas.

Pathology

Histology

- The fimbriated end of the fallopian tube may show focal stromal proliferations that are not mass forming and are associated with minor changes in the overlying benign epithelium, and these foci may be a millimeter or less in dimension. These are synonymous with microscopic or "early" adenofibromas. Larger lesions have a more well-developed glandular component and are macroscopically visible.

Immunopathology (Including Immunohistochemistry)

- The stromal compartment within an adenofibroma typically marks positive for CD10 and inhibin (as their ovarian counterparts do).

Main Differential Diagnosis

- Paratubal cystadenoma—This arises within a paratubal cyst.
- Leiomyoma (stromal compartment only)—A discrete lesion with smooth muscle differentiation.

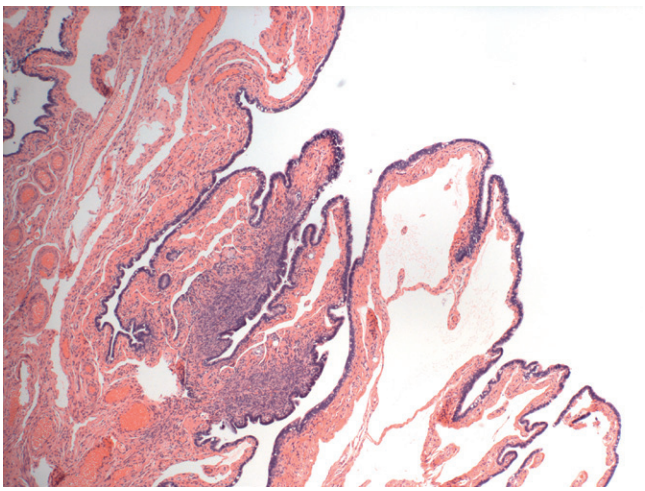


FIGURE 1

Microscopic adenofibroma with stromal condensation and minimal change in the overlying epithelium.

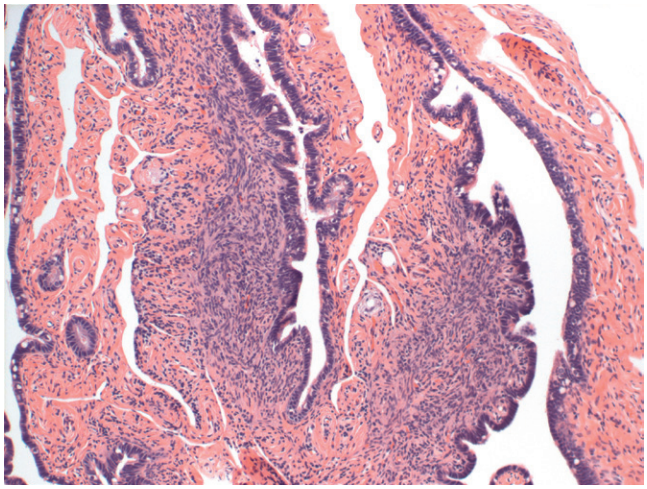


FIGURE 2
At higher magnification the stroma abuts the epithelium.

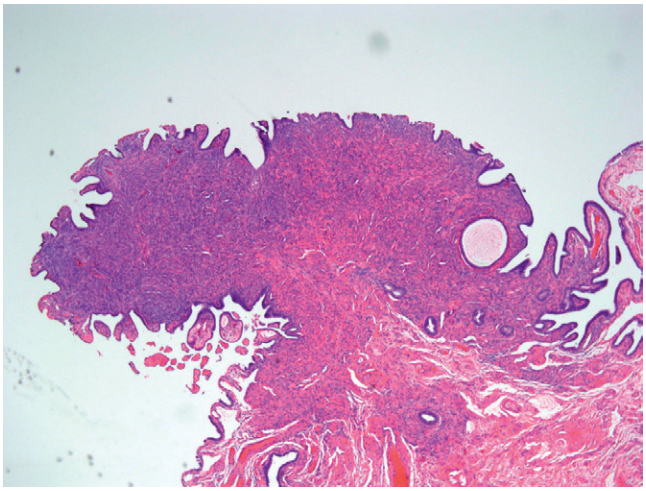


FIGURE 3
A larger adenofibroma with slight papillary change in the overlying epithelium.

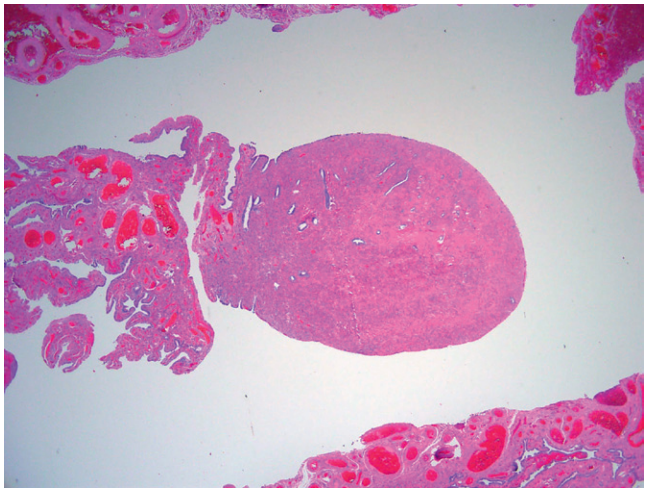


FIGURE 4
This fimbrial adenofibroma has a predominance of fibrous stroma.

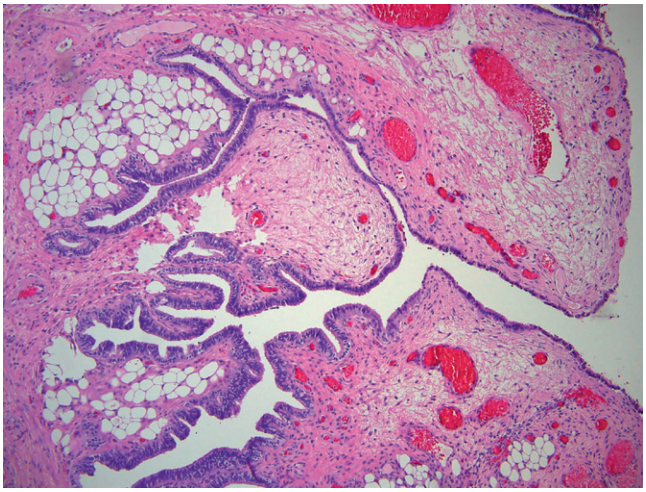


FIGURE 5
This adenofibroma contains adipose tissue.

BENIGN EPITHELIAL HYPERPLASIA (SECRETORY CELL OUTGROWTHS)

Definition—Benign, self-limited clonal proliferations of tubal secretory-type cells with variable ciliation.

Clinical Features

Epidemiology and Pathogenesis

- Secretory cell outgrowths (SCOUTs) are common proliferations seen most commonly in the sixth and seventh decades of life but may be found earlier.
- They are increased somewhat in fallopian tubes of women with borderline or malignant serous tumors. However, whether they have a direct relationship to serous neoplasia is unknown.
- SCOUTs are presumably an outgrowth from a specialized progenitor cell in the fallopian tube.

Presentation

- SCOUTs are encountered as an incidental finding during the pathologic examination of the fallopian tubes.

Prognosis and Treatment

- SCOUTs require no treatment and pose no risk to the patient. They are an incidental finding.

Pathology

Histology

- There are two types of SCOUTs, and this is for descriptive (not diagnostic) purposes.
- Type 1 SCOUTs closely resemble normal mucosa and may be predominantly secretory or have conspicuous cilia.
- Type 2 SCOUTs are expansions of pseudostratified epithelial cells that can be more easily distinguished from the surrounding epithelium and may be "endometrioid," resembling endometrial lining.
- Occasionally SCOUTs may appear mildly papillary and call to mind a papillary neoplasm. However, the papillae are usually rather bland appearing.

Immunopathology (Including Immunohistochemistry)

- Most but not all SCOUTs are PAX2 negative.
- Type 1 SCOUTs are also ALDH1 negative.
- Type 2 SCOUTs are ALDH1 positive and, interestingly, β-catenin positive (nuclear and cytoplasmic).

Recommended Diagnostic Terminology

- If prominent, a diagnosis of benign epithelial hyperplasia is appropriate.

Main Differential Diagnosis

- p53 signatures may be similar but are p53 positive (or completely negative in some instances) and are more likely to be seen in the distal tube.
- Localized intraepithelial endometrioid carcinomas are rare but should be distinguished by the greater degree of atypia.

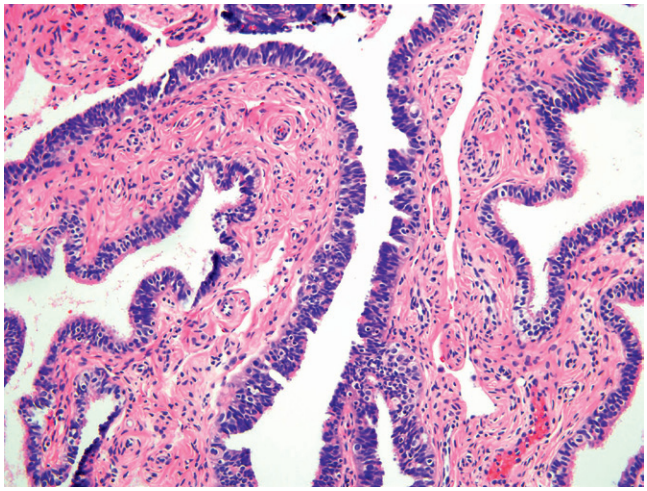


FIGURE 1

A subtle type 1 SCOUT that would not be appreciated by inspection of a hematoxylin and eosin (H&E) slide alone.

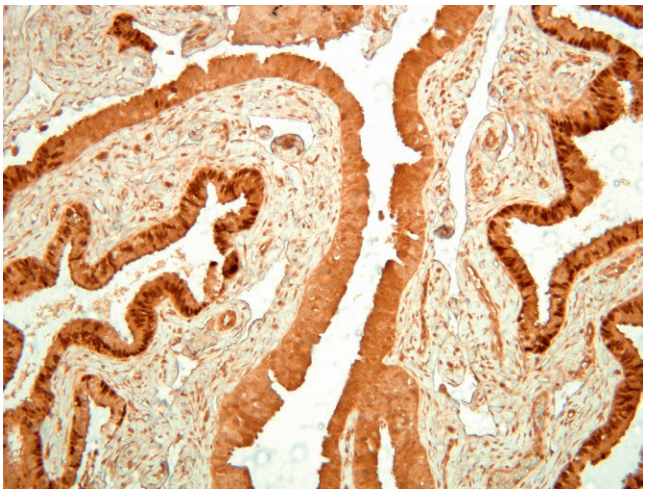


FIGURE 2

Note the discrete loss of PAX2, which highlights the epithelium.

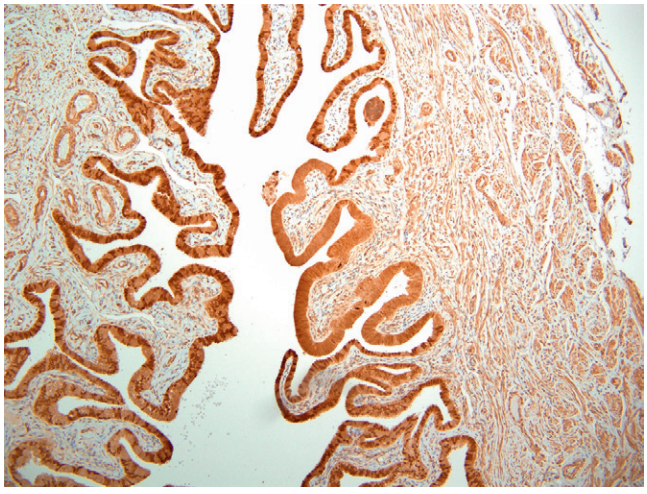


FIGURE 3

A low-power microphotograph of a PAX2-stained fallopian tube reveals a focus of slightly more pseudostratified epithelium (Type 2 SCOUT).

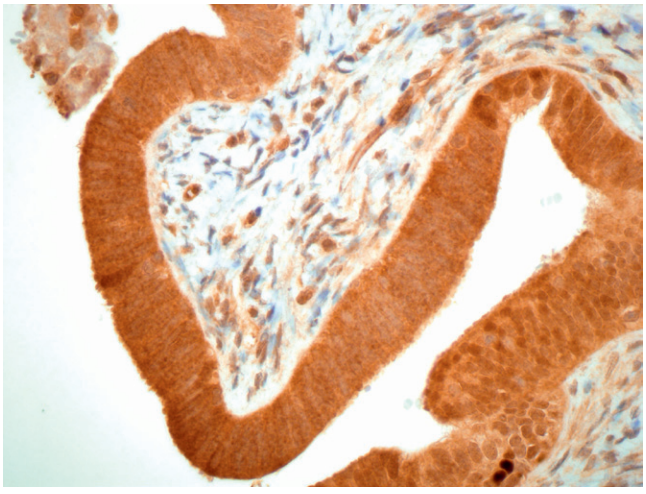


FIGURE 4

At higher magnification, note the lack of epithelial atypia despite the slight increase in thickness reminiscent of endometrioid differentiation.

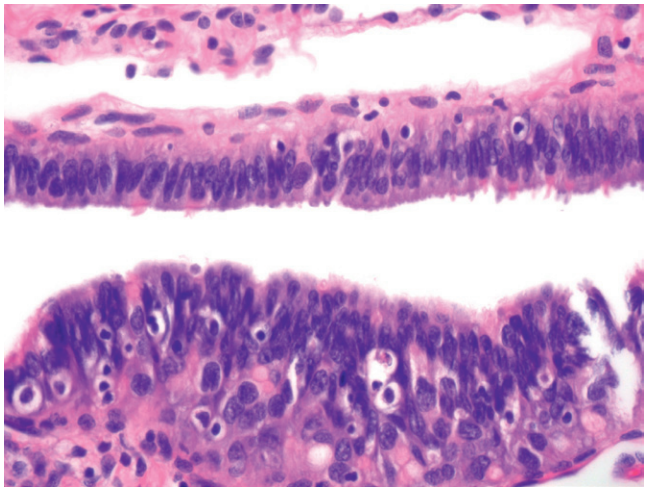


FIGURE 5

A SCOUT *(lower)* with multilayered mixed secretory and ciliated differentiation.

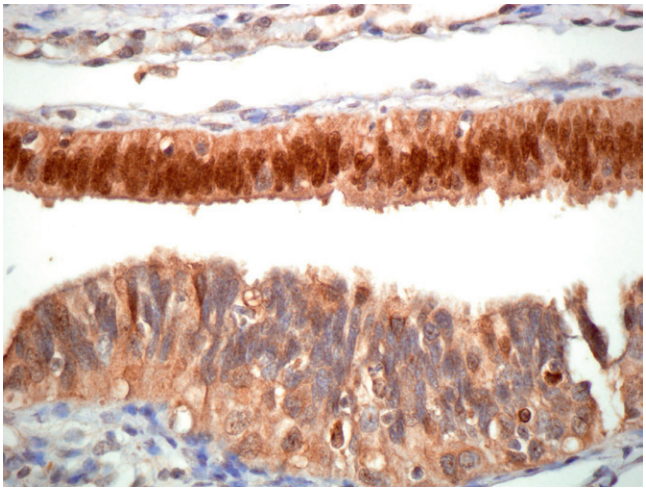


FIGURE 6

Loss of PAX2 staining highlights the same focus.

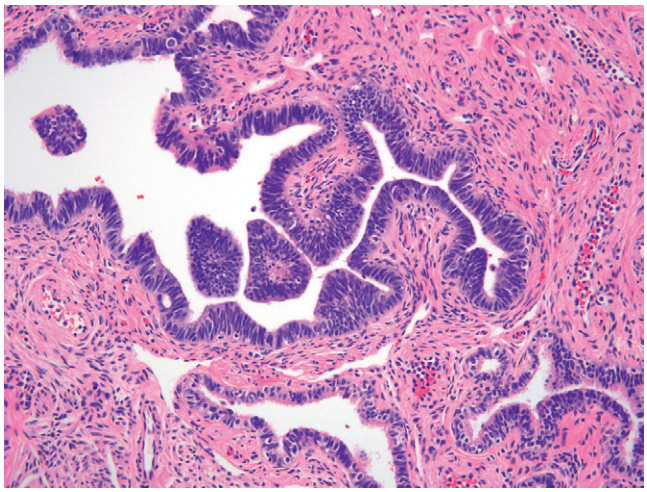


FIGURE 7

H&E-stained section shows a central focus with slight architectural complexity.

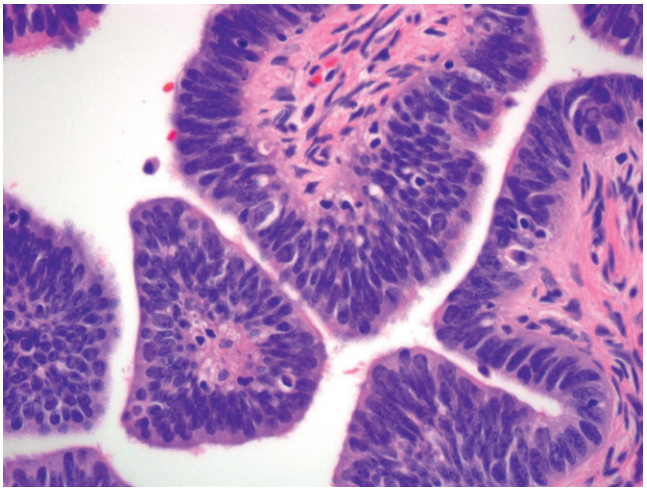


FIGURE 8

At higher power this focus takes on an appearance resembling endometrial epithelium (Type 2 SCOUT).

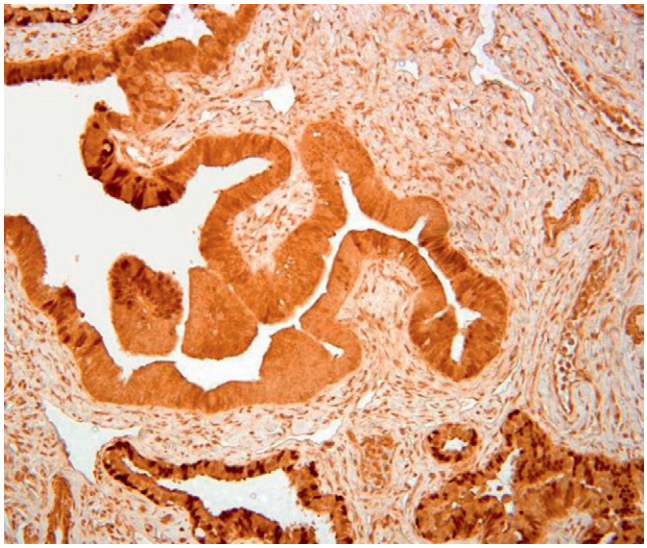


FIGURE 9

There is an absence of PAX2 staining.

p53 SIGNATURES

Definition—A limited clonal expansion of secretory cells associated with mutations in p53 exhibiting minimal or atypia. Seen as perhaps the very first step in serous carcinogenesis in the tube; often termed a "latent precursor" to pelvic serous carcinoma.

Clinical Features

Epidemiology

- p53 signatures exhibit features consistent with very early or latent serous cancer precursors. They are common (up to 70%) in thoroughly sectioned fallopian tubes of older women, predominate in the fimbria, exhibit evidence of DNA damage response, and are more frequently found in association with cancer. However, they are benign and their high frequency indicates that this entity, like many precursors, confers no risk to the patient.

Presentation

- p53 signatures are almost always an incidental finding at the time of examination of the fallopian tube that has been removed routinely or during a risk reduction procedure for an inherited BRCA1 or BRCA2 mutation.

Prognosis and Treatment

- p53 signatures require no further treatment. Although they theoretically may have a low risk of developing into a malignancy, the circumstances of their discovery (in tubes that have been removed) indicate that they are clinically insignificant.

Pathology

Histology

- The features are of a secretory cell expansion with mild atypia including
  - A continuous row of nonciliated cells
  - Variable nuclear enlargement
  - Nuclear molding (may be present)
  - Mild disturbances in nuclear orientation with preserved cell-to-cell cohesion
  - Ciliated cells, usually toward the luminal surface
- Large numbers of p53 signatures may be encountered in cases of Li-Fraumeni syndrome due to the greater likelihood of loss of p53 function (with a secondary mutation or loss of heterozygosity [LOH]).

Immunopathology (Including Immunohistochemistry)

- p53 stains are typically strongly and diffusely positive, highlighting the cells.
  - MIB1 stains typically highlight less than 20% of the cells.
  - PAX2 stains are usually but not always negative.
  - Cyclin E and p16ink4 are usually weak, patchy, or negative.

Recommended Diagnostic Terminology

- No diagnosis is required.
- If the changes are found in a risk-reducing specimen and found incidentally, the diagnosis of benign epithelial changes is permissible with the comment that the p53 stain is positive but there is no evidence of atypia or malignancy.

Main Differential Diagnosis

- Moderate or secretory cell atypia will exhibit greater degree of atypia, usually involve a larger surface area and demonstrate an increased proliferative index (low-grade serous tubal intraepithelial neoplasia or serous tubal intraepithelial lesion).
- High-grade serous tubal intraepithelial neoplasia (or serous tubal intraepithelial carcinoma) contains the above in addition to loss of polarity and epithelial cell disorganization.
- Li-Fraumeni syndrome. In this condition a germ-line mutation in p53 renders the tube prone to multiple p53 signatures. However, atypia is usually minimal.

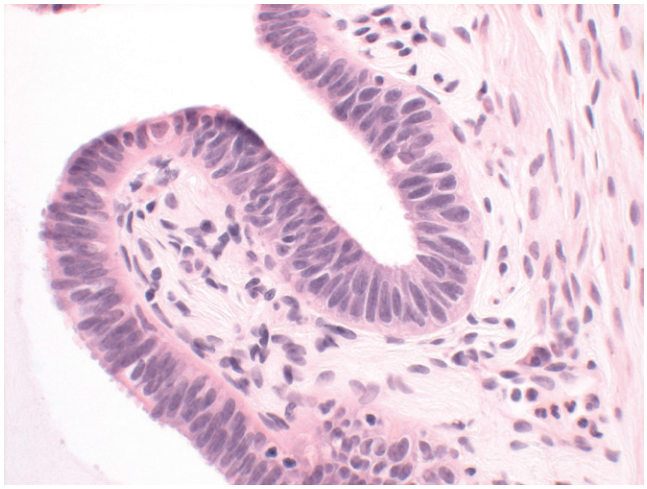


FIGURE 1

p53 signature. This entity is often limited to a portion of a tubal plica. Note the minimal nuclear enlargement and preservation of polarity. This would attract little notice in a routine specimen.

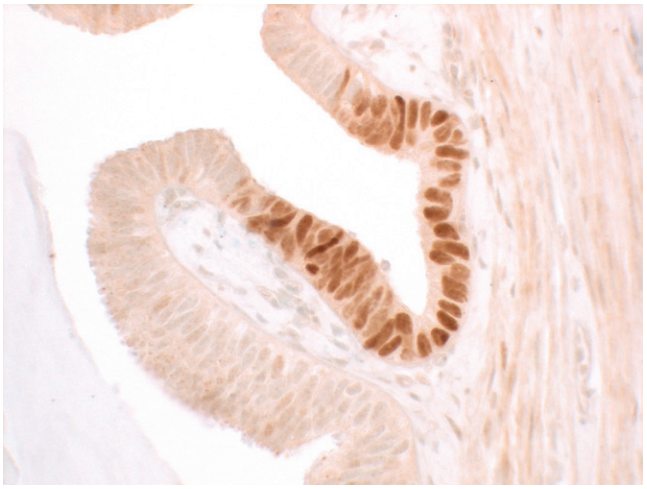


FIGURE 2

Strong nuclear staining for p53 highlights the cells.

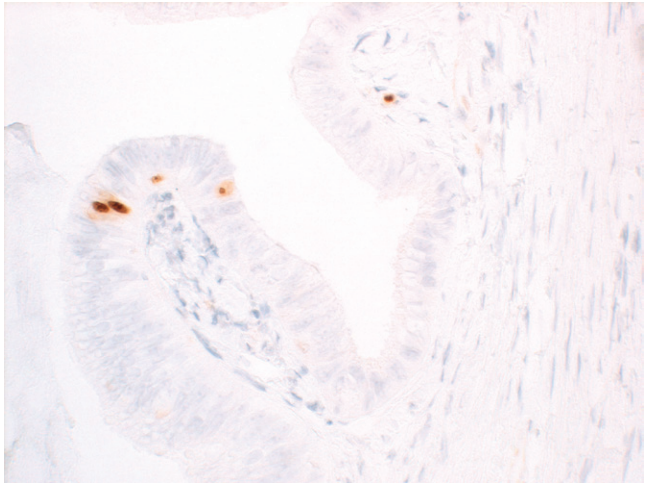


FIGURE 3

MIB1 staining typically highlights less than 20% of the cells in these mild secretory cell atypias.

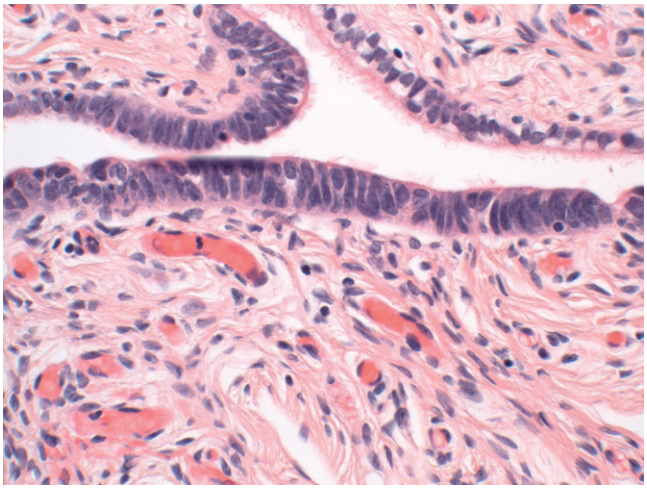


FIGURE 4

Another mild atypia (p53 signature). Note the presence of ciliated cells.

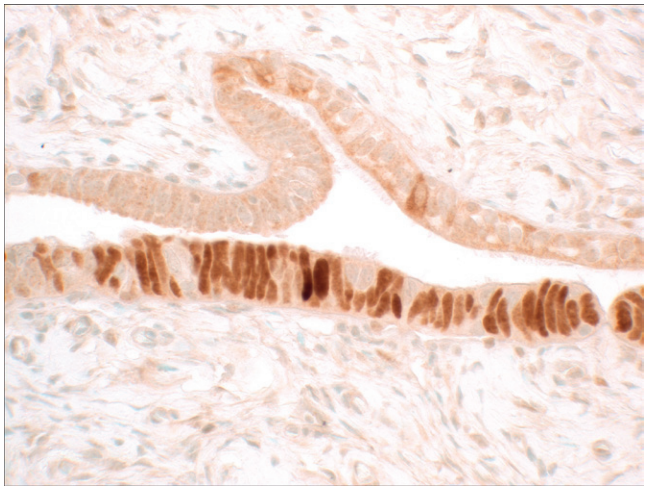


FIGURE 5

p53 staining spares the ciliated cells.

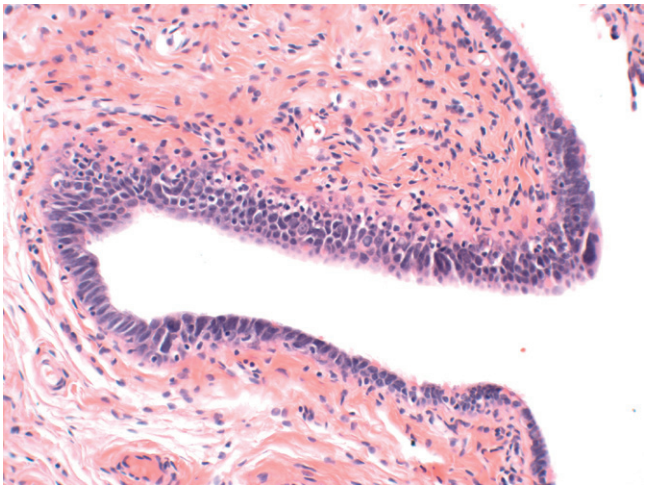


FIGURE 6

A p53 signature with greater anisokaryosis. The tangential staining lends an appearance of epithelial disorganization.

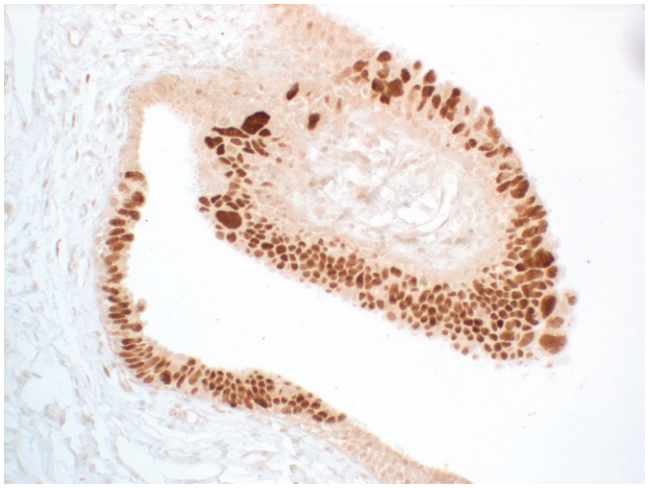


FIGURE 7

p53 staining is strong in most cells. Note the prominent nuclear enlargement in some. This by itself is not uncommon in milder forms of atypia.

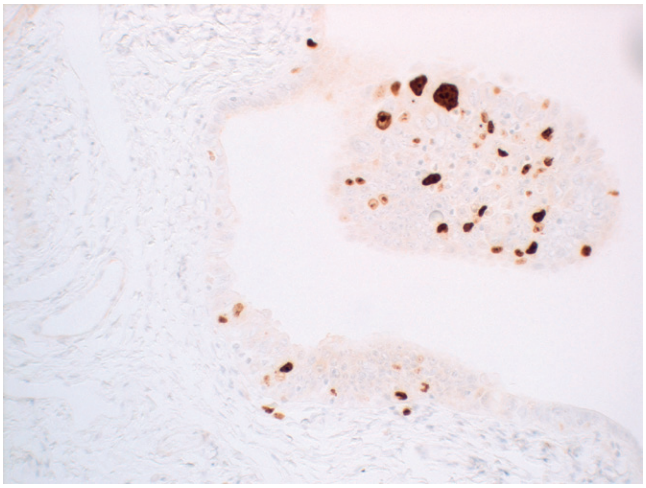


FIGURE 8

The MIB1 index is low.

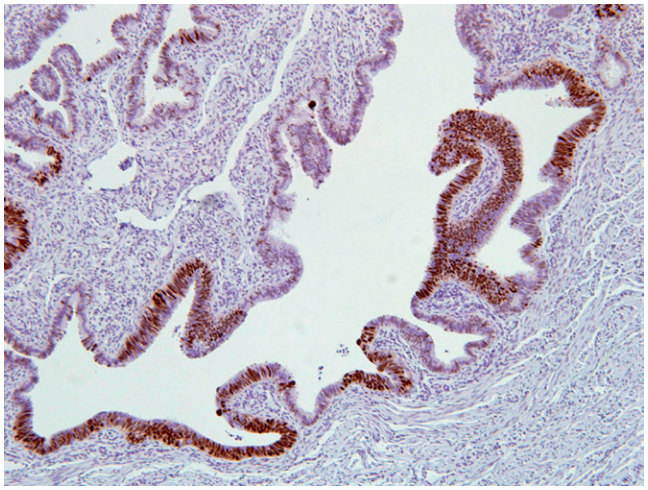


FIGURE 9

Li-Fraumeni syndrome. This p53-stained tube exhibits multiple p53 signatures. However, note that there is little atypia.

LOW-GRADE SEROUS TUBAL INTRAEPITHELIAL NEOPLASIA (SEROUS TUBAL INTRAEPITHELIAL LESION)

Definition—A serous intraepithelial neoplasm of uncertain risk that does not fulfill the criteria for serous tubal intraepithelial carcinoma (STIC).

Clinical Features

Epidemiology

- Low-grade serous tubal intraepithelial neoplasia (STIN) is synonymous with a proliferation produced when there are both a mutation and an inactivation of p53 and is similar to STIC.
- Like STICs, STINs are uncommon, found in less than 1 : 500 routine salpingectomies. It is found in less than 10% of tubes removed during risk reduction salpingo-oophorectomy (RRSO) for inherited BRCA1 or BRCA2 mutations, the percentages fluctuating as a function of patient age. It is discovered more commonly (just how commonly we do not know) in fallopian tubes of women with high-grade pelvic serous carcinoma. It can be associated with, and presumably preceded by, a benign non-atypical clonal expansion of secretory cells with p53 mutations (p53 signatures).

Presentation

- Low-grade STINs are discovered on histologic exam of the tubes, either in RRSOs or tubes removed during surgery for advanced serous carcinoma. The former are usually asymptomatic, and the latter present with the usual signs and symptoms of advanced disease. Low-grade STINs are uncommon in the asymptomatic woman without an inherited BRCA1 or BRCA2 mutation.

Prognosis and Treatment

- Low-grade STINs are removed during surgery and when found in the setting of pelvic serous cancer may imply a relationship of the tumor to the tube, particularly if the STIN is in continuity with the cancer. This would imply that the STIN was a direct precursor to invasive carcinoma if not an actual intraepithelial carcinoma.
- When found in an RRSO, low-grade STINs do not require further surgery, although thorough examination is required to exclude STIC.
- The need to test for BRCA1 or BRCA2 germ-line mutations is unclear when low-grade STINs are found incidentally. If they are particularly worrisome in appearance, testing should be considered.

Pathology

Histology

- Low-grade STIN is diagnosed using histologic criteria, but it is helpful to take advantage of ancillary tests to clarify the diagnosis. The most helpful histologic criteria include the following:
  - Cilia: Some cilia (and occasionally abundant) may be found in low-grade STINs (they are much less likely in STICs).
  - Pseudostratified epithelial growth with minimal loss of epithelial polarity.

  - The absence of marked stratification and horizontal fracture lines that would reflect conspicuous loss of polarity.
- Review by a second pathologist is encouraged if there is a difference of opinion.

Preferred Diagnostic Term

STIN with moderate atypia

- A range of terms have been proposed including low-grade STIN, serous tubal intraepithelial lesion (STIL), moderate tubal atypia, and STIN with moderate atypia. Because of the not infrequent problems in trying to separate STIL from STIC combined with the low risk of high-grade serous cancer outcome with STIC, we have found the above term to be the easiest in practice. It neither imposes an absolute exclusion of STIC (which itself imposes only a 5% to 10% risk of subsequent pelvic serous carcinoma) nor guarantees that the lower-grade lesion is completely innocuous. In either case no further treatment is likely necessary.

Immunopathology (Including Immunohistochemistry)

- The neoplastic cells are usually strongly and diffusely positive for p53 but will be conspicuously negative if the antigenic target sequence is deleted.
- Stains for p16ink4, cyclin E, EZH2, and stathmin may be positive, although not to the extent as seen in STICs. Remember, EZH2 and stathmin are *not specific and can be seen in benign epithelial hyperplasias*. Similarly PAX2 will be usually negative but not specific given it is negative in benign epithelial hyperplasias (secretory cell outgrowths [SCOUTs]) and p53 signatures.
- The MIB1 index (Ki-67) is usually modest (10% to 40%) in parts of the lesion; however, occasionally the proliferative index exceeds 50%.
- A marker of polarity (p-ERM) typically shows mostly preservation of the normal surface staining, with occasional irregular serrated luminal borders.
- Generic markers of tubal epithelium, PAX8 and WT1, will be positive.
- Use of p53 and Ki-67 is encouraged to support the diagnosis in difficult cases, but in such cases the ultimate verdict is *based on the degree of histologic certainty that the epithelium more closely resembles benign epithelium than intraepithelial carcinoma*.

Main Differential Diagnosis

- Benign epithelial hyperplasia (SCOUTs)—these may exhibit multilayering but usually include ciliated cells. Polarity is preserved.
- Reactive epithelial changes, including Arias-Stella effect—these can be striking but have normal p53 expression and a low proliferative index. Moreover, they are typically found in younger women in the setting of inflammation or pregnancy.
- p53 signatures—these are typically small and unimpressive histologically and exhibit low proliferative index. However, they may be associated with higher proliferation indices overlapping with lower-grade tubal intraepithelial neoplasms (e.g., STILs, tubal intraepithelial lesions in transition [TILTs]).
- High-grade tubal intraepithelial neoplasms (a.k.a. STICs) share features of both p53 signatures, but STICs show conspicuous loss of polarity and a proliferative index that usually (but not always) exceeds 50%.

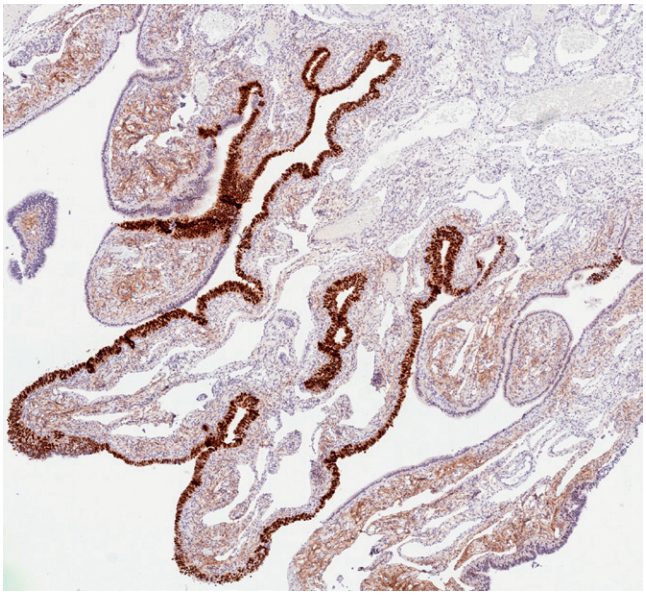


FIGURE 1

These figures underscore the difficulty in cleanly separating STIC from lesser forms of tubal intraepithelial neoplasia. Low-power view of a strongly p53-positive, expanded population of epithelial cells. Despite the strong staining, one cannot be absolutely certain that this is an STIC versus an STIL.

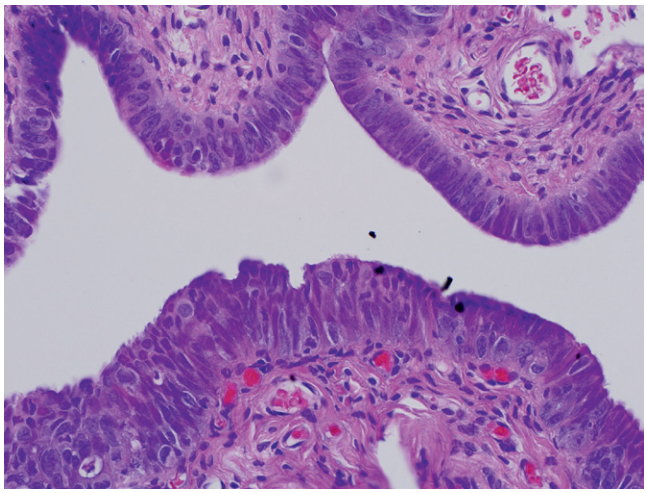


FIGURE 2

Higher magnification of the lesion in Figure 1 discloses well-polarized epithelium in the upper field with prominent nucleoli; the epithelium in the lower field is multilayered and mildly disorganized. However, note the ciliated differentiation in the center.

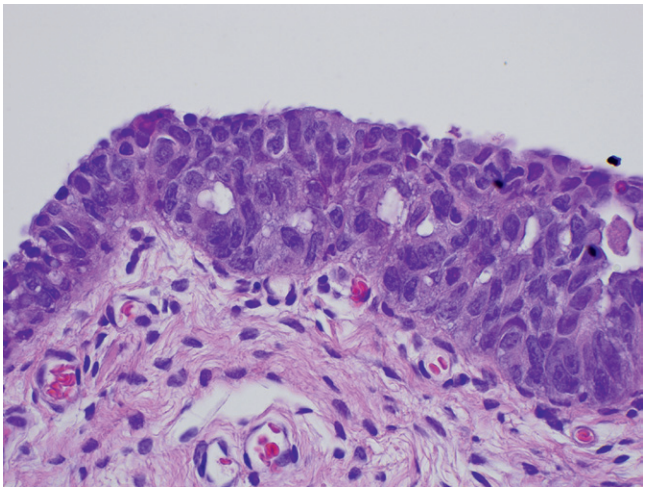


FIGURE 3

An adjacent field is more worrisome for STIC with greater irregularity in nuclear orientation near the surface. However, the sharply defined microlumina and sense of ciliated differentiation make this lesion particularly difficult to classify precisely.

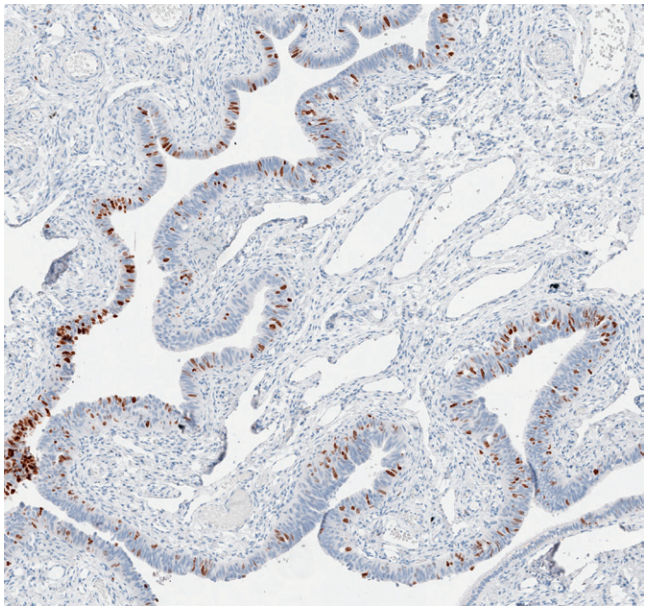


FIGURE 4

The proliferative index is moderately increased and high at the lower left.

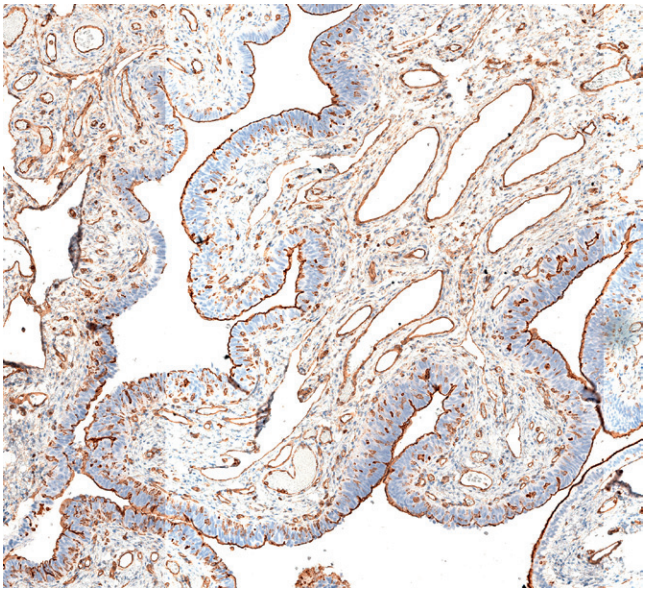


FIGURE 5

Staining with p-ERM is almost entirely luminal, similar to normal mucosa. However, there is a serrated pattern of surface staining at the lower left, a feature that we see commonly in STIC.

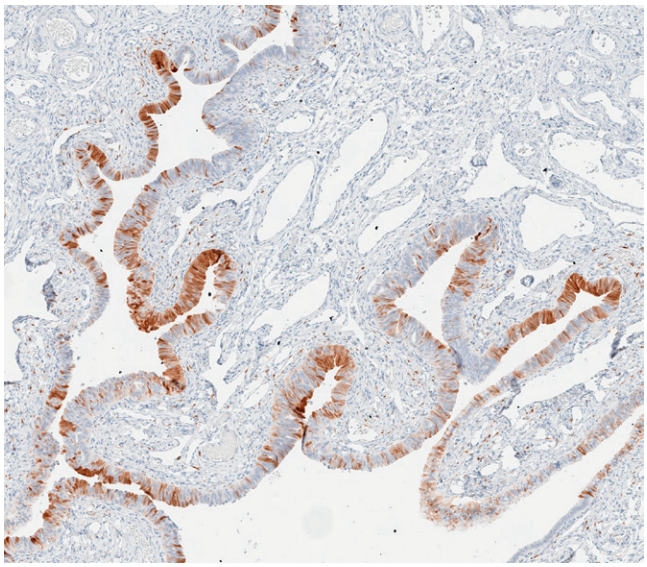


FIGURE 6

Staining for p16 is heterogeneous, more in keeping with nonmalignant epithelium, but not excluding STIC.

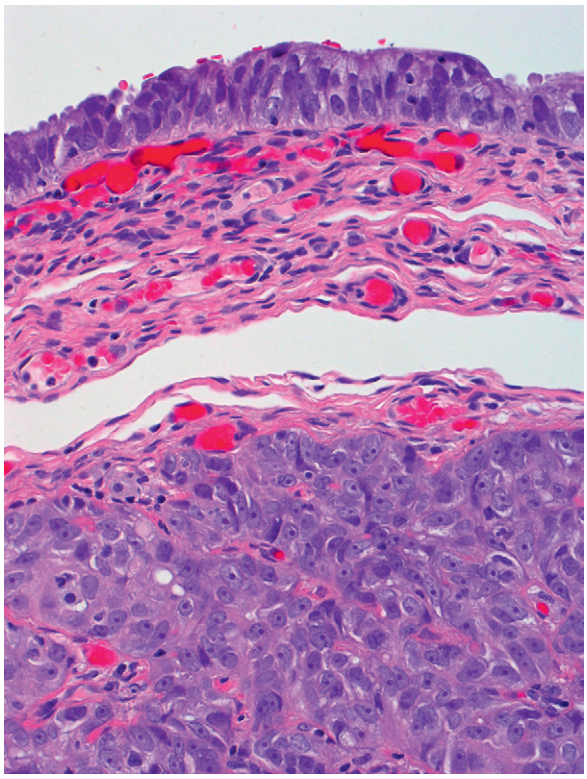


FIGURE 7

A low-grade STIN overlying an invasive carcinoma in the tube.

PAPILLARY HYPERPLASIA

Definition—An increase in thickness of the epithelial layer, occasionally forming papillary tufts within the tubal lumen.

Clinical Features

Epidemiology

- Papillary hyperplasia is an uncommon entity, and no associations have been made regarding incidence or predisposing factors. They have some resemblance to borderline serous tumors and have been proposed as a potential precursor to these tumors. However, they are not associated with most borderline tumors.

Presentation

- May be discovered incidentally at the time of examination of the tube for other reasons.

Prognosis and Treatment

- Papillary hyperplasia is benign, and no further treatment is warranted.

Pathology

Histology

- The histologic appearance can vary, likely due to different etiologies. Some are associated with tubal inflammation, in which case the lining cells closely resemble the adjacent tube with pseudostratified ciliated and secretory cells. The underlying stroma may form papillary fronds that project into the tubal lumen. These papillomas are differentiated from normal plica in that they are more architecturally complex compared with the background tube. Of note, cases of acute salpingitis may be accompanied by a florid epithelial hyperplasia that is benign. Other papillary lesions may more closely resemble mesothelium, with a cuboidal appearance.

Immunopathology (Including Immunohistochemistry)

- Calretinin stains will be negative or focally positive.

Main Differential Diagnosis

- Normal fallopian tube—tube has a plicate rather than papillary architecture.
- Papillary adenofibromas of the fallopian tube—these are associated with a prominent dense stroma that is often immunopositive for inhibin and calretinin, similar to ovarian stroma.
- Borderline serous tumors of the tube—these may overlap with this entity but typically form cystic masses rather than single intraluminal foci.
- Salpingoliths—psammomatous calcification can be encountered in the tube, associated with some alterations in tubal architecture. They are often seen in association with regionally located borderline tumors of the ovary or peritoneum.
- Serous tubal intraepithelial carcinoma—marked atypia and p53 positive (or null [from a deletion mutation]).

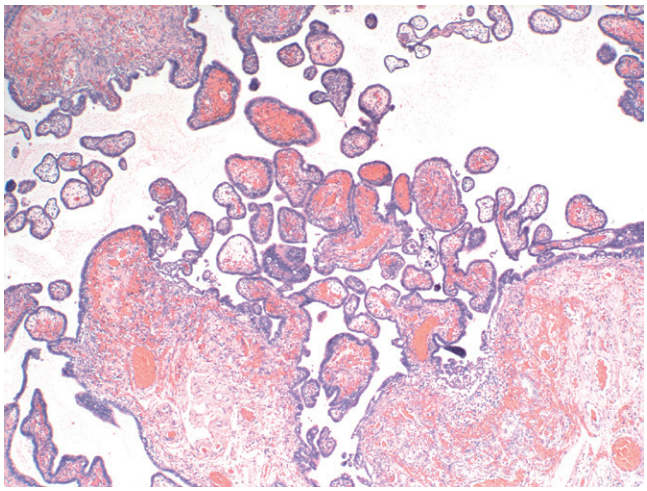


FIGURE 1

Papillary hyperplasia associated with inflammation. Note the small diameter papillae in contrast to larger tubal plicae.

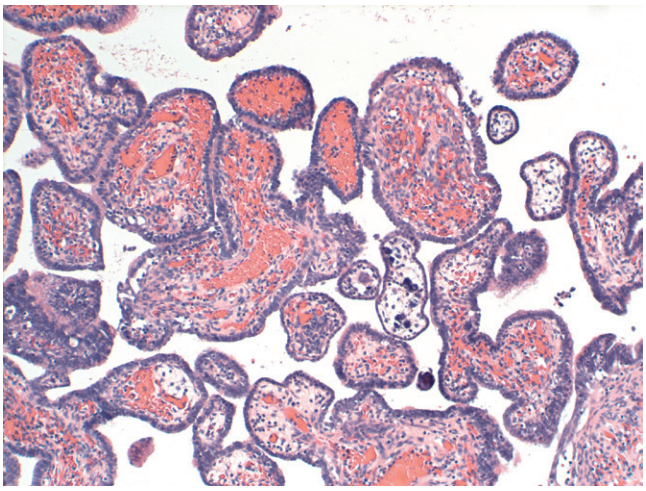


FIGURE 2

Papillary hyperplasia of the tube. Occasional calcification is present *(center)*.

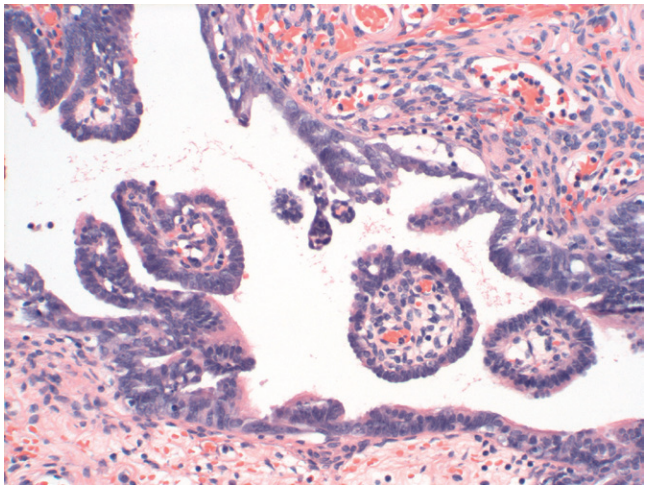


FIGURE 3

Papillary hyperplasia of the tube. Note the small, free-floating papillae.

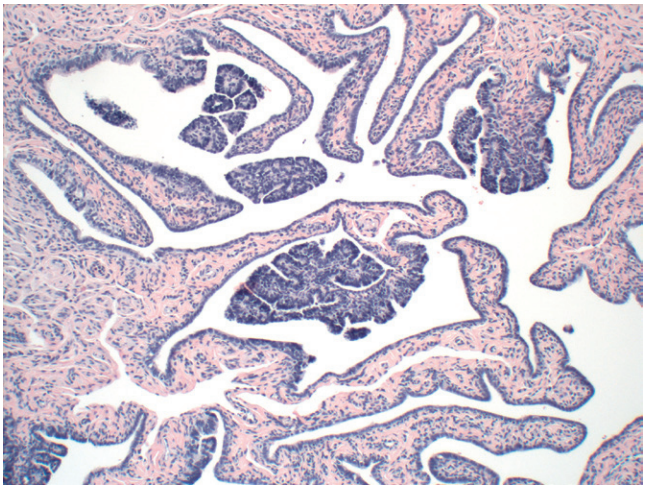


FIGURE 4

Papillary hyperplasia, present as multiple small outgrowths of ciliated and secretory cells.

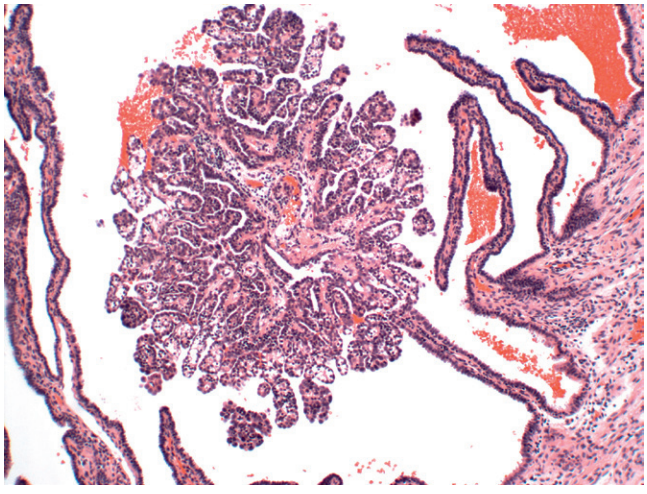


FIGURE 5

Papillary hyperplasia (a.k.a. papilloma). Note the appearance resembling a small borderline serous tumor of the tube.

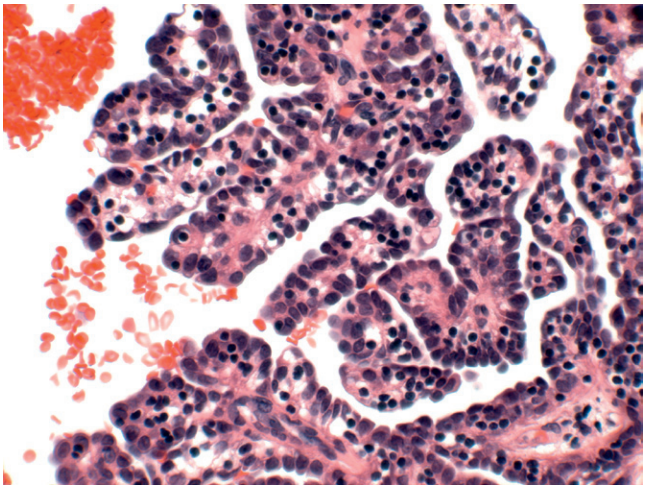


FIGURE 6

Papillary hyperplasia. At higher magnification the lining is composed of non-descript cuboidal cells.

HIGH-GRADE SEROUS TUBAL INTRAEPITHELIAL NEOPLASIA (SEROUS TUBAL INTRAEPITHELIAL CARCINOMA)

Definition—Intramucosal (noninvasive) serous carcinoma. Undisputable origin of pelvic serous cancer when found in isolation or with early invasion. A plausible candidate of origin when found in association with advanced disease.

Clinical Features

Epidemiology

- Serous tubal intraepithelial carcinoma (STIC) is rare, found in less than 1 : 1000 routine salpingectomies. It is found in from 1% to 12% of tubes removed during risk reduction salpingo-oophorectomy (RRSO) for inherited BRCA1 or BRCA2 mutations, the percentages increase with increasing patient age. It is discovered in up to 50% of fallopian tubes of women with high-grade pelvic serous carcinoma. It can be associated with, and presumably preceded by, a benign clonal expansion of secretory cells with p53 mutations (p53 signatures). Depending on the study, up to 30% of women with a carcinoma arising in the fallopian tube (with STIC) harbor a BRCA1 or BRCA2 mutation.

Presentation

- STICs are discovered on histologic exam of the tubes, either in RRSOs or tubes removed during surgery for advanced serous carcinoma. The former are usually asymptomatic and the latter present with the usual signs and symptoms of advanced disease. STIC is very uncommon in the asymptomatic woman without an inherited BRCA1 or BRCA2 mutation. Discovery of STIC is maximized using a protocol that thoroughly examines the distal fallopian tube (SEE-FIM protocol).

Prognosis and Treatment

- STICs are removed during surgery and when found in the setting of pelvic serous cancer are important as indicators of a tubal primary. When found in an RRSO they may or may not prompt further surgery (such as omentectomy or hysterectomy) to exclude residual disease. When found incidentally in nonmalignant circumstances, testing for BRCA1 or BRCA2 should be seriously considered to determine if other family members are at risk. If there is no evidence of immediate spread and pelvic washings are negative, the risk of subsequent pelvic serous cancer is low (under 10%) and in most institutions will not result in chemotherapy. Patients must be counseled that there is always some recurrence risk in a patient with a germ-line BRCA1/2 mutation.

Pathology

Histology

- STIC is diagnosed using histologic criteria, but it is helpful to take advantage of ancillary tests to clarify the diagnosis. The most helpful histologic criteria include the following:
  - Absence of cilia: The cell involved is a secretory cell.
  - An (slightly) irregular growth pattern with variable epithelial thickness, sometimes subtle.
  - Loss of normal nuclear orientation, imparting an appearance of abnormal polarity.
  - In extreme examples, horizontal fracture lines with exfoliation.
  - High nuclear-to-cytoplasmic (N/C) ratio.
- Features that may be present but are not specific are as follows:
  - Multilayered epithelium, which can be seen with any admixture of ciliated and secretory cells.

  - Nuclear molding, which often occurs focally in the tubal lining.
  - Nuclear enlargement (anisokaryosis), which is common in ciliated epithelium.
- Review by a second pathologist is encouraged if there is a difference of opinion.

Preferred Diagnostic Term

STIC (or intramucosal serous carcinoma), with the mention that up to 10% of these lesions will recur.

Immunopathology (Including Immunohistochemistry)

- The neoplastic cells are usually strongly and diffusely positive for p53 but will be conspicuously negative if the antigenic target sequence is deleted.
- Stains for p16ink4, cyclin E, EZH2, and stathmin are often positive; however, EZH2 and stathmin are *not specific and can be seen in benign epithelial hyperplasias* as can loss of PAX2 and ALDH1.
- The MIB1 index (Ki-67) is usually over 50% in parts of the lesion; however, STICs with low proliferative index can occur.
- A marker of polarity (p-ERM) typically shows loss of normal surface staining, highlighting irregular serrated luminal borders often with single cell membranous staining.
- Generic markers of tubal epithelium, PAX8, WT1, and CK7 will be positive.
- Use of p53 and Ki-67 is encouraged to support the diagnosis in difficult cases, but in such cases the ultimate verdict is *based on the degree of histologic certainty that the epithelium is malignant.*

Main Differential Diagnosis

- Benign epithelial hyperplasia (secretory cell outgrowths [SCOUTs])—these may exhibit multilayering but usually include ciliated cells. Polarity is preserved.
- Reactive epithelial changes, including Arias-Stella effect—these can be striking but have normal p53 expression and a low proliferative index. Moreover, they are typically found in younger women in the setting of inflammation or pregnancy.
- p53 signatures—these are typically small and unimpressive histologically, and exhibit low proliferative index. However, they may be associated with higher proliferation indices overlapping with lower-grade tubal intraepithelial neoplasms (e.g., serous tubal intraepithelial lesion [STIL], tubal intraepithelial lesions in transition [TILTs]).
- Lower-grade tubal intraepithelial neoplasms (a.k.a. tubal intraepithelial lesions or TILTs) share features of both p53 signatures and STICs and may signify the beginning of a transition from benign to malignant. Key distinguishing features are a casual appearance of benign pseudostratified epithelium with preserved polarity and a proliferative index under 25%.

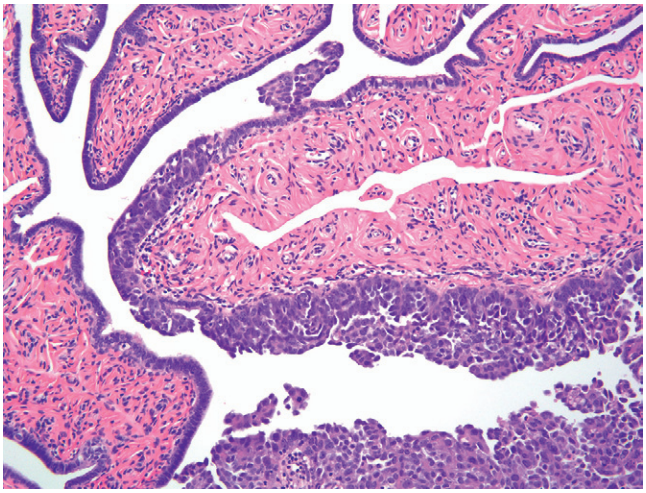


FIGURE 1

A classic STIC with multilayered epithelium and loss of polarity with horizontal fracture lines in the epithelium and exfoliation.

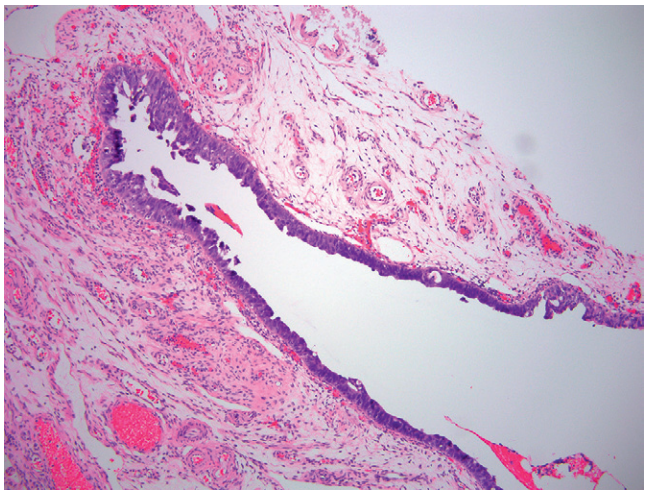


FIGURE 2

This STIC shows disorganized multilayered growth in the upper left, trailing off toward the lower right with a thinner epithelium that still displays a loss of normal cell orientation.

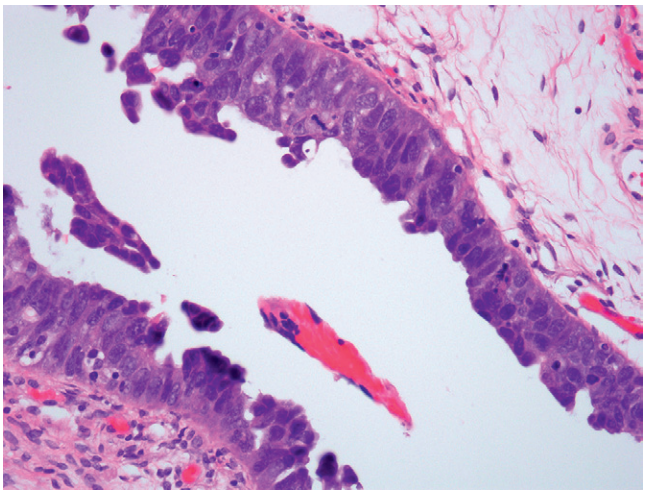


FIGURE 3

Higher power view of the STIC depicted in Figure 2.

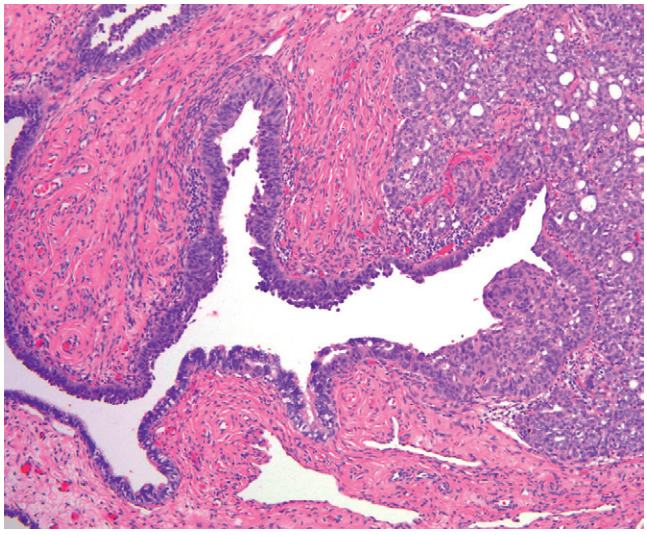


FIGURE 4

STIC *(center left)* merging with invasive serous carcinoma *(right)*.

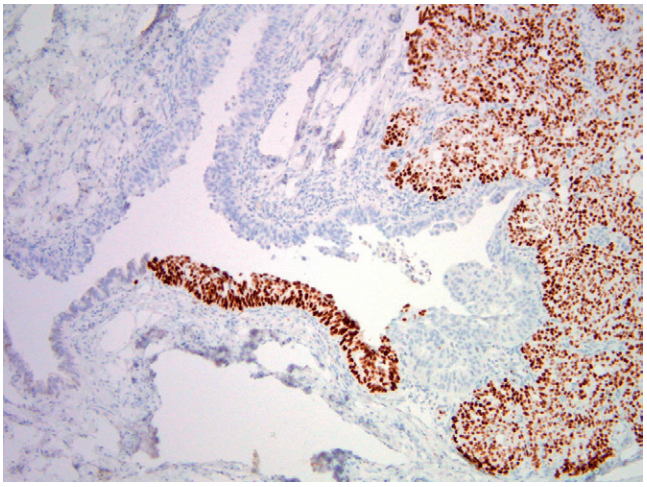


FIGURE 5

Strong p53 staining highlights part of the STIC and the cancer. The remainder of the STIC is negative, consistent with deletion of the gene encoding the protein recognized by the antibody.

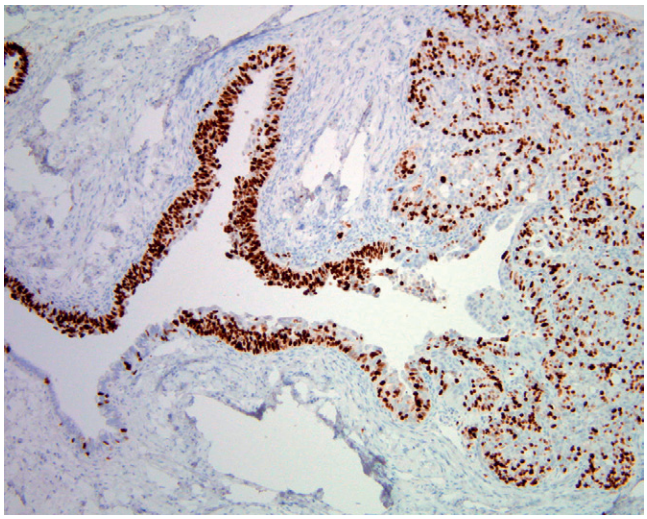


FIGURE 6

Note the strong MIB1 staining throughout both the STIC and invasive cancer. This can be highly variable from lesion to lesion, with occasional STICs having a low proliferative index.

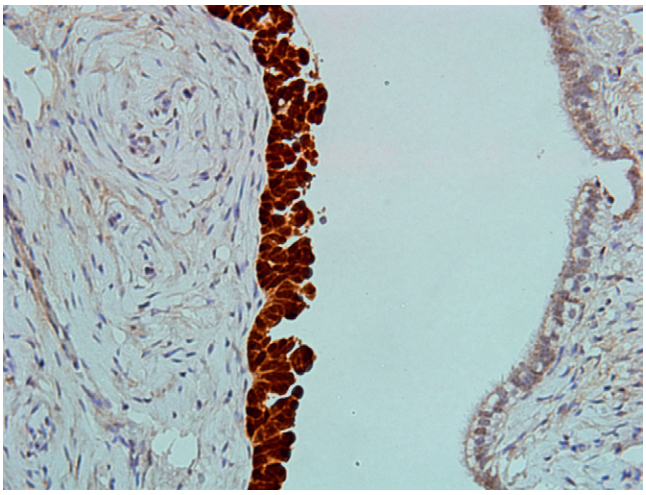


FIGURE 7

An STIC *(left)* highlighted by strong p53 staining. Note that p53 staining alone is not sufficient for a diagnosis of malignancy (also present in premalignant atypias and p53 signatures).

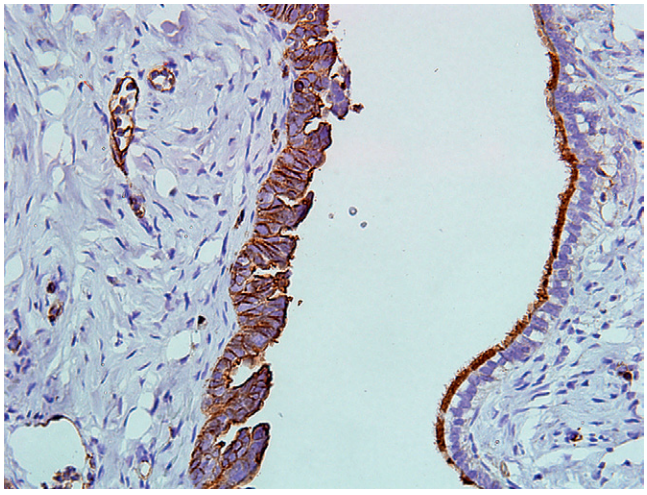


FIGURE 8

Staining for p-ERM, a marker of cell polarity, is abnormal in the STIC, tracing its irregular contour and highlighting the cell borders. Note the strictly luminal distribution in the normal epithelium *(right)*.

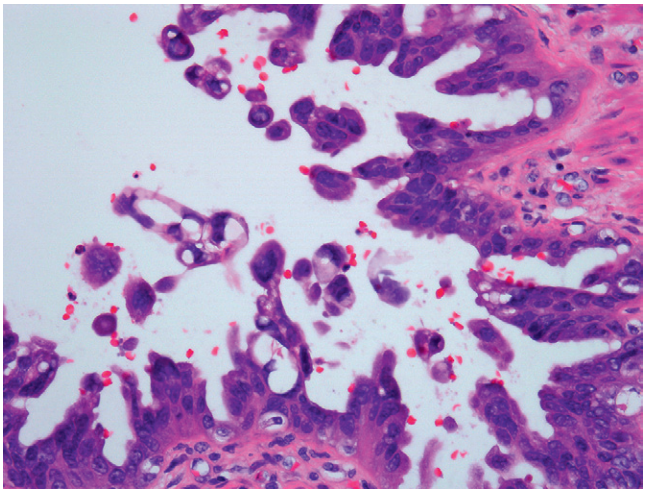


FIGURE 9

Arias-Stella reaction in a tube from a postpartum woman. This can be confused with STIC but lacks proliferative activity and will show normal p53 staining.

THE RISK REDUCING SALPINGO-OOPHORECTOMY

Definition—A procedure designed to remove the tubes and ovaries prior to the development of malignancy in women at high risk for ovarian cancer (BRCA1/2 germ-line mutations).

Clinical Features

Epidemiology

- Heterozygous germ-line mutations in BRCA1 or BRCA2 occur in approximately 1 in 400 women in the general population and 1 in 40 women of Ashkenazi Jewish descent.
- Lifetime risk of a pelvic fimbrial ovarian cancer is estimated at 40% and 10% for BRCA1 and BRCA2 mutation carriers respectively, without surgical intervention.
- The vast majority of carcinomas are variants of high-grade serous carcinoma including "SET" (solid, endometrioid-like and transitional) patterns.

Presentation

- All fallopian tubes and ovaries should be submitted for pathologic evaluation and completely sectioned. The sectioning and extensively examining the fimbria (SEE-FIM) protocol, which provides for extensive and thin sectioning of the distal one third of the tube, will maximize detection of small neoplasms.
- In about 95% of risk reduction salpingo-oophorectomies (RRSOs) no abnormality will be found. Virtually all RRSOs in asymptomatic women are grossly unremarkable.
- If a small cancer is present in the fimbria, it may be detected as a small 1 to 2 mm nodule on palpation.
- In some cases, examination of the peritoneal fluid will disclose malignant cells.

Prognosis and Treatment

- RRSO will reduce the risk of cancer by approximately 80% to 90%. Residual risk of developing malignancy following RRSO is estimated at approximately 1% to 5%, depending on the study.
- Most institutions do not treat women with intraepithelial carcinoma alone. From 1% to 10% will be followed by a pelvic serous cancer.
- Importantly, recurrences following risk reduction surgery will often not be detected for several (2 to 5) years.
- If either invasion or local spread is found at RRSO, treatment with combination chemotherapy will usually be instituted, and up to 50% will recur over the next 5 years. Short- to intermediate-term survival is high (>80%); 10-year survival approximately 25% to 35%.

Pathology

Histology

- In 5% to 10% of RRSOs an early carcinoma is detected and will be classified as a tubal primary in about 80% (see chapters on tubal intraepithelial neoplasia). Virtually all carcinomas will be found in the distal one third of the fallopian tube, including the fimbria, infundibulum, and nearby tubal segment.
- A range of tubal abnormalities will be encountered. Most are high-grade intraepithelial neoplasia (serous tubal intraepithelial carcinoma [STIC]). Others will consist of atypias that fall short of STIC and are variously classified as low-grade tubal intraepithelial neoplasia, tubal intraepithelial lesion, or moderate atypias. Occasionally, *endometrioid* intraepithelial carcinomas can be seen.
- If STIC is suspected, the following should be searched for:
  - Absence of cilia: The cell involved is a secretory cell.
  - A slightly irregular growth pattern with variable epithelial thickness, sometimes subtle.
  - Loss of normal nuclear orientation, imparting an appearance of abnormal polarity.
  - In extreme examples, horizontal fracture lines with exfoliation.
  - High nuclear-to-cytoplasmic (N/C) ratio.
- Features that are not particularly helpful are:
  - Multilayered epithelium, which can be seen with any admixture of ciliated and secretory cells.

  - Nuclear molding, which often occurs focally in the tubal lining.
  - Nuclear enlargement (anisokaryosis), which is common in ciliated epithelium.
- In difficult cases, staining for p53 and Ki-67 may be helpful, but the diagnosis is ultimately based on histologic features. Review by a second pathologist is encouraged if there is a difference of opinion.

Preferred Diagnostic Terminology

- Terminology for high- and low-grade tubal intraepithelial neoplasia is sufficient (see respective chapters).
- If STIC alone is found, the risk of recurrence (1% to 10%) should be specified.
- If STIC and/or invasive carcinoma or spread are documented, this should be specified as it increases the recurrence risk to up to nearly 50%.
- If the specimen is entirely normal histologically or contains a lower-grade atypia, no diagnosis is necessary other than benign epithelial changes. However, a note should be added that even in the absence of a neoplasm there is still a small (1% to 5%) risk of a subsequent pelvic cancer, which is greater than the general population.
- Terms such as tubal dysplasia and p53 signature should not be used, or if they are, should be qualified with a carefully written explanation to distinguish them from higher-risk (STIC) lesions.

Immunopathology (Including Immunohistochemistry)

- Use of p53 and Ki-67 is encouraged to support the diagnosis in difficult cases, but in such cases the ultimate verdict is *based on the degree of certainty that the epithelium is malignant.*

Main Differential Diagnosis

- These are detailed in the appropriate chapters on tubal intraepithelial neoplasia.

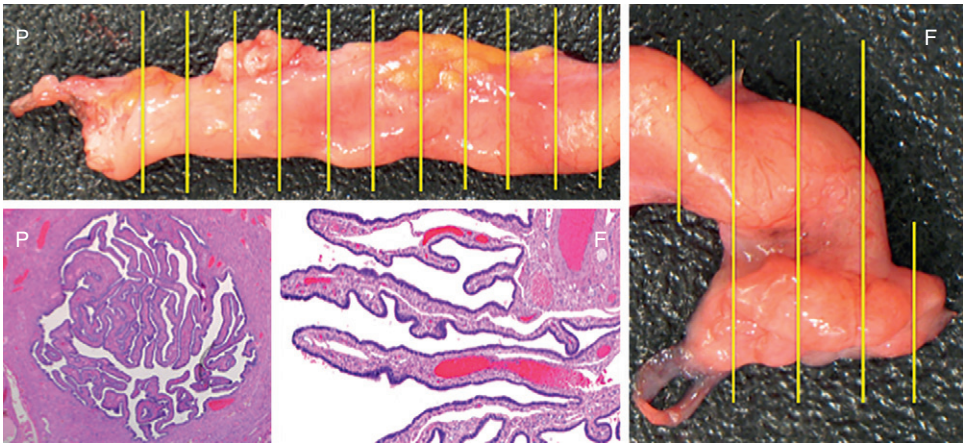


FIGURE 1

The SEE-FIM sectioning protocol specifies complete tubal sectioning and multiple sections of the fimbria..

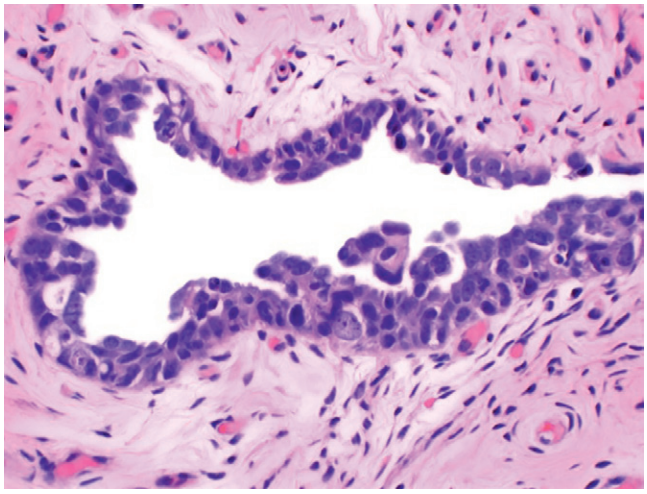


FIGURE 2

A typical STIC found in an RRSO.

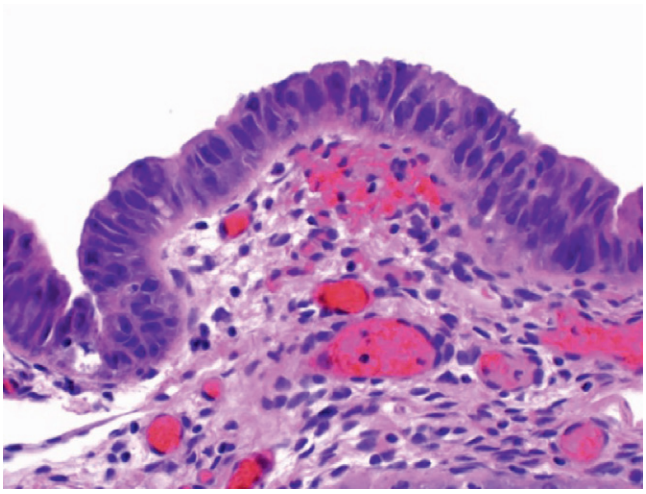


FIGURE 3

A low-grade tubal intraepithelial neoplasm with lesser atypia (serous tubal intraepithelial lesion [STIL] or tubal intraepithelial lesion in transition [TILT]).

SALPINGOLITHS

Definition—Psammous calcifications in the lumen and plica of the fallopian tube.

Clinical Features

Epidemiology

- Uncommon.
- Approximately one half are associated with low-grade serous tumors of the ovary (borderline or low-grade malignancies).

Presentation

- Discovered incidentally at the time of examination of the tube for other reasons.
- When found in association with low-grade serous tumors, they are usually at higher stage perhaps because salpingoliths signify a form of spread from the primary tumor.

Prognosis and Treatment

- Depends entirely on the associated epithelial lesion.
- Incidentally discovered salpingoliths require immediate workup, but periodic follow-up is prudent given the association with low-grade serous tumors.

Pathology

Histology

- Numerous concentric calcifications are situated in the plical stroma.
- Calcifications may be bare or surrounded by scant cytoplasm.
- Location in the lamina propria suggests lymphatic spread from the primary tumor.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- The main issue is whether the salpingoliths are incidental or associated with a benign or malignant tumor. This is resolved usually by analysis of the remainder of the adnexa.
- Primary borderline or malignant serous tumor originating in or involving the tube. This is confirmed if there is a proliferating neoplastic epithelium associated with psammous calcifications.

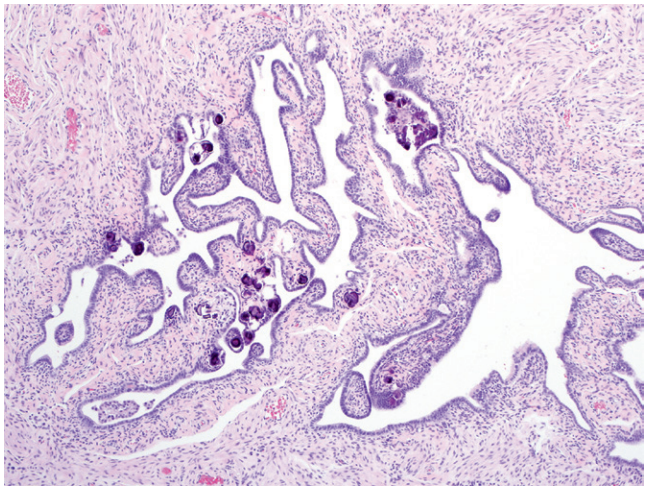


FIGURE 1

Salpingoliths at low magnification. Note the predominance in the lamina propria.

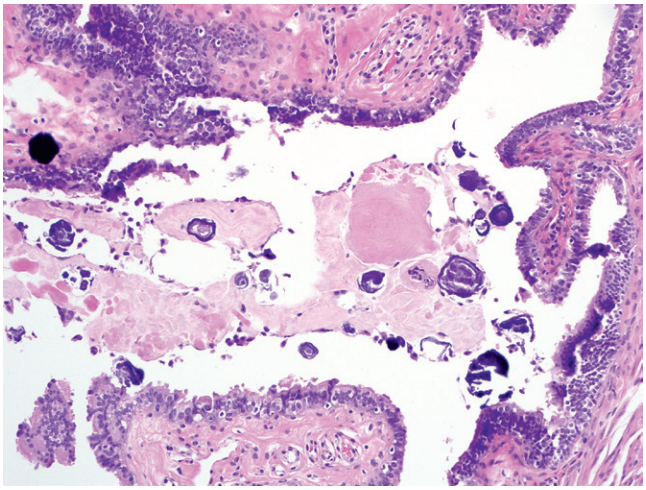


FIGURE 2

Salpingoliths. In some areas they may present as intraluminal calcifications.

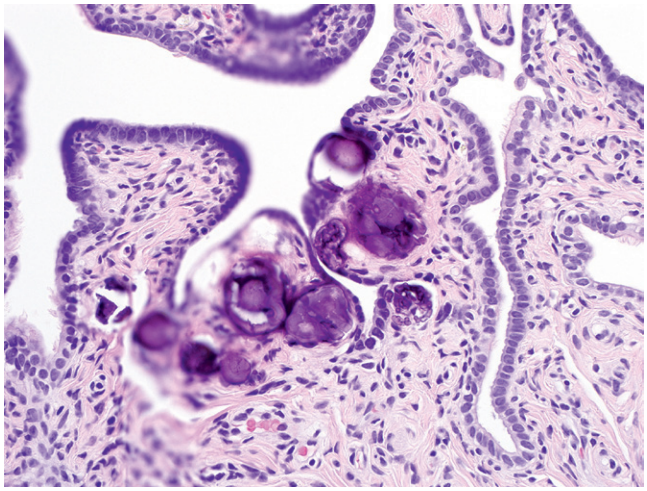


FIGURE 3

Salpingoliths at higher magnification. Note the distinctive location in the stroma. This raises the intriguing question of whether they were transported by lymphatics versus directly incorporated from the lumen.

ADENOCARCINOMA OF THE FALLOPIAN TUBE

Definition—Adenocarcinoma arising in the tubal mucosa.

Clinical Features

Epidemiology

- Historically a small fraction (5% or less) of pelvic serous carcinomas relative to the ovary; however, with the attention being paid to the distal tube (using the section and extensively examine the fimbriated end [SEE-FIM] protocol) as a source of many high-grade serous carcinomas, the incidence is presumed to be much higher.
- Linked to chronic tubal inflammation.
- Up to 30% have been reported to be associated with BRCA1 or BRCA2 germ-line mutations.

Presentation

Two major presentations are as follows:

- A bulky, sausage-shaped tube filled with tumor. This is presumed to occur when the distal fallopian tube is closed by peritubal or tubal-ovarian adhesions.
- A microscopic intramucosal carcinoma (serous tubal intraepithelial carcinoma [STIC]) that (presumably) spreads by direct exfoliation onto the pelvic surfaces.

Prognosis and Treatment

- Generally seen as synonymous with high-grade serous carcinoma of the ovary or pelvis in terms of outcome, which is dependent on stage at presentation.
- Stage I tumors confined by fimbrial adhesions have a much better prognosis.

Pathology

Histology

- Classic criteria for diagnosis as a tubal carcinoma include (1) intramucosal carcinoma; (2) absence of a coexisting endometrial carcinoma of same histology; and (3) minimal parenchymal involvement of the ovaries, with primarily surface involvement. Each of these has a caveat. First, not all intramucosal carcinomas can necessarily be assumed to be sites of origin in the absence of a lesser precursor condition (such as a low-grade serous tubal intraepithelial neoplasia [STIN]/serous tubal intraepithelial lesion [STIL]). Coexisting tubal and endometrial carcinomas can be concurrent primary tumors in some instances. There is no evidence that a cystic tumor in the ovary is necessarily more likely to be a primary ovarian tumor than a surface implant given recent data indicating that ovulating mice are highly prone to cystic metastases from pelvic carcinomas (via entry of repairing ovulation sites).
- Most tumors are high-grade müllerian carcinomas including those with classic high-grade serous carcinoma and solid, endometrioid-like, and transitional (SET) patterns. Occasional endometrioid lesions in the tube have been described but primary low-grade endometrioid carcinomas of the tube are uncommon and many likely come from endometriosis.

Immunopathology (Including Immunohistochemistry)

- The neoplastic cells are usually strongly and diffusely positive for p53 but will be conspicuously negative if the antigenic target sequence is deleted.

- Generic markers of tubal epithelium, PAX8, WT1, and CK7 will be positive.

Main Differential Diagnosis

- Metastatic carcinomas of the gastrointestinal and pancreaticobiliary tracts—these are usually mucin producing.
- Metastatic carcinomas from the uterus and/or ovary—determining origin may be difficult, but at present a dominant ovarian mass in the absence of a tubal STIC may favor an ovarian origin. Endometrial carcinomas that invade the myometrium are generally held to be primary in the setting of a coexisting STIC or carcinoma.
- Female adnexal tumor of wolffian origin—may mimic a low-grade endometrioid adenocarcinoma. These are typically inhibin and calretinin positive.

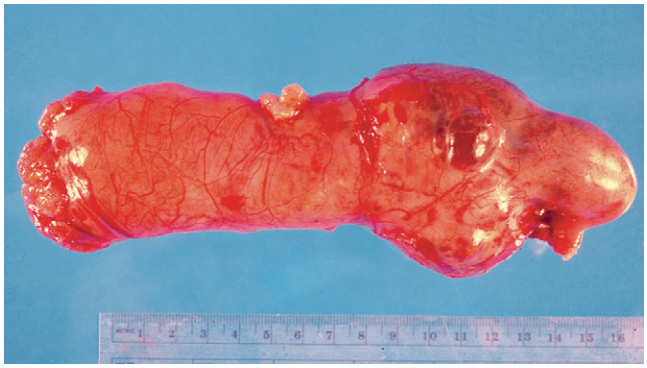


FIGURE 1

Typical sausage-shaped tube filled with a seemingly confined serous carcinoma.

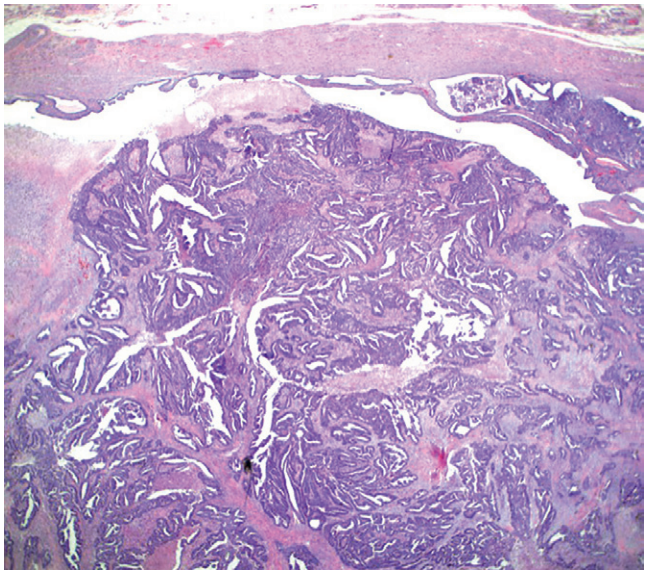


FIGURE 2

Low-power magnification of a fallopian tube distended by carcinoma. This is not specific for a tubal origin by itself.

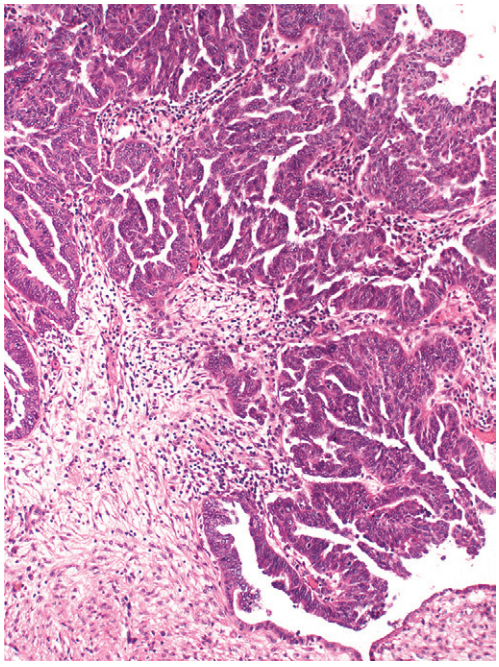


FIGURE 3

Exophytic high-grade serous carcinoma.

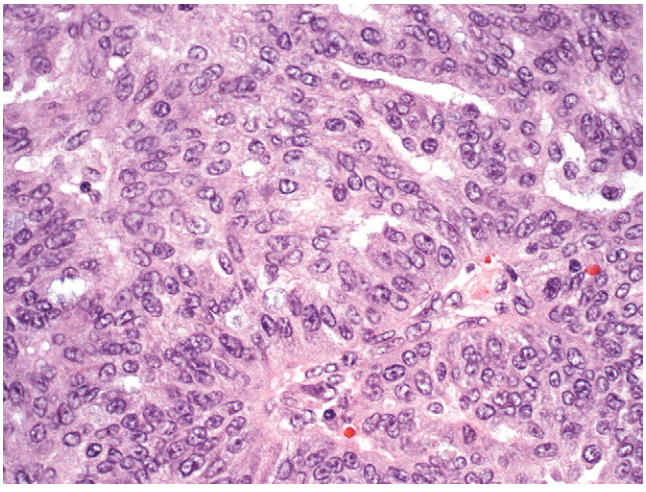


FIGURE 4

Endometrioid differentiation in a high-grade müllerian carcinoma (SET type).

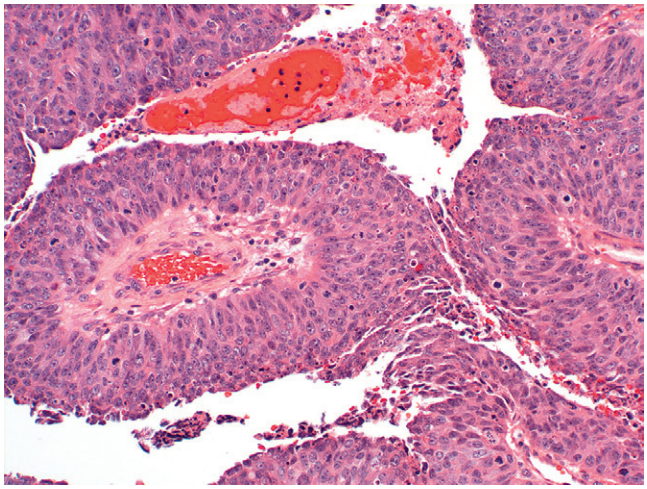


FIGURE 5

Transitional pattern in a high-grade müllerian carcinoma of the tube (SET type).

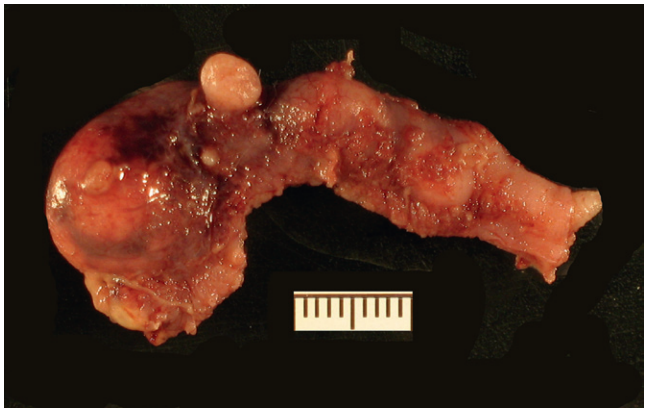


FIGURE 7

Small endometrioid carcinoma in the distal tube in a patient with endometrial adenocarcinoma. This would be designated as a metastasis in most cases.

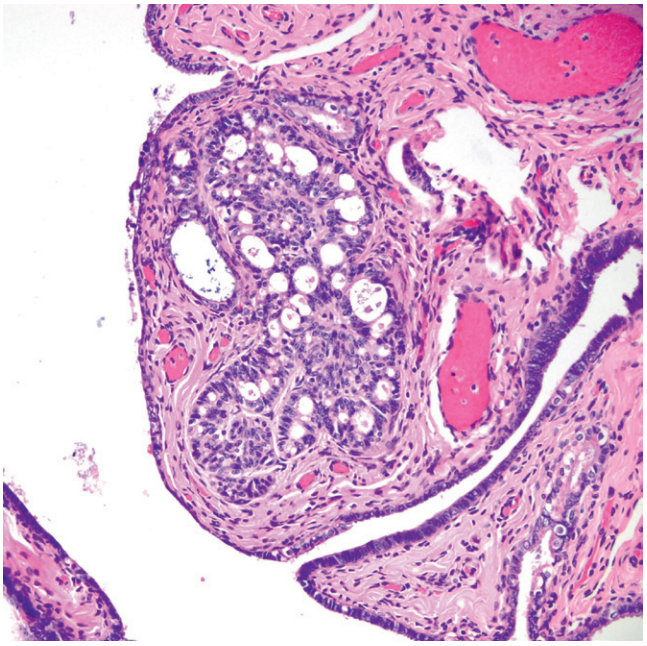


FIGURE 6

Small focus of endometrioid atypia involving a plica. This was the only abnormality in this patient, indicating that lower-grade endometrioid differentiation can occur in the fallopian tube and possibly give rise to endometrioid carcinomas. However, these are quite rare.

ENDOSALPINGEAL IMPLANTS FROM REMOTE TUMORS

Definition—Intraepithelial neoplasms of presumed nontubal origin.

Clinical Features

Epidemiology

- Uncommon but a function of the thoroughness to which the tube is examined.
- Can be seen with both gynecologic and nongynecologic tumors.
- Mucosal involvement will be seen in about one third of cases where the tube is involved.
- Colon and breast are the most common sites of origin.

Presentation

- Discovered incidentally during tubal examination.
- Clinical features related to the nature of the tumor of origin.

Prognosis and Treatment

- Depends on the biologic behavior of the original tumor.

Pathology

Histology

- Tumor cells are in the mucosa, lending the appearance of an "intraepithelial" neoplasm.
- Degree of atypias varies depending on the nature of the tumor.
- Bland-appearing mucinous epithelium is seen in cases with either gynecologic or intestinal (appendiceal) tumors.
- The absence of a clear precursor condition, although with bland lesions this may be impossible to exclude.

Immunopathology (Including Immunohistochemistry)

- PAX8 and WT1 may be helpful in differentiating gastrointestinal and other sites from a primary lesion of the fallopian tube, but both may be negative in mucinous lesions even if from the female genital tract.

Main Differential Diagnosis

- Primary tubal intraepithelial carcinoma with mucinous differentiation—diagnosis of exclusion (must rule out concomitant gastrointestinal including appendiceal primary).
- Mucinous metaplasia of fallopian tube epithelium—again this is a diagnosis of exclusion.

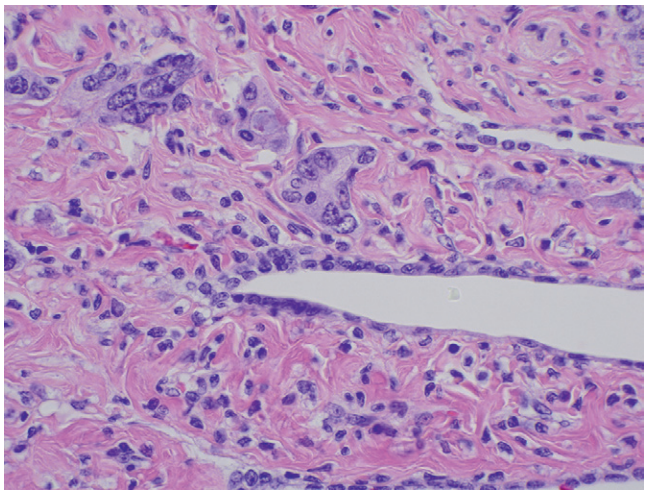


FIGURE 1

Metastatic colonic carcinoma present in lymphatics beneath a normal tubal mucosa.

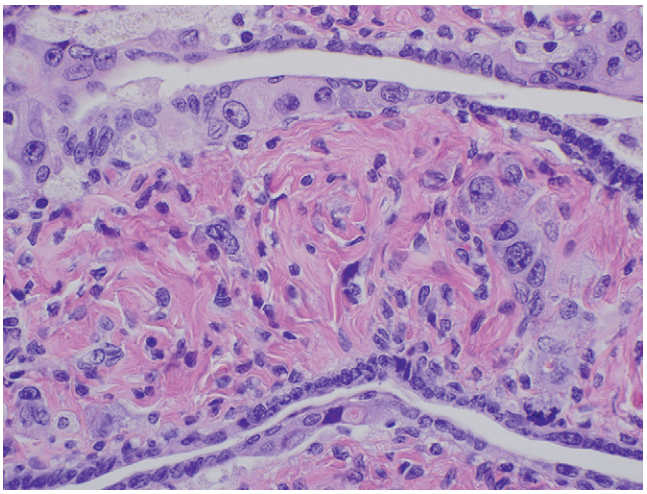


FIGURE 2

Here the tumor cells have migrated onto the mucosa, displacing normal epithelial cells. In this case there is no question that the tumor is from another site, but this illustrates the potential for intraepithelial spread in such tumors.

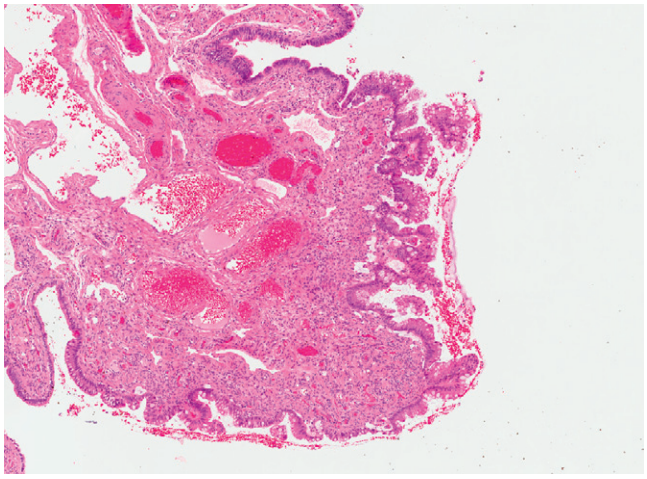


FIGURE 3

Tumor implant on the fimbrial mucosa from a low-grade mucinous tumor of the appendix.

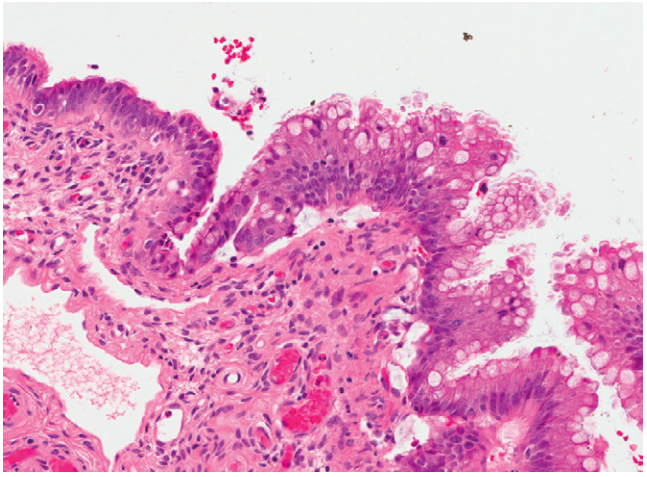


FIGURE 4

At higher magnification the metastatic epithelium is virtually indistinguishable from what would be expected if this were a mucinous metaplasia.

FEMALE ADNEXAL TUMOR OF WOLFFIAN ORIGIN

Definition—A low-grade neoplasm that is thought to arise in the mesonephric remnants of the broad ligament.

Clinical Features

Epidemiology

- Female adnexal tumors of (probable) wolffian origin (FATWOs) are rare neoplasms, and no clinical or demographic associations have yet been made regarding their origin.

Presentation

- FATWOs usually present as unilateral, expansile tumors arising in the broad ligament but may be seen less commonly in the fallopian tube, ovary, and adjacent peritoneal region. The patient may describe mass effect symptoms if the tumor is large enough or may be completely asymptomatic.
- FATWOs present as solid or solid and cystic masses.

Prognosis and Treatment

- FATWOs are considered low-grade malignancies, and after conservative surgical excision, the patient can be closely followed. About 20% have an adverse outcome and concern is raised when there is capsular invasion, necrosis, and increased mitotic counts.

Pathology

Histology

- Histologically, FATWOs closely resemble mesonephric tumors of the cervix. Histologic patterns include solid to spindled with variable amounts of retiform tubule formation. In solid tumors, irregular cleftlike spaces may form. Nuclear grade is low and necrosis should be rare or absent.

Immunopathology (Including Immunohistochemistry)

- FATWOs stain positive for calretinin, cytokeratin, and vimentin. EMA and CEA are negative in the neoplastic cells.

Main Differential Diagnosis

- Adenomatoid tumor—this tumor has a regular pattern of small mesothelial lined acini.
  Metastatic adenocarcinoma—endometrioid carcinomas in particular may mimic this when they have a spindled component.
  Sarcoma (solid/spindled variant)—calretinin and cytokeratin stains should exclude this entity.
- Sex cord stromal tumors may mimic this neoplasm; however, Sertoli-Leydig cell tumors are not seen in the broad ligament. Granulosa cell tumors can be and the distinction is based on histology and the cytologic features (nuclear grooves) when present.

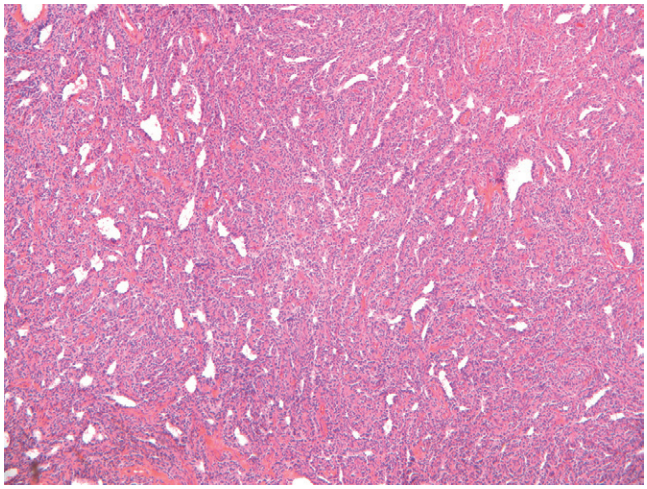


FIGURE 1

FATWO. Note the monomorphic population of cells with ill-defined spaces.

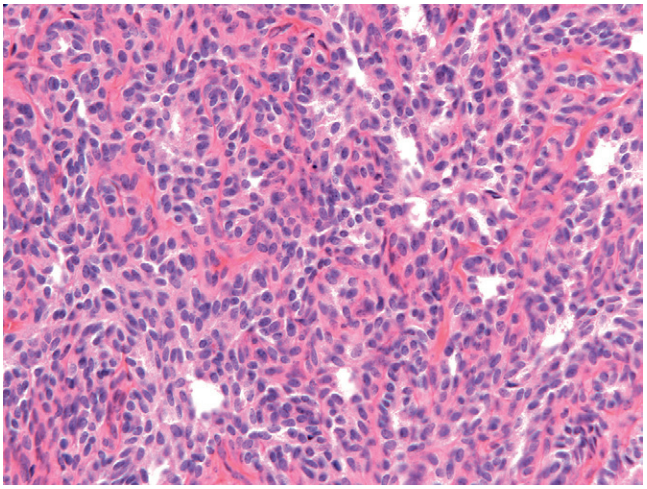


FIGURE 2

At higher magnification the nuclei are uniform and slightly fusiform with minimal coarsening of the chromatin.

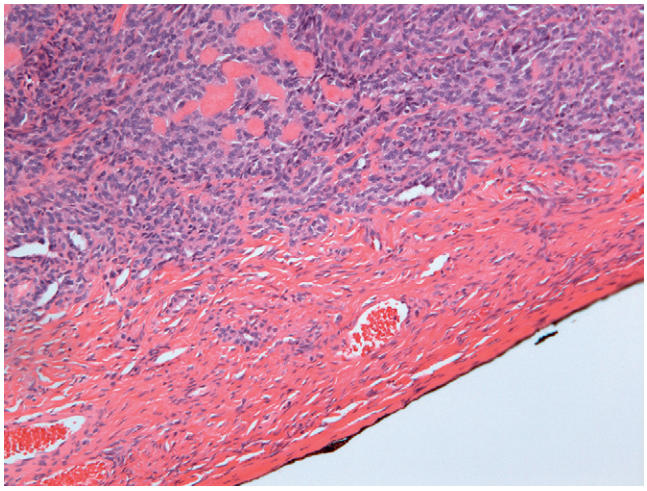


FIGURE 3

The border of the tumor and benign stroma.

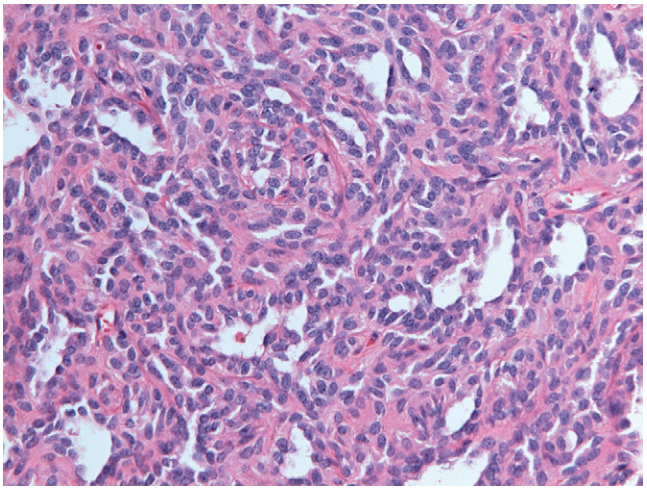


FIGURE 4

At high magnification the glands form a small slitlike space.