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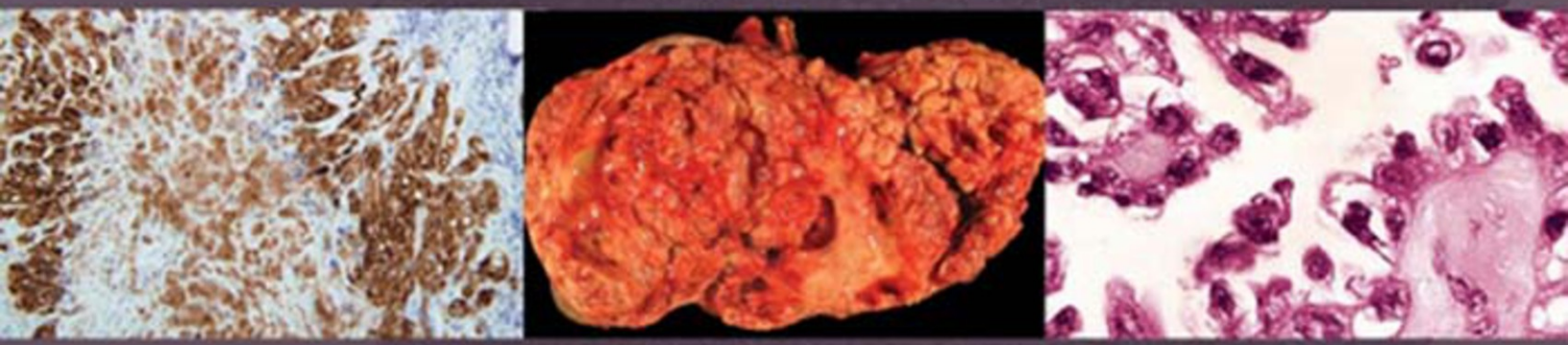
HIGH-YIELD PATHOLOGY

Gynecologic and Obstetric Pathology

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



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Gynecologic and Obstetric Pathology

HIGH-YIELD PATHOLOGY

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GYNECOLOGIC AND OBSTETRIC PATHOLOGY:
HIGH-YIELD PATHOLOGY

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PREFACE

Navigating the Seven "Cs" of Decision Making in Pathology

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

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

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

Christopher P. Crum, MD

CONTENTS

B. Endometrial Glandular Neoplasia and Its Mimics

C. Mesenchymal Lesions of the Uterus

SECTION 5

Ovary

TANGENTIALLY SECTIONED OVARIAN FOLLICLE

PITFALL

Definition—A benign sectioning artifact that can be mistaken for neoplasia.

Clinical Features

Epidemiology

- Reproductive-age women.

Presentation

- Found incidentally on examination of the ovaries.

Prognosis and Treatment

- Not neoplastic and of no clinical import unless misdiagnosed as neoplasia.

Pathology

Histology

- Tangentially sectioned follicles will display theca cells only in a somewhat discrete microscopic nodule.
- Theca cells are enlarged and fusiform.
- Mitotic figures are common but normal appearing.

Immunopathology (Including Immunohistochemistry)

- Noncontributory but are inhibin positive.

Main Differential Diagnosis

- Microscopic thecoma-fibroma. These will appear more discrete.
- Metastatic carcinomas. These can be distinguished by cytokeratin stains if needed. In general, serial sections will likely reveal the follicle for what it is.

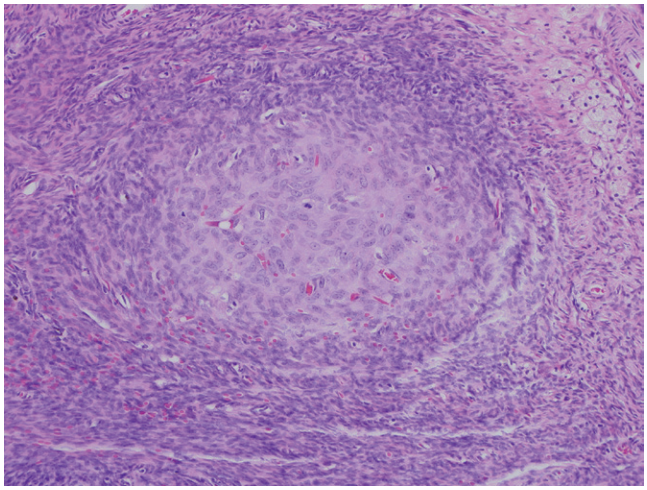


FIGURE 1

Tangentially sectioned follicle. Note the pale appearance of the theca externa.

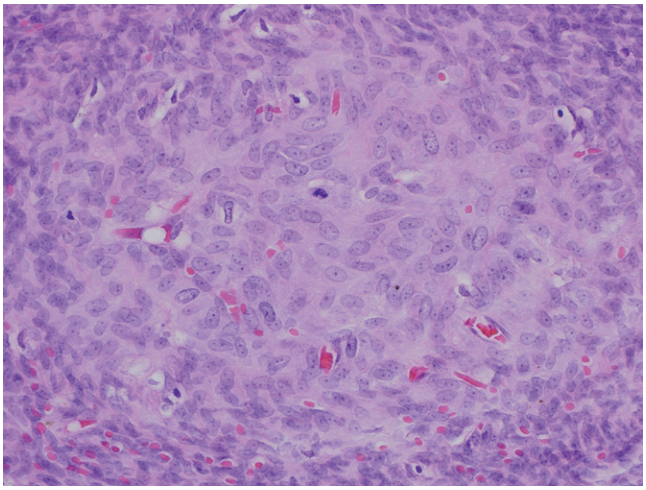


FIGURE 2

Tangentially sectioned follicle. At higher magnification the theca externa cells exhibit ovoid nuclei and open chromatin.

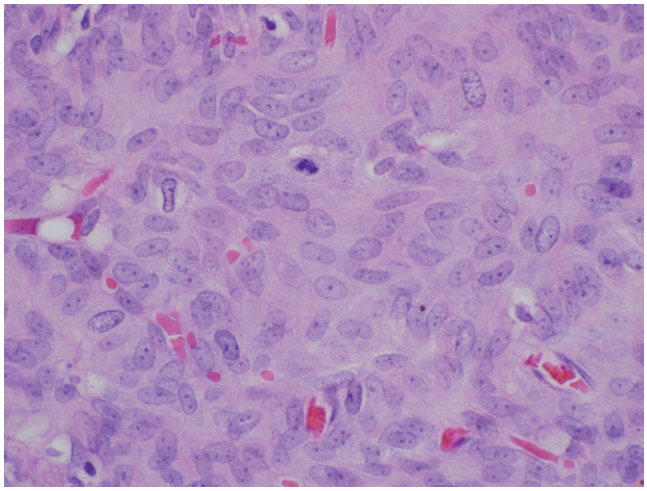


FIGURE 3

Tangentially sectioned follicle. At higher magnification the theca externa cells exhibit ovoid nuclei and open chromatin.

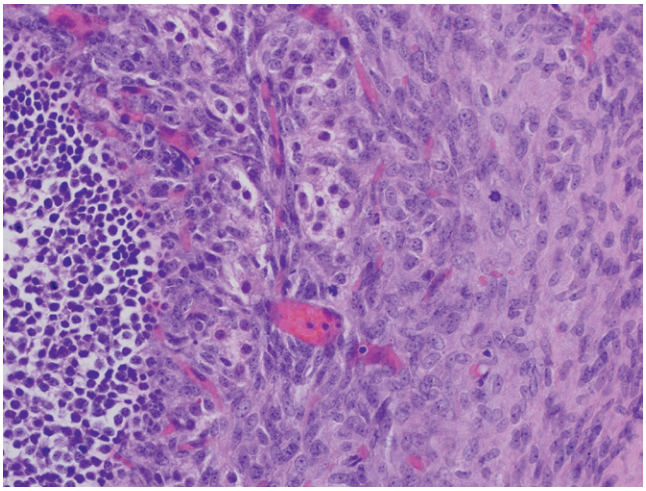


FIGURE 4

Follicles in which orientation permits distinction of the different layers. Note the theca externa on the right and the mitotic activity.

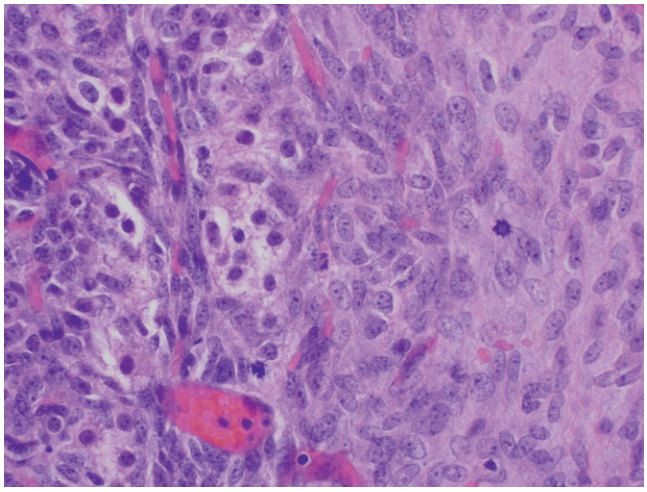


FIGURE 5

Higher magnification delineating the theca interna *(right)* and externa *(left)* of a follicle.

THE OVARY IN PREGNANCY

Definition—A constellation of findings in the ovary during gestation.

Clinical Features

Epidemiology

- Related to the pregnancy state.
- Linked to the effects of gonadotropins on the ovarian cortex.
- Can be particularly pronounced during multiple-gestation pregnancies and hydatidiform moles.

Presentations

- Corpus luteum of pregnancy.
- Theca-lutein hyperplasia of pregnancy (TLHP): Presents with variable enlargement of ovaries during pregnancy, typically bilateral.
- Hyperreactio luteinalis: Bilateral multicystic ovaries.
- Solitary luteinized cyst (discussed separately).

Prognosis and Treatment

- Excellent; these are incidental benign lesions.

Pathology

Histology

- Corpus luteum of pregnancy: A distinct cerebriform contour, hyaline droplets, and vacuoles.
- TLHP: Varies from focal to extensive. Thecal cells are expanded and merge with luteinized stromal cells to form small nodules (sometimes called pregnancy luteoma). Variable and less-pronounced luteinization of the granulosa cells.
- Hyperreactio luteinalis: A variant of TLHP in which there are in addition numerous follicle cysts giving rise to a multicystic ovary.

Immunopathology (Including Immunohistochemistry)

- Not usually necessary.

Main Differential Diagnosis

- Steroid-producing tumors—these are single unilateral uninodular solid tumors. Here the distinction between a luteoma and a "pregnancy luteoma" becomes blurred. Pregnancy is believed by some to be synonymous with TLHP. However, if the tumor is single, solid, and unilateral, the term steroid cell tumor is more apt.

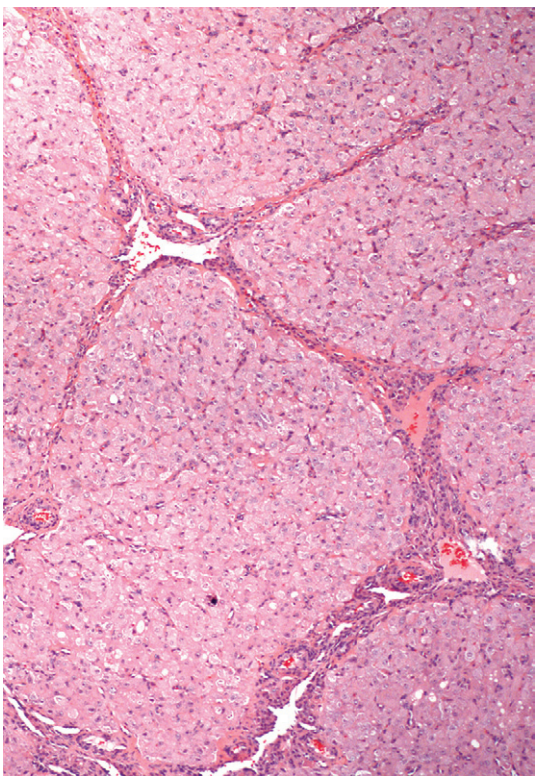


FIGURE 1

Corpus luteum of pregnancy. Low-power image with cerebriform contour.

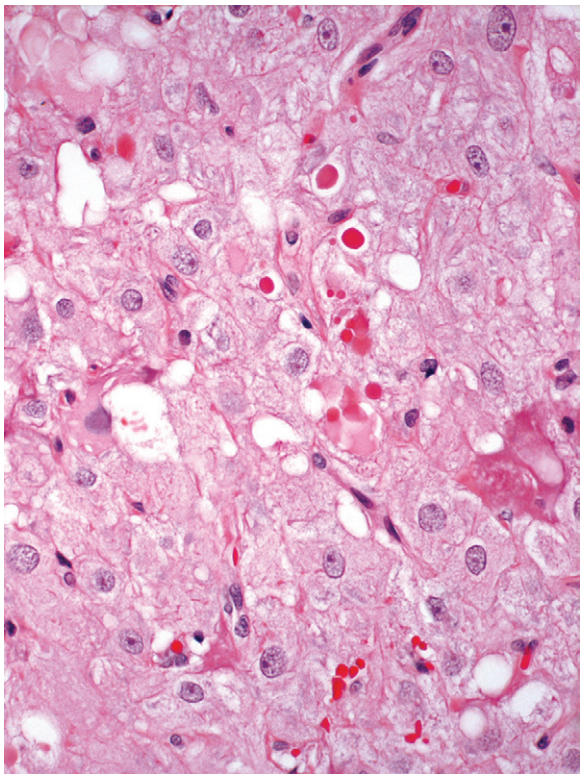


FIGURE 2

Corpus luteum of pregnancy. At higher power the characteristic vacuoles and hyaline droplets are seen.

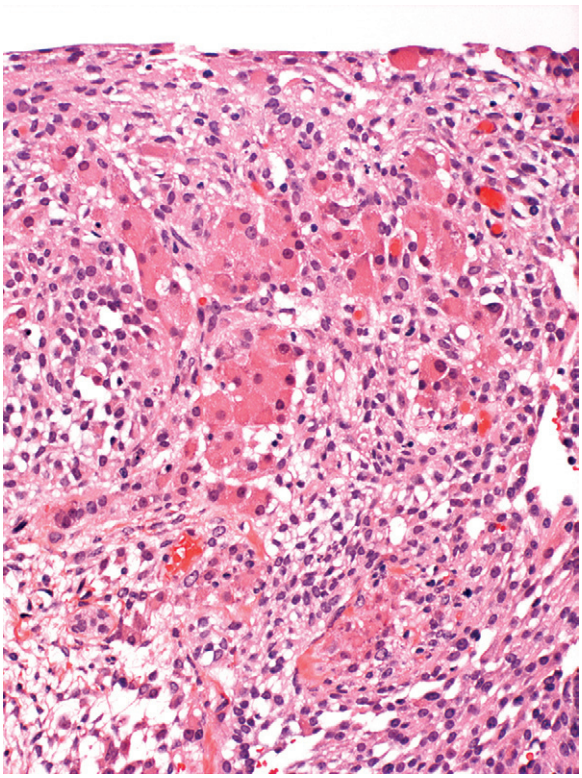


FIGURE 3

TLHP. Prominent coalescing thecal and stromal luteinized cells.

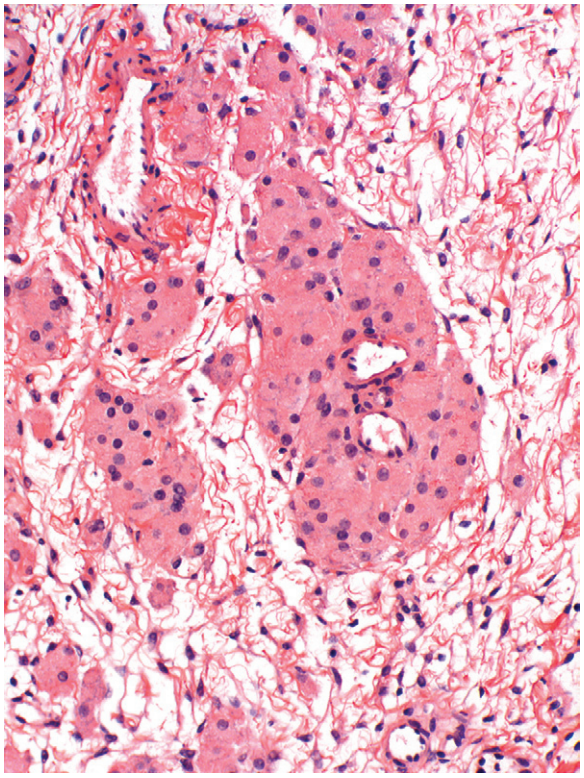


FIGURE 4

TLHP. Plump luteinized stromal cells.

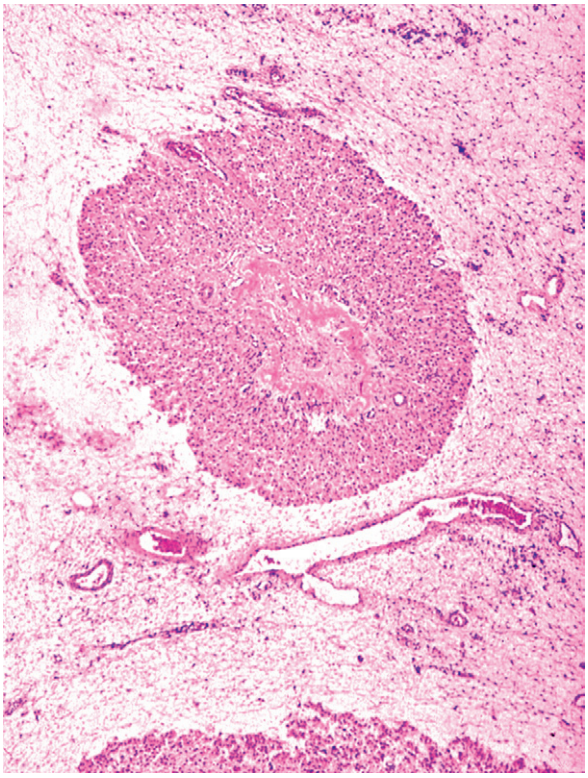


FIGURE 5

Nodular TLHP, characterized by microscopic nodular aggregates of hyperplastic thecal cells.

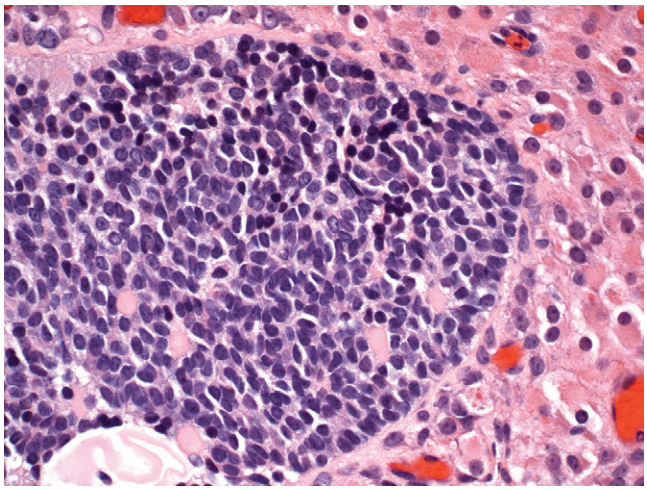


FIGURE 6

Granulosa cell proliferation in the ovary during pregnancy.

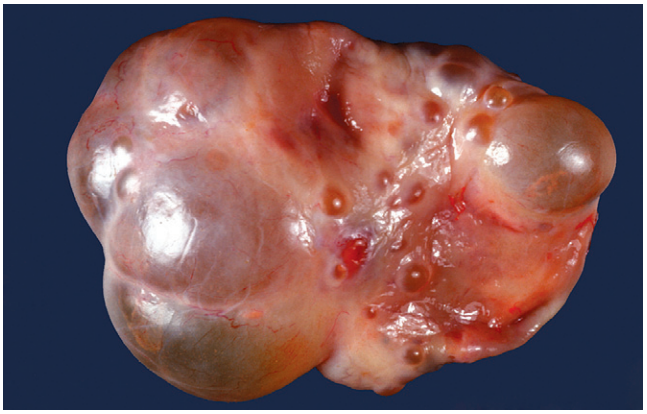
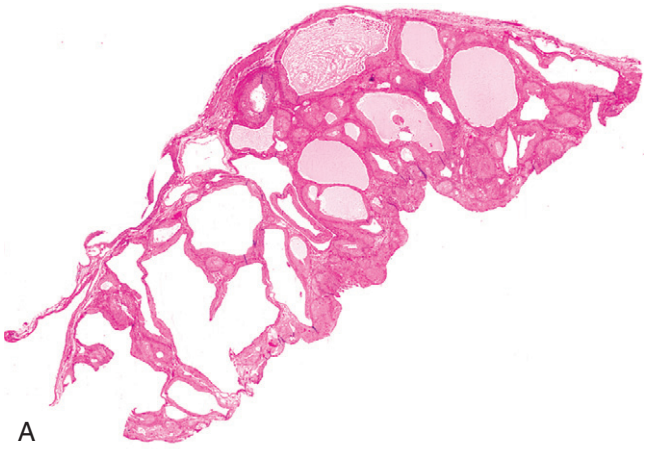


FIGURE 7

Hyperreactio luteinalis. The characteristic features are bilateral expansion of the ovaries by multiple cysts.



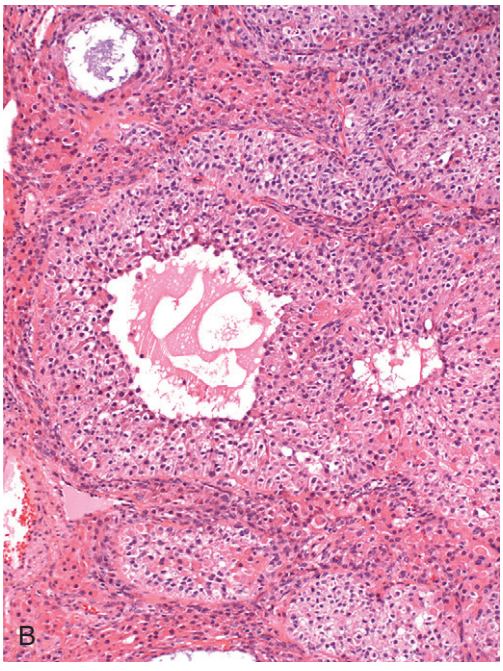


FIGURE 8

Hyperreactio luteinalis. **A,** Low-power microphotograph depicts multiple cystic follicles. **B,** The follicles are lined by luteinized cells.

SOLITARY LUTEINIZED FOLLICLE CYST

Definition—Benign incidental ovarian cyst most often noted in pregnant women.

Clinical Features

Epidemiology

- Uncommon to rare.
- Most often noted in pregnant or recently postpartum women.
- Can also be seen in nonpregnant, usually reproductive-age, women.

Presentation

- May be found on imaging or the patient may present with pelvic discomfort.
- Hormonal derangement has not been reported in association with these cysts.
- Most are incidentally noted at the time of cesarean section or ultrasound examination of the ovaries/pelvis.

Prognosis and Treatment

- Excellent; these are incidental benign lesions.

Pathology

Histology

- Gross examination is characterized by a thin-walled cyst filled with watery fluid.
- Median size of these cysts is 2.5 cm.
- At low power the cyst is lined by several layers of eosinophilic luteinized cells.
- At high power both a granulosa and theca cell layer can usually be appreciated.
- Occasional cells with nuclear atypia can be appreciated and are sometimes dramatic, but the overall nuclear-to-cytoplasmic (N/C) ratio remains very low.
- Mitotic activity is typically absent but rare studies have reported seeing some mitotic activity.

Immunopathology (Including Immunohistochemistry)

- Not usually needed, although inhibin and calretinin might be helpful in excluding an epithelial lesion. Reticulin stains will highlight the individual cells.

Main Differential Diagnosis

- Cystic ovarian epithelial tumor.
- Follicle cyst.

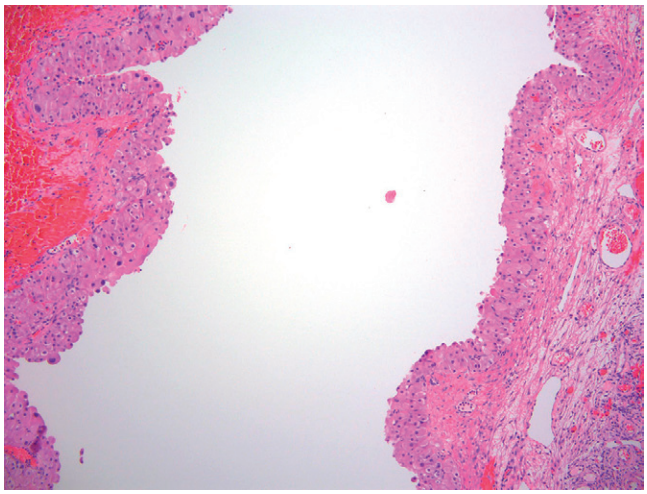


FIGURE 1

Solitary luteinized follicle cyst. At low power the cyst lining is seen, and it is composed of cells with abundant eosinophilic cytoplasm.

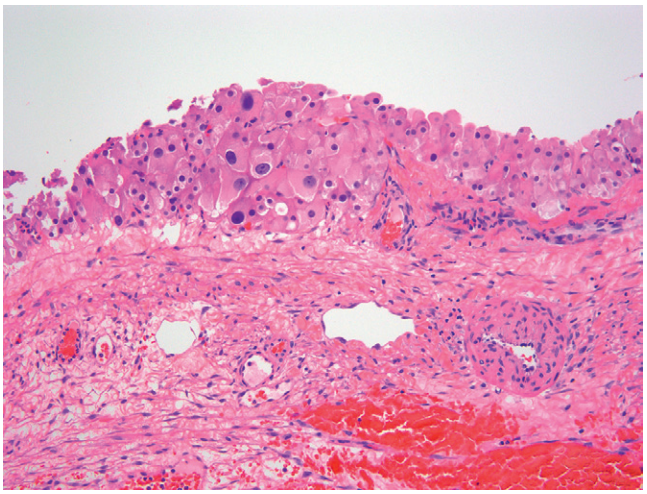


FIGURE 2

Solitary luteinized follicle cyst. In this example, at high power, cells with marked nuclear atypia are seen. Note the preserved, low N/C ratio and the absence of mitotic activity.

POLYCYSTIC OVARIAN SYNDROME

Emily E.K. Meserve, MD, MPH

Definition—An apparent congenital disorder characterized by ovulatory dysfunction and biochemical evidence of androgen excess, often with polycystic ovaries detected by ultrasound.

Clinical Features

Epidemiology

- First described by Stein and Leventhal.
- Can be seen in generations of families, suggesting an autosomal mode of inheritance in such cases.
- However, no single gene has been consistently linked to this disorder.
- Underlying defect is hyperandrogenism associated with ovulatory dysfunction, follicular arrest, and oligomenorrhea.
- Most common endocrinopathy in reproductive-age women, affecting from 2% to 20% of this group and up to 3.5% of women worldwide.

Presentation

- Criteria for the clinical diagnosis include a variation on the following: (1) oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea, (2) clinical or biochemical evidence of androgen excess, and (3) polycystic ovaries as defined by ultrasound (Rotterdam criteria). However, 20% of otherwise normal reproductive-age women have polycystic ovaries and up to 25% of women with signs of polycystic ovarian syndrome (PCOS) will have normal-appearing ovaries.
- Gross examination of the ovaries generally demonstrates increased ovarian size/volume and number of follicles. Often the cystic follicles appear blue through the semitranslucent overlying ovarian cortex.
- Women with PCOS often have normal or only mildly elevated serum luteinizing hormone (LH) and/or follicle stimulating hormone (FSH) levels. Importantly, however, the serum LH is often increased relative to the FSH resulting in an elevated LH : FSH ratio, especially during the follicular phase of the menstrual cycle, which is sufficient to disrupt ovulation.

Prognosis and Treatment

- The most common therapy used to induce ovulation is clomiphene, which has a success rate in achieving pregnancy of over 80%.
- Other manifestations are managed by weight loss, reducing hyperinsulinemia, and suppressing endometrial hyperplasia (oral contraceptives).

Pathology

Histology

- Histologic examination demonstrates increased thickness of cortical and subcortical stroma, thickened and collagenized tunica, increased number of developing and atretic follicles, and multiple cystic follicles (1 to 2 mm) with theca-lutein hyperplasia. A normal number of primordial follicles will be present. A subset of patients show stromal hyperplasia and/or hyperthecosis. Often there is a relative paucity of evidence of recent ovulation including few corpora lutea. These findings are all in keeping with the spectrum of changes seen in long-term exposure to excess androgen, such as in female to male transsexual ovaries.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Granulation tissue.
- Recurrent adenocarcinoma (in clinically appropriate setting).

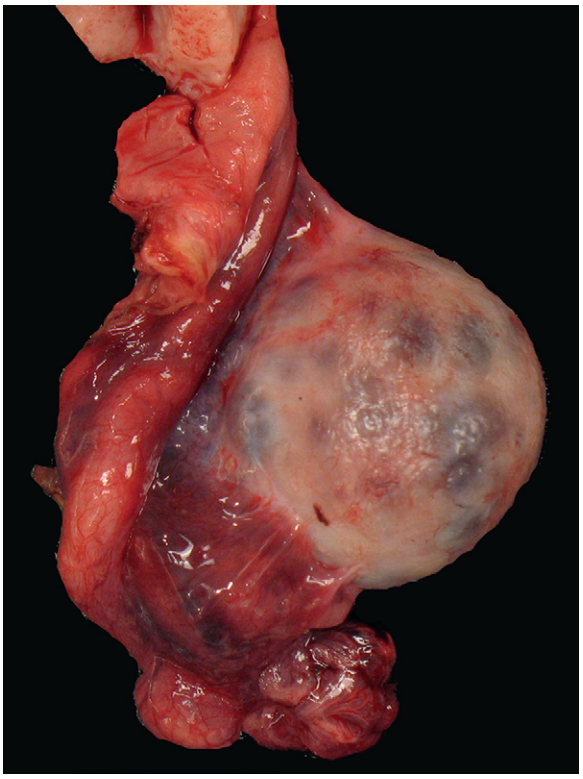


FIGURE 1

Gross examination of ovaries from a patient with PCOS, showing bluish cysts under the cortex.

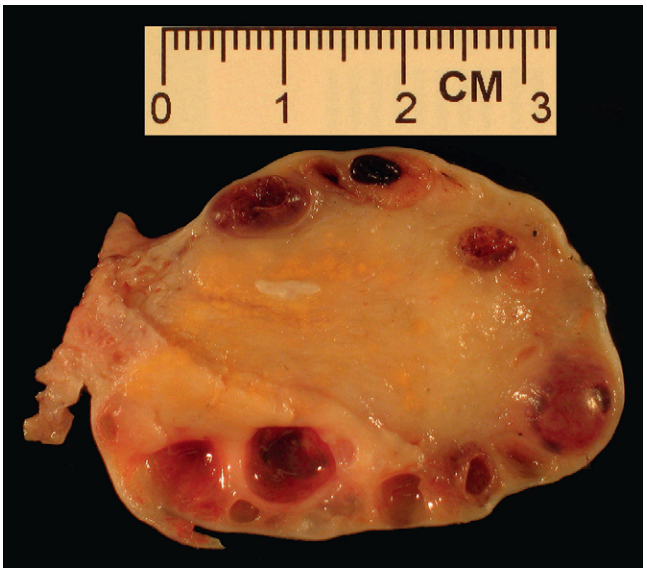


FIGURE 2

Section of ovaries demonstrating features of PCOS; note the increased number of subcortical cystic follicles.

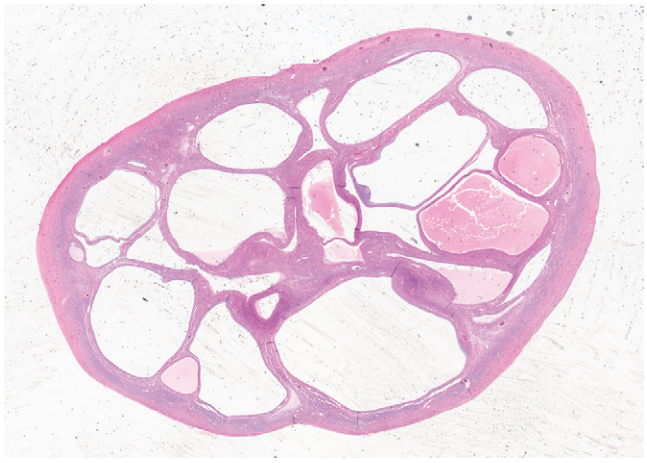


FIGURE 3

Whole mount section of PCOS ovary with cystic follicles.

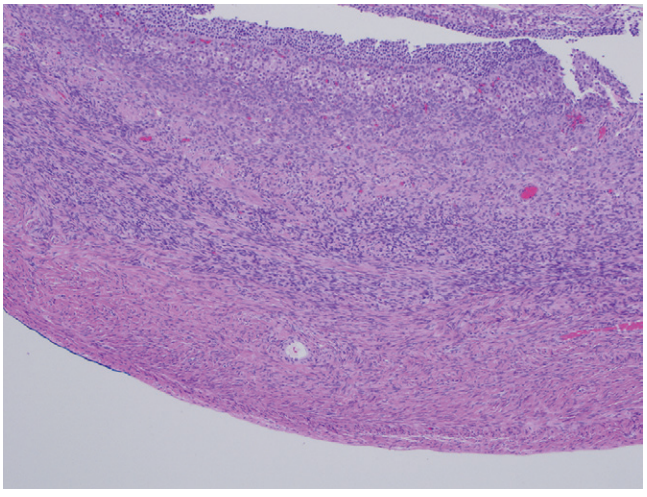


FIGURE 4

Thickened, collagenized, superficial cortex seen in PCOS.

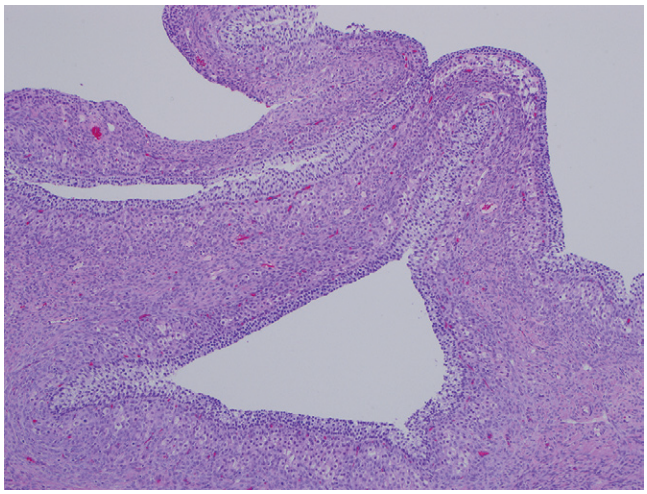


FIGURE 5
Multiple luteinized cystic follicles seen in PCOS.

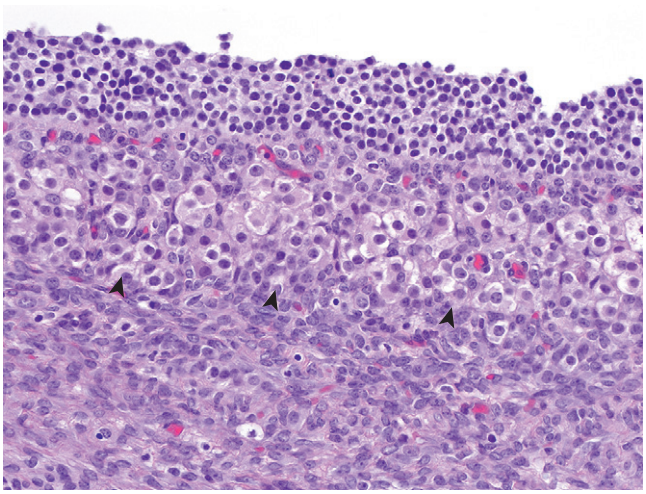


FIGURE 6
Higher magnification of cystic follicle in PCOS with expanded and luteinized theca cell layer *(arrows).*

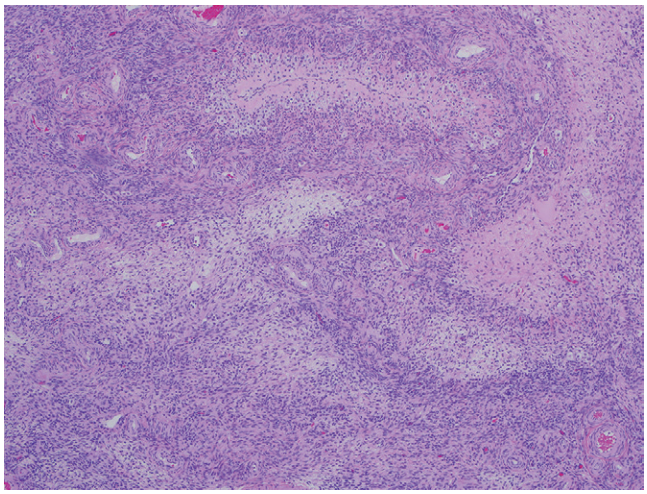


FIGURE 7
Multiple atretic follicles are common in PCOS.

CORTICAL STROMAL HYPERPLASIA AND HYPERTHECOSIS

Definition—An expansion of the ovarian cortex and medulla by a benign proliferation of ovarian cortical stromal cells and associated luteinized cells. Cortical stromal hyperplasia (CSH) is a mild form seen at menopause; stromal hyperthecosis is a more pronounced variant associated with symptoms comparable to polycystic ovarian syndrome.

Clinical Features

Epidemiology

- Seen in perimenopausal or postmenopausal women.
- May less commonly be seen as part of the clinical spectrum of polycystic ovarian syndrome (PCOS).

Presentation

- Imaging studies will reveal a diffuse symmetric enlargment of the ovaries.
- The most common symptomatic presentation is of hyperestrogenic sequelae including abnormal uterine bleeding, occasionally with endometrial intraepithelial neoplasia (EIN) or endometrial adenocarcinoma. CSH is considered to confer an increased risk for endometrial carcinoma; however, it can be found in at least one third of ovaries at menopause.
- Rarely, virilizing symptoms attributable to excess androgen production are present when there is more pronounced stromal cell luteinization (hyperthecosis). Insulin resistance is also a manifestation.

Prognosis and Treatment

- Cortical stromal hyperplasia with mild stromal luteinization is usually an incidental finding requiring no further treatment.
- Hyperthecosis accompanied by excess androgen effects is managed by oophorectomy or GnRH-agonist therapy. In premenopausal women management is similar to that for PCOS.

Pathology

Histology

- The findings should always be bilateral and symmetrical.
- Grossly, the ovaries appear slightly larger than would be expected for the patient's age, and on cut section the medulla and cortex appear expanded by a nodular, light brown to tan tissue.
- At low power the histologic appearance is strikingly different than an atrophic ovary, which would be expected in most cases (based on patient age).
- The atrophic ovarian cortex is not appreciated, and instead a diffuse to nodular proliferation of ovarian cortical stromal cells is apparent at low power.
- The cortical stromal cells are spindled, with elongated oval nuclei and scant lightly eosinophilic cytoplasm, with minimal amounts of intercellular collagen.
- Mitoses are infrequent.
- The "hyperthecosis" component is named for the small clusters, nests, and single luteinized cells that are associated with the spindled stromal cells.
- The luteinized cells are large, with relatively abundant clear to eosinophilic cytoplasm and centrally placed nuclei with prominent nucleoli.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Stromal hyperthecosis and/or stromal hyperplasia alone—isolated stromal hyperthecosis has been described as a separate entity and is the extreme form of this disorder and quite rare. Similarly stromal expansion without luteinized stromal cells can occur but it is unusual to not find occasional luteinized stromal cells.
- Hilus cell hyperplasia—this is limited to the hilar region.
- Fibroma-thecoma—this will present as a discrete mass. In some cases, stromal hyperthecosis will be more fibrous in appearance, and the distinction from fibroma-thecoma is essentially one of distribution.
- Stromal luteoma— this is a homogeneous lesion with a monomorphic population of cells with abundant cytoplasm, rather than the admixture of spindled stromal cells and luteinized cells.

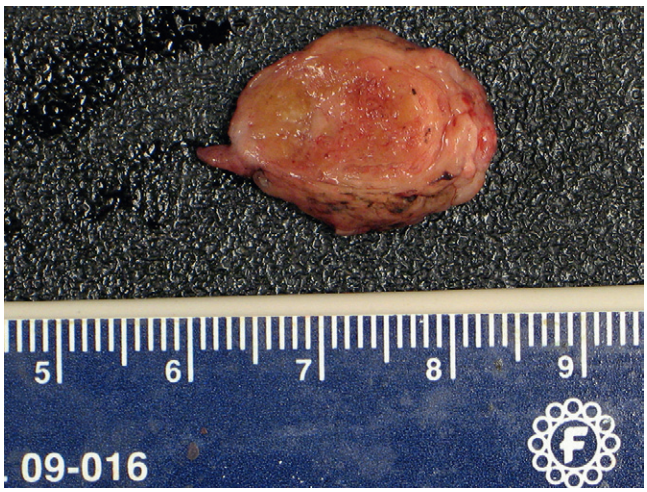


FIGURE 1

Stromal hyperplasia with luteinized stromal cells. Gross appearance. The ovary is larger than would be expected for a postmenopausal woman. The ovarian medulla and cortex appear expanded by vaguely nodular tan to brown tissue.

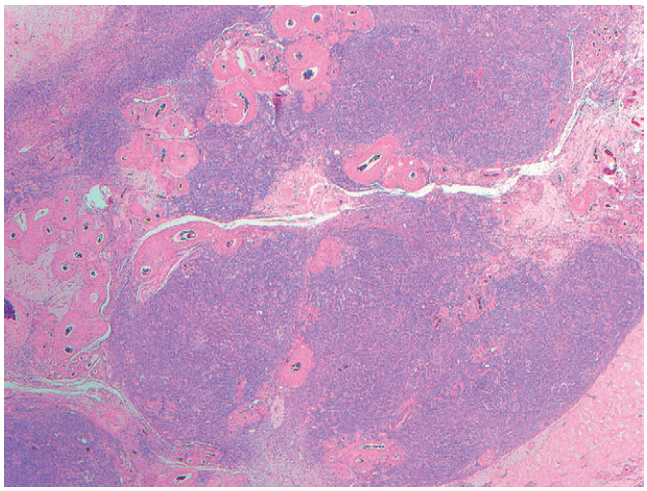


FIGURE 2

Stromal hyperplasia and hyperthecosis. A nodular proliferation of stromal cells within the medulla is apparent at low power.

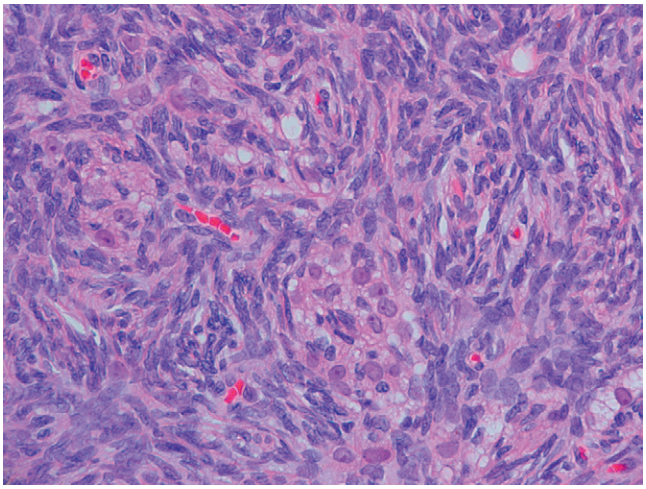


FIGURE 3

Stromal hyperplasia and hyperthecosis. At high power, single cells and small nests of luteinized cells are easily appreciated within the nodules of spindled stromal cells. The luteinized cells are epithelioid, with large round nuclei, prominent nucleoli, and eosinophilic cytoplasm.

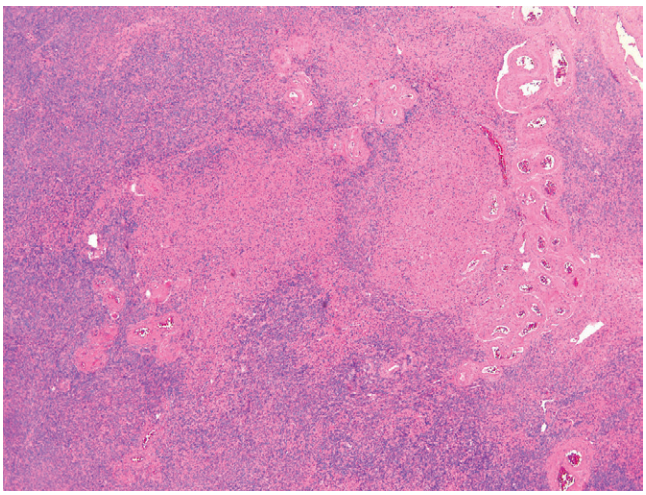


FIGURE 4

Stromal hyperplasia and hyperthecosis. In some cases the proliferation of luteinized cells is more exuberant and can have a nodular appearance at low power *(center)*. The eosinophilic areas in the center are composed of luteinized cells.

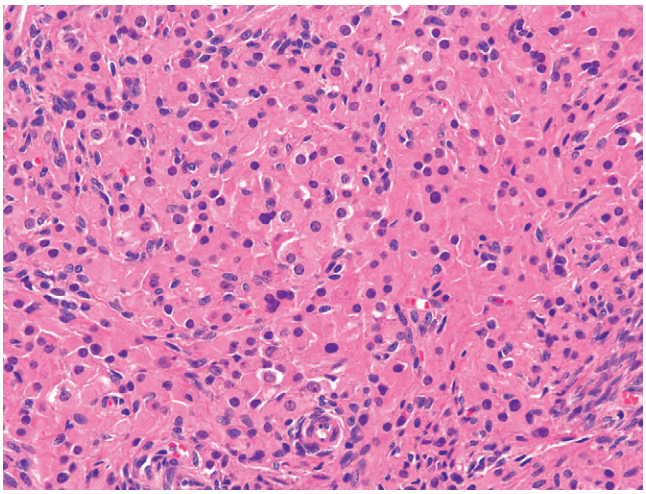


FIGURE 5

Stromal hyperplasia and hyperthecosis. At high magnification the nodules of luteinized cells are identical to those seen singly and in small nests.

ENDOMETRIOMA WITH MUCINOUS METAPLASIA

Definition—Endometriotic epithelium with focal noncomplex mucinous differentiation.

Clinical Features

Pathogenesis

- Occurs in endometriotic cysts. Probably a very early neoplastic change akin to other lesions associated with endometriomas, such as müllerian mucinous cystadenomas, adenofibromas, and well-differentiated endometrioid adenocarcinomas.

Presentation

- An incidental finding in endometriotic cysts.

Prognosis and Treatment

- The prognosis is excellent, and outcome is uneventful as this process, when not complex or mass forming, is not associated with neoplasia.
- No treatment is required, but the endometrioma should be *liberally sampled* to exclude any more advanced process.

Pathology

Histology

- A bland mucinous epithelial lining without gland formation. Mild epithelial complexity is not uncommon.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Müllerian (sero) mucinous cystadenomas form larger cysts with more prominent architecture and with mucinous and often tubal differentiation. The tumors do not contain endometrial stroma in direct continuity with the mucinous proliferation, although endometrial stroma may be found in the adjacent cyst wall.

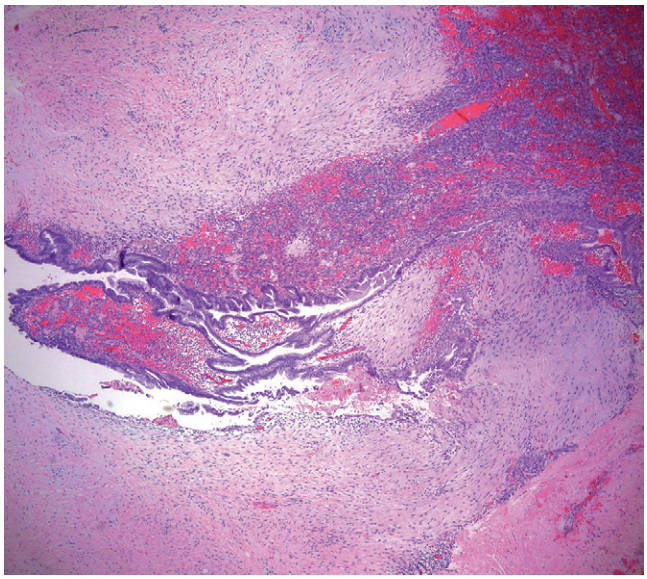


FIGURE 1

Endometrioma with mucinous differentiation. A low-power photomicrograph of a cyst wall with prominent endometrial stroma, the middle and right of the picture.

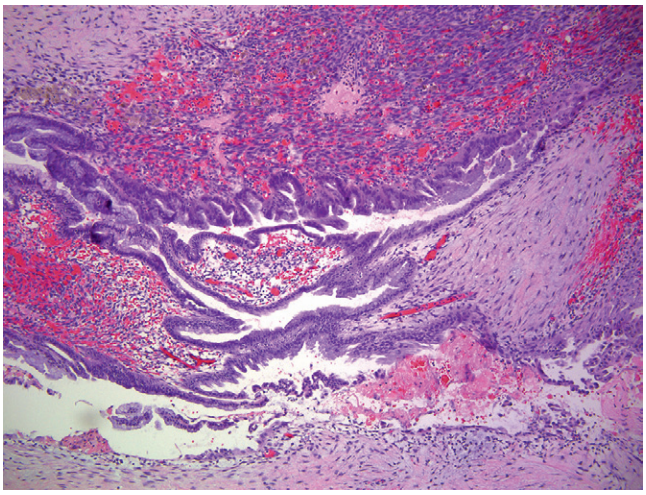


FIGURE 2

Endometrioma with mucinous differentiation. At higher magnification the stroma can be seen to abut the overlying mucinous metaplasia.

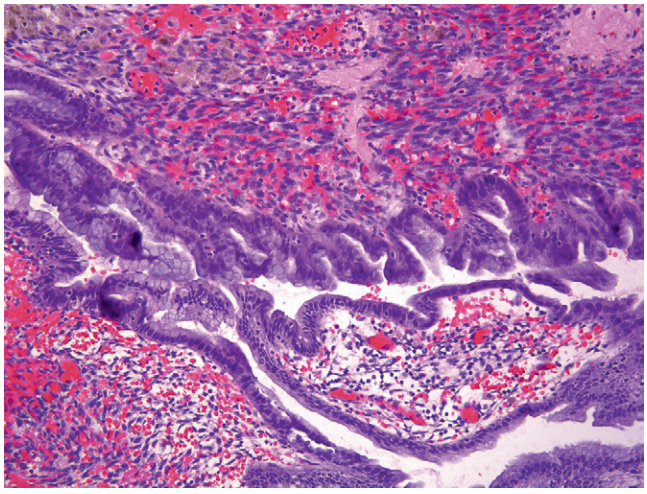


FIGURE 3

Endometrioma with mucinous differentiation. Note the lack of complex epithelial growth.

ENDOMETRIOMA WITH ATYPIA

Definition—Endometriotic epithelium with noncomplex architecture and nuclear atypia.

Clinical Features

Pathogenesis

- Occurs in endometriotic cysts. Possibly a very early neoplastic change akin to other lesions associated with endometriomas, such as müllerian mucinous cystadenomas, adenofibromas, and well-differentiated endometrioid adenocarcinomas. Can be associated with mutations in ARID1A.

Presentation

- An incidental finding in endometriotic cysts.

Prognosis and Treatment

- The prognosis is excellent and outcome uneventful as this process, when not complex or mass forming, is not associated with neoplasia.
- No treatment is required, but the endometrioma should be *liberally sampled* to exclude any more advanced process.

Pathology

Histology

- The hallmark is nuclear enlargement and hyperchromasia. The nuclear/cytoplasmic ratio remains relatively low.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Arias-Stella effect in endometriotic cysts—these could be associated with pregnancy.
- Clear-cell carcinoma—the cells in this entity would harbor a higher nuclear/cytoplasmic ratio and often would be associated with adenofibromas.

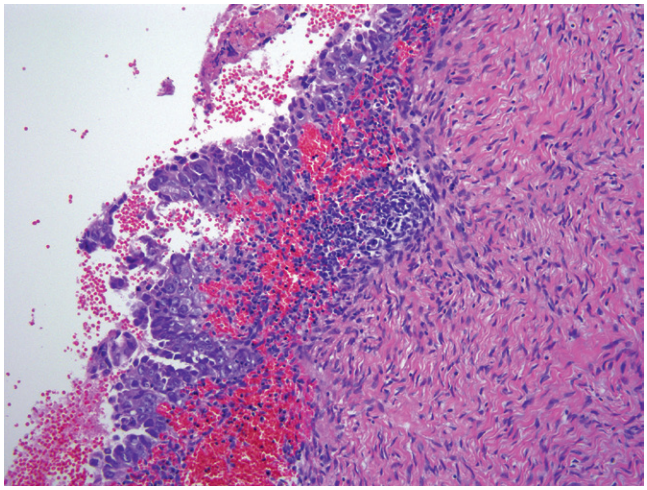


FIGURE 1

Endometrioma with epithelial atypia. A low-power photomicrograph of a cyst wall with prominent endometrial stroma *(the middle and right of the picture).*

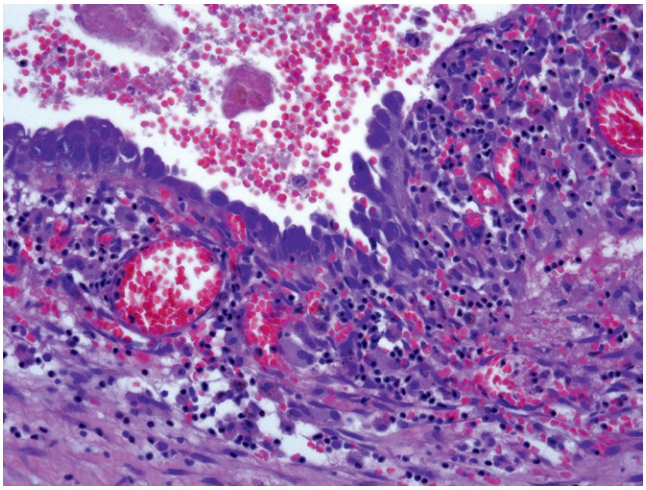


FIGURE 2

Endometrioma with atypia. At higher magnification the stroma can be seen to abut the overlying atypical epithelium.

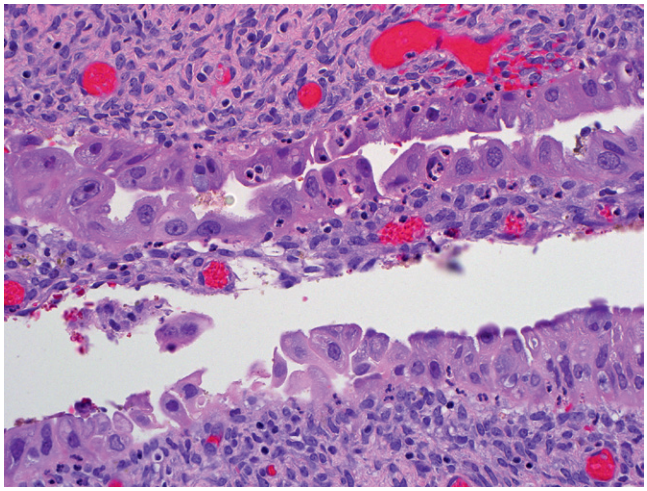


FIGURE 3

Endometrioma with atypia. Note the relatively low nuclear/cytoplasmic ratio.

DECIDUALIZED ENDOMETRIOMA

PITFALL

Definition—A variant of endometrioma that may be confused with malignancy on ultrasound.

Clinical Features

Epidemiology

- Relatively common.
- Seen during pregnancy.

Presentation

- May be a prior history of endometriosis.
- Ovarian enlargement or cyst during pregnancy.
- The presence of mural nodules, usually but not always smoothly lobulated.
- May be interpreted on imaging studies as *potentially malignant.*

Prognosis and Treatment

- Because these lesions are occasionally interpreted on ultrasound as possibly malignant, they may inspire greater anxiety on the part of the physician and patient.
- Once the diagnosis of endometrioma is made, the risk or likelihood of concomitant malignancy is low in young patients.
- Outcome is uneventful, but rare cases in pregnancy can rupture (with rare deaths) and require surgery to control hemorrhage.

Pathology

Histology

- Grossly, decidualized endometriotic cysts are notable for their thickened surface, often with a cobblestone appearance due to the prominent decidual changes.
- The range in size is broad, and the cyst diameter can be anywhere from a few millimeters to many centimeters, with a cyst wall that varies in thickness.
- At low magnification the cyst wall is lined by a prominent decidualized endometrium.
- Endometrial glands may be inconspicuous.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Corpus luteum of pregnancy—these are lined by luteinized granulosa cells with a classic lobulated appearance.
- Xanthomatous pseudotumor—this variant of endometriosis is lined by foamy macrophages that might be confused with the decidualized endometrium lining endometriosis.

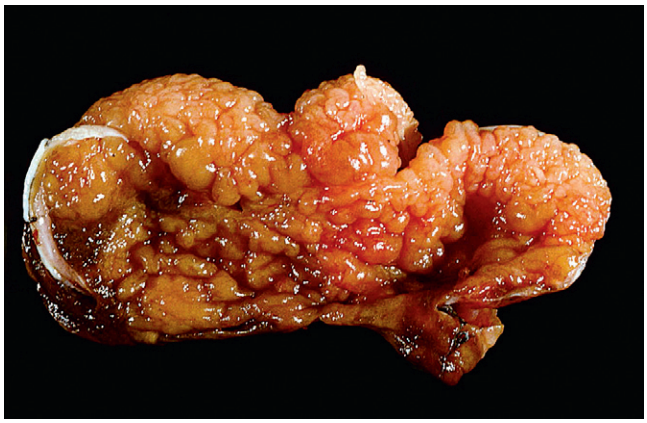


FIGURE 1

Decidualized endometrioma. Gross image. Note the thickened lining of decidualized endometrium with a vague cobblestone appearance.

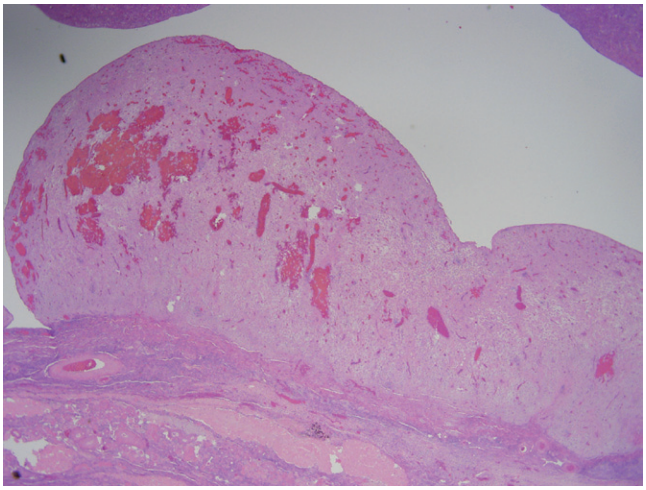


FIGURE 2

Decidualized endometrioma. At low magnification the decidualized stromal cells are most conspicuous.

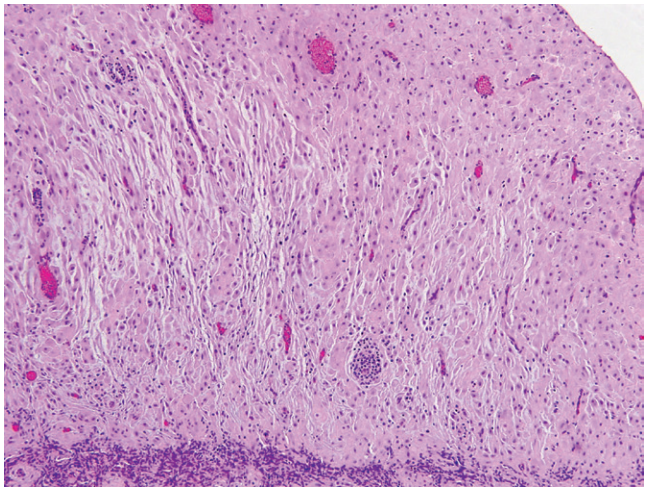


FIGURE 3

At higher magnification the polyhedral decidualized cells are uniformly arranged.

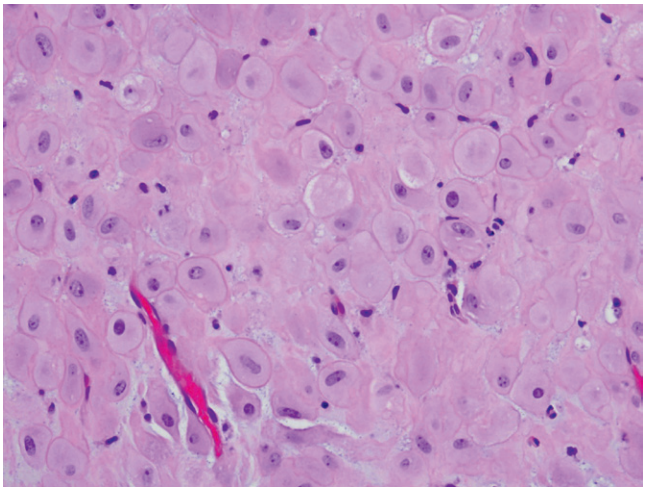


FIGURE 4

The decidualized stroma forms a characteristic pavement of non-overlapping cells.

SEROUS CYSTADENOMAS AND CYSTADENOFIBROMAS

Definition—A benign epithelial or epithelial stromal tumor with a serous (ciliated) epithelial component.

Clinical Features

Epidemiology

- Common; among the most frequently encountered of the benign epithelial tumors.
- Can be seen at any age, most commonly in postmenopausal women.
- Average age at presentation is in the mid-50s.
- May be associated with endometriosis.

Presentation

- Ovarian mass ranging from cystic (cystadenoma) to cystic and solid (adenofibroma) or both (cystadenofibroma).
- Frequently bilateral.

Prognosis and Treatment

- Outcomes should be uneventful.
- Occasionally adenofibromas will have foci of adenocarcinoma, but such cases have an excellent prognosis.
- Surgical excision is adequate treatment.

Pathology

Histology

- Cystadenomas are typically encysted without surface involvement.
- (Cyst) adenofibromas can involve the surface and occasionally may be associated with benign regional implants.
- Tumors may be confined to the ovary or adjacent (paraovarian) region. Sometimes they may be associated with fimbrial adenofibromas, which are morphologically identical.
- On histologic examination the fibromatous component consists of small bland spindled cells with short nuclei arranged in fascicles and storiform patterns, similar to a fibroma.
- The cystic spaces are irregularly shaped and are uniformly present throughout the stroma.
- The spaces are lined by benign epithelial cells resembling salpingeal epithelium.
- The epithelial cells are columnar to cuboidal and often pseudostratified.
- Nuclear atypia is not present in the glandular or stromal components.
- Endometrial-type stroma is not present, but some of these tumors may merge histologically with endometrioid adenofibromas or mucinous tumors.
- Psammomatous calcifications may be noted, particularly in the stromal component.
- Varying degrees of ischemic-type necrosis and stromal calcification may be seen.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Borderline serous tumor—there should be complex epithelial architecture.
- Extensive cortical inclusion cysts—this distinction is based on degree and how discrete the changes are.
- Paratubal cysts—these have an identical lining but possess a cyst wall with loose connective rather than densely fibrotic tissue. Smooth muscle should be focally evident.
- Hydrosalpinx—the presence of plicae and a well-developed wall of smooth muscle.

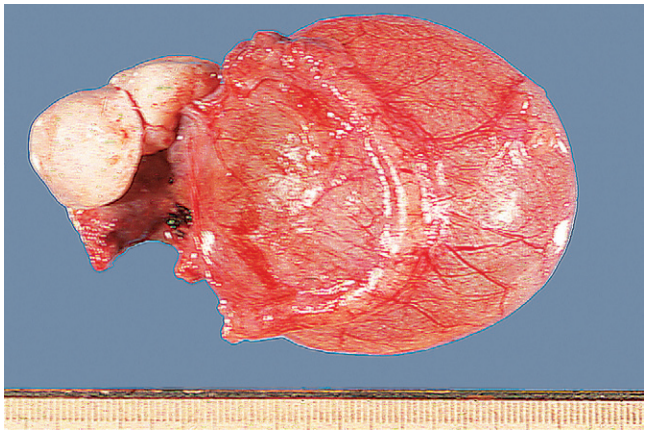


FIGURE 1

Paratubal cystadenofibroma, seen here as a unilocular cyst.

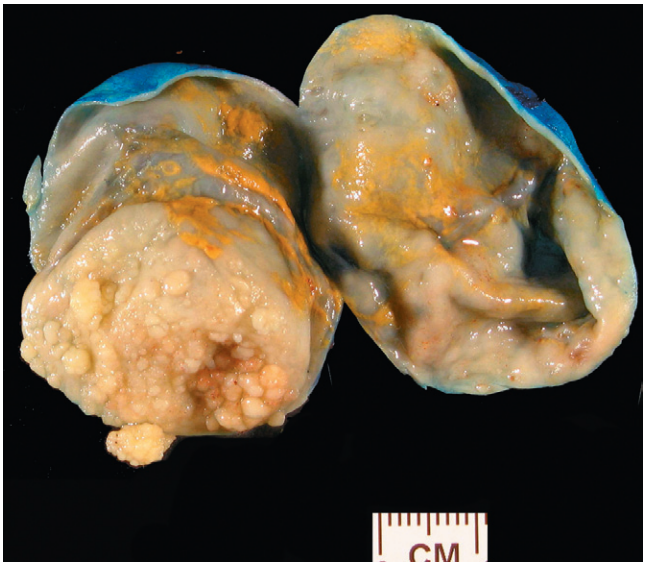


FIGURE 2

Serous cystadenoma. Note the mildly irregular cyst lining.

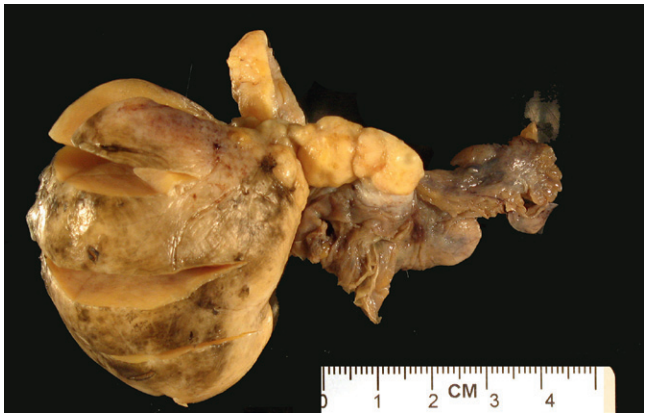


FIGURE 3

Adenofibroma of the ovary. This tumor resembles a fibroma due to the predominance of stroma.

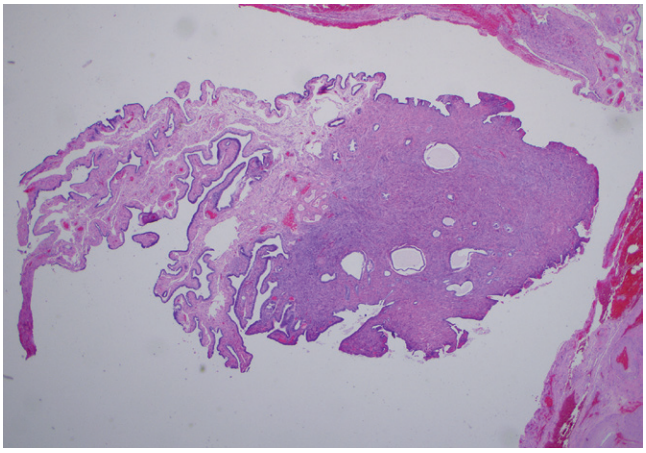


FIGURE 4

Serous adenofibroma of the tubal fimbria. These are sometimes associated with ovarian tumors of the same histology.

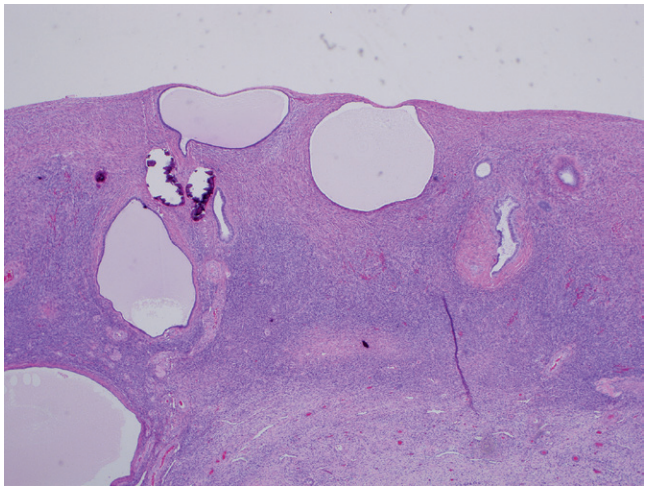


FIGURE 5

Ovarian cortical inclusion cysts are sometimes prominent and may suggest an incipient cystadenofibroma. The distinction from a cyst (adenofibroma) is based on the discrete nature of the latter.

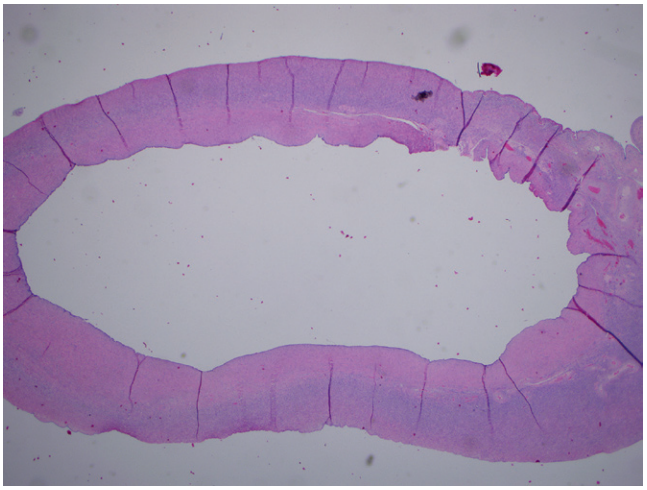


FIGURE 6

Serous cystadenoma. Note in particular the dense fibrous wall, which distinguishes this from a hydrosalpinx or paratubal müllerian cyst.

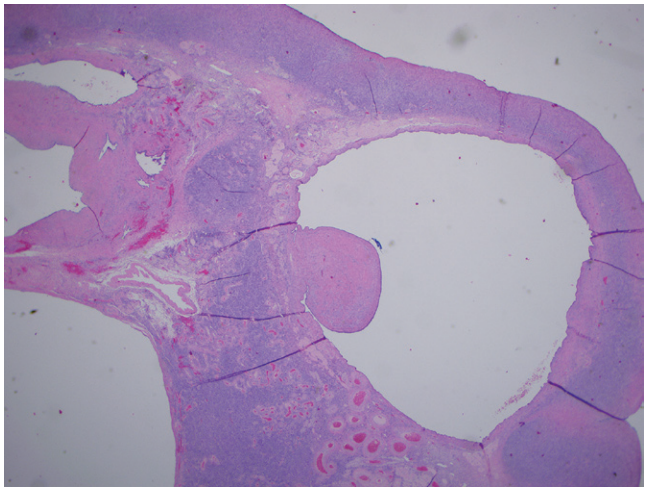


FIGURE 7

A serous cystadenofibroma. Note the nodular excrescence and abundance of stroma.

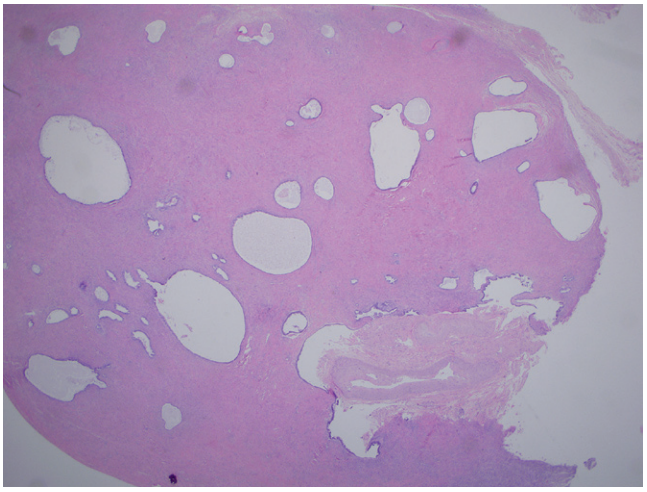


FIGURE 8

Serous adenofibroma, with a well-organized fibrous nodule punctuated by small epithelial-lined cysts.

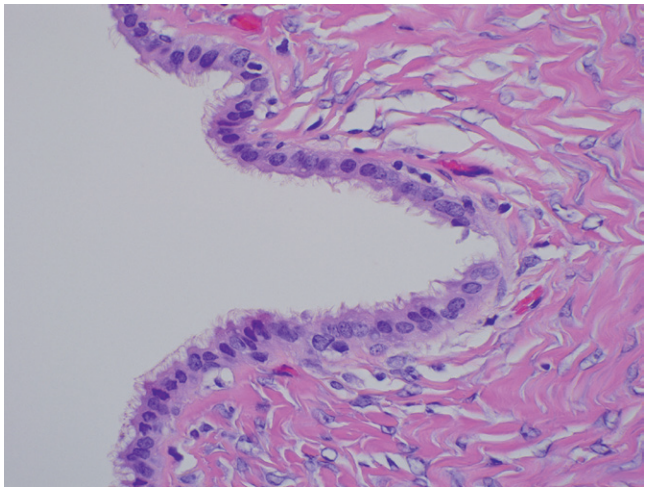


FIGURE 9

The lining of these benign serous tumors is typically uncomplicated with conspicuous cilia.

CORTICAL INCLUSION CYSTS

Definition—Ovarian cortical inclusion cysts (CICs) lined by either mesothelium (ovarian surface epithelium [OSE]) or müllerian epithelium.

Clinical Features

Epidemiology

- Very common.
- Found in the majority of ovaries in postmenopausal women.
- Associated with increasing age.
- Most plausible origin is entrapped tubal epithelium or shed cells from the fimbria. Another proposed mechanism is transdifferentiation of OSE.

Presentation

- Usually an incidental finding.
- Occasionally a very large inclusion cyst will be removed as a cystectomy.

Prognosis and Treatment

- These cysts are incidental benign findings.
- CICs are postulated to give rise to epithelial tumors of the ovary, the most likely being mucinous and low-grade serous tumors.

Pathology

Histology

- The cyst lining may be flat to cuboidal with minimal cytoplasm.
- Cysts may be lined by ciliated epithelium resembling the fallopian tube.
- Nuclear atypia is generally absent.
- Mitoses are not seen.

Immunopathology (Including Immunohistochemistry)

- Noncontributory for diagnostic purposes. However, there is considerable interest in whether the epithelium is derived from the tube or the mesothelial covering of the ovary. The immunophenotype is typically müllerian (PAX8 positive) but occasional examples can be found where there is co-expression of both mesothelial (Calretinin) and müllerian (PAX8) markers, which prompts some speculation that the OSE is unique and capable of both mesothelial and müllerian differentiation (or transdifferentiation).

Main Differential Diagnosis

- Cystic follicle—these can be lined by very thin layers of residual theca cells and be misclassified as CICs. Alternatively cystic follicles or ovulation sites can be populated with OSE/endosalpingiosis.
- Unilocular serous cystadenoma: This is an arbitrary distinction, but the diagnosis of cystadenoma will be considered when the cyst exceeds 1 cm and is associated with a fibrous wall.

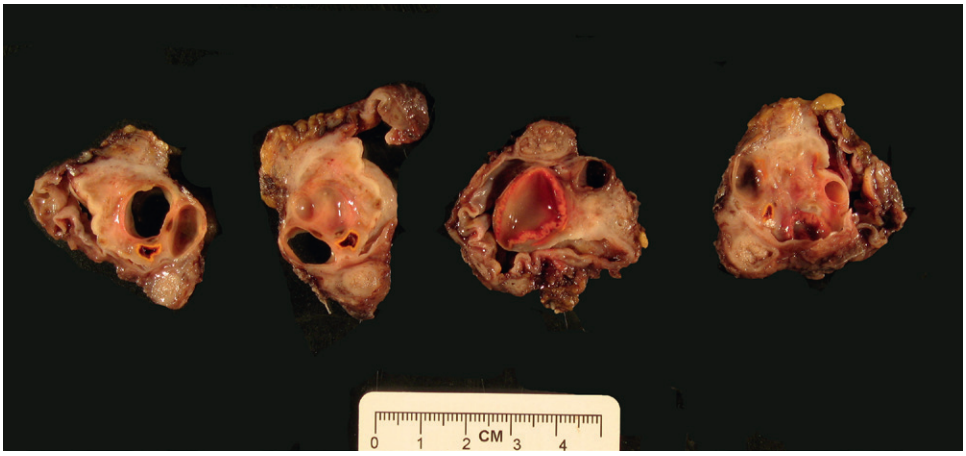


FIGURE 1

CICs associated with a corpus luteum *(center)*.

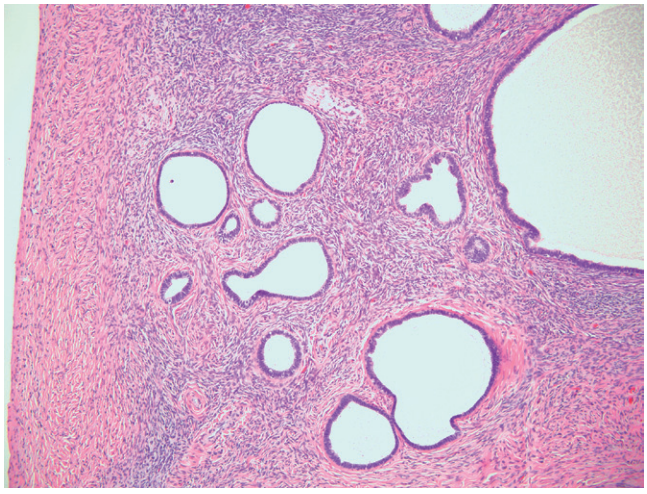


FIGURE 2

CICs. This low-power image shows several cysts within the ovarian cortex.

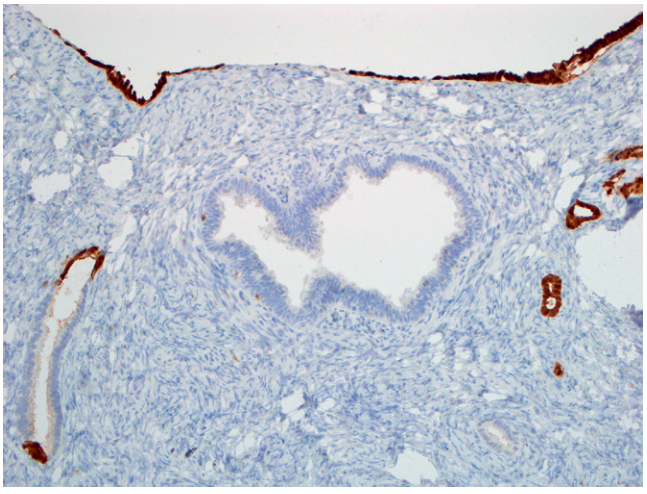


FIGURE 3

CICs stained with calretinin. Note the OSE stains positive while the cysts do not, typical of müllerian CICs.

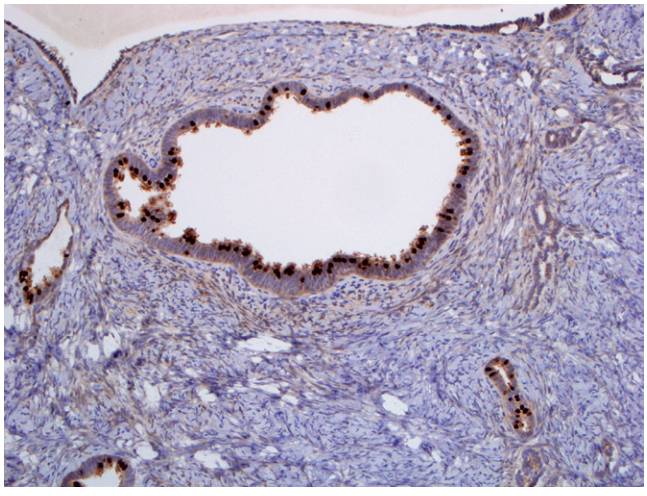


FIGURE 4

A serial section of (of Figure 3) stained with FOXJ1, a marker of ciliated cells. Note the müllerian CICs stain positive in contrast to the OSE.

ENDOSALPINGIOSIS

Definition—The presence of epithelium resembling fallopian tube epithelium outside the fallopian tube.

Clinical Features

Epidemiology

- Endosalpingiosis has been noted in up to 7% of reproductive-age women.
- It can be found in association with other pelvic pathologic processes including endometriosis, infection (pelvic inflammatory disease), neoplasm, and tubal processes, such as hydrosalpinx.

Presentation

- Occasionally patients may present with pelvic pain; however, the majority of cases are asymptomatic and may be found incidentally at the time of surgery. May be seen in pelvic or aortic lymph nodes removed during a staging procedure.

Prognosis and Treatment

- Some authors have pointed out a possible association between endosalpingiosis and low-grade serous tumors; however, this has not been proven.
- Currently no further treatment is warranted.

Pathology

Histology

- Endosalpingiosis is commonly a microscopic finding; however, mass lesions have been described.
- Typically the lesions are glandular or tubular structures lined by cuboidal epithelium with variable amounts of cilia.
- The glands should be bland with no increase in mitoses (opposed to low-grade serous carcinoma), and no surrounding desmoplasia or endometrial-like stroma should be appreciated.

Immunopathology (Including Immunohistochemistry)

- Noncontributory for diagnostic purposes, although the distinction of endosalpingiosis from mesothelium may be of interest in studies. Endosalpingiosis should stain for PAX8, a müllerian epithelial marker, and for FOXJ1, tubulin, and p73, markers of ciliated epithelial cells.

Main Differential Diagnosis

- Implants of low-grade serous carcinoma or a serous borderline tumor—these entities should manifest with more complex/papillary architecture and will be associated with desmoplasia (both) or evidence of tissue replacement by tumor (carcinomas). Endosalpingiosis typically manifests with more uniform glandlike structures and conspicuous ciliation.
- Endometriosis—this entity is associated with endometrial stroma and/or evidence of old hemorrhage (hemosiderin).
- Metastasis from low-grade adenocarcinoma—this can occur when endosalpingiosis involves lymph nodes.

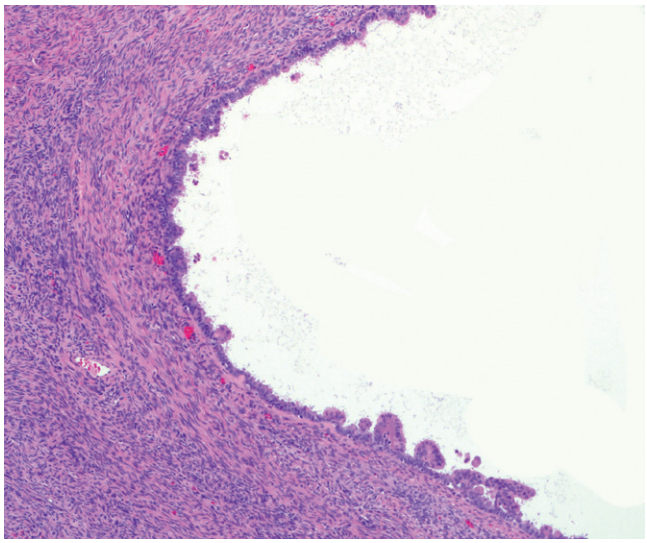


FIGURE 1

Endosalpingiosis. This focus in the ovarian cortex exhibits small papillary like structures.

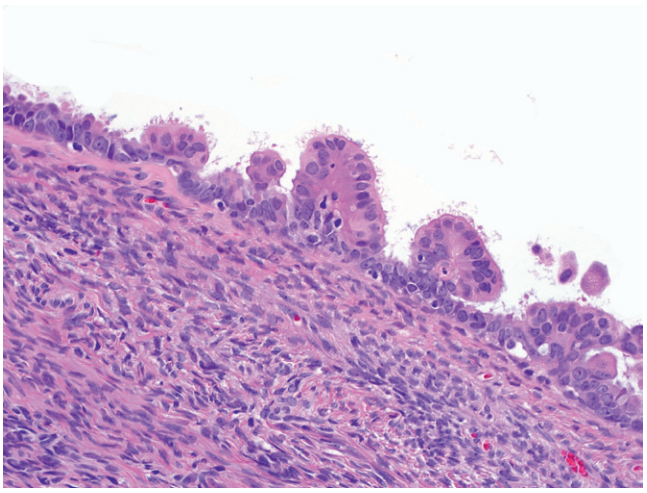


FIGURE 2

Endosalpingiosis. At higher magnification the papillary structures seen in Figure 1 exhibit an eosinophilic cytoplasm and cilia.

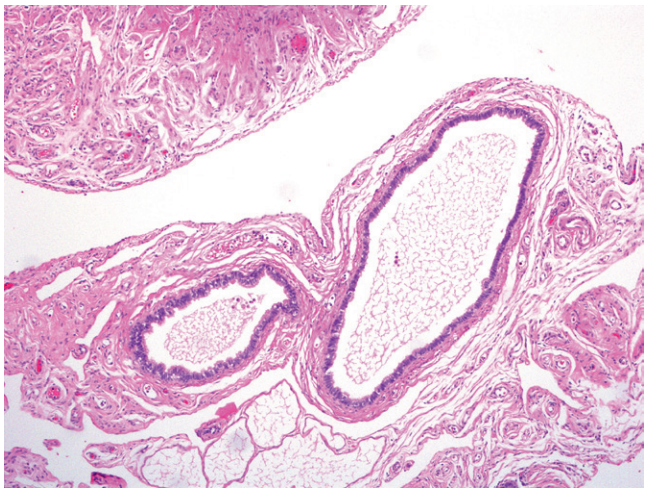


FIGURE 3

Endosalpingiosis. This focus in the mesosalpinx depicts uniform glandlike structures surrounded by loose stroma.

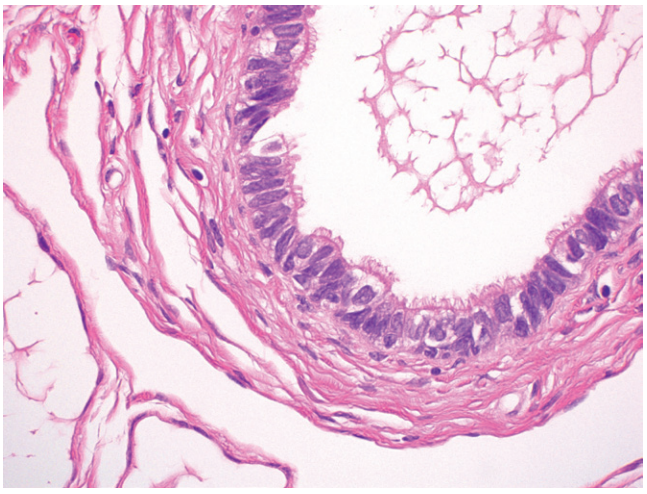


FIGURE 4

Note the conspicuous cilia lining this focus of endosalpingiosis (seen in Figure 3).

MALAKOPLAKIA

Definition—A granulomatous disease of uncertain etiology characterized by histiocytic infiltrates (von Hansemann cells) with calcified inclusions (Michaelis-Gutmann bodies).

Clinical Features

Epidemiology

- Most often associated with the urinary tract with a female preponderance (4 : 1). There is no relationship to gender in other sites.
- Wide age range, but the typical patient is older, with an overall mean age of 50 years.
- Invariably associated with some underlying chronic disorder, including organ transplantation, allergic conditions, chemotherapy, acquired immunodeficiency syndrome (AIDS), malignancy, chronic inflammatory or infectious conditions, and malnutrition.
- The cause is obscure, but theories include an underlying infection with an abnormal immune response that could include the inability of macrophages to digest and eliminate bacteria because of lysosomal defect, leading to the inclusions seen in the cells.

Presentation

- Typically found incidentally in the context of an underlying disorder. In the gynecologic tract, abnormal bleeding is the most common.
- When seen grossly the lesions are soft tan to yellow nodules, plaques, or bands.

Prognosis and Treatment

- Depends on the underlying disorder, which includes a range of diseases (see earlier).
- Antibiotic therapy has been shown to be effective.

Pathology

Histology

- The appearance will vary depending on the age of the lesions, ranging from predominantly inflammatory early on, to the development of the prominent histiocytic infiltrate with Michaelis-Gutmann bodies, and terminating in fibrosis.
- Michaelis-Gutmann bodies are diagnostic but not always present depending on the age of the lesion. These are discrete targetoid structures in which dot-forming, calcified debris is present in the cytoplasm of the macrophages.

Immunopathology (Including Immunohistochemistry)

- Numerous CD68 positive histiocytes.
- Gram stains may be positive for gram-negative bacteria.

Main Differential Diagnosis

- Other granulomatous diseases, including tuberculosis and sarcoid.

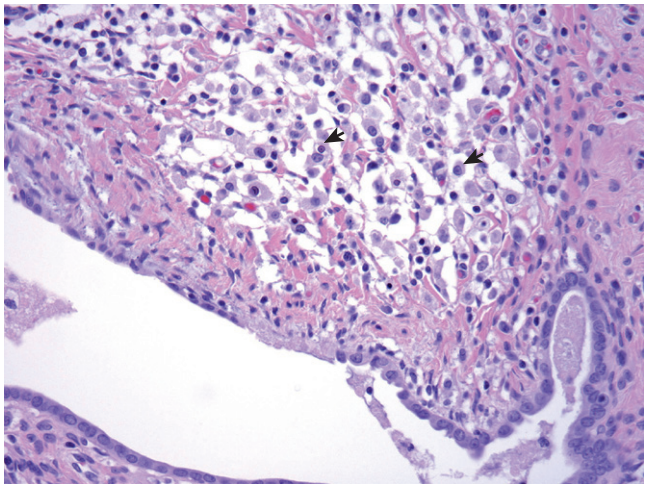


FIGURE 1

Malakoplakia in the gynecologic tract associated with chronic diverticulitis. In this image of the tubal mucosa there is a prominent macrophage response with a few targetoid Michaelis-Gutmann bodies *(arrows)*.

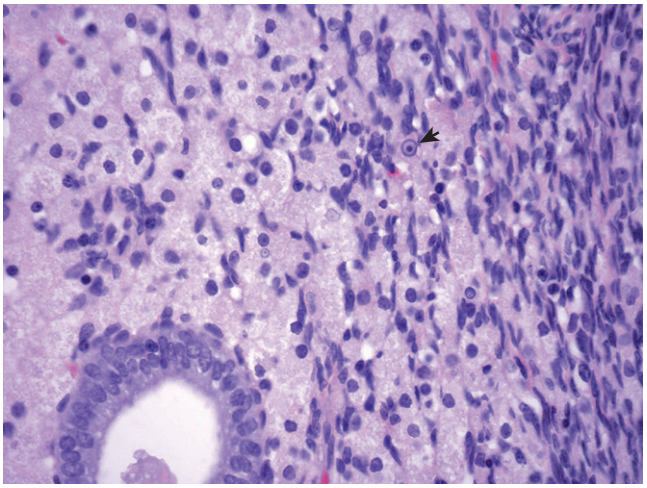


FIGURE 2

Malakoplakia in the gynecologic tract associated with chronic diverticulitis. This microscopic field in the endometrium exhibits a classic targetoid Michaelis-Gutmann body *(arrow)*.

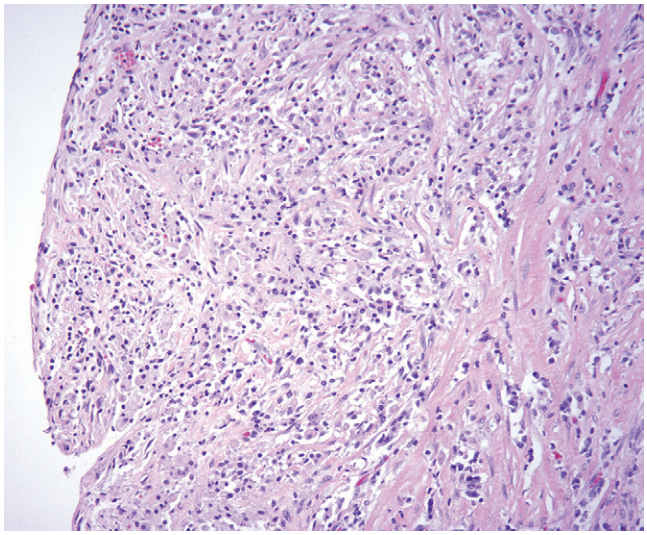


FIGURE 3

Malakoplakia in an inflammatory pseudocyst of the ovary from the same patient. Note that this lesion is more developed with some fibroblastic response.

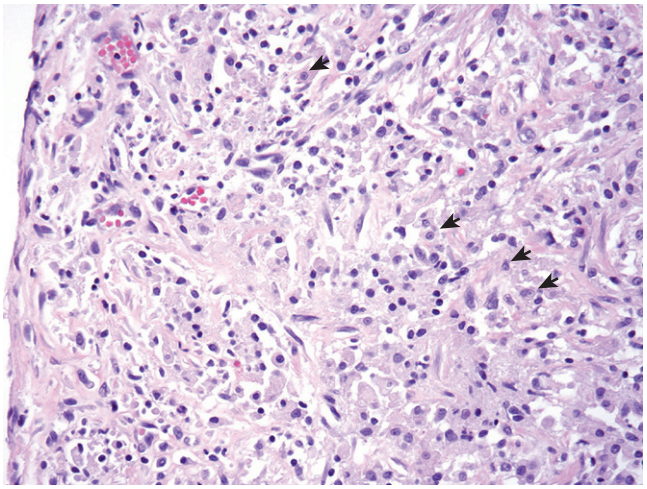


FIGURE 4

At higher magnification a few Michaelis-Gutmann bodies can be appreciated *(arrows)*.

HIGH-GRADE SEROUS CARCINOMA, CLASSIC TYPE

Brooke E. Howitt, MD

Definition—A pelvic serous carcinoma with papillary architecture and high nuclear grade.

Clinical Features

Epidemiology

- Approximately 15% associated with *BRCA1* or *BRCA2* germline mutation.
- Predominant in the sixth and seventh decades of life.
- Approximately 1% of women will develop this malignancy in their lifetime.
- Associated with nulliparity and talc exposure.
- Approximately 40% to 50% associated with a detectable tubal intraepithelial carcinoma in the distal fallopian tube.

Presentation

- Pelvic discomfort, bloating, and frequent urination.
- Pelvic mass on physical exam or on ultrasound.

Prognosis and Treatment

- Forty percent 5-year survival.
- Managed with surgical debulking and chemotherapy with platinum-based agents and taxol.

Pathology

Histology

- Papillary or micropapillary architecture.
- High nuclear grade.
- Patterns of spread are frequently infiltrative.
- Tumor is often associated with psammomatous calcifications.

Immunopathology (Including Immunohistochemistry)

- Immunostains for p16, WT1, and PAX8 are typically positive.
- p53 is typically strongly and diffusely positive (>75% of tumor cells), or may be entirely negative (consistent with null phenotype).

Main Differential Diagnosis

- SET pattern of serous carcinoma—this pattern is frequently admixed with classic morphology.
- Low-grade serous carcinoma—less nuclear atypia with uniformity; p53 is *wild-type*.
- High-grade endometrioid adenocarcinoma—columnar tumor cells lacking exfoliative growth; squamous differentiation indicates endometrioid-type carcinoma. May also overexpress p53.
- Other metastatic carcinomas—should be considered in a limited biopsy specimen; use of immunohistochemistry (PAX8, WT-1) to confirm the diagnosis.

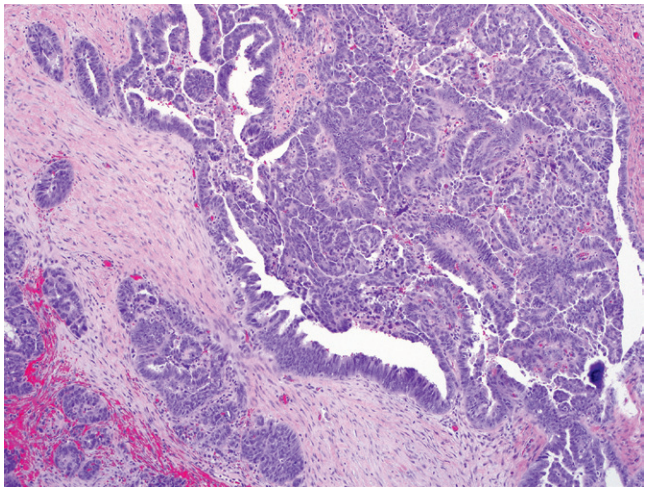


FIGURE 1

High-grade serous carcinoma, classic type. Note the poorly formed glands, papillary architecture, and dark blue appearance due to the high nuclear-to-cytoplasmic ratio.

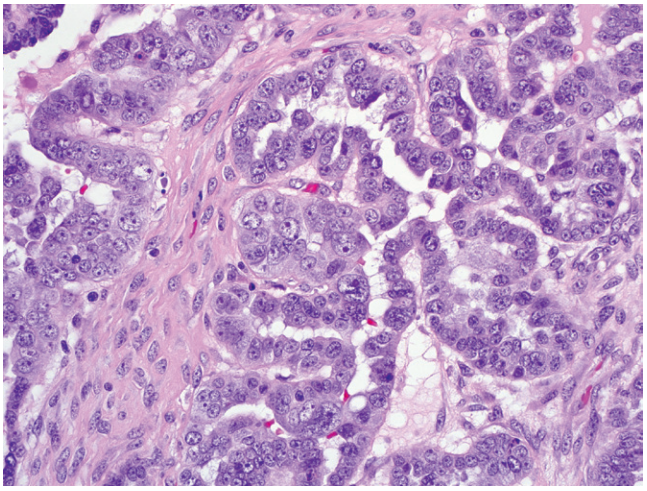


FIGURE 2

High-grade serous carcinoma, classic type. Here there is a semblance of gland architecture, but note the lining cells are largely single layer and cuboidal.

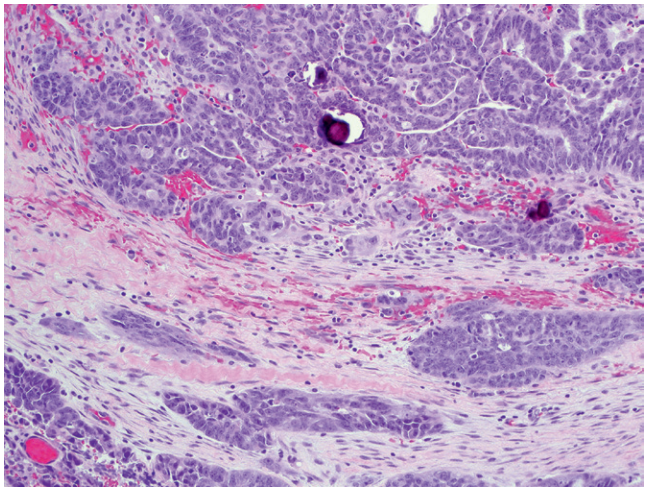


FIGURE 3

High-grade serous carcinoma, classic type. Scattered psammomatous calcifications are seen here. A dense fibrotic response is also characteristic.

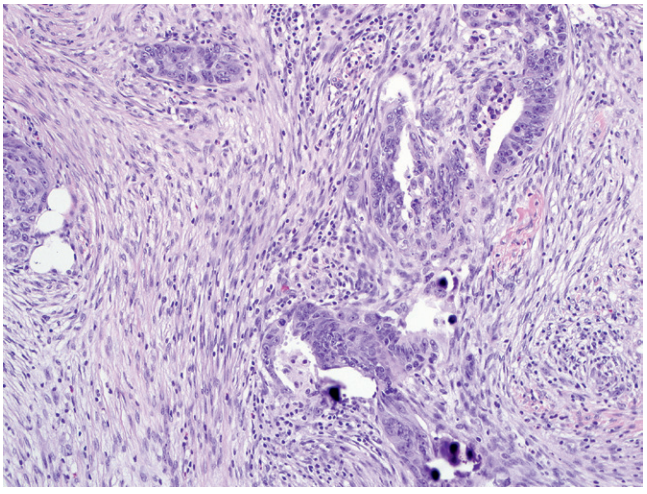


FIGURE 4

High-grade serous carcinoma, classic type. Typical area of invasion with a strong desmoplastic response and poorly formed glandular architecture.

HIGH-GRADE SEROUS CARCINOMA WITH "SET" PATTERNS

Brooke E. Howitt, MD

Definition—A distinctive constellation of patterns (solid, endometrioid-like, and transitional [SET]). Defined (arbitrarily) as greater than 50% of the tumor.

Clinical Features

Epidemiology

- Frequently associated with *BRCA1* or *BRCA2* germline mutation (approximately 50%).
- This pattern is seen less frequently (about 25%) in sporadic serous carcinomas, and may be associated with somatic mutations in *BRCA1* or *BRCA2*.
- Younger mean age than classic serous carcinomas.
- Lower frequency of associated serous tubal intraepithelial carcinoma than classic serous carcinoma.

Presentation

- Similar to most serous carcinomas, but may present at a younger age.
- Somewhat less frequently detected incidentally or in risk-reducing salpingo-oophorectomies relative to classic serous carcinoma.

Prognosis and Treatment

- Based on preliminary data, these tumors trend toward a more favorable response to chemotherapy and short- to intermediate-term outcome.
- Managed like other high-grade serous carcinomas.

Pathology

Histology

- Three patterns, including solid, endometrioid like, and transitional.
- Lower frequency of papillary architecture and micropapillary architecture.
- Patterns of spread are often less infiltrative.
- Tumor-infiltrating lymphocytes also seen.
- Necrosis ("comedo-type") is frequently present and may be extensive.
- May be associated with a serous tubal intraepithelial carcinoma, but less commonly than classic serous carcinoma.

Immunopathology (Including Immunohistochemistry)

- Usually noncontributory. Immunostains for p53, p16, WT1, PAX8, etc. are typically strongly positive, similar to classic serous carcinoma.

Main Differential Diagnosis

- Classic serous carcinoma—this pattern may be present to some degree as well.
- High-grade and solid endometrioid adenocarcinoma—less prominent nucleoli; lacks other areas of classic serous carcinoma. Squamous differentiation indicates endometrioid pattern of adenocarcinoma.

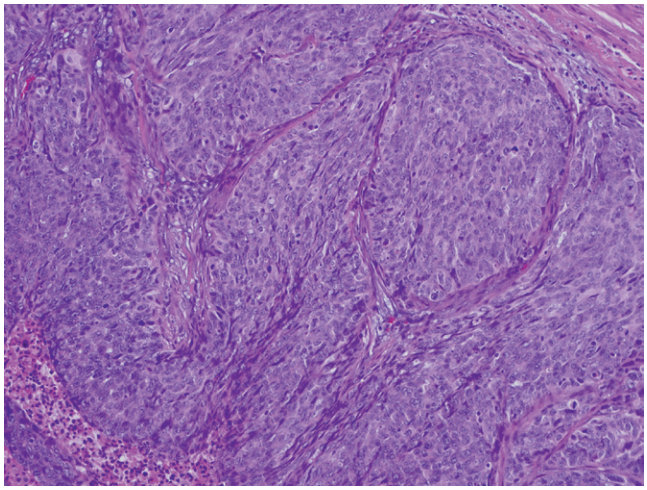


FIGURE 1

High-grade serous carcinoma, SET type. This field depicts a predominantly *solid* pattern with elongated nuclei in a nested background.

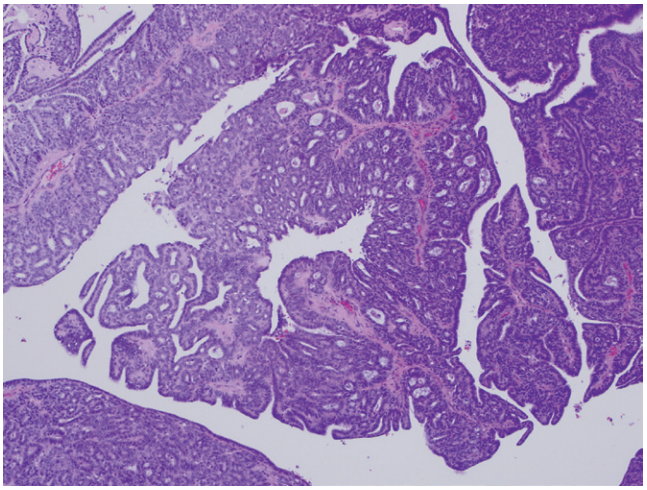


FIGURE 2

High-grade serous carcinoma, SET type. Low-power microphotograph showing gland architecture that closely mimics endometrioid carcinoma.

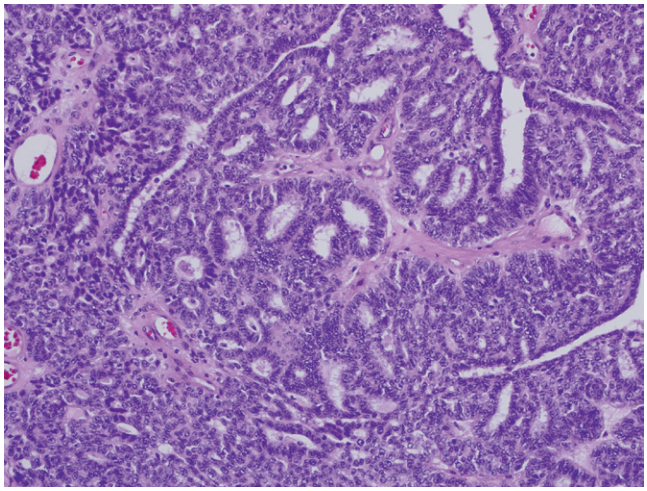


FIGURE 3

High-grade serous carcinoma, SET type. Higher-power microphotograph showing some multilayering with elongated nuclei, similar to endometrioid adenocarcinoma.

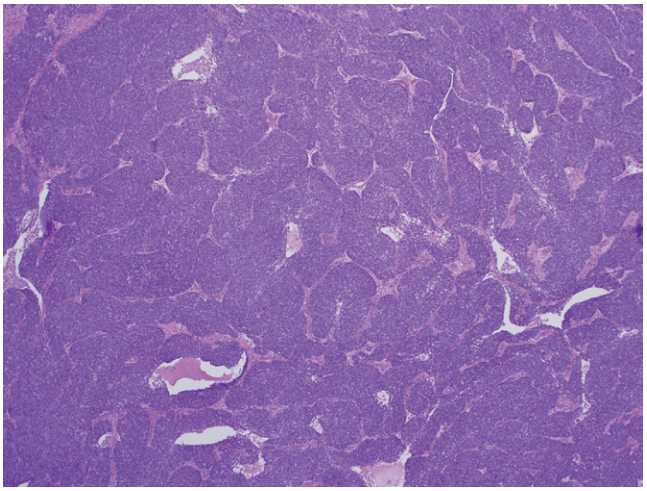


FIGURE 4

High-grade serous carcinoma, SET type. Low- and higher-power images of a tumor with transitional features.

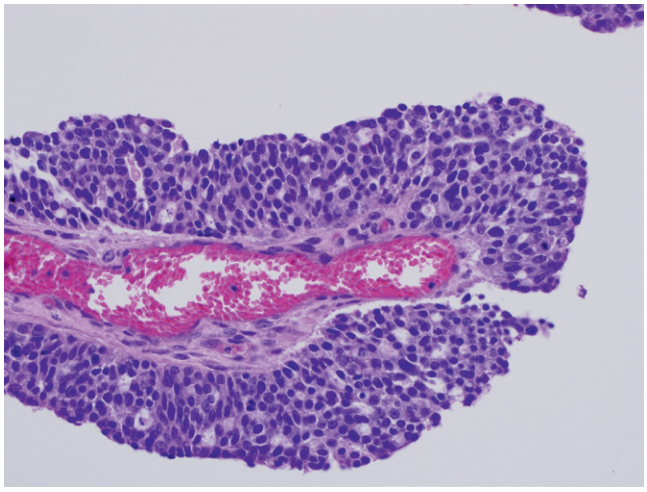


FIGURE 5

High-grade serous carcinoma, SET type. Low- and higher-power images of a tumor with transitional features.

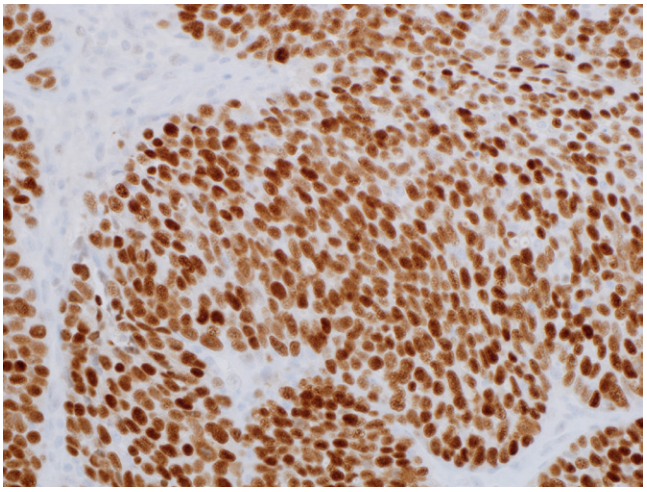


FIGURE 6

High-grade serous carcinoma, SET type. These tumors invariably contain p53 mutations, similar to classic serous carcinomas.

LOW-GRADE ENDOMETRIOID ADENOCARCINOMA WITH SQUAMOTRANSITIONAL OR SPINDLE FEATURES

Definition—A distinct variant of low-grade endometrioid carcinoma with a spindled or squamotransitional phenotype.

Clinical Features

Epidemiology

- Similar to other low-grade endometrioid adenocarcinomas.
- Associated with endometriosis of the ovary.

Presentation

- Abdominal mass and ovarian enlargement.

Prognosis and Treatment

- As any low-grade endometrioid adenocarcinoma.

Pathology

Histology

- Three intersecting patterns can be seen, including conventional endometrioid adenocarcinoma, a whirled spindled cell pattern that may appear almost morule like, and a more papillary pattern with fusiform cells giving the illusion of transitional differentiation.
- Uniform nuclear morphology and low proliferative index.
- Expansile growth pattern.

Immunopathology (Including Immunohistochemistry)

- May be helpful. Inhibin will be negative as will be CK20. Immunostains for p53, p16, WT1, PAX8, and CK7 will be heterogeneous.

Main Differential Diagnosis

- Higher-grade carcinoma with transitional differentiation: greater nuclear atypia, higher nuclear-to-cytoplasmic (N/C) ratio with more nuclear pleomorphism, and p53 positive (or completely absent).
- Variants of granulosa cell or Sertoli cell tumors—inhibin positive.
- Proliferative Brenner tumor—these will not have background endometrioid differentiation and typically demonstrate a more delicate papillary rather than nested histology.

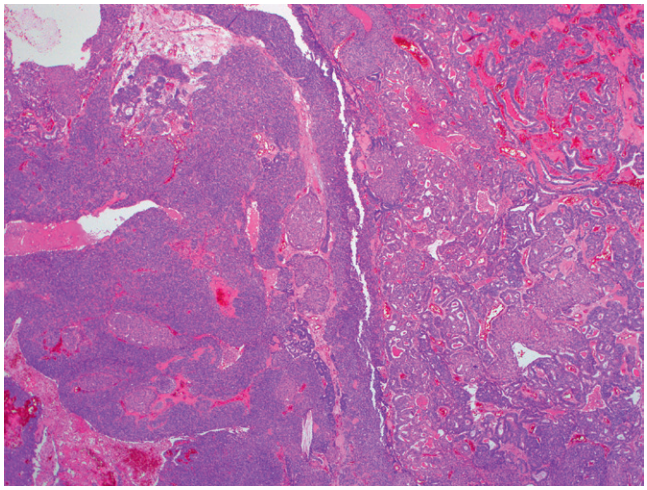


FIGURE 1

Low-grade endometrioid adenocarcinoma of the ovary with transitional features. The more conventional glandular pattern on the right merges with a transitional pattern on the left.

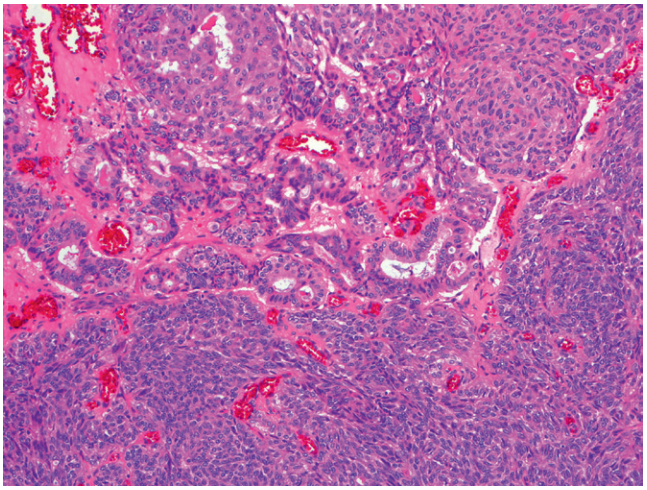


FIGURE 2

Low-grade endometrioid adenocarcinoma of the ovary with transitional features. In this field some glandular differentiation is seen centrally, with vague morule-like histology above and more spindle cell growth below.

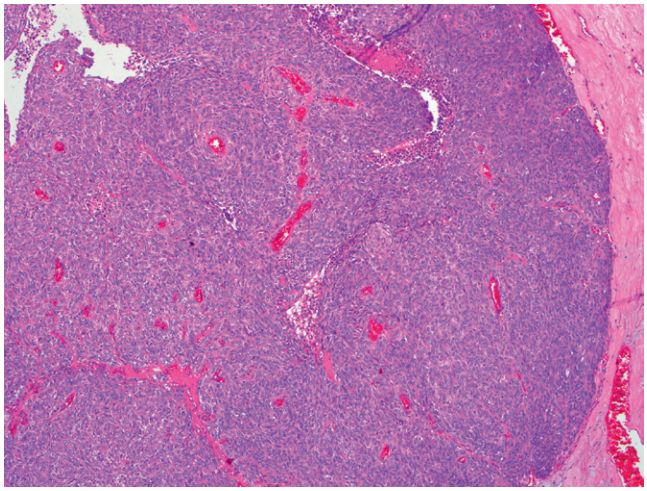


FIGURE 3

A field showing transitional growth alone. Note that the papillary architecture gives way to a more nested growth pattern.

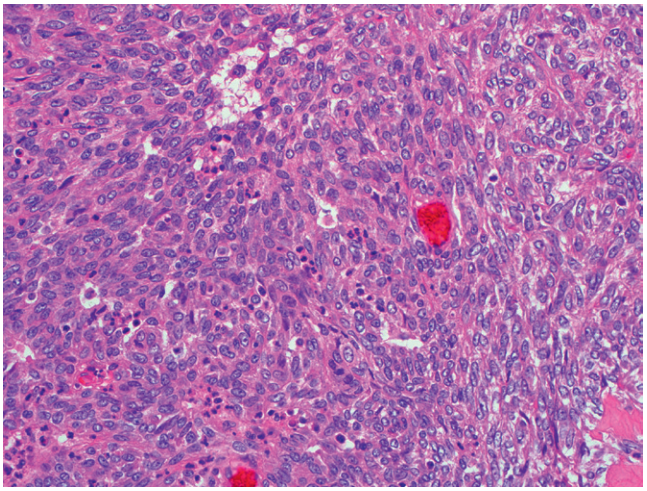


FIGURE 4

An area of solid growth. Note the uniform nuclear features.

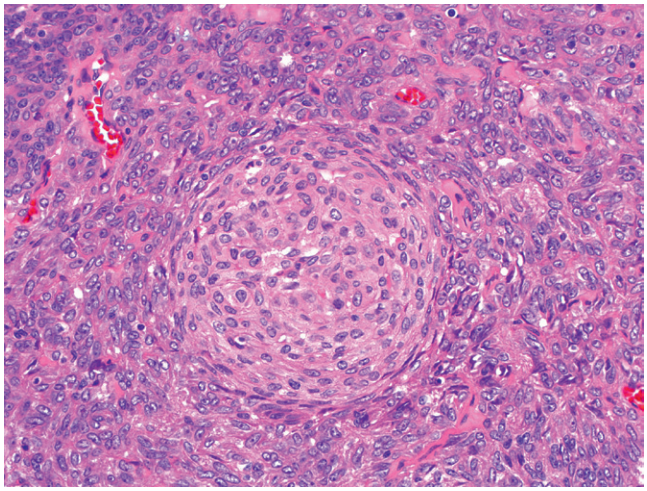


FIGURE 5

In this field a morule-like focus is seen *(center).*

CARCINOSARCOMA

Definition—An ovarian malignancy with mixed epithelial and mesenchymal differentiation.

Clinical Features

Epidemiology

- Rare tumors, comprising less than 4% of epithelial ovarian carcinomas.
- Presumed to arise in most cases from a single neoplastic clone.
- Can be associated with endometriosis, but can coexist with any epithelial cell type.
- Present at an older age than most epithelial carcinomas, in the seventh and eighth decades.

Presentation

- Presentation typically that of ovarian carcinoma in general.
- Majority (75% or more) present with advanced-stage (III or IV) disease.
- Over 90% will have spread beyond the ovary.
- Over two thirds will have ascites.
- Over half have nodal metastases.
- Up to 90% will have an elevated Ca125.

Prognosis and Treatment

- Prognosis is poor; there is a high recurrence rate and mortality due to high stage at presentation, with the median survival less than 1 year.
- A more favorable outcome for stage I, with average survival of 6 years.
- Heterologous tumors have in some reports been linked to worse survival, but data are not consistent.
- Treated as any high-grade carcinoma, with surgical debulking and chemotherapy.

Pathology

Histology

- Mixed epithelial and mesenchymal differentiation.
- Epithelial component can be endometrioid, serous, clear cell, or undifferentiated.
- Mesenchymal component can be homologous or heterologous.
- Metastases typically contain both epithelial and mesenchymal elements.

Immunopathology (Including Immunohistochemistry)

- Immunostains may be helpful in establishing or excluding mesenchymal differentiation but are usually not necessary (cytokeratins).

Main Differential Diagnosis

- Spindle cell differentiation in adenocarcinoma—can be excluded by cytokeratin stains.
- Adenosarcoma of the ovary—lacks the malignant epithelial component.

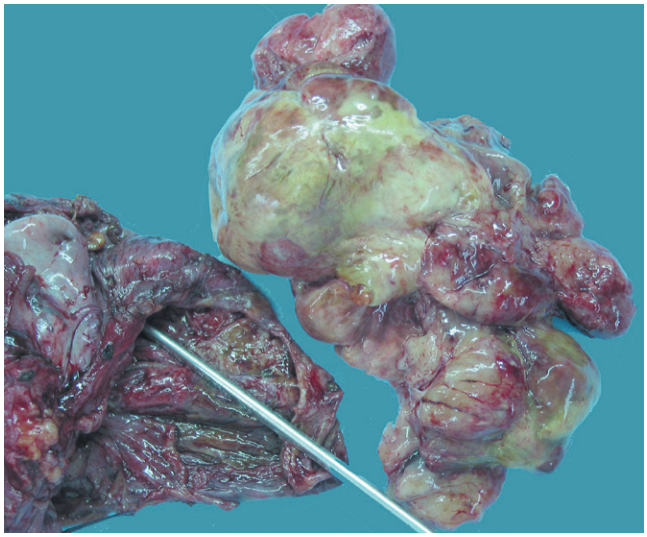


FIGURE 1

Carcinosarcoma of the ovary, seen here as a fleshy mass that was associated with the endometriotic cyst on the left. A probe designates the partially opened cyst wall.

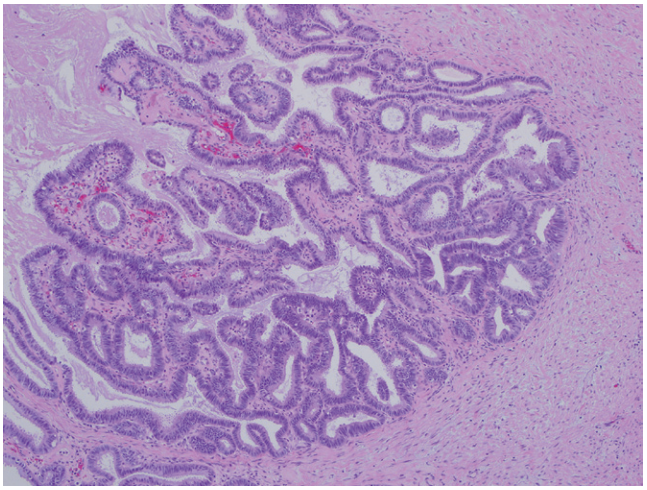


FIGURE 2

Carcinosarcoma of the ovary. The focus is a preexisting proliferative (borderline) endometrioid adenofibroma.

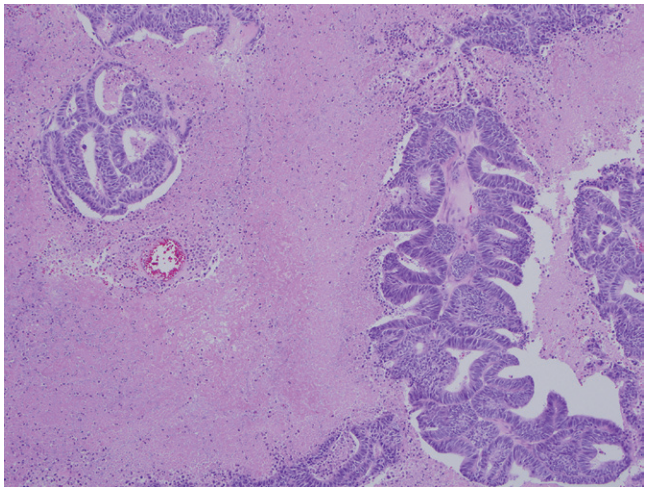


FIGURE 3

This focus contains a well-differentiated adenocarcinoma, albeit with some necrosis.

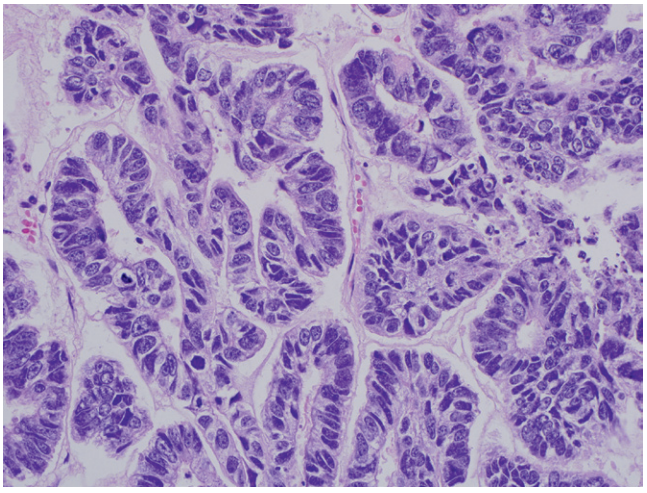


FIGURE 4

As is typical of carcinosarcomas, this epithelial focus is higher grade, with marked nuclear atypia.

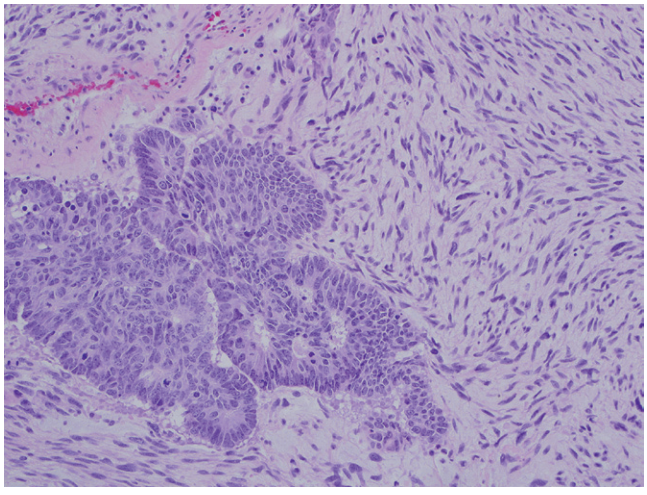


FIGURE 5

The epithelial *(left)* and mesenchymal *(right)* components are juxtaposed.

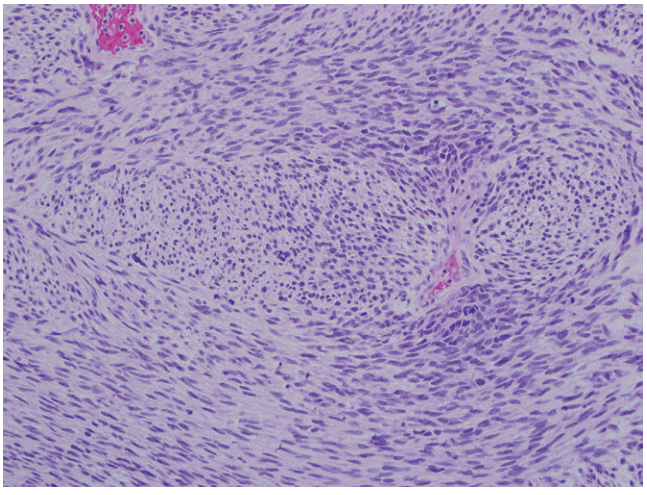


FIGURE 6

The mesenchymal component is a spindle cell malignancy resembling a leiomyosarcoma.

ADENOSARCOMA OF THE OVARY

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

Clinical Features

Epidemiology

- Rare.
- Occurs over a wide age range with a mean of 54 years.

Presentation

- Most cases present with abdominal discomfort and distension.
- Tumors are unilateral in over 90% of cases.
- Tumor frequently ruptures during surgery.
- Predominantly solid tumor. Size varies widely with a mean of 14 cm in the study by Eichorn et al.
- Most are stage I (65%) or II (28%) when discovered.

Prognosis and Treatment

- Most treated with total abdominal hysterectomy and contralateral adnexectomy.
- Over 75% recur at a mean of 2.6 years.
- Five-, ten-, and fifteen-year survival rates were 64%, 46%, and 30%, respectively.
- Poor prognostic indicators include age below 53, tumor rupture, and high-grade tumors or those with high-grade sarcomatous overgrowth.
- Often treated with chemotherapy, but the benefit is uncertain.

Pathology

Histology

- Solid component ranges from fibrous (mimicking adenofibroma) to sarcomatous in appearance.
- Numerous small cysts punctuate the solid background, lined by columnar or metaplastic epithelium.
- Phyllodiform architecture, similar to other adenosarcomas, may be present.
- Periepithelial or subepithelial stromal condensation with variable atypia and mitotic activity.
- The sarcomatous component can vary widely, mimicking endometrial stroma or smooth muscle but may be heterologous. Sex cord–like differentiation may be present.
- Sarcomatous overgrowth can occur with marked atypia.

Immunopathology (Including Immunohistochemistry)

- No specific markers are needed (or particularly useful), although some may highlight different differentiation patterns in the stroma.

Main Differential Diagnosis

- Ovarian adenofibroma—should not display the architecture or stromal features.
- Carcinosarcoma—should display both malignant stroma and epithelium.

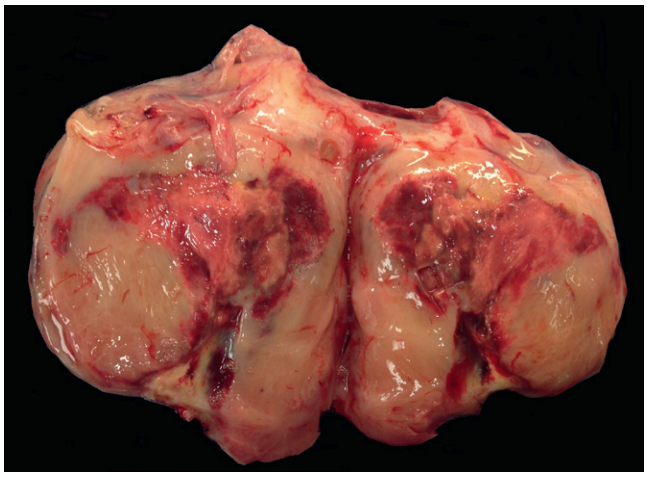


FIGURE 1

Recurrent ovarian adenosarcoma presenting as a fleshy mass in the peritoneum.

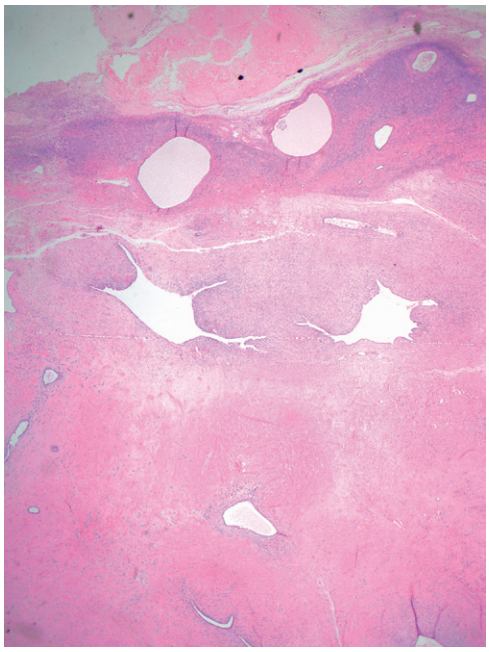


FIGURE 2

Ovarian adenosarcoma. Note the normal ovarian cortex above, with cortical inclusions. The malignant tumor is below.

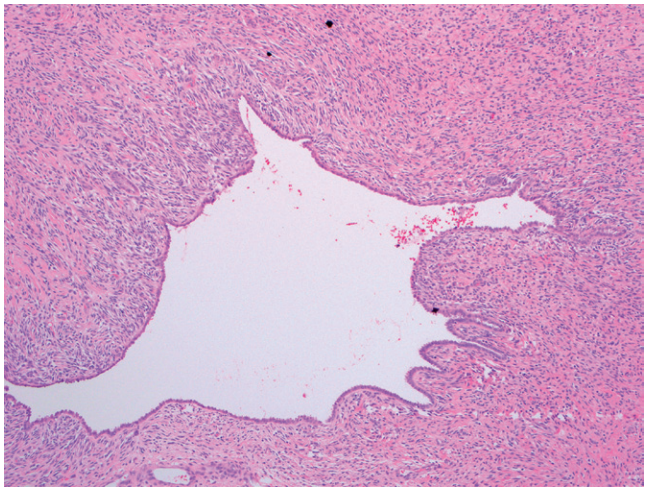


FIGURE 3

Ovarian adenosarcoma. An irregular cystic space lined by a low columnar epithelium is surrounded by a subtle condensation of spindled cells.

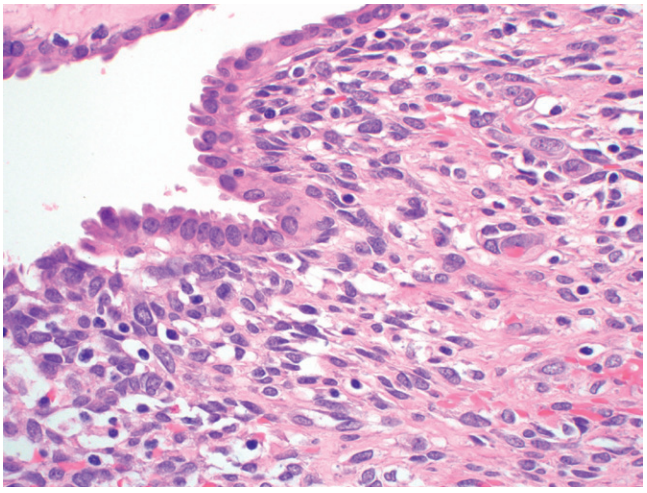


FIGURE 4

Ovarian adenosarcoma. At higher magnification the subepithelial spindled cells exhibit nuclear crowding, enlargement, and hyperchromasia.

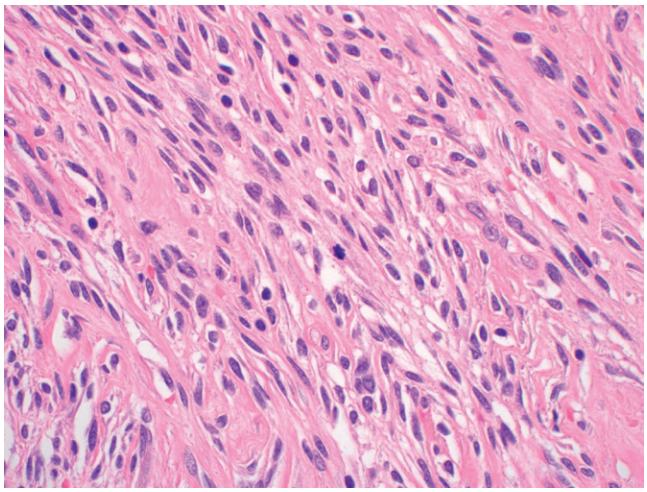


FIGURE 5

Ovarian adenosarcoma. This field shows moderate atypia with mitotic activity.

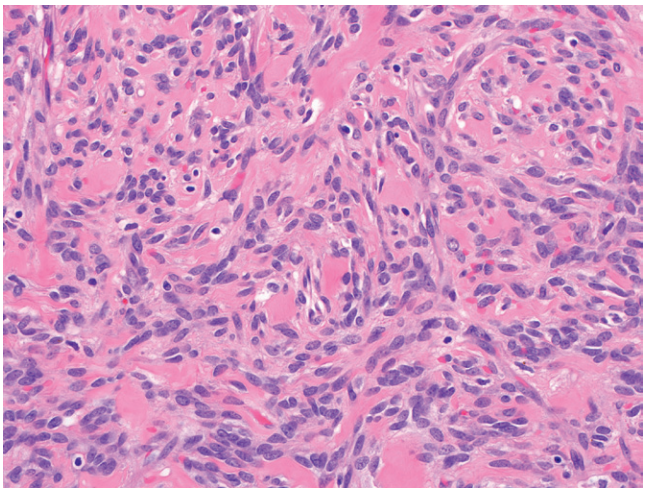


FIGURE 6

Ovarian adenosarcoma. This field resembles smooth muscle differentiation. Such stromal heterogeneity is common in these tumors and may necessitate careful examination to identify the diagnostic areas.

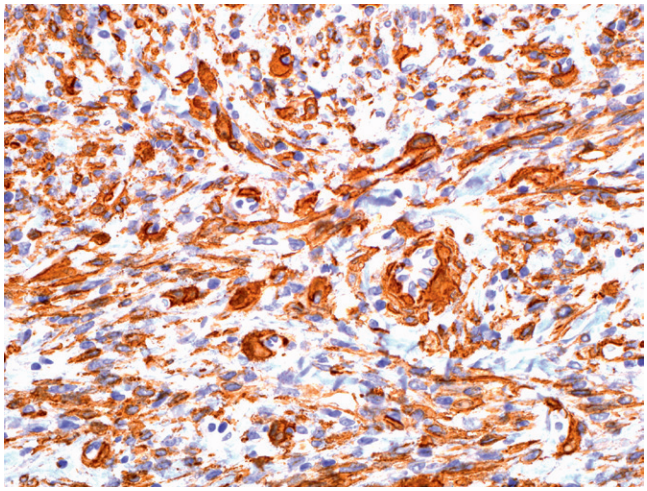


FIGURE 7

A stain for smooth muscle actin is strongly positive, underscoring the unreliability of such stains for excluding other tumors with smooth muscle differentiation.

SEROUS BORDERLINE TUMOR (SBT)

Definition—A proliferative serous tumor of the ovary conferring a small (less than 5%) risk of adverse outcome.

Clinical Features

Epidemiology

- The most common epithelial tumor of the ovary. Predominates in the fourth to sixth decades of life, but can be seen at virtually any age.
- These tumors can be associated with endometriosis but more often are seen as part of a continuum merging with müllerian ovarian cortical inclusions.
- There is no known relationship to BRCA, a familial syndrome or p53 mutations.

Presentation

- Usually as a large, multicystic mass with papillary growth, either lining the cyst lumens or on the surface. From one third to one half will be bilateral. Peritoneal implants occur in some cases.

Prognosis and Treatment

- Prognosis is excellent in the absence of frank stromal invasion or invasive implants on the peritoneum (which would define a well-differentiated serous carcinoma).

Pathology

Histology

- Cardinal features include a low-power appearance of multiple papillary structures with a mild to moderate degree of epithelial complexity. The lining epithelium typically contains ciliated cells, but this appearance can merge with both endometrioid and mucinous differentiation, the latter often termed "seromucinous" differentiation.
- Fibrosis with entrapment of epithelium, either in the cyst wall or ovarian surface, is not uncommon.
- Confluent epithelial growth, either in the form of microacinar or micropapillary architecture, can be seen. In the absence of invasive implants, these findings do not significantly alter prognosis.
- Microinvasion, defined as small papillary clusters of eosinophilic tumor cells in spaces totaling less than 5 mm in diameter, is found in up to 10% of SBTs. It may be associated with a greater risk of invasive implants, but in their absence confers no appreciable increase in the risk of adverse outcome over SBTs.
- Lymph node metastases can also be seen with serous borderline tumors (SBTs) but does not independently alter the prognosis in the absence of an infiltrative pattern that would suggest low-grade serous carcinoma.
- Tumors in pregnant patients may show exuberant epithelial proliferation and microinvasion.

Immunopathology (Including Immunohistochemistry)

- Usually noncontributory. PAX8 (positive) and calretinin (negative) immunostains might aid in sorting out rare cases that resemble well-differentiated mesothelioma.
- In cases with exuberant growth or moderate nuclear atypia, wild-type p53 staining can help to rule out high-grade serous carcinoma.

Main Differential Diagnosis

- Rare mesotheliomas can overlap with SBT and may be difficult to distinguish based on immunophenotype.
- Well-differentiated serous carcinomas—look for stromal invasion or extensive confluent or micropapillary growth.
- Rare high-grade serous carcinomas might mimic SBT at low magnification due to well-developed papillae with a thin epithelial covering. Higher power inspection will confirm the high nuclear grade.

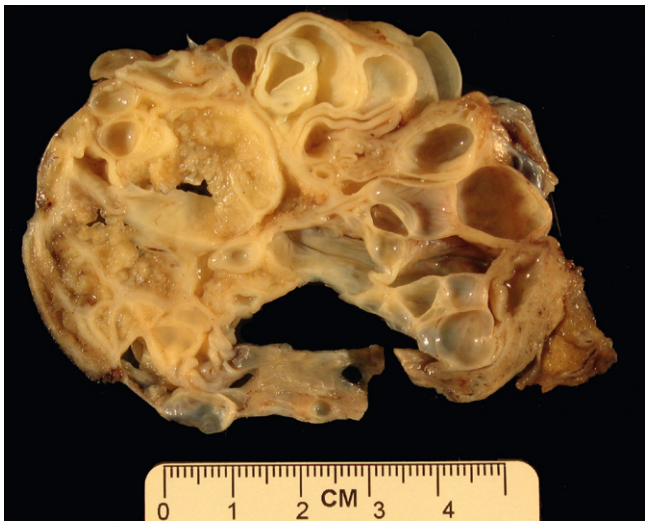


FIGURE 1

SBT presenting as multiple cysts, some of which are filled with papillary growth.

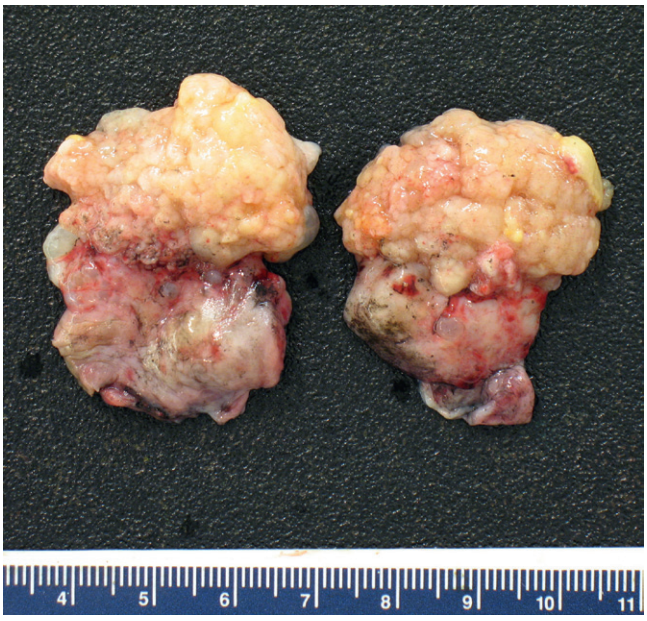


FIGURE 2

SBT involving the ovarian surface.

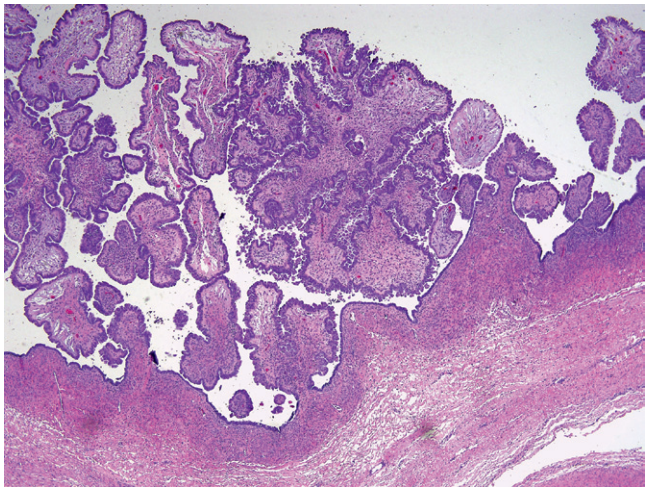


FIGURE 3

Low-power view of papillary growth lining a cyst in an SBT.

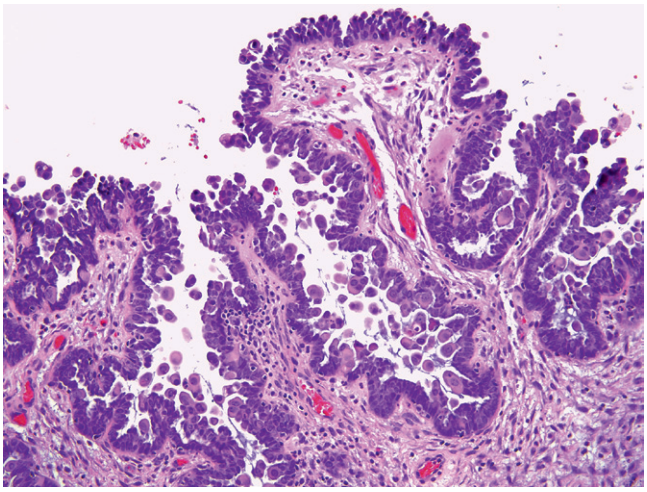


FIGURE 4

Cyst lining of an SBT. Note the pink cells with variable ciliated differentiation.

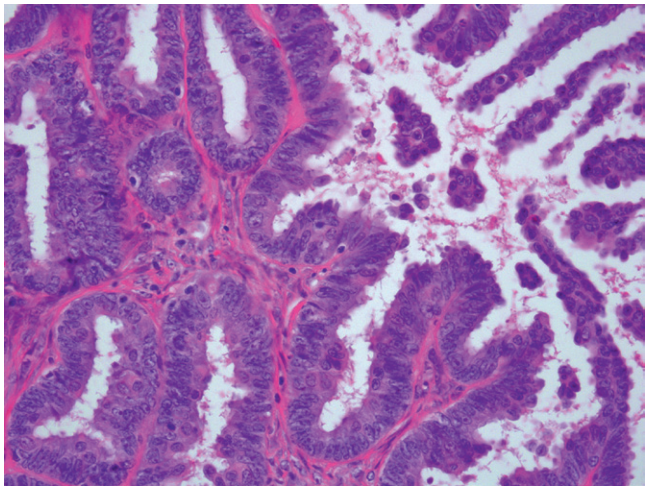


FIGURE 5
Ciliated cell differentiation in an SBT.

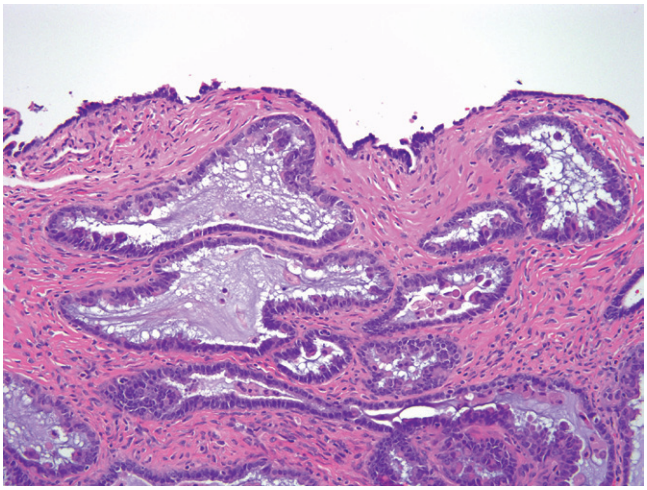


FIGURE 6
Surface ovarian involvement by an SBT.

SEROUS BORDERLINE TUMOR WITH COMPLEX ARCHITECTURE

Definition—A serous borderline tumor (SBT) with evidence of early, noninfiltrative carcinoma.

Clinical Features

Epidemiology

- Associated with the most common epithelial tumor of the ovary. Predominates in the fourth to sixth decades of life, but can be seen at virtually any age.
- Viewed as early malignant change on the surface of the papillae.
- An intermediate biology between SBT and well-differentiated invasive serous carcinoma.

Presentation

- Presents as a unilateral or bilateral low-grade serous tumor.
- Surface involvement may be present, and implants may or may not be detected.
- Nodular macroscopic growth is much less common.

Prognosis and Treatment

- Prognosis is comparable to SBT if invasive implants are not found.
- Associated statistically with a higher likelihood of coexisting invasive implants.

Pathology

Histology

- Complex architecture can manifest as either a micropapillary, microacinar, or cribriform pattern. In the micropapillary pattern, epithelial cells surround a prominent, nonbranching fibrous stalk and protrude radially as long, thin micropapillae without stromal cores so that the low-power appearance resembles a Medusa head. Length of the papillae should be at least five times the width. When the micropapillae merge, they take on a ramifying appearance; alternatively, the pattern can take on a cribriform pattern. The epithelial cells in these foci generally differ from those in other areas or in ordinary borderline tumors in that the cells are monomorphous and "clonal appearing" with scant cytoplasm. Cilia may be retained, particularly in the areas of cribriform growth. Nuclei are round and slightly more hyperchromatic than in the usual borderline tumor.

Immunopathology (Including Immunohistochemistry)

- Usually noncontributory. PAX8 and calretinin immunostains might aid in sorting out rare cases that resemble well-differentiated mesothelioma.

Diagnostic terminology

- SBT with low-grade intraepithelial carcinoma *or*
- SBT with complex (micropapillary/microacinar) architecture.
- Note: In the absence of invasive, recurrence risk for this tumor is comparable to that of a conventional borderline tumor.

Main Differential Diagnosis

- Some borderline tumors are complex but will fall short of the degree of papillary change described.
- Rarely a high-grade serous carcinoma will manifest with either micropapillae or cribriform architecture. Careful scrutiny of the cytology is important.

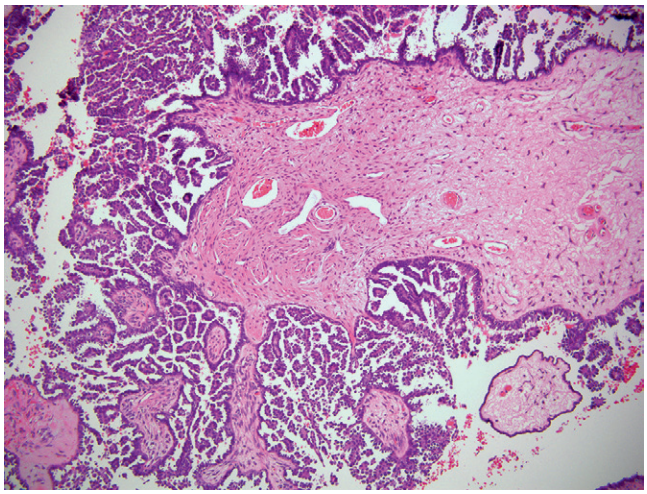


FIGURE 1

Pseudomicropapillary change in a borderline tumor. The papillae are interrupted with individual cell clusters suspended in space.

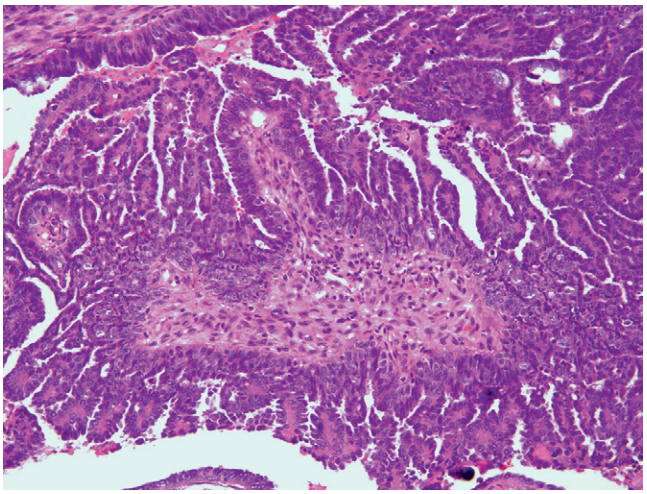


FIGURE 2

Micropapillary architecture in an SBT with noninterrupted (nonbranching) papillae.

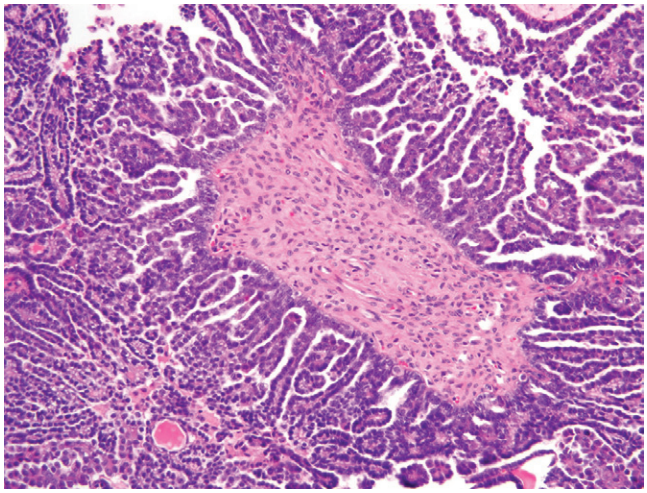


FIGURE 3

Micropapillary architecture in an SBT with noninterrupted (nonbranching) papillae.

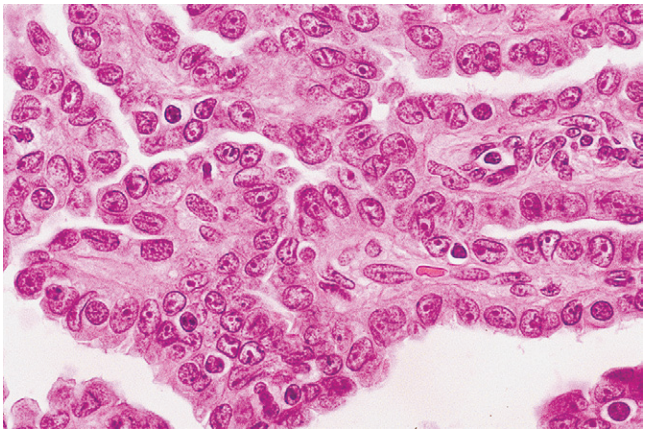


FIGURE 4

Micropapillary growth pattern in an SBT at higher magnification. The nuclei are monomorphous. In this case they are vesicular with small nucleoli.

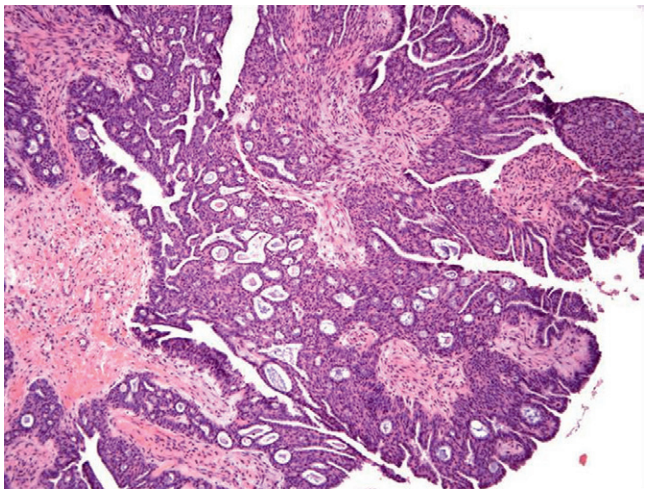


FIGURE 5

Confluent growth with microacinar architecture.

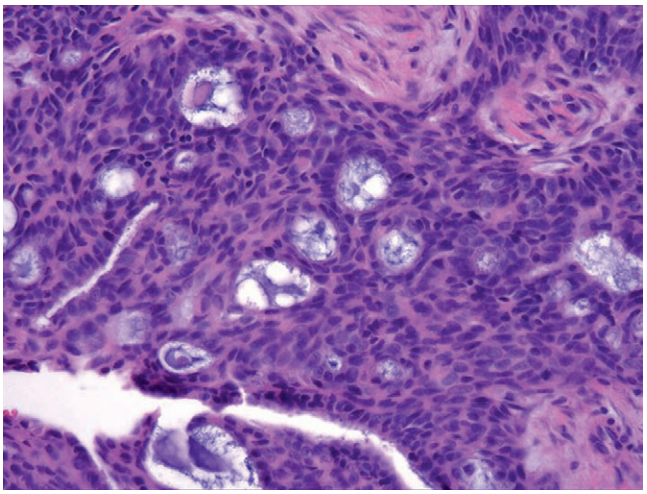


FIGURE 6

Microacinar growth at higher magnification.

LOW-GRADE INVASIVE SEROUS CARCINOMA OF THE OVARY

Definition—An invasive low-grade serous carcinoma.

Clinical Features

Epidemiology

- The less common serous carcinoma. Predominates in the fourth to sixth decades of life, but can be seen at virtually any age.
- Can arise in a serous borderline tumor (SBT) or SBT with complex architecture (intraepithelial carcinoma).
- Associated with mutations in regulators of the MAPK pathway (KRAS, BRAF, ERBB2) in about two thirds of tumors.

Presentation

- One third to one half are bilateral. Often associated with an SBT.
- Large unilocular or multilocular cystic mass.
- May respond to withdrawal of estrogen replacement. There have been responses to tamoxifen and aromatase inhibitors. MEK inhibitors are being investigated as well.

Prognosis and Treatment

- Prognosis is a function of stage. Tumors involving peritoneal surfaces have a poor prognosis with less than 50% 5-year survival.
- Typically responds poorly to conventional chemotherapy but regimens targeting the MAPK pathway have shown responses in some patients.

Pathology

Histology

- Low-grade serous carcinomas are often associated with areas that merge morphologically with SBTs.
- Combine the features of both extensive papillary architecture (often with many psammoma bodies) and evidence of stromal invasion. The latter may consist of infiltrating glandlike structures or, more commonly, multiple papillae projecting into a space or embedded in a fibrous stroma that may also contain glands, cysts, irregular islands of tumor cells, or cribriform glands.
- Often the invasive papillae are suspended in space. Nuclei are uniform, round, or oval with evenly distributed chromatin, with or without a prominent nucleolus.
- Cilia are usually not conspicuous, but ciliated differentiation (tubulin, FOXJ1) can be found.
- Peritoneal invasion by low-grade serous carcinoma is an extension of the spectrum of invasive implants, but the abundance of metastatic deposits and its nuclear morphology are more in keeping with a frankly malignant process. This can take the form of numerous nests of invasive tumor, more loosely arranged clusters of papillae, the latter of which might be delicate and might mimic a noninvasive implant.
- A rare variant, psammocarcinoma, is seen on the peritoneal surfaces and, despite the predominance of psammomatous calcifications, destructively infiltrates the adjacent tissues.

Immunopathology (Including Immunohistochemistry)

- Usually noncontributory. PAX8 and calretinin immunostains might aid in sorting out rare cases that resemble well-differentiated mesothelioma. However, we have seen hybrid tumors that share both immunophenotypes.

Main Differential Diagnosis

- Pseudoinvasion in areas of SBT.
- SBT with complex architecture (no invasion).
- Microinvasion in an SBT (less than 10 square mm).
- Well-differentiated mesothelioma (most will be PAX8 negative/calretinin positive).

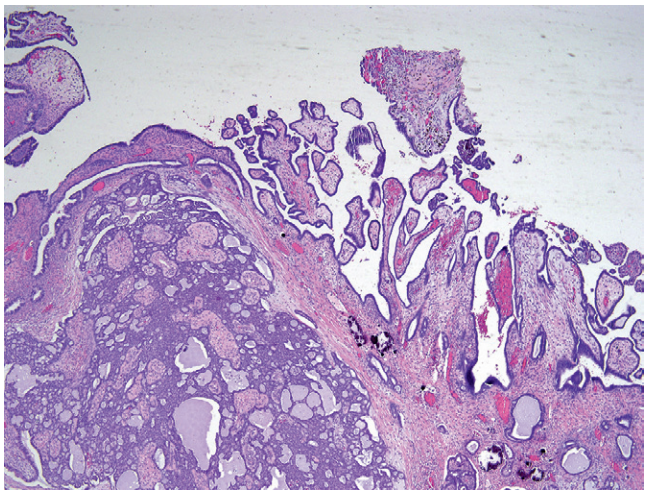


FIGURE 1

Low-grade serous carcinoma. Note the blunt, nonbranching surface papillae. This paradoxically low architectural complexity is commonly seen with low-grade serous carcinomas. Note also the confluent growth in the stroma, an expansile/replacement pattern of invasion.

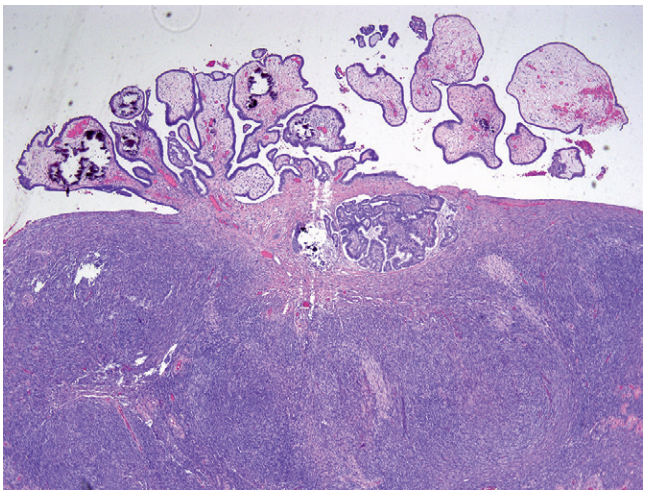


FIGURE 2

A metastasis to a contralateral ovary again demonstrates a low architectural surface complexity with subsurface invasion.

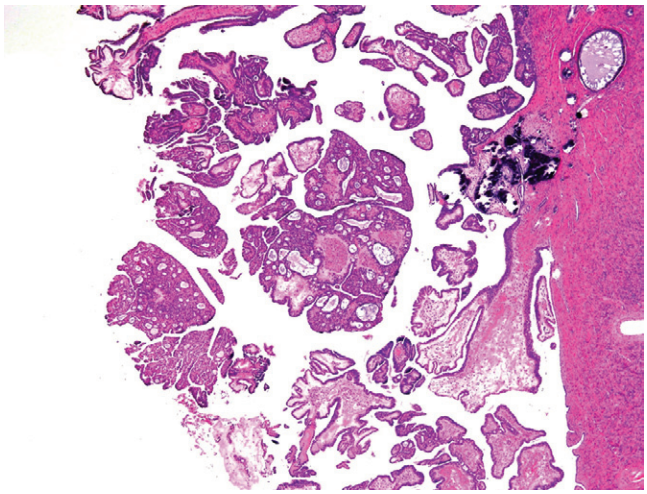


FIGURE 3

Cortical invasion by a low-grade serous carcinoma with expansile and infiltrative growth and retraction artifact.

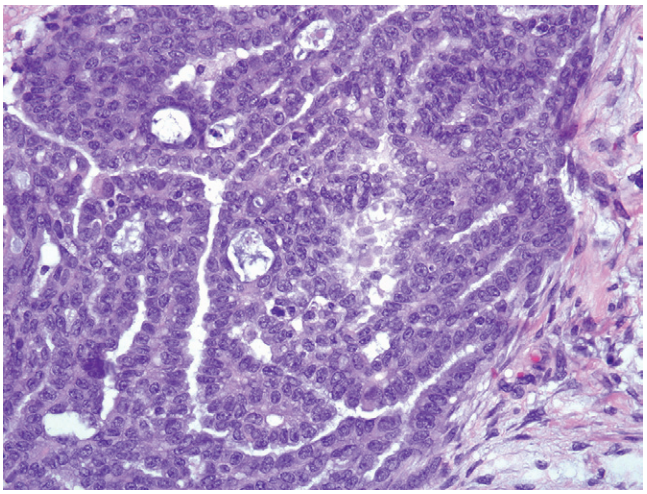
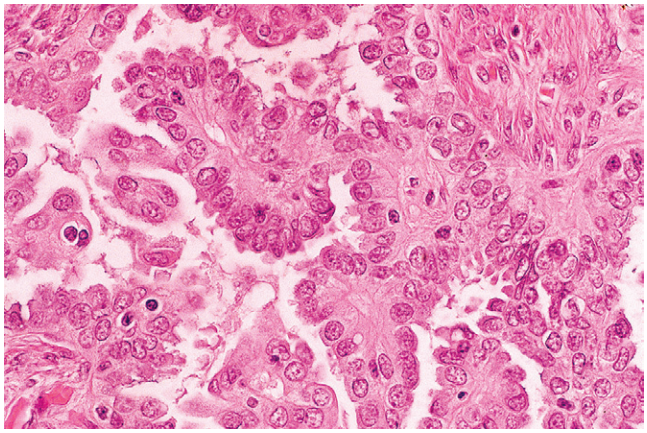


FIGURE 4

High-power image of low-grade serous carcinoma, papillary and solid patterns. There is mild atypia with inconspicuous cilia.



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High-power image of low-grade serous carcinoma, papillary and solid patterns. There is mild atypia with inconspicuous cilia.

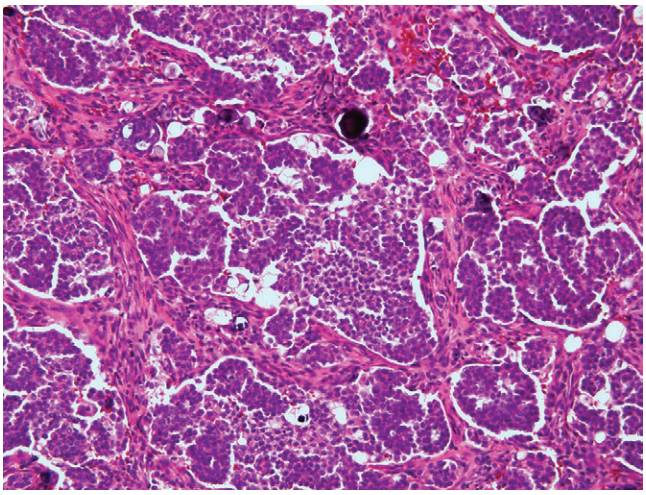

FIGURE 6

High-density papillary growth in a peritoneal metastasis of low-grade serous carcinoma.

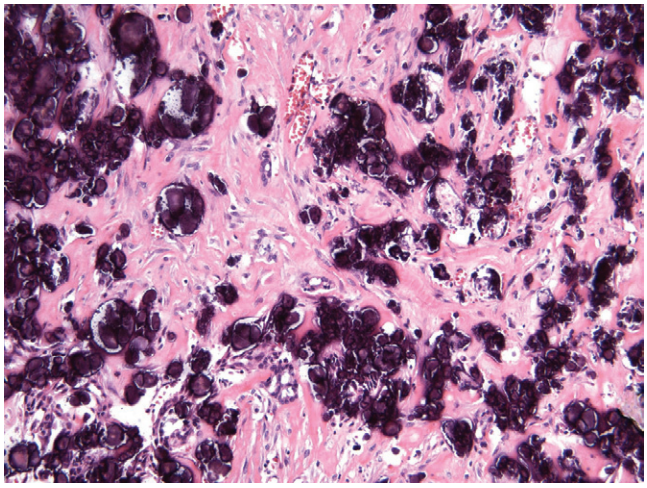

FIGURE 7

Psammocarcinoma (low-grade serous carcinoma with abundant psammomatous calcifications) infiltrating omental fibrous tissue.

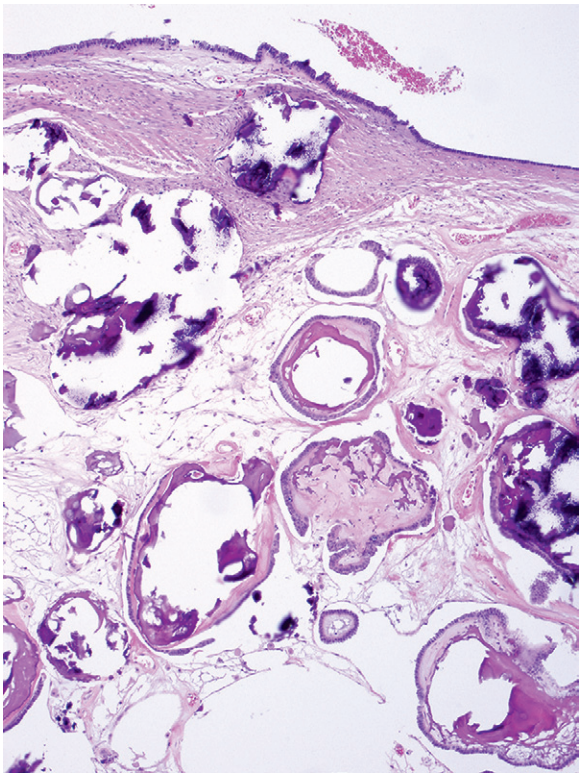

FIGURE 8

An uncommon variant of low-grade serous carcinoma in which large discrete papillae are suspended in the stroma, surrounded by an unlined retracted stroma. Note the numerous calcifications, suggesting that this focus is evolving toward a picture similar to that in Figure 7.

INVASIVE IMPLANTS OF LOW-GRADE SEROUS TUMOR

Definition—Low-grade serous tumor implants with high risk of a malignant or adverse outcome.

Clinical Features

Epidemiology

- Predominates in the fourth to sixth decades of life, but can be seen at virtually any age.
- Classically associated with borderline serous tumors, but also associated with frankly malignant low-grade serous carcinomas of the ovary.
- Comprises growth on mesothelial surfaces with high risk of adverse outcome.

Presentation

- Usually seen as small granular deposits on the serosal or omental surfaces.
- Nodular macroscopic growth can be present.

Prognosis and Treatment

- Prognosis is guarded, with up to 60% risk of recurrence and death.
- Empirically approached as evidence of a low-grade serous carcinoma, irrespective of the primary tumor histology. Felt to rarely respond to conventional chemotherapy. Newer therapies for low-grade serous carcinomas targeting the MAPK pathway (MEK inhibitors) may produce some benefit.
- There is evidence that some of these are estrogen sensitive and respond to withdrawal of hormone replacement or to aromatase inhibitors.

Pathology

Histology

- Invasive implants are composed of cells and cell patterns similar to those of well-differentiated serous carcinomas. A key finding is a high density of papillary or solid growth relative to stroma.
- They are almost always associated with stromal desmoplasia but, in addition, have an irregular, infiltrative-appearing border. They appear to invade underlying structures or replace fatty tissue rather than sitting indolently on the peritoneal surface or between fat lobules.
- If underlying tissue is absent in a biopsy specimen, the lesion is classified as noninvasive by default. However, either a micropapillary pattern alone or solid epithelial nests surrounded by clear spaces or clefts in a fibrous stroma are sufficient to consider an implant invasive in the absence of an obvious infiltrative pattern. Such patterns may be associated with a primary tumor with micropapillary architecture.

Immunopathology (Including Immunohistochemistry)

- Usually noncontributory. PAX8 and calretinin immunostains might aid in sorting out rare cases that resemble well-differentiated mesothelioma.

Main Differential Diagnosis

- Desmoplastic noninvasive implants—these can be difficult to distinguish, particularly in small samples. The gland density should be low relative to the background stroma, without retraction artifact.
- Endosalpingiosis—presents as small glands within the stroma or lymph nodes.
- Mesothelial cells—these can form small papillae and can be associated with calcifications. Calretinin positive.

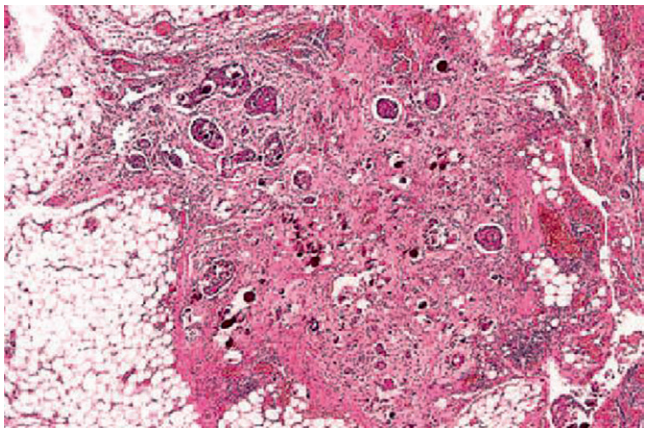

FIGURE 1

Invasive epithelial implants of serous borderline tumor (SBT). Numerous epithelial islands are present in a fibrous and edematous stroma. The lesion appears to be expanding into and replacing the omental fat.

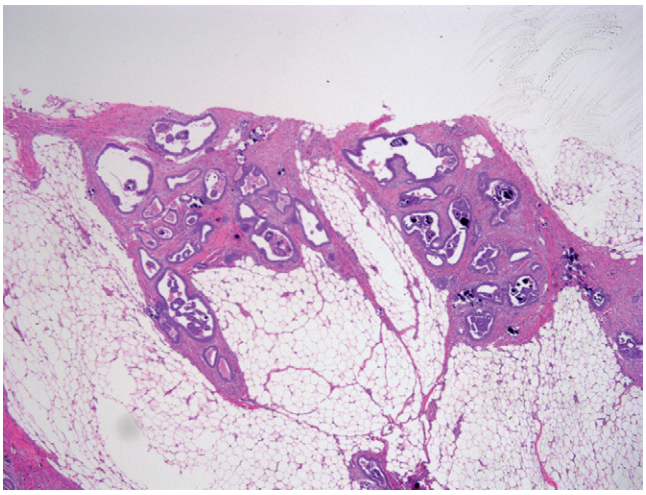

FIGURE 2

Invasive implants with complex epithelial growth associated with dense fibrous stroma.

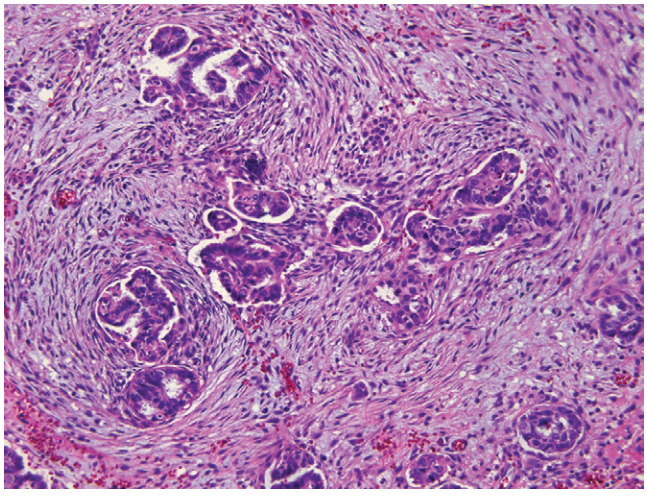

FIGURE 3

Desmoplastic invasive implant infiltrating fibrous stroma.

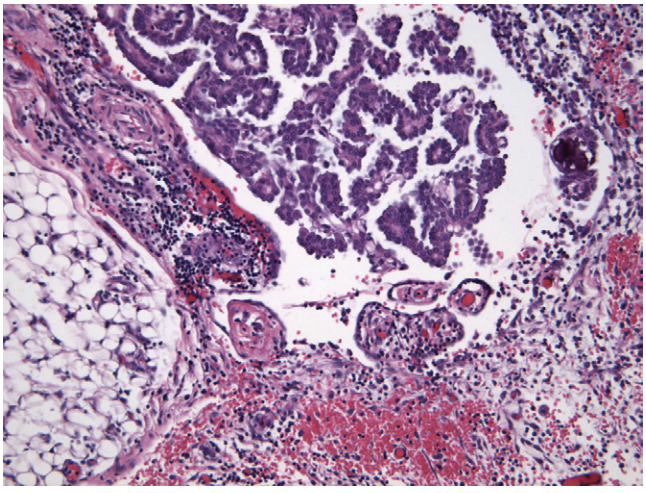

FIGURE 4

Implant with complex micropapillary architecture.

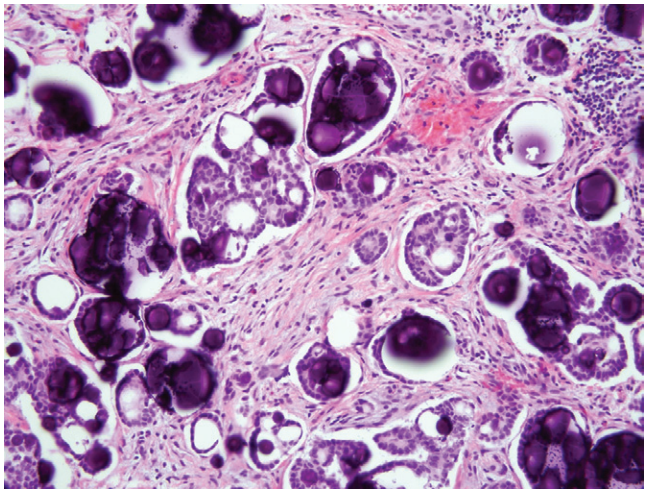

FIGURE 5

Prominent retraction artifact is also a characteristic seen in invasive implants.

MUCINOUS CARCINOMA

Definition—A malignant mucinous tumor arising in the ovarian cortex.

Clinical Features

Epidemiology

- The least common of the major malignant epithelial tumors, accounting for about 2.4% of all primary malignant epithelial tumors of the ovary.
- Average age in the sixth decade.
- Associated with borderline mucinous tumors.
- Associated with RAS mutations.

Presentation

- Can be encountered at any age.
- Usually unilateral, but not always.
- Typically a solid and multicystic mass without obvious surface involvement.
- Estrogenic or androgenic manifestations in some due to the activation of adjacent ovarian stromal cells.

Prognosis and Treatment

- Most are stage I, with a good prognosis and only 11% recurrence rate.
- Advanced stage tumors carry a poor (less than 10%) survival.

Pathology

Histology

Two histologic patterns are seen.

- The *expansile* pattern composed of confluent glands or cysts filled with malignant-appearing epithelium with minimal intervening stroma and fine papillae with minimal stroma. Lining is composed of tall columnar cells with mucin, including goblet cells. Separation from borderline may be difficult, but invasion is considered if the area of involvement is greater than 10 square millimeters or at least 3 mm in one dimension.
- The *infiltrative* pattern consists of a more classical admixture of irregularly arranged neoplastic mucinous epithelium amid a desmoplastic or fibromatous stroma. Additional patterns include colloid carcinoma-like or signet-ring cells.

Immunopathology (Including Immunohistochemistry)

- Intestinal mucinous carcinomas can be positive for CK7, CK20, and CDX2, although staining with the latter two should be considerably less than that of CK7. PAX8 may or may not be positive but is a helpful indicator of an ovarian origin if positive.

Main Differential Diagnosis

- Metastatic intestinal, pancreatic, or biliary tree carcinoma—these should be considered if the tumor is bilateral, is multinodular, involves the surface, and shows extensive vascular invasion or a wide range of patterns including small tight glands with marked atypia and signet-ring cells. However, note that some primary tumors are bilateral and may express considerable CK20 and CDX2.
- Borderline mucinous tumors—if there is invasion by cohesive glands with minimal stromal response, it may be very difficult to exclude a borderline intestinal tumor. Careful attention to the cytologic features in the cyst lining is helpful in that the lining cells in malignant tumors will be uniformly atypical and not demonstrate the spectrum of benign and borderline morphology seen in nonmalignant tumors.

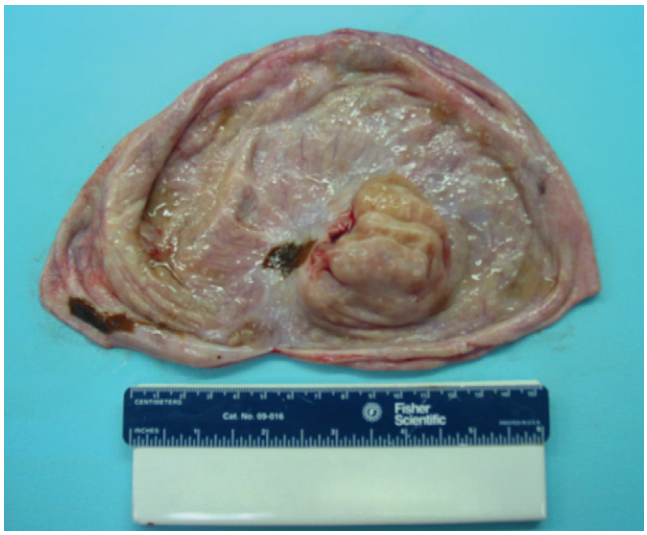

FIGURE 1

Mucinous carcinoma of the ovary arising in a borderline tumor. This tumor is a single cyst with a central tumor nodule.

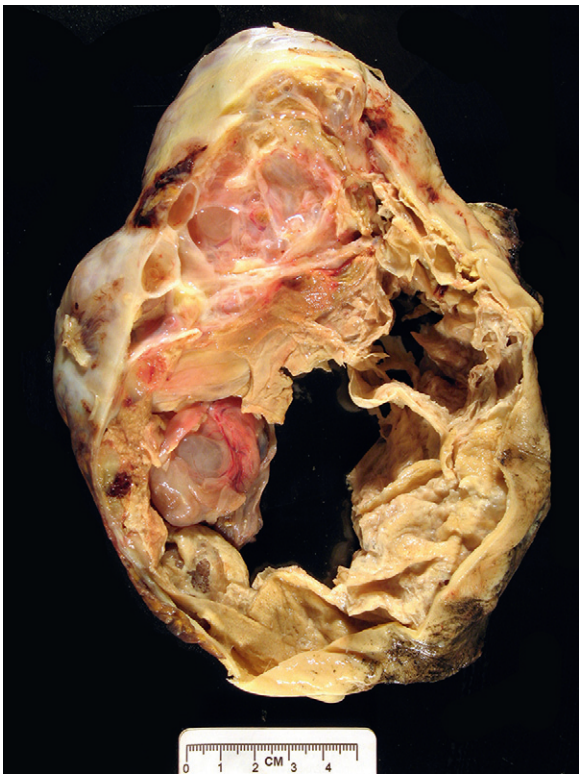

FIGURE 2

Mucinous carcinoma. This is more typical, with multiple cysts and focal solid growth.

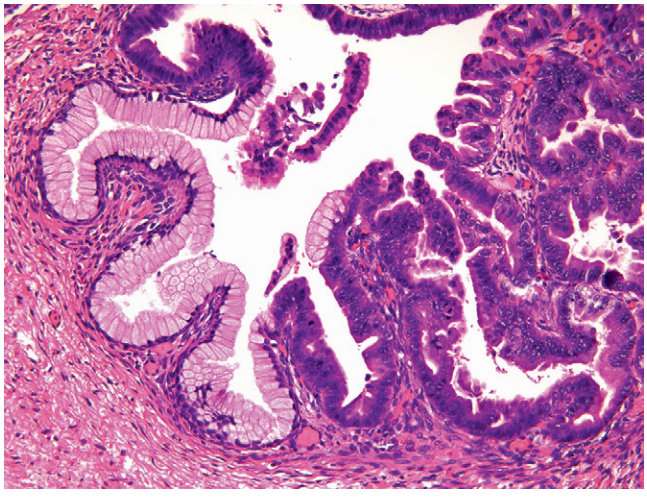

FIGURE 3

Junction of benign and malignant mucinous epithelium, not uncommon in these tumors.

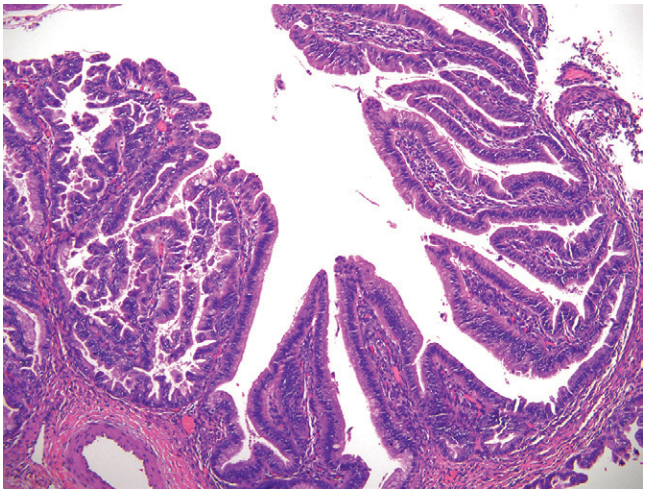

FIGURE 4

Mucinous carcinoma. In this medium-power magnification there is expansile growth with intracystic exophytic growth. This pattern portends a favorable outcome.

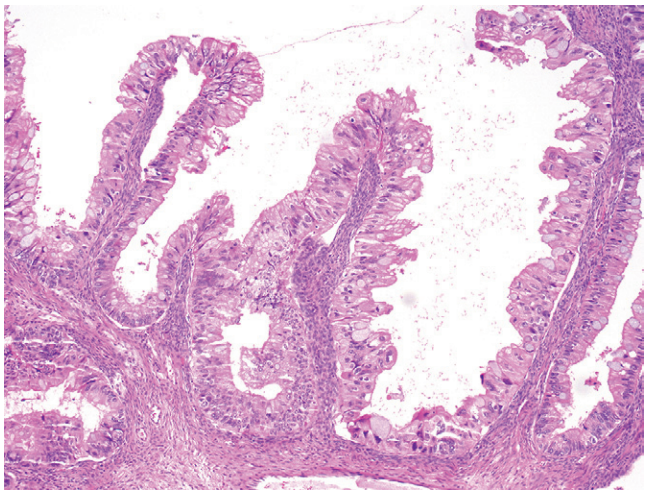

FIGURE 5

A somewhat more subtle variant of malignant epithelium, again with an expansile growth pattern and papillary architecture.

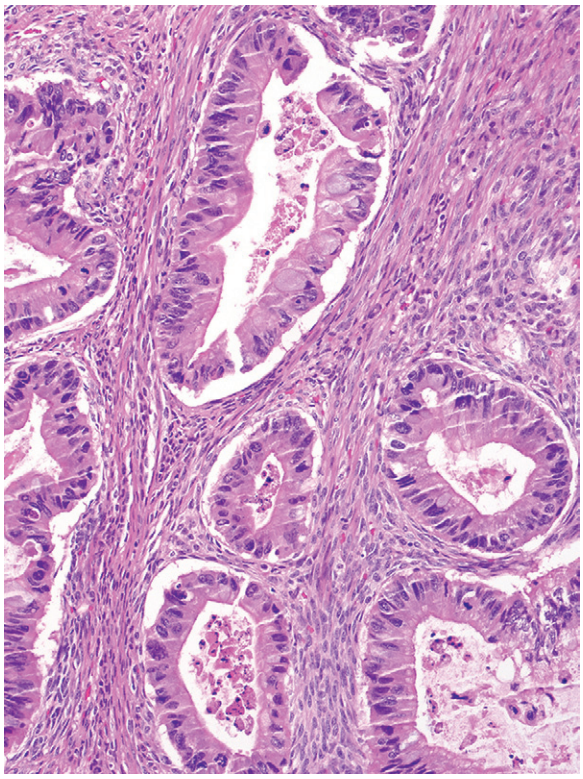

FIGURE 6

Malignant glands in stroma with retraction artifact.

MUCINOUS TUMORS WITH MURAL NODULES

Definition—Mucinous tumors containing nodular foci in the cyst wall of altered mesenchymal and/or epithelial differentiation.

Clinical Features

Epidemiology

- Extremely uncommon; tendency toward women in the fifth and sixth decades.
- Associated with both borderline and malignant mucinous tumors.
- Etiology is unclear; however, one recent paper noted different codon 12 k-ras mutations in a mucinous tumor and its mural nodule, suggesting that both may have originated in a mucinous precursor cell followed by clonal divergence.

Presentation

- Typically found incidentally in a mucinous tumor.
- Generally uniform to variegated, yellow, pink, or red in appearance.
- Hemorrhage and necrosis may be present.
- Mural nodules may be single or multiple and range from less than 1 cm up to 30 cm.

Prognosis and Treatment

- Benign mural nodules will have an uneventful outcome.
- Outcome of malignant nodules varies but in general is poor. Risk of tumor-related death in patients with either anaplastic carcinomatous or sarcomatous nodules exceeds 50%. In small series of patients with stage IA tumors, 5-year disease-free survival has been as high as 100%.

Pathology

Histology

- Three categories of benign nodules have been described. (1) Pleomorphic and epulis-like type, with osteoclast-like multinucleated giant cells, extravasated red blood cells (RBCs), and pleomorphic spindled cells similar to aneurysmal bone cysts. (2) Pure spindle cell population with no or few giant cells. (3) Multinucleated cells with ground-glass cytoplasm and thin fibrous bands. A resemblance to sarcoma (i.e., sarcoma like) is noted, but these nodules are sharply circumscribed and do not invade vessels.
- Malignant nodules include the following: (1) Anaplastic carcinoma with pleomorphic cells with markedly enlarged nuclei with prominent nucleoli and abundant eosinophilic cytoplasm, the latter sometimes imparting a rhabdoid appearance. Both epithelioid and spindle cells may be present and will stain with cytokeratin antibodies. (2) Sarcomatous and carcinosarcomatous mural nodules are even rarer, and fibrosarcomas, rhabdomyosarcomas, and pleomorphic undifferentiated sarcomas have been reported.

Immunopathology (Including Immunohistochemistry)

- Cytokeratins will stain both spindle and epithelial components.

Main Differential Diagnosis

- Benign and malignant can be confused with each other.

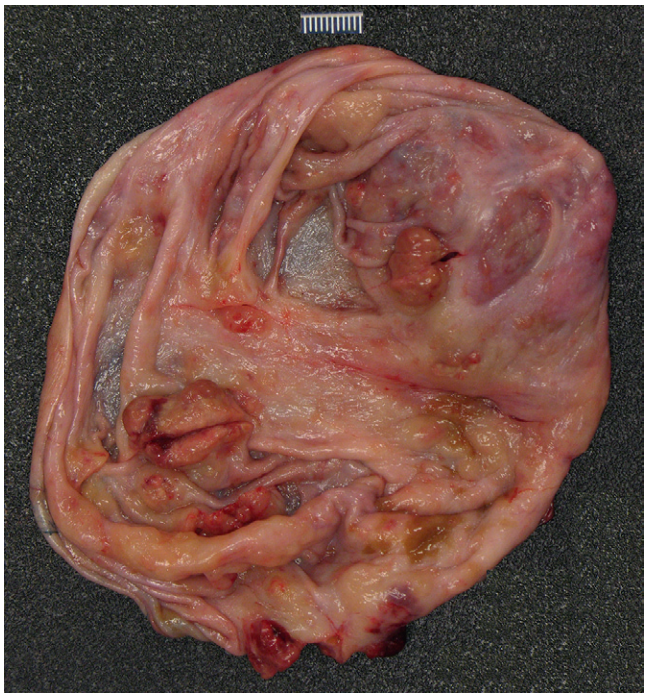

FIGURE 1

Low-grade mucinous tumor with mural nodules. Note several raised lesions in the wall of this tumor.

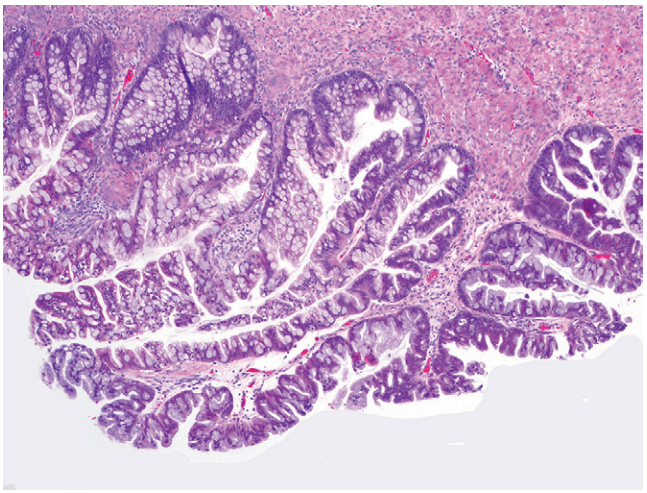

FIGURE 2

The tumor appears as a well-differentiated mucinous carcinoma without stromal invasion.

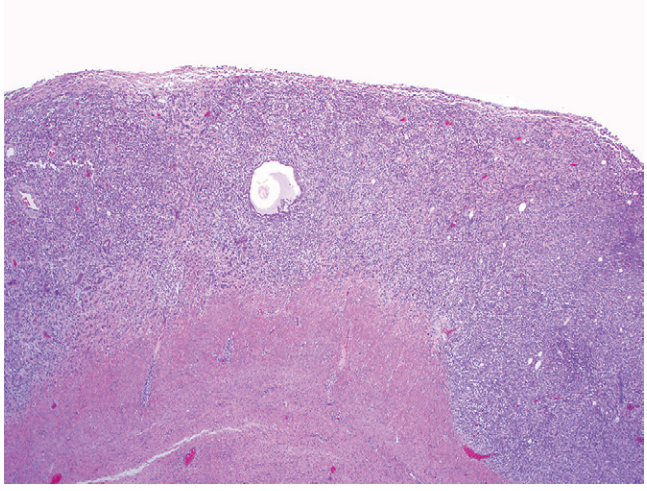

FIGURE 3

Mural nodule from above tumor, seen as a plaquelike lesion on the cyst wall.

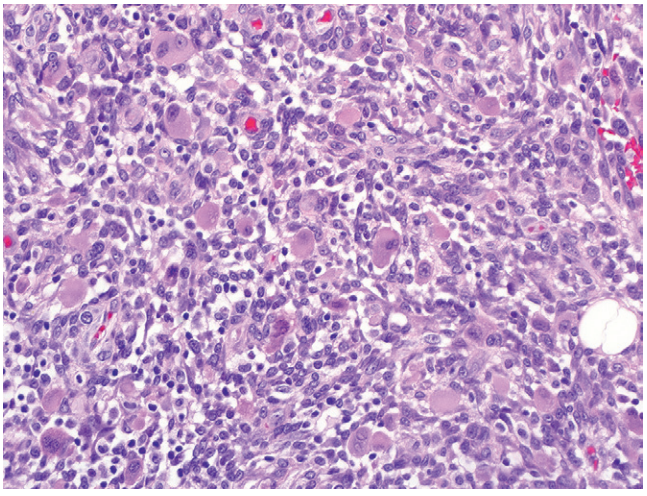

FIGURE 4

At higher magnification there is an epithelioid population with scattered eosinophilic cells.

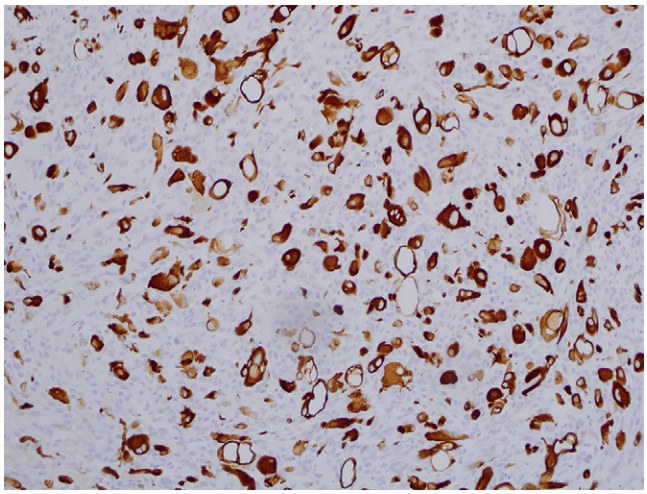

FIGURE 5
Immunostains for cytokeratin are strongly positive.

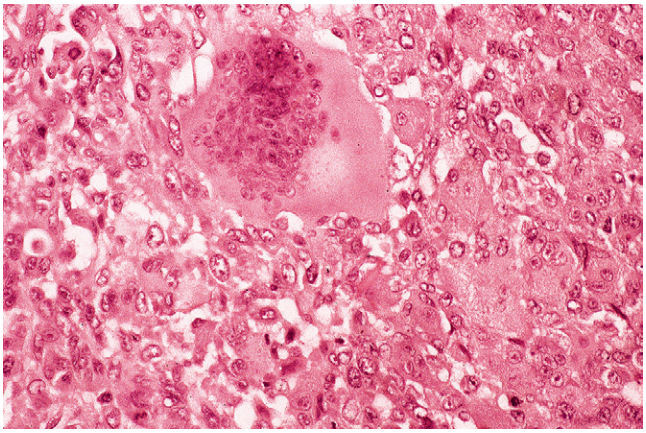

FIGURE 6
A benign nodule with numerous multinucleated cells.

MUCINOUS BORDERLINE TUMOR

Definition—An atypical proliferative mucinous tumor with intestinal differentiation, without stromal invasion or intraepithelial carcinoma.

Clinical Features

Epidemiology

- The second most common epithelial tumor of the ovary and 12% to 15% of ovarian tumors. Approximately 10% of mucinous tumors are borderline. The average age is in the sixth decade, but borderline tumors can be encountered over a wide age range.

Presentation

- Usually as a large, multicystic mass. The solid component should be principally fibrous, but mucin-producing epithelium can produce both soft and fibrous areas.

Prognosis and Treatment

- Prognosis is excellent in the absence of frank stromal invasion. There is minimal risk of bilaterality, but this can rarely be seen in primary tumors.
- A coexisting neoplasm in the appendix should be ruled out.

Pathology

Histology

- In addition to benign-appearing areas with a single layer of mucinous columnar cells with benign-appearing, basally located nuclei, other areas are characterized by the presence of epithelial cells that are crowded, stratified, and often form either stroma-free papillary tufts or papillae with thin fibrous cores.
- The nuclei are slightly enlarged and hyperchromatic and have increased mitotic activity, most noticeable at the base of the papillae.
- The epithelium has the morphologic appearance of intestinal epithelium with goblet cells and sometimes Paneth cells.
- Neuroendocrine cells are also present but may require special stains for visualization.
- The gland and cyst lumens contain mucin, sometimes admixed with histiocytes and inflammatory cells.

Immunopathology (Including Immunohistochemistry)

- Positive for CK7, and variable for CK20, PAX8, and CDX2.

Main Differential Diagnosis

- Well-differentiated metastatic mucin-producing adenocarcinomas of the appendix and pancreaticobiliary tree—usually smaller, multinodular, involving the ovarian surface, and including pseudomyxoma.

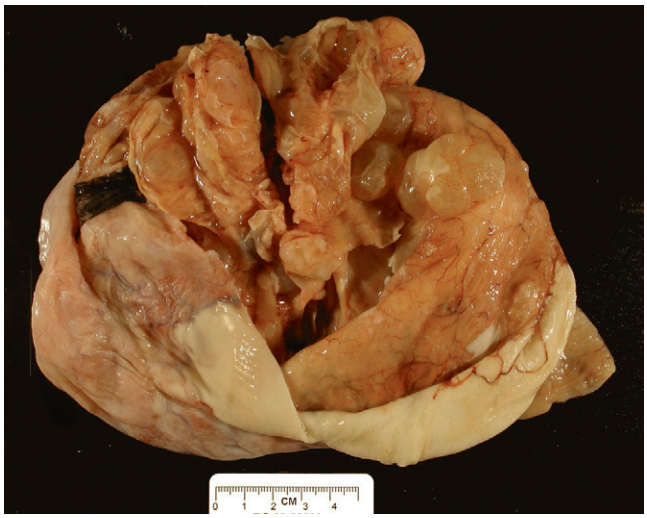

FIGURE 1

Gross pathology of a mucinous borderline tumor with soft fleshy excrescences that contain small cysts filled with mucin.

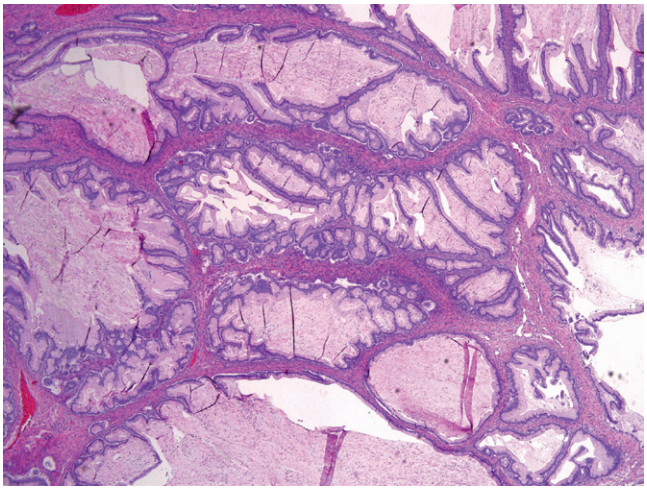

FIGURE 2

Mucinous borderline tumor. At low magnification there are abundant contiguous cysts with mild epithelial complexity.

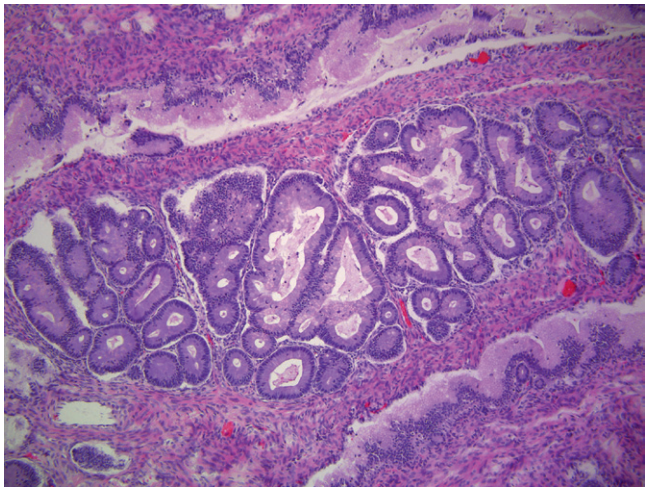

FIGURE 3

Mucinous borderline tumor. This field displays minimal atypia.

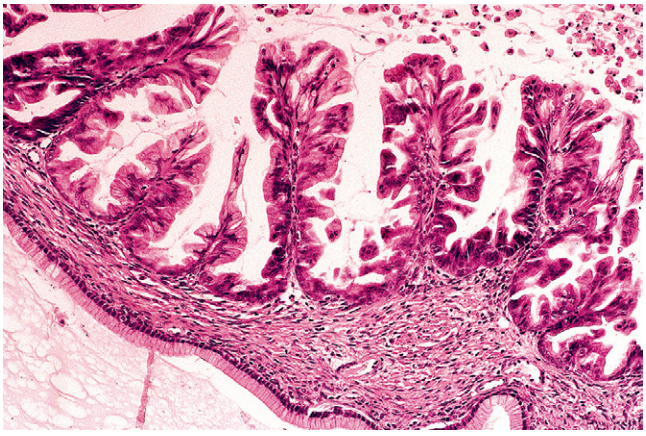

FIGURE 4

Mucinous borderline tumor. At higher magnification there are uniform papillae with mild epithelial complexity, modest atypia, and thin stromal cores.

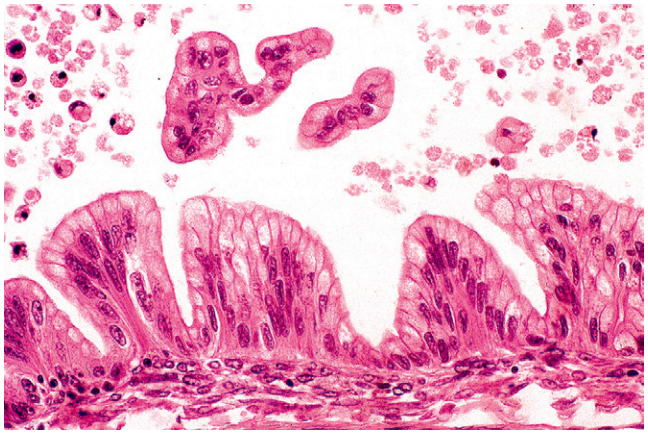

FIGURE 5

Mucinous borderline tumor. Intestinal-type differentiation is present, with mucin-producing epithelium and modest atypia.

MUCINOUS BORDERLINE TUMOR WITH INTRAEPITHELIAL CARCINOMA

Definition—Marked intramucosal atypia in a borderline mucinous tumor of the ovary.

Clinical Features

Epidemiology

- The second most common epithelial tumor of the ovary and 12% to 15% of ovarian tumors. Approximately 10% of mucinous tumors are borderline. The average age is in the sixth decade, but borderline tumors can be encountered over a wide age range.

Presentation

- Usually as a large, multicystic mass. The solid component should be principally fibrous, but mucin-producing epithelium can produce both soft and fibrous areas.

Prognosis and Treatment

- Prognosis is excellent if the atypia is confined to the surface and is not accompanied by frank stromal invasion. No further therapy is warranted but thorough sampling of the tumor is indicated to exclude invasion. Undersampling of a more ominous component may explain the small risk of recurrence, approximately 5%. There is minimal risk of bilaterality, but this can rarely be seen in primary tumors.

Pathology

Histology

- Features of a borderline tumor will virtually always be present, but rarely an intraepithelial carcinoma will emerge from a benign-appearing epithelium.
- The epithelial cell nuclei appear cytologically malignant (significant nuclear enlargement, nuclear hyperchromasia, often prominent nucleoli), but there is no obvious stromal invasion.
- In most cases there is prominent stratification of the malignant-appearing cells with stroma-free papillae or a cribriform pattern of growth.

Immunopathology (Including Immunohistochemistry)

- Positive for CK7 and variable for CK20, PAX8, and CDX2.

Main Differential Diagnosis

- Well-differentiated metastatic mucin-producing adenocarcinomas of the appendix and pancreaticobiliary tree—usually smaller, multinodular, involving the ovarian surface, and including pseudomyxoma.
- Metastatic colonic carcinoma can present with a similar level of atypia within large cysts. However, confluent neoplastic glands are usually seen as well.

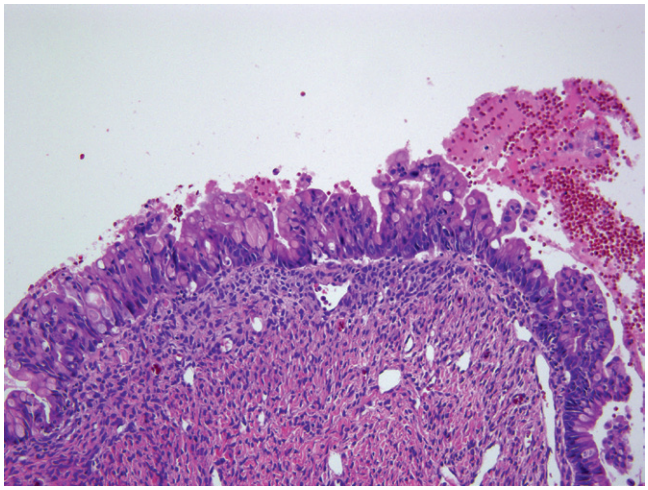

FIGURE 1

Intraepithelial carcinoma in a mucinous tumor. This focus is notable for prominent epithelial stratification.

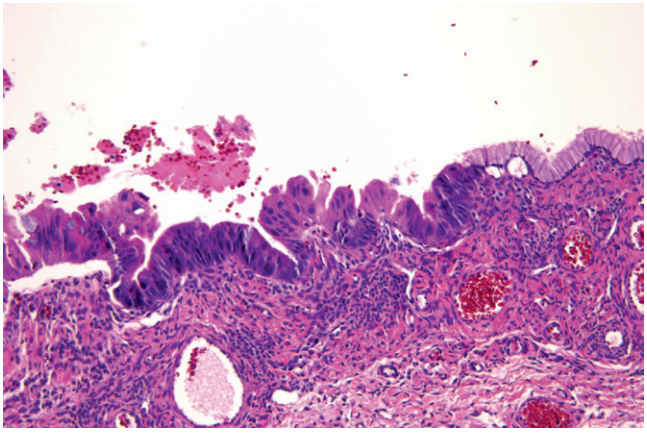

FIGURE 2

Intraepithelial carcinoma in a mucinous tumor. At this magnification the marked hyperchromasia characterizes the transition to intraepithelial carcinoma from the benign epithelium on the right.

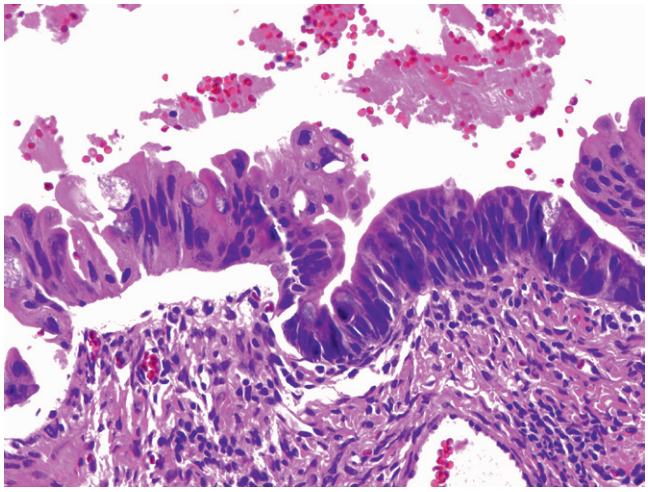

FIGURE 3

Intraepithelial carcinoma in a mucinous tumor. A higher magnification illustrates the marked nuclear atypia in this focus.

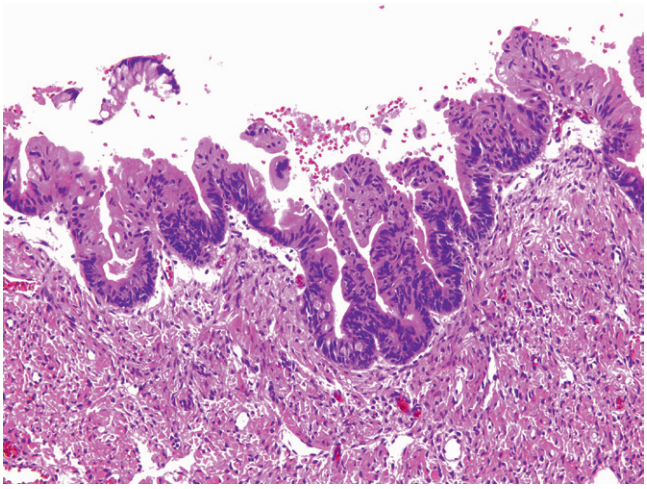

FIGURE 4

Intraepithelial carcinoma in a mucinous tumor. Another focus contains a blend of both marked atypia and stratification.

LOW-GRADE ENDOMETRIOID ADENOCARCINOMA

Definition—An adenocarcinoma typically derived from endometriosis and displaying well to moderate differentiation.

Clinical Features

Epidemiology

- Approximately 40% of low-stage tumors are associated with endometriosis. Those with endometriosis tend to be younger than those without.
- Approximately 5% associated with Lynch syndrome.
- Associated with PTEN and ARID1 mutations.

Presentation

- Generally low grade and low stage.
- Will be found in 5% to 7% of women with uterine endometrioid carcinoma.
- Women presenting with ovarian endometrioid adenocarcinomas have a ~20% risk of a concurrent endometrial endometrioid adenocarcinoma.

Prognosis and Treatment

- Prognosis relative to high-grade serous adenocarcinomas is good.
- Eighty percent present as stage I or II but can be multifocal with involvement of both ovaries.
- Grade I or II tumors have a 5-year disease-free survival approaching 80%.
- Stage I grade II tumors will often receive chemotherapy; thus nuances of grading might impact on management.
- When spread occurs, it is typically to the pelvic surfaces or lymph nodes.
- Management is similar to serous carcinomas, with combination chemotherapy and hormonal therapy if the tumor recurs.

Pathology

Histology

- The typical finding is an encapsulated tumor that is often associated with an adenofibroma or endometriotic cyst.
- Tumor is arranged in well-demarcated glands, but other patterns, including cordlike or ribbonlike sertoliform growth, can be seen, as well as squamotransitional or mucinous differentiation.

Immunopathology (Including Immunohistochemistry)

- Will be inhibin negative and strongly pan-keratin positive. Might be variably positive for CK7, however. Should have normal (heterogeneous) p53 expression.

Main Differential Diagnosis

- Sertoli, granulosa cell tumor or other sex cord tumors—these will be considered if there is a spindled or sex cord–like pattern in the epithelial tumor. They can be excluded by staining for inhibin or calretinin.
- Metastatic colonic carcinoma—this can be difficult to separate on frozen section if there is extensive necrosis. CK20/PAX8 stains will be helpful and should be strongly positive/negative.
- Insular carcinoid tumor—these tumors can be arranged in bland-appearing glands and can mimic endometrioid carcinoma. The distinctive nuclear features and highly uniform population blending acini and cordlike growth are helpful distinguishing features. They will also exhibit staining for neuroendocrine markers.

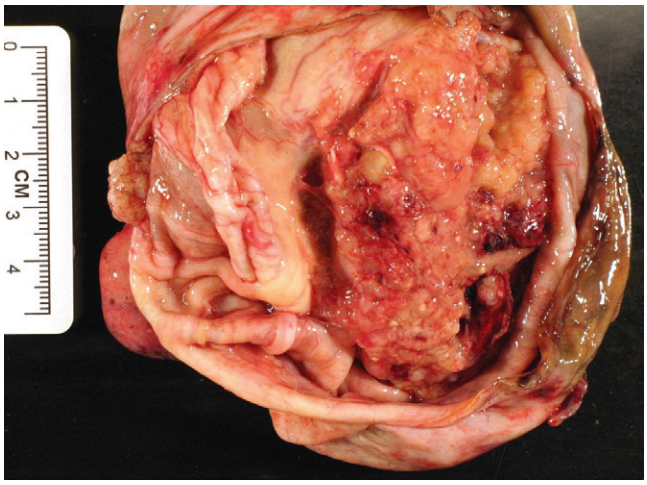

FIGURE 1

A tumor within a large cyst.

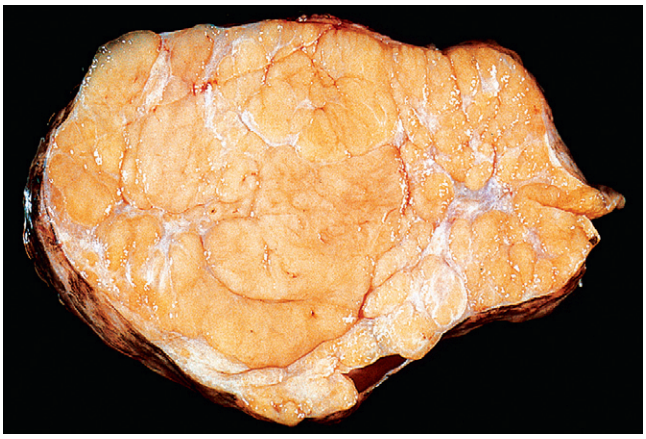

FIGURE 2

A more solid tumor that might mimic a sex cord stromal tumor given the somewhat yellow appearance.

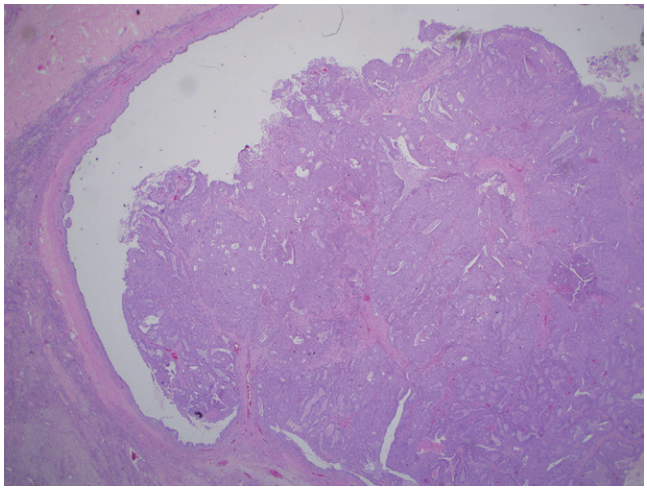

FIGURE 3

At low magnification this endometrioid carcinoma is associated with an endometriotic cyst.

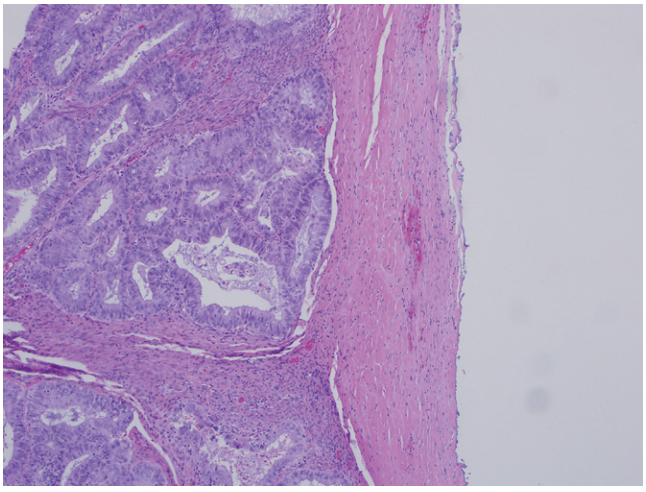

FIGURE 4

Low-grade endometrioid carcinomas typically (but not always) are encapsulated without surface involvement.

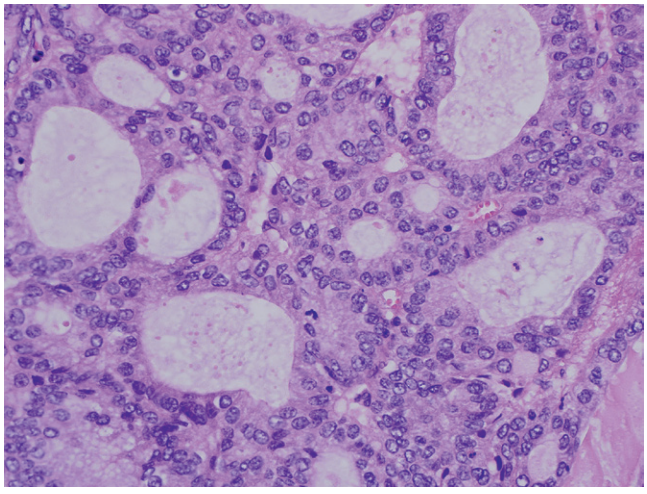

FIGURE 5

Higher magnification showing the typical neoplastic endometrioid glands with pseudostratified epithelium.

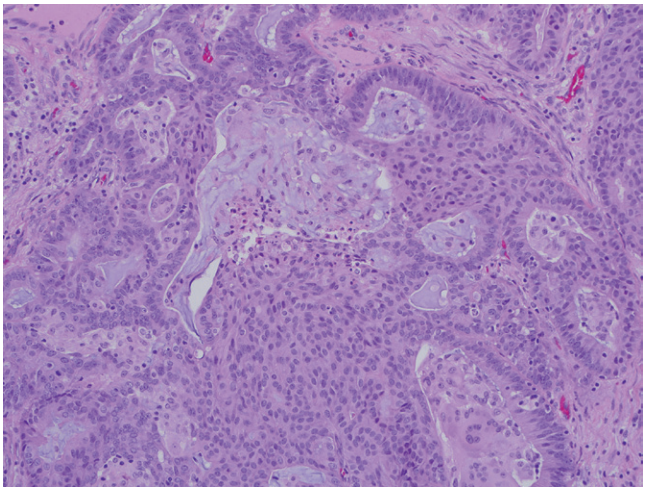

FIGURE 6

From 10% to 20% of low-grade endometrioid ovarian carcinomas *(shown here)* coexist with a similar tumor in the uterus (see Figure 7). Despite the identical features including squamous differentiation, the likelihood is high that the tumors are separate primaries.

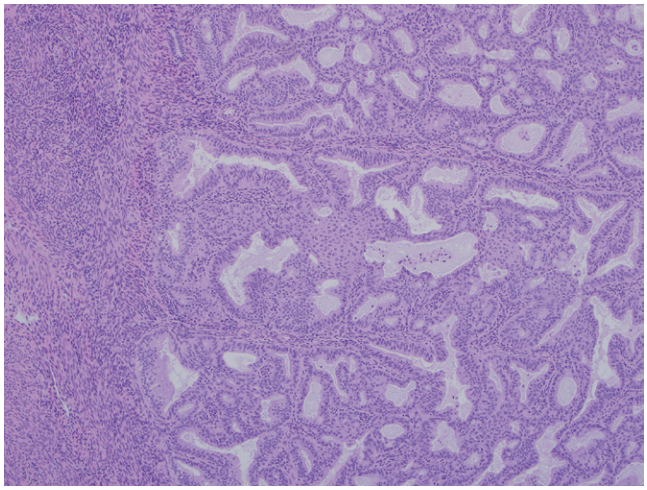

FIGURE 7

From 10% to 20% of low-grade endometrioid ovarian carcinomas (see Figure 6) coexist with a similar tumor in the uterus *(shown here)*. Despite the identical features including squamous differentiation, the likelihood is high that the tumors are separate primaries.

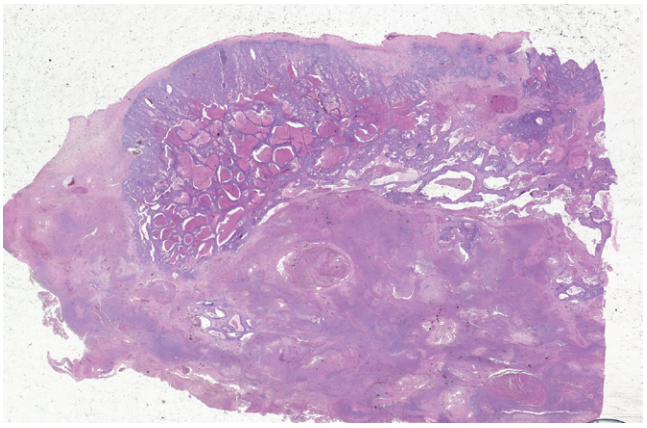

FIGURE 8

A low-magnification image of a section from a large tumor with extensive necrosis (seen at higher power in Figure 9). Such features can make the distinction from colonic carcinoma difficult on frozen-section analysis.

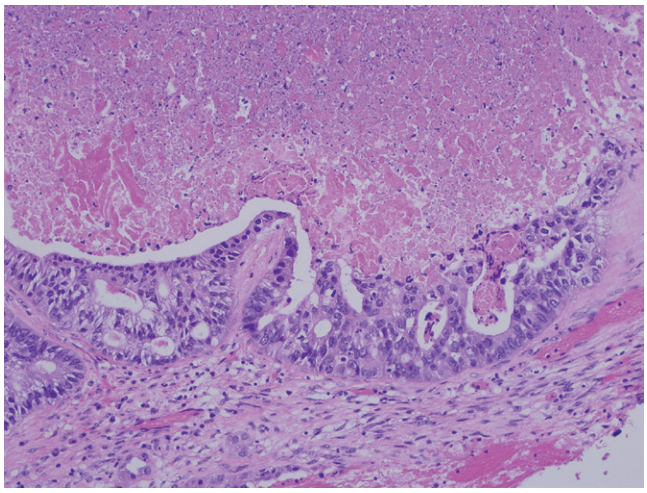

FIGURE 9

The large tumor with extensive necrosis seen in Figure 8 is shown at higher power.

ENDOMETRIOID ADENOFIBROMA

Definition—A benign epithelial and stromal tumor with an endometrioid epithelial component.

Clinical Features

Epidemiology

- Rare; these lesions represent less than 1% of all benign ovarian tumors.
- Most common in postmenopausal patients or women in their late reproductive years.
- Average age at presentation is in the mid-50s.
- May be associated with endometriosis.

Presentation

- Ovarian mass.
- The majority of cases are unilateral.

Prognosis and Treatment

- Excellent.
- There have been no reports of recurrent tumors.
- Surgical excision is adequate treatment.

Pathology

Histology

- Gross examination is notable for a firm mass with a smooth surface.
- On cut section the tumor is firm with a variable number of cystic spaces; these cystic spaces may contain hemorrhagic debris, mucin, or serous fluid.
- The cystic spaces can be relatively large, up to several centimeters in diameter.
- On histologic examination the fibromatous component consists of small bland spindled cells with short nuclei arranged in fascicles and storiform patterns, similar to a fibroma.
- The cystic spaces are irregularly shaped and are uniformly present throughout the stroma.
- The spaces are lined by benign epithelial cells resembling endometrium.
- The epithelial cells are columnar to cuboidal and often stratified.
- The cells typically have elongated nuclei with moderate to abundant amounts of cytoplasm.
- Similar to endometrial epithelium seen elsewhere, the cells may be focally mucinous, exhibit squamous metaplasia in the form of squamous morules, or have scattered ciliated cells. Those with morular metaplasia are usually termed proliferative or borderline endometrioid adenofibromas.
- Nuclear atypia is not present in the glandular or stromal components.
- Endometrial-type stroma is not present.
- Psammomatous calcifications may be noted, particularly in the stromal component.
- Varying degrees of ischemic-type necrosis and stromal calcification may be seen.

Immunopathology (Including Immunohistochemistry)

- Noncontributory. Establishing an endometrioid origin with special stains is not usually needed.

Main Differential Diagnosis

- Proliferative or borderline endometrioid tumor—these contain greater gland crowding with some complexity, often with squamous morules.
- Metastatic low-grade endometrioid adenocarcinoma—this might be an issue if the patient has an endometrial or contralateral endometrioid adenocarcinoma but can usually be excluded on histologic exam.

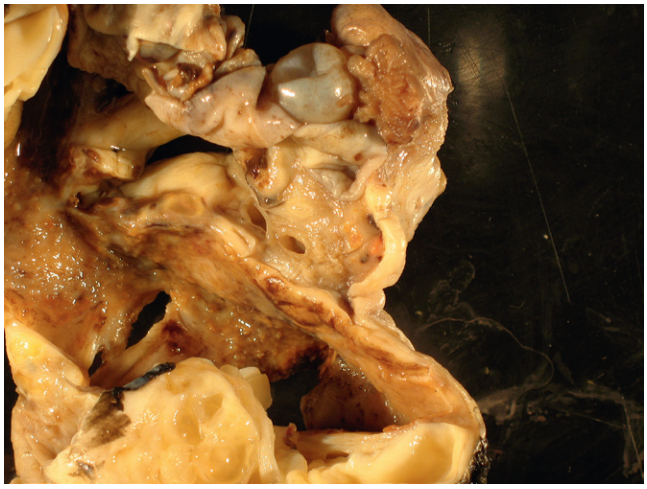

FIGURE 1

Endometrioid adenofibroma. Gross photograph showing varying-sized cystic spaces lined by minimal amounts of hemorrhagic material.

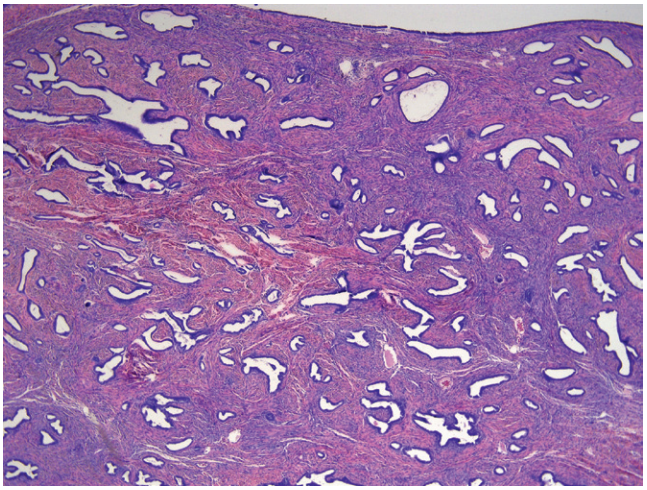

FIGURE 2

Endometrioid adenofibroma. Low-power image showing numerous irregularly shaped glands distributed evenly throughout a fibromatous stroma. Note the absence of solid epithelial growth or endometrial stroma.

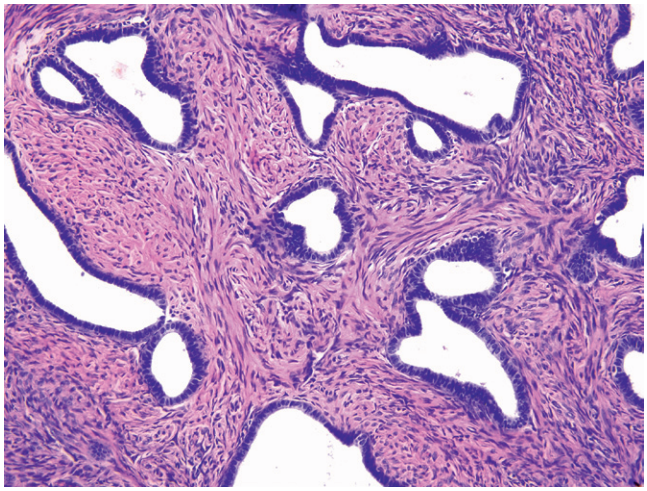

FIGURE 3

Endometrioid adenofibroma. High-power image showing the epithelial component. Note the bland columnar cell nuclei and the variably cellular stroma.

PROLIFERATIVE (BORDERLINE) ENDOMETRIOID ADENOFIBROMA

Definition—Noninvasive epithelial and stromal tumors with an atypical endometrioid epithelial component.

Clinical Features

Epidemiology

- Uncommon but not exceedingly rare; less than 200 reported cases but most pathologists will encounter at some point in their practice.
- Similar to other endometrioid tumors, patients are typically at the end of their reproductive period or postmenopausal.
- The average age at diagnosis is in the mid-50s.
- At least one fourth of cases are associated with endometriosis.

Presentation

- Ovarian mass, usually unilateral.

Prognosis and Treatment

- Excellent; recurrences are exceedingly rare when the tumor is not accompanied by a frank carcinoma.
- Two cases of potential peritoneal implants at the time of initial surgery have been reported, but autochronus endometriosis could not be excluded.
- Surgical excision is adequate therapy.

Pathology

Histology

- Gross examination is characterized by a solid and cystic mass with variable amounts of hemorrhage.
- The low-power histologic examination reveals a fibrous stroma with variable numbers of proliferative endometrioid glands scattered about.
- The epithelial cells are stratified and proliferative, with nuclear atypia that can be either mild or marked.
- The glandular architecture is variable and ranges from purely glandular (frequently with squamous morule formation), to papillary, to a combination of both.
- The glandular type of proliferation can be adenofibromatous or may consist of numerous closely packed endometrioid glands.
- The papillary growth patterns are usually villous, lack extensive branching, and project into the cystic spaces of the tumor.
- If the epithelial changes are limited to nuclear atypia, then the tumor is often referred to as a "proliferative endometrioid tumor with atypia;" if the epithelial component resembles a low-grade endometrial endometrioid carcinoma, then the tumor is often referred to as a "borderline endometrioid tumor." These distinctions have unclear clinical significance.
- By definition, stromal invasion, typified by a desmoplastic stromal response, is absent.
- In some cases there is a robust proliferation of endometrioid epithelium without intervening stroma; if this area exceeds 5 mm, some would call this microinvasion; however, recurrences have not been reported in these tumors.
- Our definition of microinvasion is limited to those tumors with one or more invasive foci, defined as irregularly shaped invasive-appearing glands with a desmoplastic stromal response, smaller than 10 mm^2.
- Tumors with a clearly invasive pattern, or those with such a degree of confluent growth that the pathologist judges it to be invasive, should be termed as such.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Low-grade endometrioid carcinoma—this diagnosis is made when there is a loss of gland integrity or confluent epithelial growth.
- Endometriosis with atypia—this is defined as epithelial atypia and may be confused (or associated) with early clear-cell carcinoma. It is not characterized by glandular expansion.

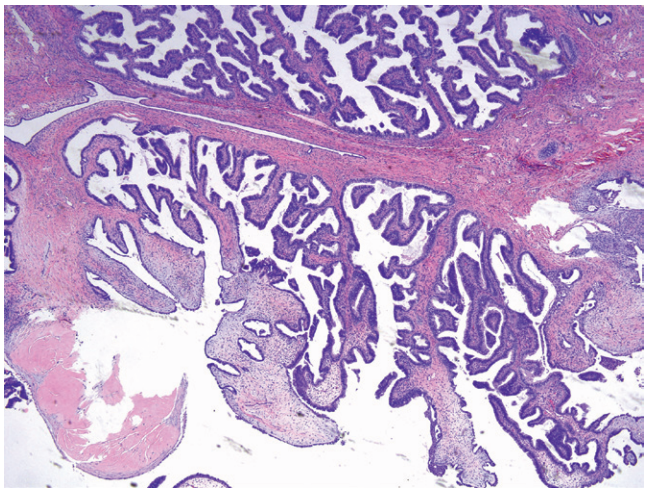

FIGURE 1

Borderline endometrioid adenofibroma. At low power note the presence of innumerable papillary growths into a cystic space.

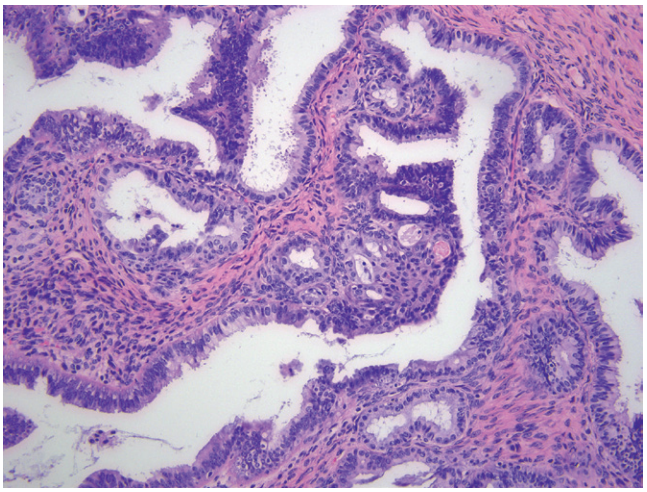

FIGURE 3

Borderline endometrioid adenofibroma. Note the focus of cribriform growth in the center of the image.

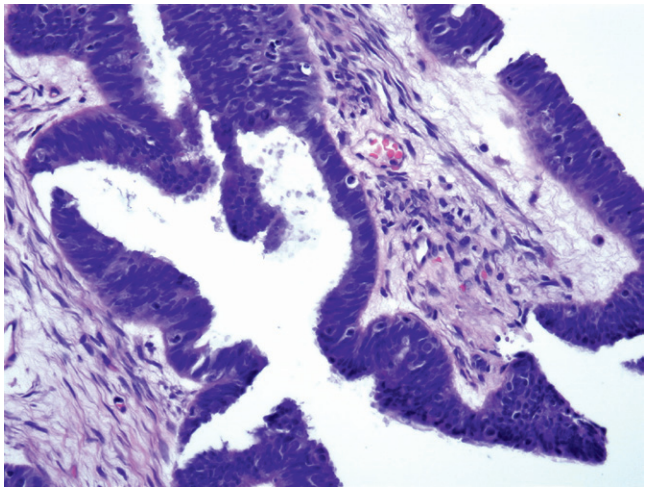

FIGURE 2

Borderline endometrioid adenofibroma. At high power note the stratified epithelium, which resembles endometrial endometrioid adenocarcinoma. There is mild nuclear atypia.

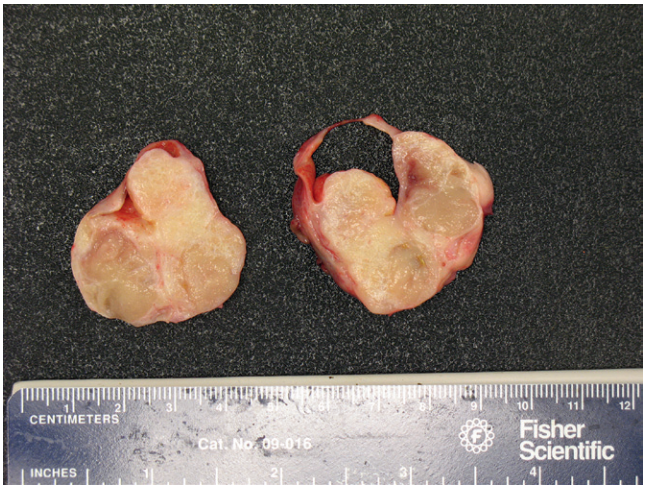

FIGURE 4

Borderline endometrioid adenofibroma with endometrioid adenocarcinoma. The borderline component is present at the top of the specimen, near the cystic structure. The nodules of carcinoma are present at the lower portion and are distinguished by their more gelatinous or fleshy appearance.

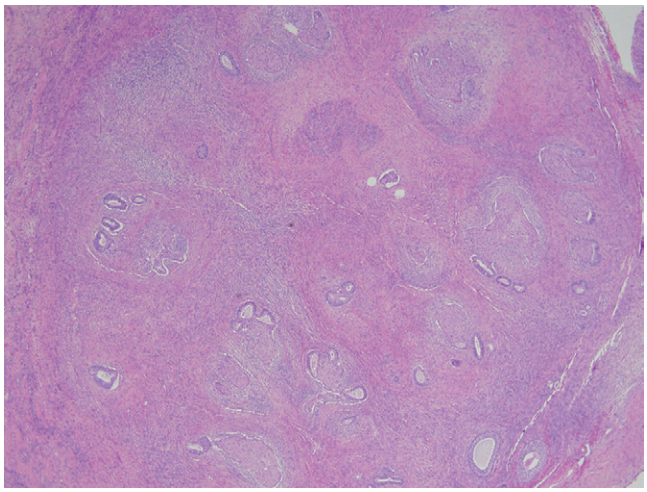

FIGURE 5

Borderline endometrioid adenofibroma. In this low-power image, note the irregular nests of epithelial proliferation scattered about the ovarian stroma.

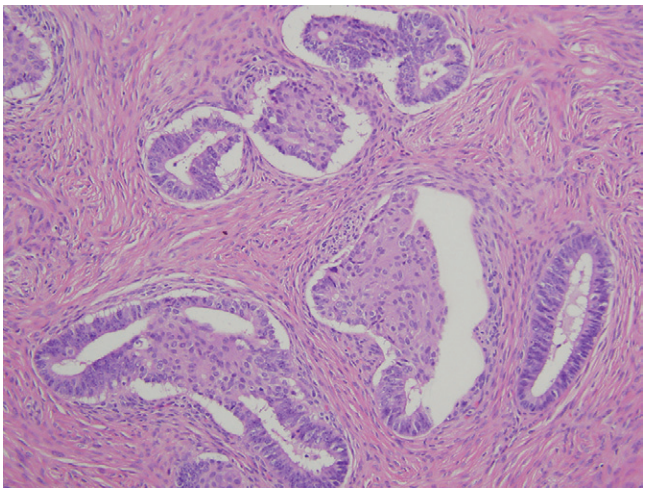

FIGURE 6

Borderline endometrioid adenofibroma. At higher power the same tumor seen in Figure 5 is composed of endometrioid glands with prominent squamous morule formation. The epithelial cells are mildly atypical and proliferative.

MÜLLERIAN MUCINOUS AND SEROMUCINOUS TUMORS OF THE OVARY

Definition—A morphologic spectrum of tumors arising in endometriosis and displaying a müllerian (rather than intestinal) phenotype.

Clinical Features

Epidemiology

- Rare, reports limited to small series.
- Associated with borderline neoplasia usually serous or mucinous.
- Most present in the fourth and fifth decades.
- Considered a derivation of endometrioid differentiation (endometriotic cysts).

Presentation

- Unilateral or bilateral.
- Parvilocular or multilocular. The appearance is often that of an endometrioid cyst with foci of excrescences.
- Frequently bilateral, likely because of the association with endometriosis.

Prognosis and Treatment

- Prognosis depends on the grade, although most müllerian mucinous tumors, including carcinomas, fare well in short-term follow-up.
- Monitoring of the contralateral ovary is necessary if fertility sparing surgery is performed, given the risk of a contralateral tumor.

Pathology

Histology

Benign and borderline tumors

- Benign tumors display an endocervical-like population.
- The low-power microscopic appearance of borderline tumors is that of broad bulbous papillae, associated with cell stratification and epithelial tufting, and similar to that of serous tumors.
- The papillae are lined by both mucinous columnar cells resembling those of the endocervix and stratified polygonal eosinophilic cells.
- Acute inflammatory cells present in the epithelial cell cytoplasm and in the extracellular mucin.
- Adjacent endometriosis or an endometriotic cyst is often seen.
- Nuclear atypia is mild; intraepithelial carcinoma and microinvasion are rare but have been reported with favorable outcome.
- Pseudoinvasion may be seen with benign-appearing mucinous cells within mucin or histiocytes secondary to rupture, a feature also seen in intestinal mucinous tumors.
- Hybrid tumors with ciliated differentiation (so-called seromucinous tumors) are an extension of this tumor type, with a similar behavior.

Malignant müllerian mucinous cystadenocarcinomas

- Very uncommon.
- Like borderline tumors, these are seen in the fourth and fifth decades.
- Most have expansile invasion, less commonly infiltrative invasion with desmoplasia.
- No recurrences were seen on short-term follow-up in one series of four women treated with chemotherapy.
- Rare reports have described squamous carcinomas arising in müllerian mucinous tumors.

Immunopathology (Including Immunohistochemistry)

- Usually not necessary. CK7 and/or PAX8 staining are helpful in establishing an ovarian origin. CK20 is usually absent or nearly so. ER and PR are typically positive.

Main Differential Diagnosis

- Borderline or low-grade malignant endometrioid tumors—the two may merge in some cases.
- Borderline serous tumors—some serous tumors can appear quite "secretory." The presence of clear-cut mucinous differentiation segregates the mucinous, or if admixed with tubal differentiation, seromucinous tumors from the pure serous borderline tumors.

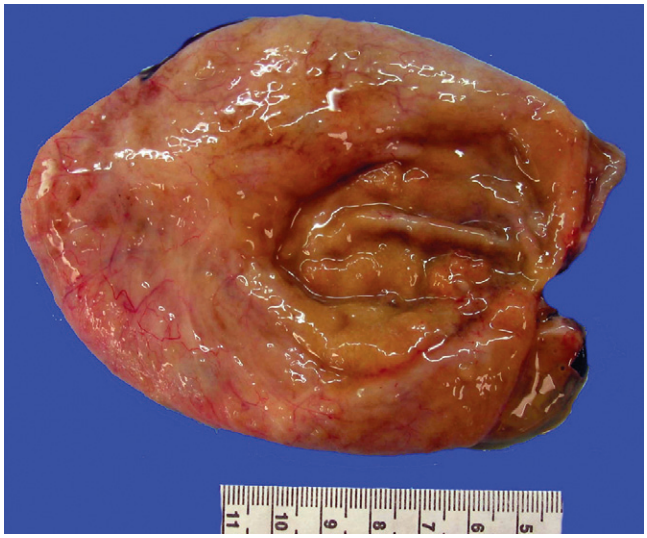

FIGURE 1

Mucinous cystic tumor, müllerian (endocervical) type in a unilocular cyst, presumably arising from an endometrioma.

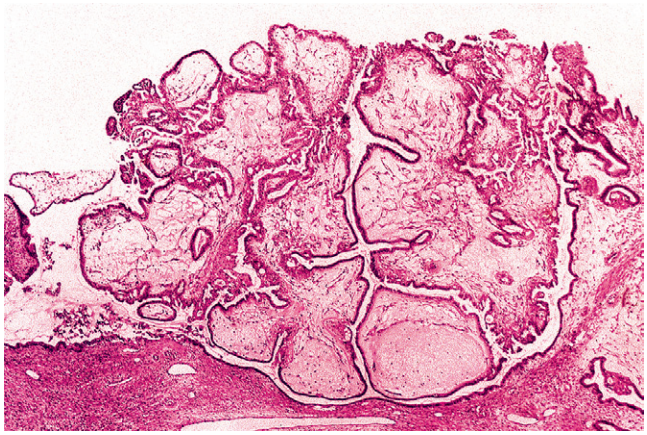

FIGURE 2

Endocervical-like mucinous borderline tumor. The low-power appearance mimics a serous borderline tumor with bulbous papillae.

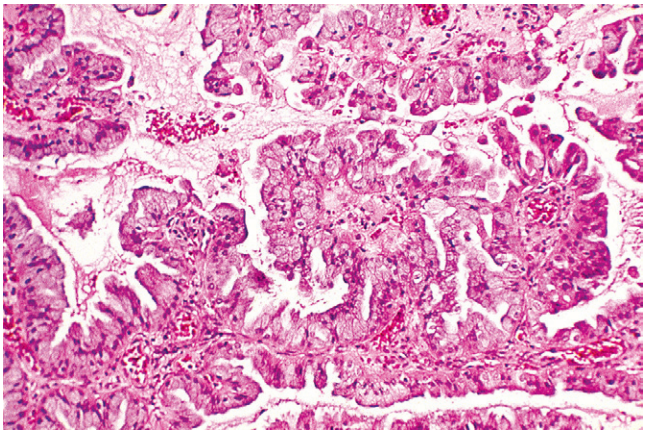

FIGURE 3

Endocervical-like mucinous borderline tumor. The papillae are lined by benign-appearing mucinous cells that resemble those of the endocervix.

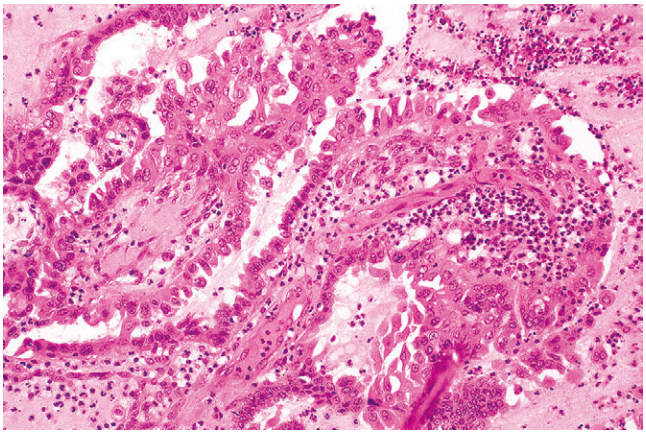

FIGURE 4

Endocervical-like mucinous borderline tumor. In this focus highly stratified eosinophilic cells line the papillae. There are numerous leukocytes in the papillae and in the mucin.

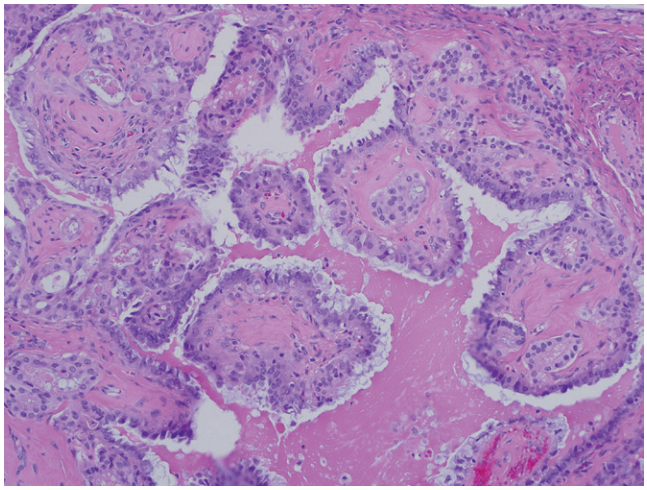

FIGURE 5

Seromucinous borderline tumor showing a mixture of phenotypes.

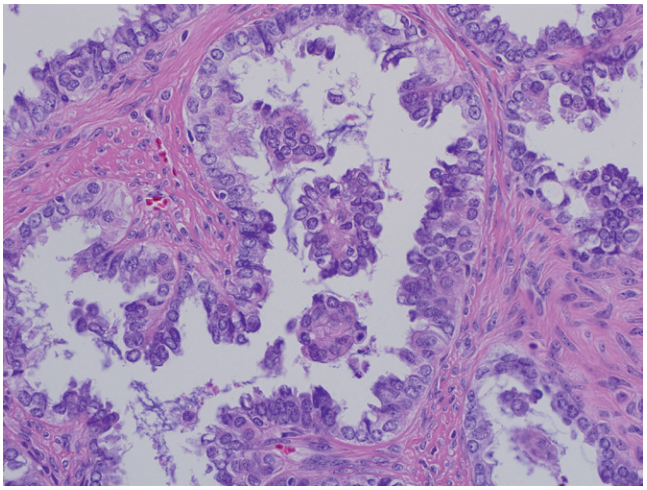

FIGURE 6

Seromucinous borderline tumor showing focal prominent ciliated differentiation.

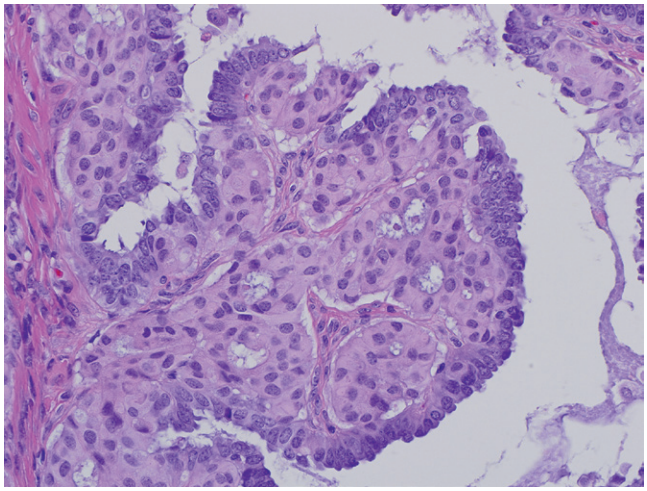

FIGURE 7

Seromucinous borderline tumor showing eosinophilic cells with mucin reminiscent of both endocervical and tubal differentiation.

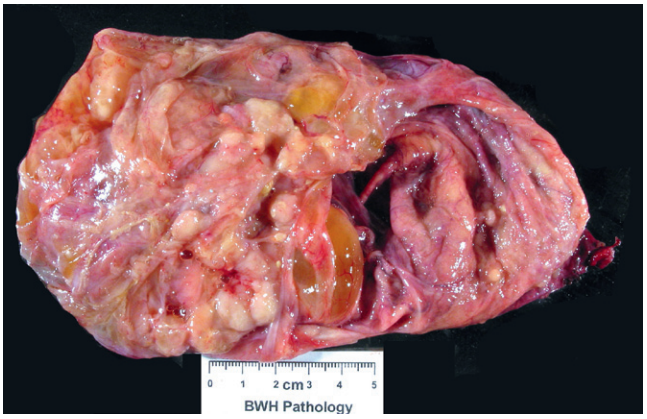

FIGURE 8

Malignant mucinous carcinoma arising in an endometrioma.

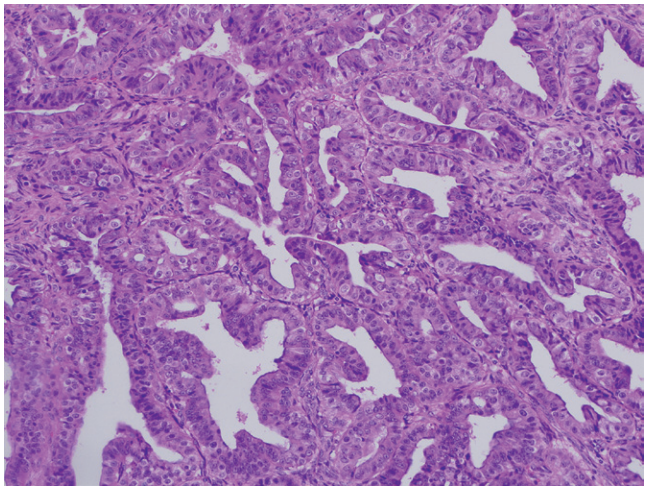

FIGURE 9

Malignant müllerian mucinous carcinoma with a resemblance to endometrioid carcinoma.

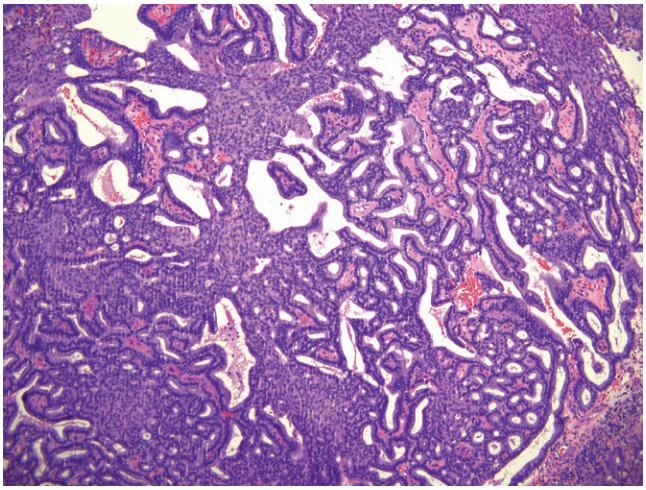

FIGURE 10

Malignant müllerian mucinous carcinoma with squamous metaplasia.

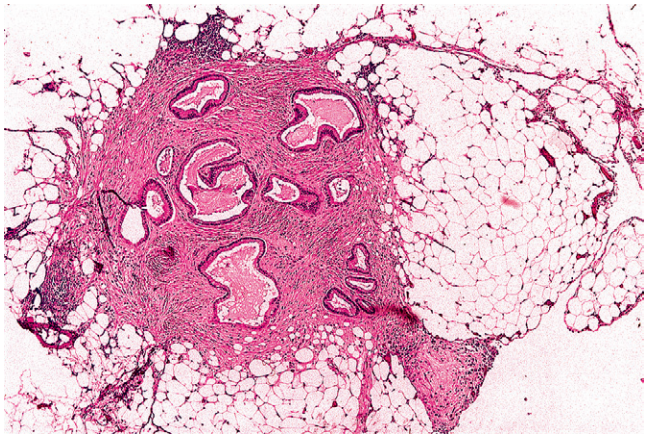

FIGURE 11

Omental implant from an endocervical-like mucinous borderline tumor. Cysts and glands are set in a desmoplastic stroma. The overall appearance is that of an invasive implant.

BENIGN BRENNER TUMOR

Definition—A benign ovarian tumor composed of cells resembling transitional epithelium of the urinary tract.

Clinical Features

Epidemiology

- Uncommon but seen periodically in practice.
- Brenner tumors may represent up to 5% of benign epithelial tumors of the ovary.
- Present in a wide range of patients, from 30 to 70 years of age.

Presentation

- Brenner tumors are most often an incidental finding in an ovary removed for another reason.
- Can rarely present as a large unilateral ovarian mass (up to 20 cm).
- Approximately one third of cases present as a component of, or adjacent to, another ovarian tumor such as a teratoma, serous cyst, or mucinous cyst.

Prognosis and Treatment

- Brenner tumors are benign and with rare exceptions not associated with recurrent or progressive disease.
- Excision is adequate and appropriate treatment.

Pathology

Histology

- On gross examination, Brenner tumors are well-demarcated, gritty white nodules that may be solid or solid and cystic.
- Low-power examination shows regularly distributed nests of epithelial cells set within a fibrous stroma.
- The stroma often contains spiculated calcifications, and plump luteinized cells may be seen.
- The epithelial cells are arranged in solid or cystic nests or islands, or occasionally a trabecular pattern.
- Most often the epithelial cells have relatively abundant pale or eosinophilic cytoplasm and characteristic elongated, oval nuclei with a groove (coffee bean nucleus).
- The nests of cells resemble transitional-type (urothelial) epithelium with small cystic central spaces.
- Occasionally the center of the cyst or island may be lined with ciliated, mucinous, or nonspecific glandular cells.
- If an associated tumor (mucinous, serous, or dermoid cyst) is present, then the two components are well demarcated from each other, although they are often abutting each other without intervening ovarian stroma.
- To be termed a mixed Brenner and mucinous tumor (for example), the two components must be clearly separate discrete areas since Brenner tumors can have mucinous epithelium.
- Epithelial atypia is lacking.

Immunopathology (Including Immunohistochemistry)

- Positive for uroplakin.
- Negative for inhibin and CK20.

Main Differential Diagnosis

- Borderline Brenner tumor—due to the transitional appearance of both lesions, although architecturally, borderline Brenner tumors are usually distinct.
- Granulosa cell tumor—due to the grooved cells, immunohistochemistry is different and the growth patterns are distinct.
- Carcinoid—salt and pepper nuclei usually distinguish this entity easily.

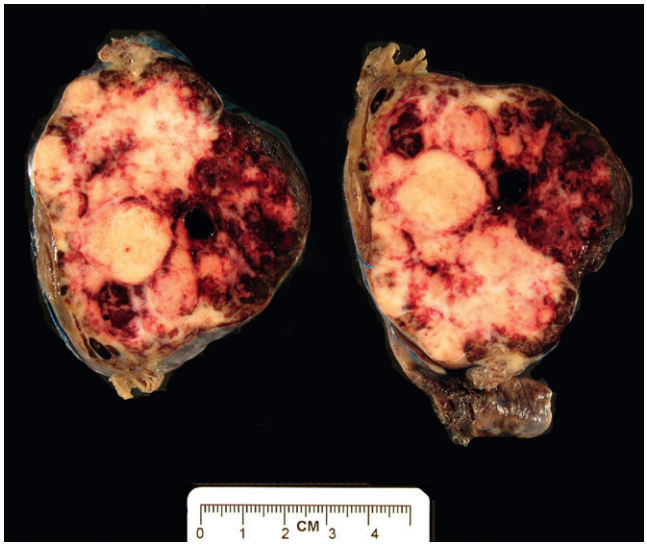

FIGURE 1

Brenner tumor. Gross photograph showing the characteristic white lesion with areas of hemorrhage. The texture is gritty. There are areas of cysts and hemorrhage.

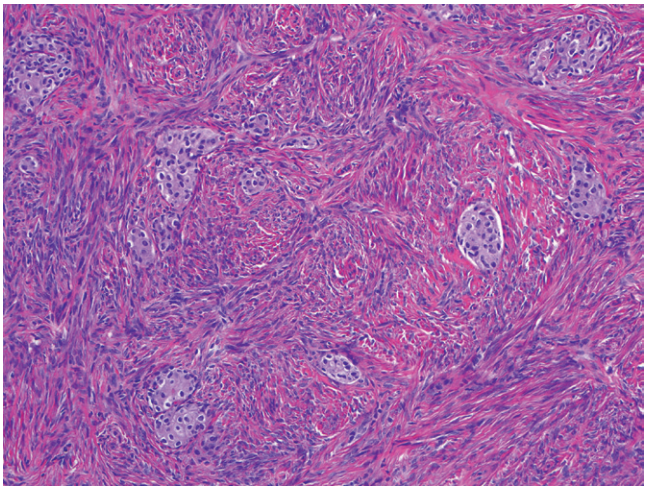

FIGURE 2

Brenner tumor. At low power a nest of transitional appearing cells is present in ovarian stroma. The nest is well circumscribed and does not appear to be invasive.

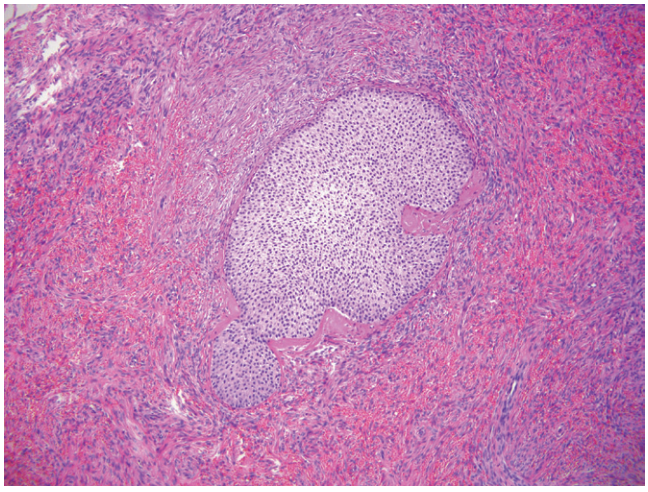

FIGURE 3

Brenner tumor. Another focus with a large nest of transitional-type cells.

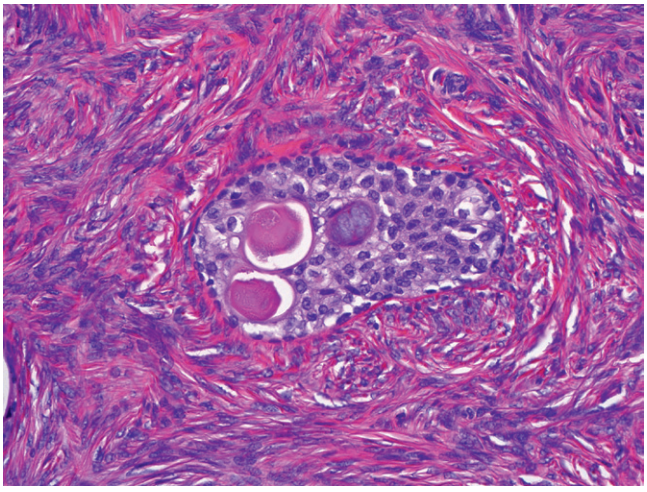

FIGURE 4

Brenner tumor. This nest contains small concentric secretions emblematic of mucinous differentiation.

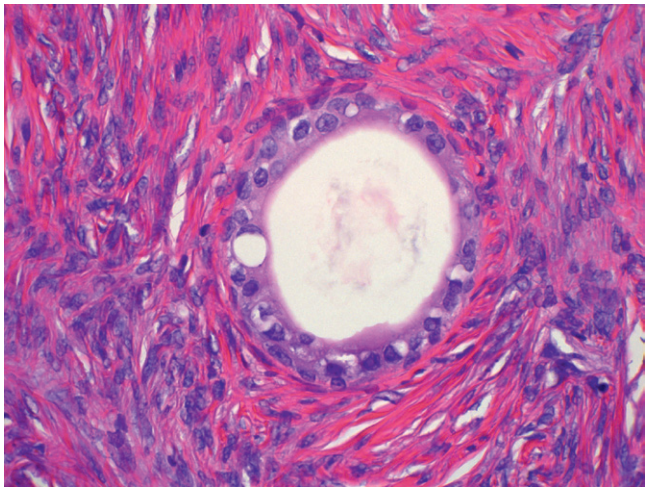

FIGURE 5

Brenner tumor. This focus appears intermediate between columnar and transitional.

MALIGNANT BRENNER TUMOR

Definition—An invasive ovarian carcinoma with a transitional growth pattern that contains areas of benign or borderline Brenner tumor.

Clinical Features

Epidemiology

- Rare.
- Can present at a range of ages, but the mean age is in the 60s.

Presentation

- Unilateral solid and cystic ovarian mass; less than 15% are bilateral.
- Calcifications may be noted on imaging of the mass.
- Over 75% of patients are stage I at the time of presentation.

Prognosis and Treatment

- Few cases have been reported.
- Most tumors are confined to the ovary at the time of diagnosis and resection.
- Often treated as any high-grade ovarian malignancy with chemotherapy and debulking.

Pathology

Histology

- Histology is characterized by the presence of an invasive carcinoma associated with a background or component of benign or borderline Brenner tumor.
- The invasive component may consist of transitional cell carcinoma (high or low grade), squamous cell carcinoma, undifferentiated carcinoma, or any combination of the three.
- The invasive area typically has some areas of glandular differentiation.
- Stromal calcification is often present in association with the invasive component.
- The cells themselves are frankly malignant, with large pleomorphic nuclei and often with a high mitotic rate.

Immunopathology (Including Immunohistochemistry)

- Positive for uroplakin, WT1, and cytokeratin 7.
- Negative for cytokeratin 20.

Main Differential Diagnosis

- Ovarian transitional cell carcinoma—these are high-grade serous carcinomas; no benign. Brenner component will be encountered.
- Metastatic/locally advanced transitional cell carcinoma of the urinary bladder.
- Borderline Brenner tumor—there is a lack of stromal infiltration and atypia.
- Endometrioid carcinoma with transitional or spindle cell differentiation—this may be the most difficult because the tumor will typically present with more bland-appearing histology, similar to Brenner tumors.

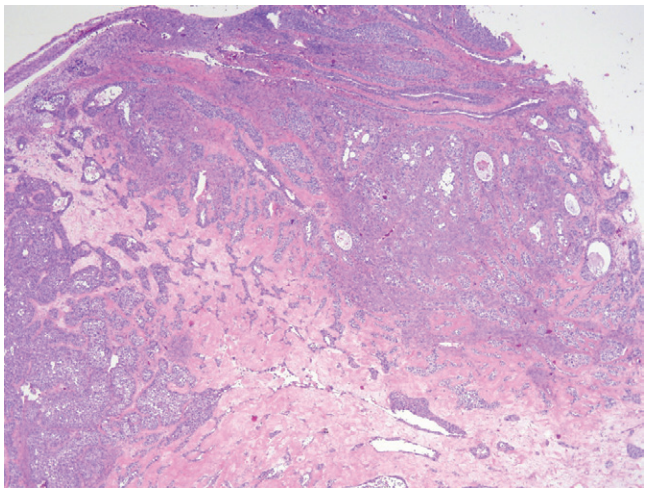

FIGURE 1

Malignant Brenner tumor. Low-power image shows a solid and focally cystic neoplasm with areas of ovarian and hyaline stroma.

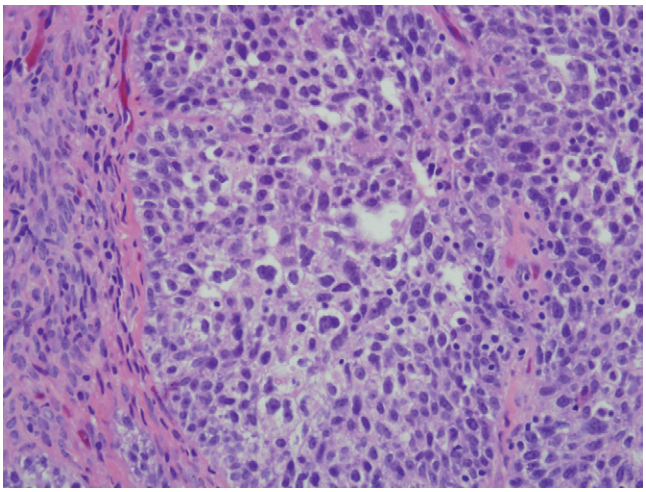

FIGURE 2

Malignant Brenner tumor. Marked atypia with pleomorphic hyperchromatic nuclei.

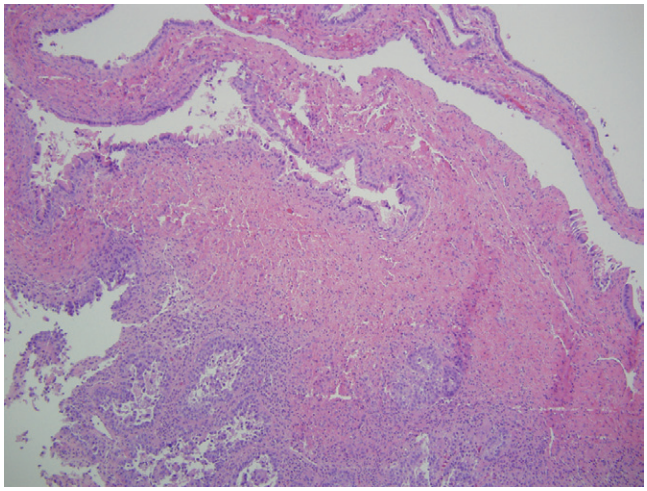

FIGURE 3

Malignant Brenner tumor. Foci of invasive carcinoma *(lower half of the image)* adjacent to a focus of benign Brenner tumor with mucinous features *(top half of the image)*.

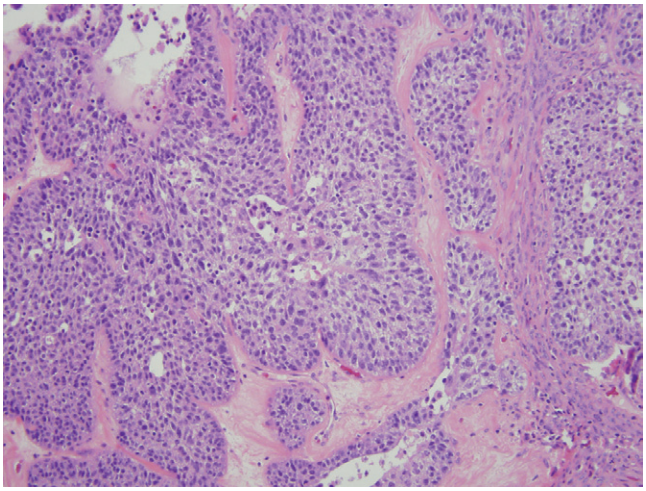

FIGURE 4

Malignant Brenner tumor. Invasive appearing nests of carcinoma with severe atypia.

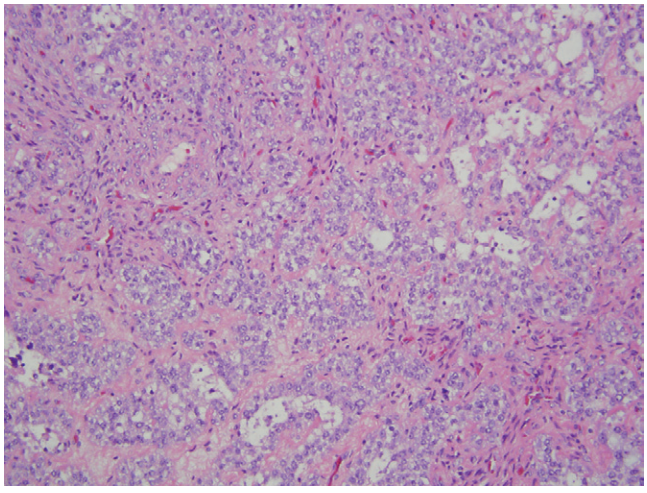

FIGURE 5

Malignant Brenner tumor. Frankly invasive nests of epithelial cells, which have a vaguely transitional morphology.

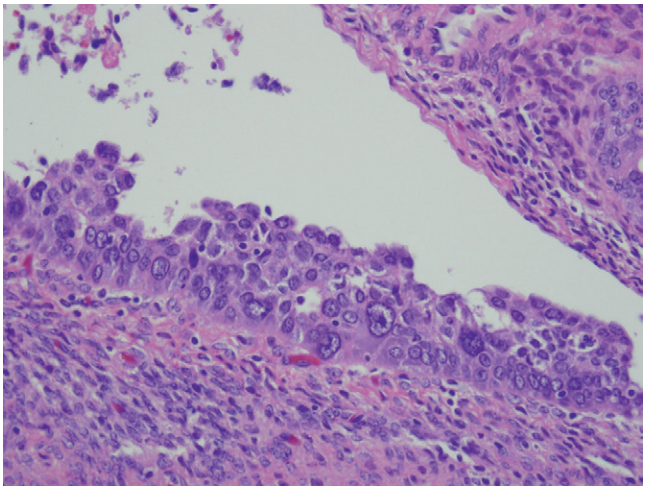

FIGURE 6

Malignant Brenner tumor. A flat focus of markedly atypical cells.

CLEAR-CELL CARCINOMA

Definition—A malignant, endometriosis-associated epithelial tumor.

Clinical Features

Epidemiology

- Uncommon.
- Distinct gene expression profile.
- Present in postmenopausal women with a mean age in the 50s.

Presentation

- Unilateral ovarian mass in more than 95% of patients.
- Rare cases are associated with a paraneoplastic syndrome consisting of hypercalcemia. This is the most common ovarian cancer to present with thromboembolic disease.
- Frequently arise in the setting of endometriosis and/or an adenofibroma.

Prognosis and Treatment

- At least 40% of patients present with stage I disease (confined to the ovary).
- Data conflict on whether clear-cell carcinoma has a worse prognosis than other ovarian epithelial-stromal tumors with early-stage tumors. However, with more advanced disease, clear-cell cancers are very resistant to conventional chemotherapy. Mammalian target of rapamycin (MTOR) inhibitors are being evaluated as treatment for these tumors.
- In some studies, tumors contained within a cyst have the better prognosis than those associated with adenofibromatous masses.

Pathology

Histology

- On gross examination these tumors are often both cystic and solid; the solid component is soft and tan/brown.
- In early-stage tumors, endometriosis can often be identified nearby.
- On microscopic examination the characteristic feature of this tumor is the abundant clear cytoplasm.
- The cells may be growing in sheets, arranged in a tubuloglandular pattern, in papillae, or as a mixture of multiple patterns.
- Cells are not pseudostratified and are usually only one to two cell layers thick in any given area.
- The tumor cells have abundant cytoplasm, which is most often clear (due to glycogen accumulation) but may be eosinophilic or even granular.
- The cells often have a "hobnail" appearance, most evident when they are lining cystic spaces or the surface of papillae.
- The nuclei may be only mildly atypical or may exhibit marked pleomorphism.
- The papillary cores are characteristically hyalinized.
- In rare cases mucin-producing cells can be seen, and sometimes lymphocytes and plasma cells are prominent.

Immunopathology (Including Immunohistochemistry)

- Broad-spectrum keratins and cytokeratin 7 are positive.
- ER, PR, and Her2-neu are variably present.
- WT1 and p53 are usually negative or patchy.
- HINF1-β is a new marker that is relatively sensitive for ovarian clear-cell carcinoma. Napsin A and AMACR are less sensitive but more specific.

Main Differential Diagnosis

- Serous carcinoma—strongly p53 positive.
- Endometrioid carcinoma with clear-cell change—this differential is more commonly encountered in the uterus. Look for classic features of clear-cell carcinoma, including staining with Napsin A and AMACR.
- Dysgerminoma—different age group, lack of glandular architecture, positive for OCT3/4.
- Metastatic renal cell carcinoma—consider if the tumor is bilateral. May be CD10 positive, CK7 negative.

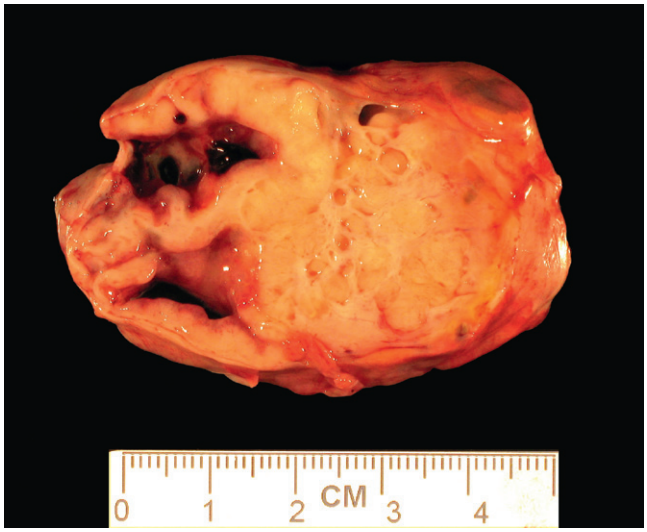

FIGURE 1

Gross image of ovarian clear-cell carcinoma. A tan to yellow, soft, predominantly solid but focally cystic mass replacing the ovary.

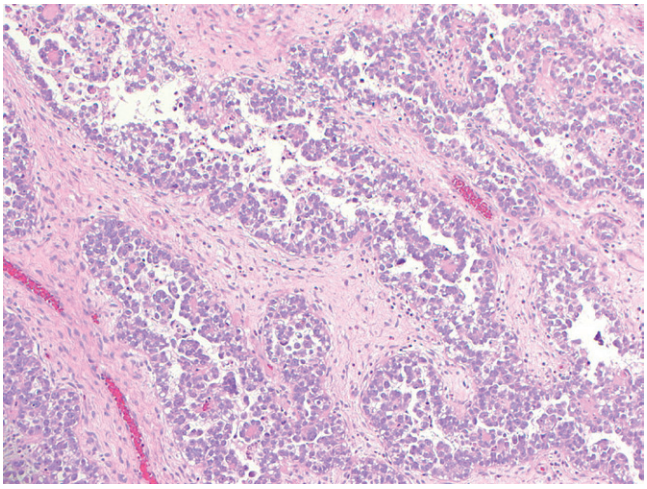

FIGURE 2

Ovarian clear-cell carcinoma. At low power the papillary growth pattern can be seen. The presence of a thin (one to two cell) layer of hobnailed cells is apparent.

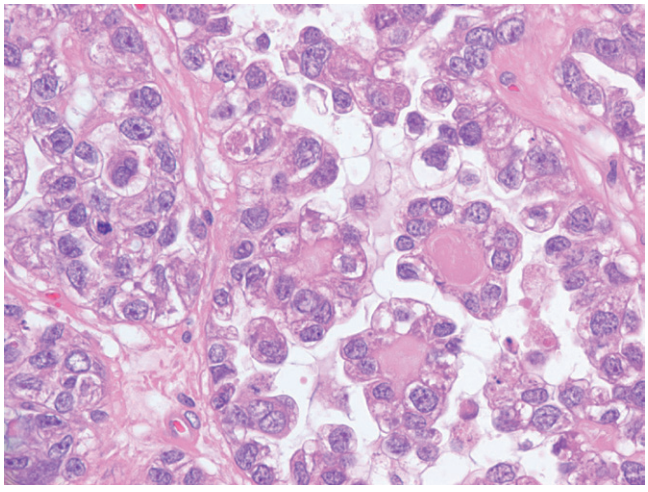

FIGURE 3

Ovarian clear-cell carcinoma. At high power, hyalinized stromal cores are apparent in the small papillae. Nuclear atypia is present in this example. Hobnailed cells are present.

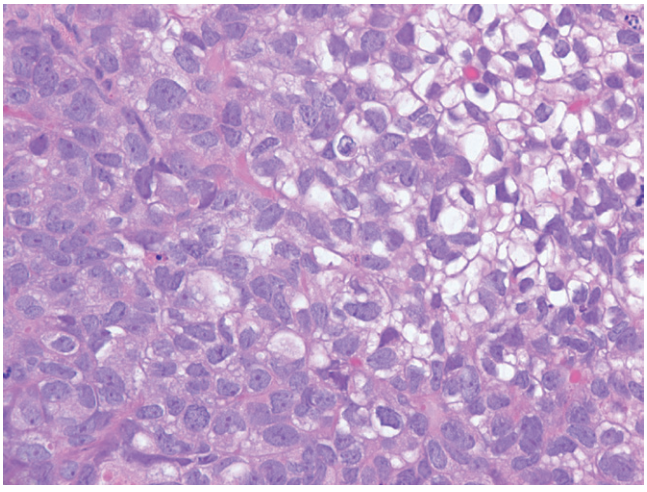

FIGURE 4

Ovarian clear-cell carcinoma. In this high-power example, solid growth is present. The characteristic cells with clear cytoplasm are present in the upper right, but tumor cells with more eosinophilic cytoplasm are noted in the left side of the image.

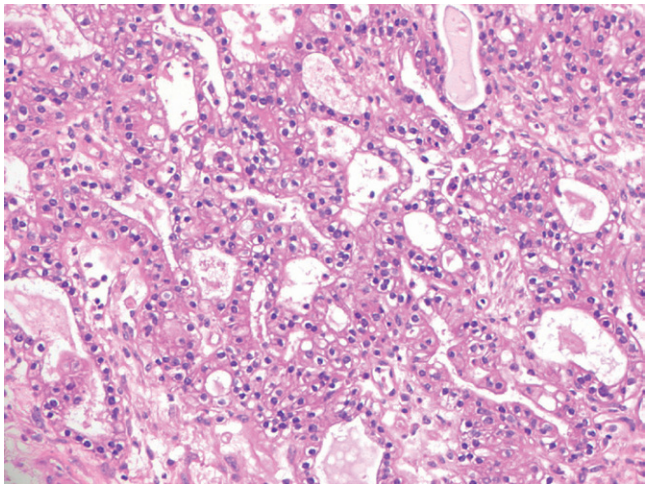

FIGURE 5

Ovarian clear-cell carcinoma. In this image a more tubular growth pattern is present. Hobnailing of the cells is not prominent, and the nuclei are small and exhibit minimal atypia.

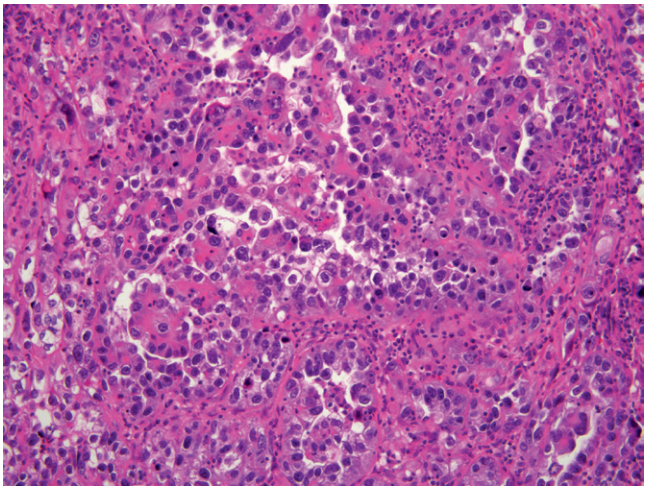

FIGURE 6

Ovarian clear-cell carcinoma. A papillary growth pattern is seen. Tumor cells have variably clear to eosinophilic cytoplasm.

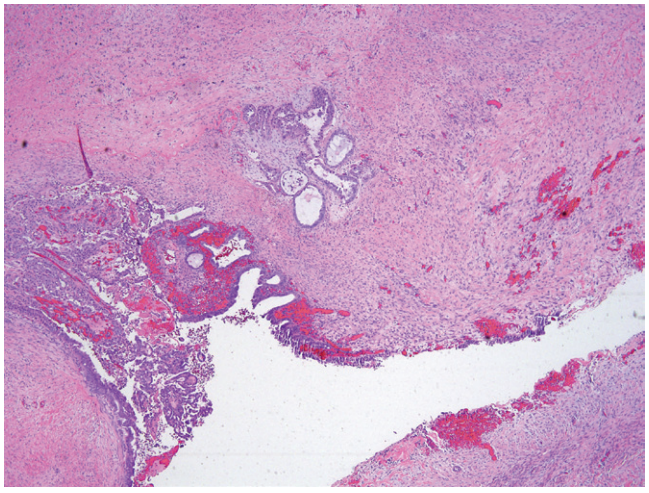

FIGURE 7

Ovarian clear-cell carcinoma arising in endometriosis.

OVARIAN ADENOCARCINOMA WITH YOLK SAC DIFFERENTIATION

Brooke E. Howitt, MD

PITFALL

Definition—A rare tumor variant with classic carcinoma and yolk sac differentiation.

Clinical Features

Epidemiology

- Extremely rare, limited to isolated reports or small case series.
- Broad age range but most are postmenopausal, averaging in the early 50s.

Presentation

- The majority present with an abdominal mass at high stage (III or greater).
- Alpha-fetoprotein may be elevated.
- Large tumor mass, averaging 17 cm in one report.

Prognosis and Treatment

- Managed with standard chemotherapy with generally poor results.
- Behaves as any poorly differentiated epithelial tumor; most survive less than 2 years. Regimens targeting germ cell tumors (BEP) are often too toxic for elderly women with these tumors.
- Reported longer-term survival seen only in patients with stage IA disease.
- Prognosis parallels other tumors with germ cell differentiation occurring in older women.

Pathology

Histology

- Non–germ-cell component can include endometrioid or clear-cell carcinoma and carcinosarcoma.
- Coexisting benign endometrioid lesions reported in some, including the contralateral ovary.
- Admixture of germ cell and epithelial elements, although the two are distinct from one another.

Immunopathology (Including Immunohistochemistry)

- Strong AFP and SAL4 immunopositivity in the yolk sac tumor (YST) component.
- Adenocarcinoma is positive for ER/PR (if endometrioid).

Main Differential Diagnosis

- YST with endometrioid differentiation—younger age, not associated with an endometrioid precursor, positive for YST markers, responds to appropriate chemotherapy.

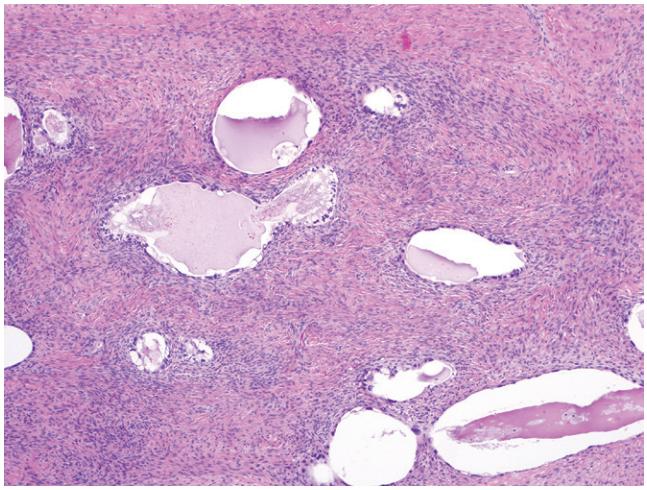

FIGURE 1

Borderline clear-cell adenofibroma in a case of mixed clear-cell carcinoma and YST of the ovary.

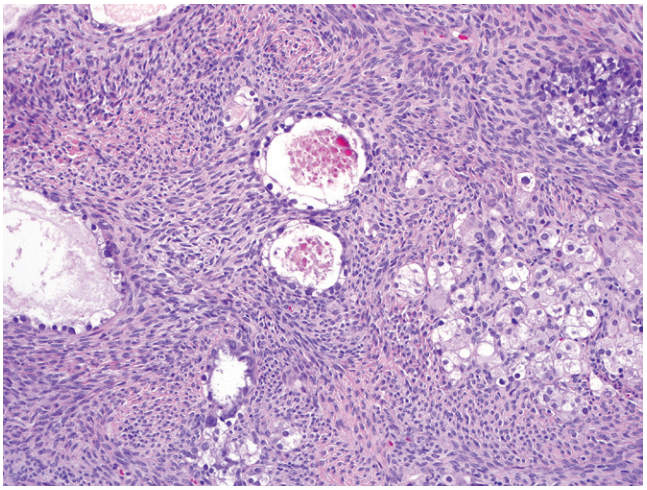

FIGURE 2

Junction of the clear-cell adenofibroma with frank clear-cell carcinoma on the right.

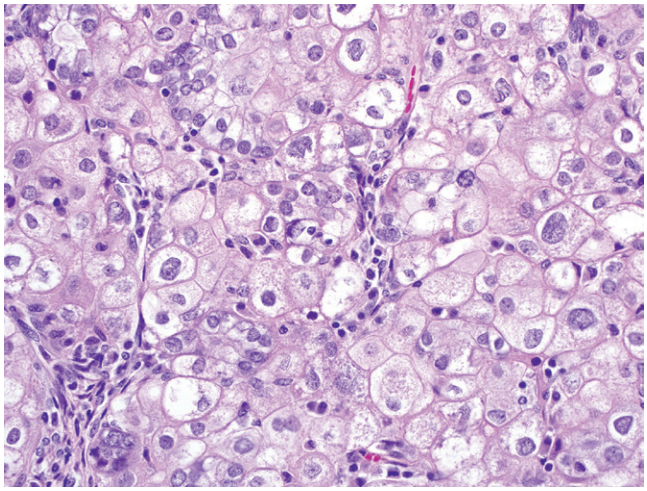

FIGURE 3

Solid growth of classic clear-cell carcinoma.

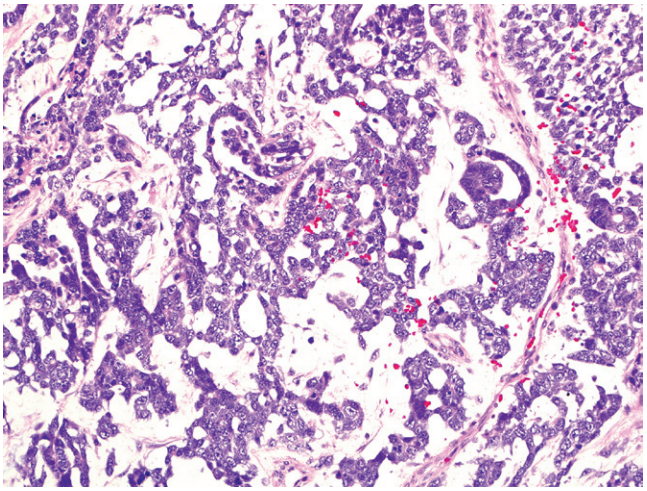

FIGURE 4

Medium magnification of the YST component with a complex but somewhat "regularly irregular" alveolar-glandular pattern.

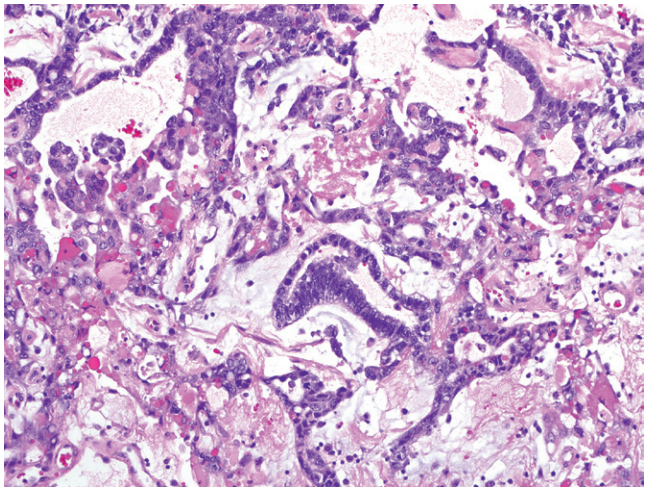

FIGURE 5

Higher magnification of the YST component with foci of glandlike differentiation. Note the numerous eosinophilic hyaline droplets.

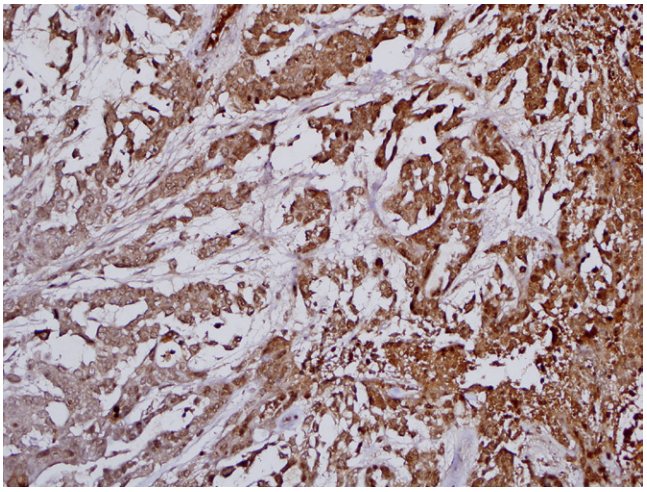

FIGURE 6

The YST component is strongly AFP positive.

BORDERLINE CLEAR-CELL ADENOFIBROMA

Definition—An early form of clear-cell neoplasia with malignant cytology and the absence of invasion.

Clinical Features

Epidemiology

- Clear-cell tumors of this type typically present as adenofibromas that can arise *de novo* or from within endometriotic cysts. Uncommon tumors comprising less than 1% of epithelial tumors.

Presentation

- Usually as a large, unilateral multicystic mass. The cysts can give a honeycomb appearance within a fibrous stroma.

Prognosis and Treatment

- Prognosis is excellent in the absence of frank stromal invasion. The significance of microinvasion is unclear, but there is no evidence at present to suggest more than a minimal risk of recurrence.

Pathology

Histology

- A cardinal feature is a low-power appearance of multiple, round, variably sized cysts within a fibrous stroma in a honeycomb pattern. The low-power image is often unimpressive because the cells lining the cysts are flattened.
- At higher magnification, enlarged, hyperchromatic nuclei, often with prominent nucleoli, should be visible to justify the diagnosis of a borderline clear-cell tumor.
- Clusters of smaller atypical glands with confluent architecture justify the diagnosis of microinvasion. This term is applied to invasive focus of less than 10 mm^2.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Clear-cell adenofibroma—this is a subjective interpretation inasmuch as it will be based on whether there is sufficient atypia to justify a diagnosis of borderline tumor. Many feel that pure benign clear-cell adenofibromas do not really exist.
- Multiloculated simple or mesothelial cyst—this misclassification is a possibility. PAX8 staining should be sufficient to confirm a clear-cell tumor.

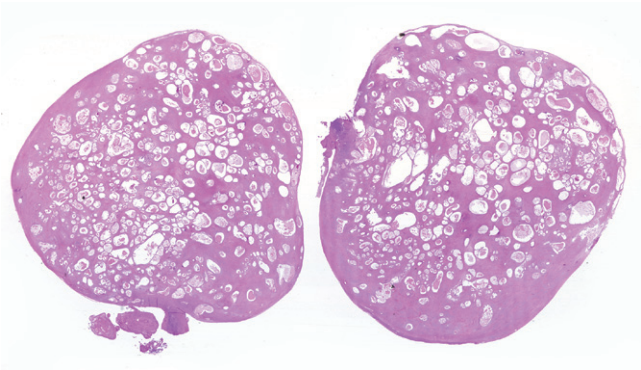

FIGURE 1

Low magnification of a borderline clear-cell adenofibroma. Note the honeycomb distribution of epithelial-lined cysts.

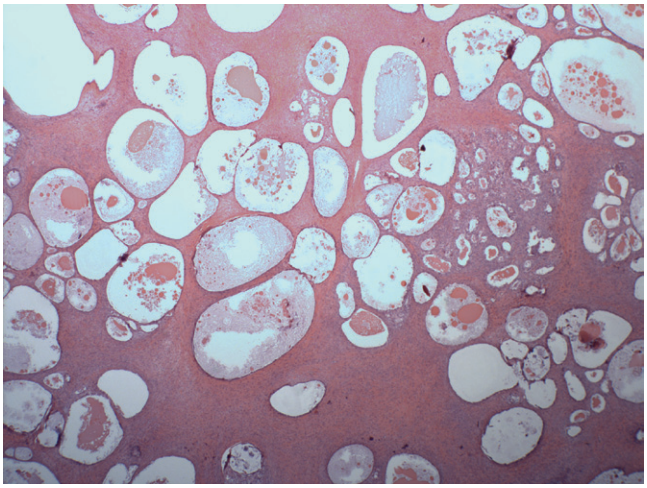

FIGURE 2

Borderline clear-cell adenofibroma. Note the focus of microinvasion at center right.

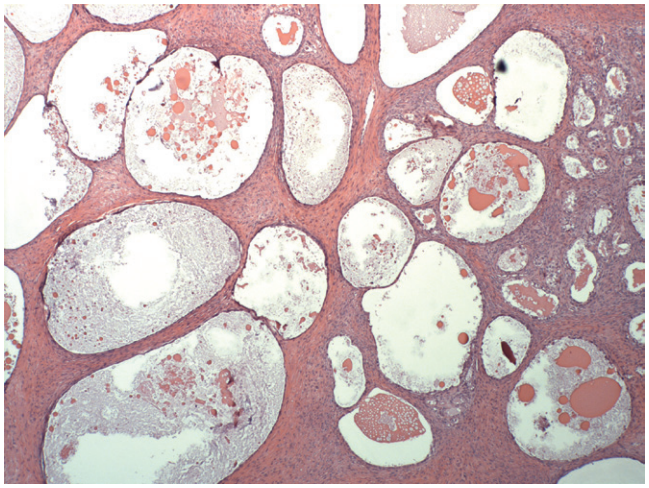

FIGURE 3

Borderline clear-cell adenofibroma. The focus of microinvasion is on the right.

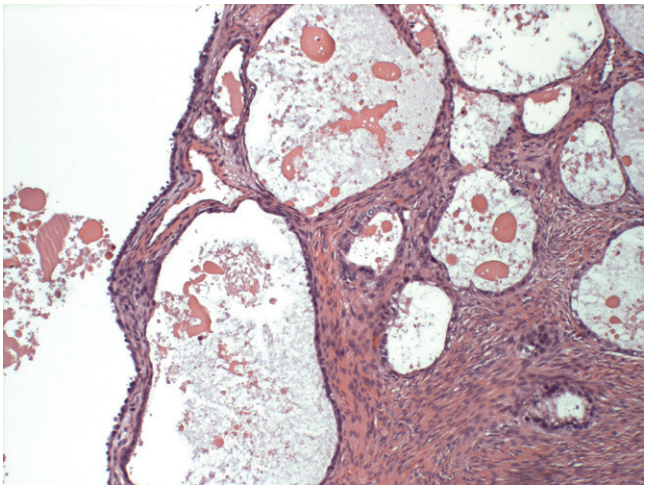

FIGURE 4

Borderline clear-cell adenofibroma. Note the nuclear enlargement in the lining cells.

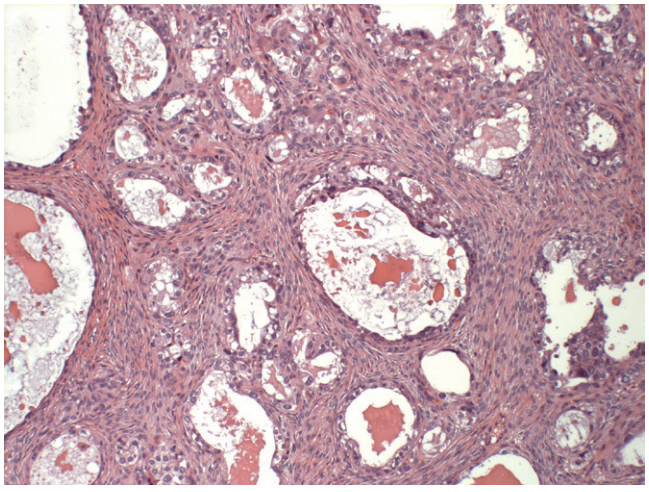

FIGURE 5

Borderline clear-cell adenofibroma. Higher magnification of the focus of microinvasion.

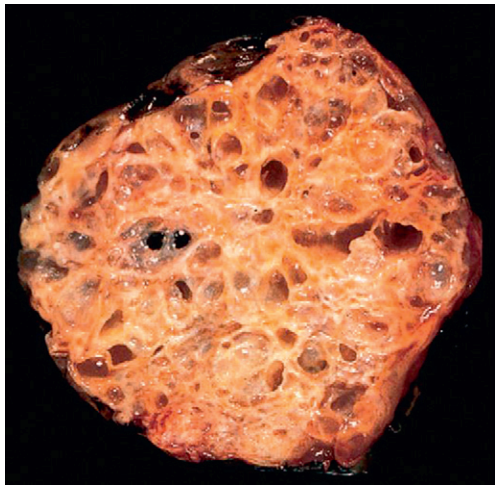

FIGURE 6

Classic honeycomb appearance of a multicystic borderline clear-cell adenofibroma.

METASTATIC CARCINOMA TO THE OVARY

Definition—Ovarian spread from remote nongynecologic epithelial neoplasms.

Clinical Features

Epidemiology

- Sixty to eighty percent of metastatic tumors are non-müllerian, including stomach (6% to 14%); colon (7% to 12%); breast (9% to 32%); and rarely lung, biliary duct, ileum, and other sites (1% to 2% each).

Presentation

Tumors typically present as pelvic masses with the following characteristics being helpful but not absolute indicators of metastatic disease.

- Small, bilateral and/or multinodular mucinous tumors suggest a metastasis.
- Homogeneous expansion of the ovarian parenchyma without cyst formation is typical of signet-ring cell tumors, breast carcinomas, and lymphomas.
- Large tumors with hemorrhage and necrosis are typical of colonic primaries.

Prognosis and Treatment

- Depends entirely on the nature of the tumor; generally poor.

Pathology

Histology

- Look for multinodularity on low magnification.
- Multiple histologic patterns including cystic glands and infiltrative tumor cells.
- Surface involvement when present in a bilateral mucin-producing tumor strongly suggests a metastatic tumor.
- Diffuse infiltration of the ovary by small tubular glands is also a departure from most of the normal epithelial patterns seen in primary ovarian tumors. Vascular space involvement is also suggestive of a metastasis.

Immunopathology (Including Immunohistochemistry)

- Immunohistochemistry may be helpful in identifying the primary site; however, there is overlap in gastrointestinal (GI), pancreatic, and ovarian tumors that may lead to confusion. The absence of SMAD4 is particularly useful to rule in a metastatic pancreatic carcinoma but is not always positive.
- Ovarian tumors are typically CK7 positive and CK20 negative, whereas colonic tumors are CK20 positive and CK7 negative.
- Appendiceal tumors may show variable levels of CK7 and CK20 expression and can be uninformative in a large number of cases.
- CDX2 staining may be patchy in ovarian and appendiceal tumors as opposed to strong staining seen in most colon tumors.

Main Differential Diagnosis

All of the following may be difficult to distinguish from primary mucinous carcinomas:

- Pancreatic mucinous tumors—can be well or poorly differentiated. SMAD4 is helpful if negative.
- Appendiceal mucinous tumors—see content on pseudomyxoma.
- Mucinous tumors from the biliary tree—can be positive for both CK7 and CK20.

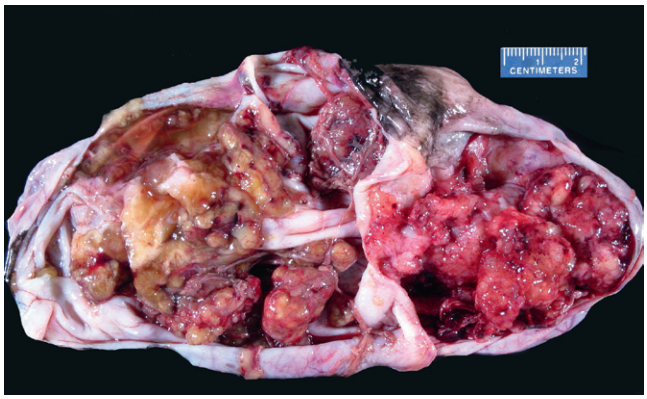

FIGURE 1

Metastatic colonic carcinoma, seen here as a multicystic mass with necrosis.

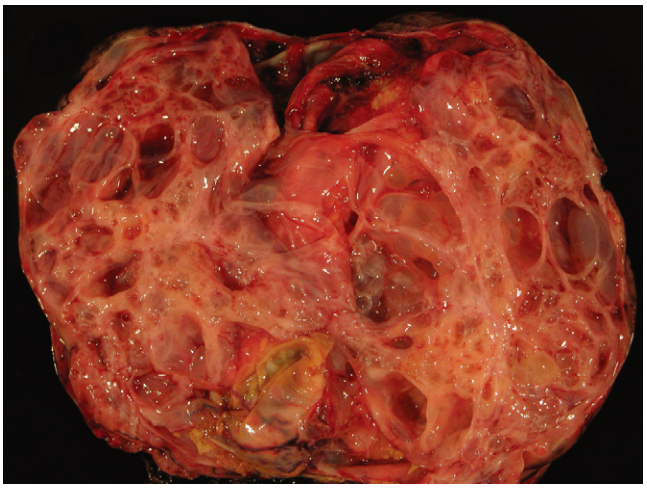

FIGURE 2

Metastatic biliary carcinoma. Note the resemblance to a low-grade mucinous tumor.

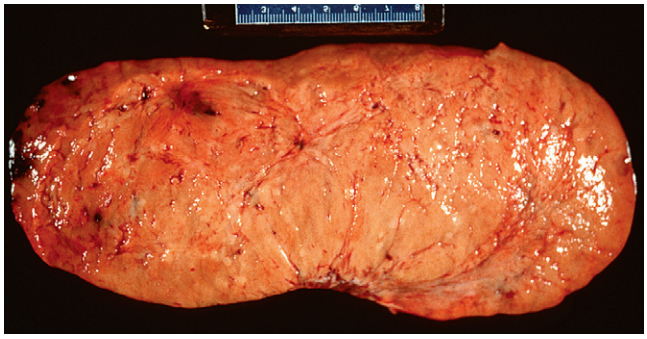

FIGURE 3

Metastatic gastric carcinoma. The ovary is diffusely expanded with a glistening surface.

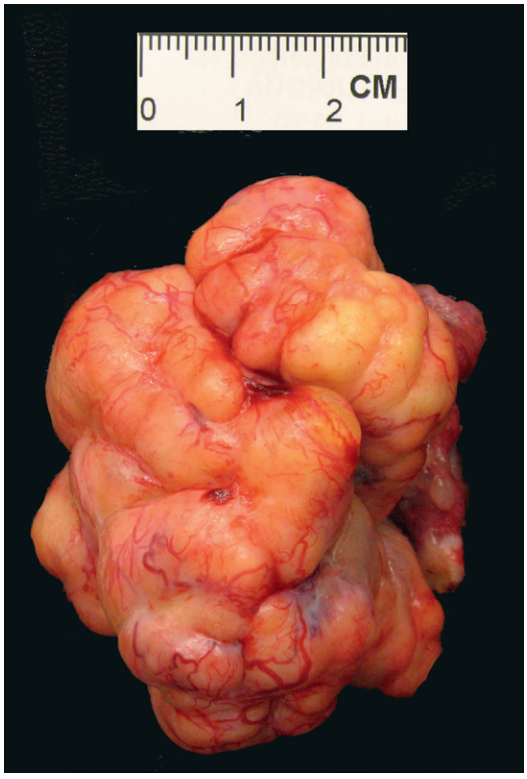

FIGURE 4

Metastatic breast carcinoma, producing a lobulated and expanded ovary.

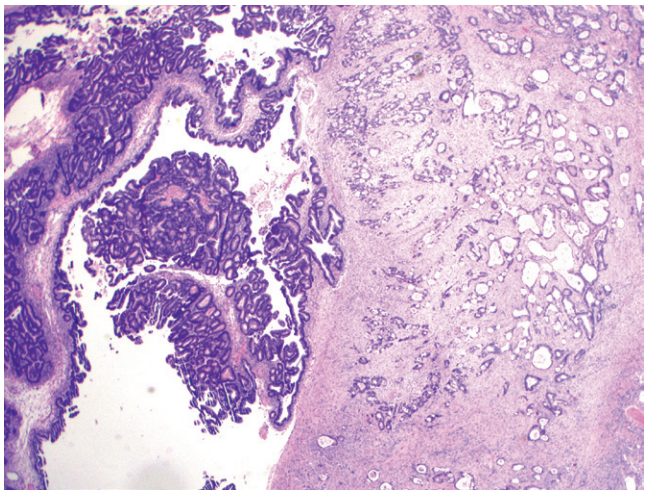

FIGURE 5

Metastatic colon cancer. Note the multiple patterns, glandular on the left and infiltrative on the right.

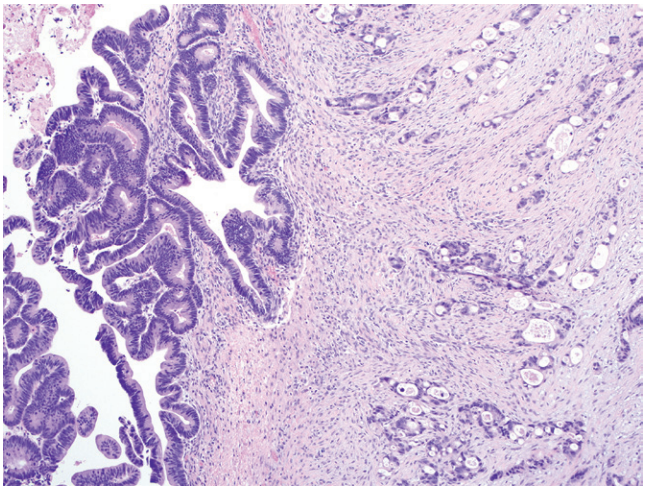

FIGURE 6

Metastatic colon cancer. Note the multiple patterns, glandular on the left and infiltrative on the right.

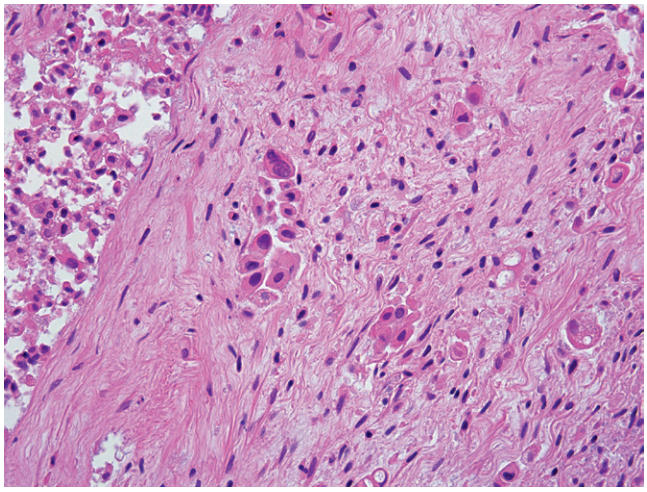

FIGURE 7

Metastatic biliary carcinoma. A typical metastatic pattern with small gland clusters.

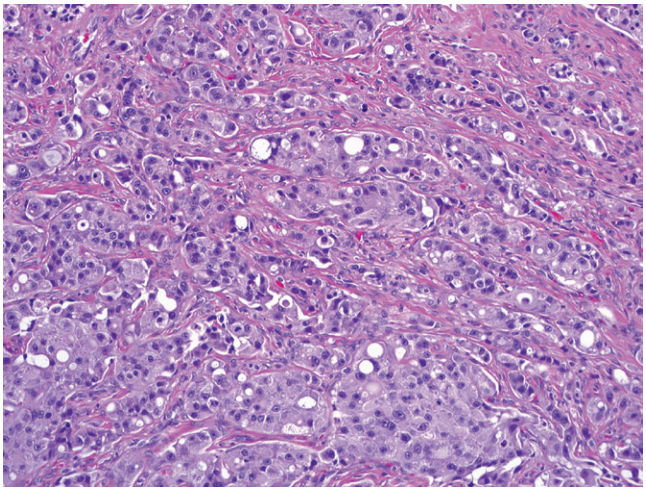

FIGURE 8

Metastatic breast carcinoma.

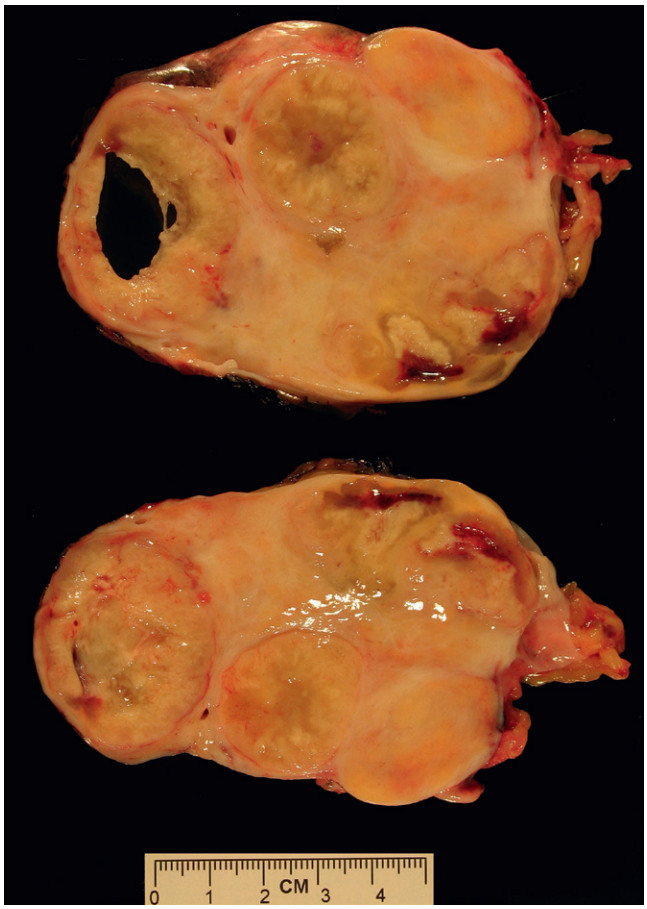

FIGURE 9

Metastatic lung carcinoma to the ovary. This can present as an occult metastasis and occur with no prior history in some cases.

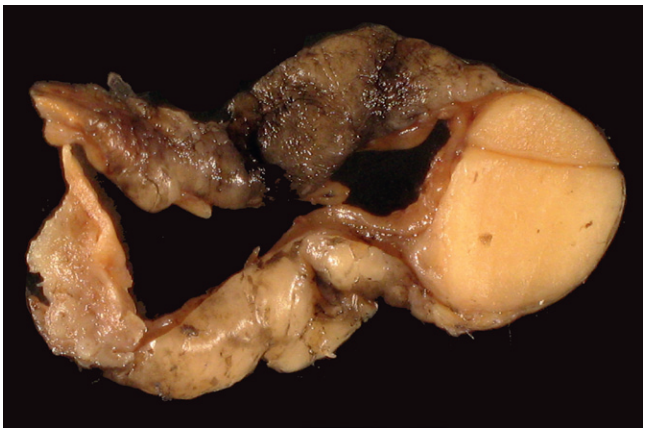

FIGURE 10

A rare example of metastatic medullary carcinoma of the thyroid to the ovary.

PSEUDOMYXOMA PERITONEI

Definition—A clinical term for increased mucin present within the abdominal cavity, typically associated with a low-grade mucinous tumor of the appendix or gastrointestinal tract.

Clinical Features

Epidemiology

- Pseudomyxoma is frequently associated with appendiceal neoplasms; however, occasional cases occur in the absence of a detectable appendiceal tumor.
- Occasionally a large bowel, pancreatic, or coexisting ovarian mass may be present.

Presentation

- Patients with pseudomyxoma typically present with increased abdominal girth; however, this is not a universal finding.

Prognosis and Treatment

- The prognosis is guarded. In patients with pseudomyxoma and a tumor of either appendiceal or ovarian origin the clinical course is protracted and may result in death.
- The higher the level of tumor burden and the higher the stage are associated with an adverse outcome.
- The currently recommended treatment is surgical excision of the tumor and drainage of the mucin with close clinical follow-up.

Pathology

Histology

- The mucin itself is comprised of acellular to highly cellular mucin.
- Two general histologic groups have been described by Ronnett et al including "adenomucinosis" in which the glandular cells appear benign and "mucinous adenocarcinoma" in which the glandular cells appear malignant. A hybrid of the two has also been described with an outcome similar to the malignant form. However, adenomucinosis may also recur and prove fatal, albeit over a more protracted course.
- The primary tumor is typically appendiceal and may show distension of the appendix with mucin.
- Ovarian involvement may be unilateral or bilateral with cyst formation and pseudomyxoma ovarii.

Immunopathology (Including Immunohistochemistry)

- Immunohistochemistry with CK7, CK20, and CDX2 may be helpful in identifying the primary site; however, there is overlap in gastrointestinal (GI), pancreatic, and ovarian tumors that may lead to confusion.
- Appendiceal tumors may show variable levels of CK7 and CK20 expression and can be uninformative in a large number of cases.
- CDX2 staining may be patchy in ovarian and appendiceal tumors as opposed to strong staining seen in most colon tumors.

Main Differential Diagnosis

All of the following may be associated with pseudomyxoma peritonei and therefore should be ruled out:

- Pancreatic mucinous tumors
- Appendiceal mucinous tumors
- Ovarian mucinous tumors
- Tubular gut mucinous tumors

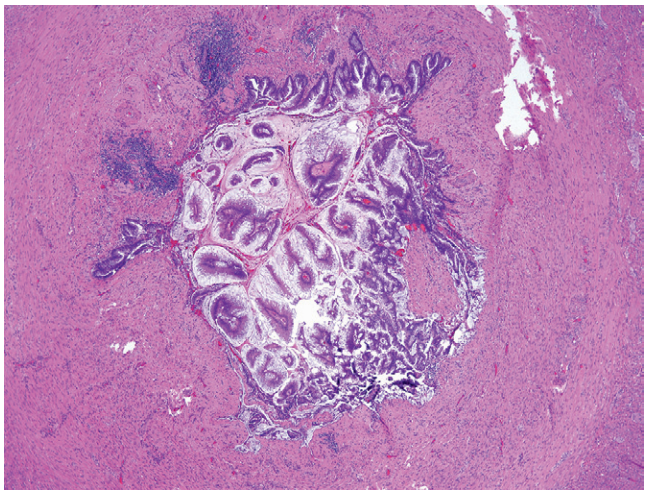

FIGURE 1

Pseudomyxoma peritonei. An appendix with luminal obliteration by a low-grade appendiceal mucinous neoplasm.

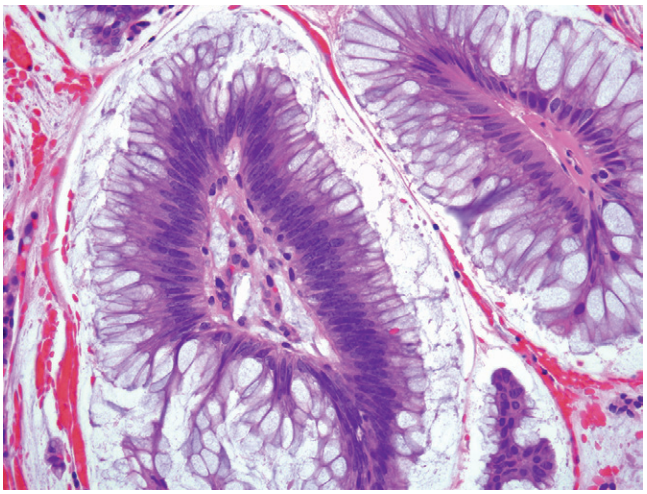

FIGURE 2

Pseudomyxoma peritonei. Low-grade appendiceal mucinous neoplasm with bland cytology.

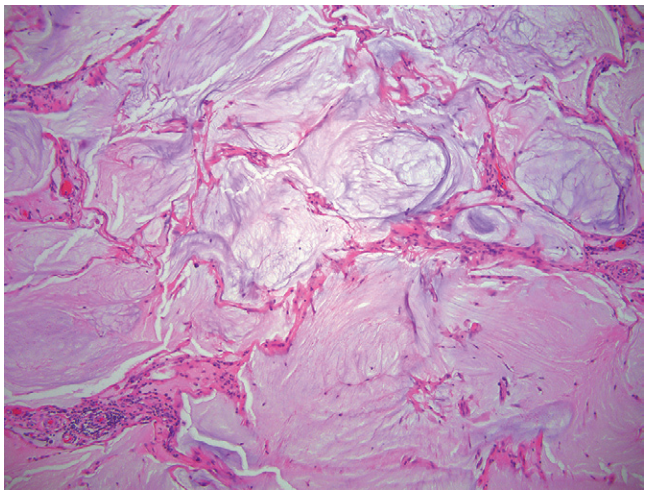

FIGURE 3

Pseudomyxoma peritonei. Pools of acellular mucin.

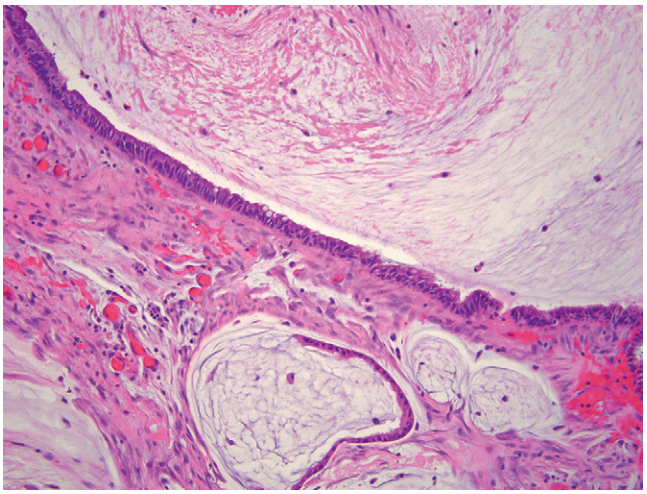

FIGURE 4

Pseudomyxoma peritonei. A peritoneal implant of epithelium from a low-grade appendiceal mucinous neoplasm.

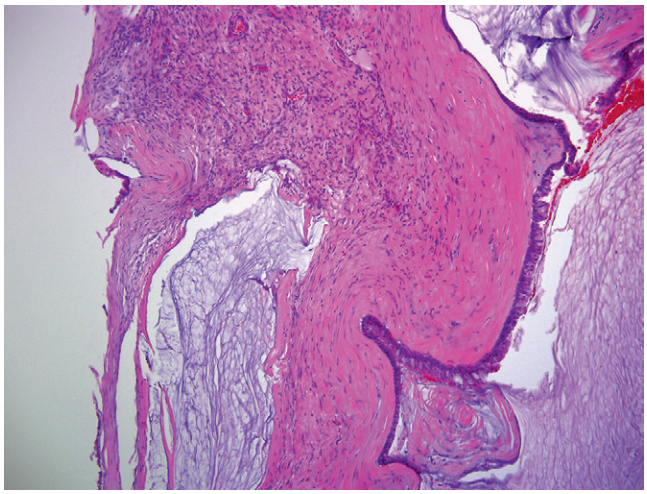

FIGURE 5

Pseudomyxoma peritonei. Ovarian involvement of a low-grade appendiceal mucinous neoplasm. The ovarian implants may closely represent a mucinous cystadenoma or borderline tumor.

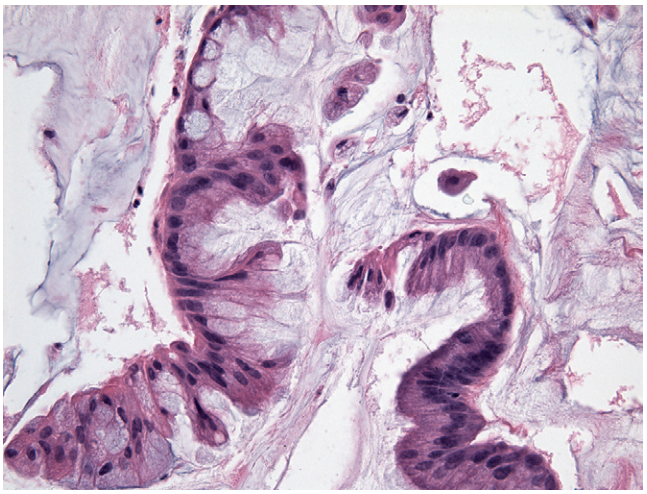

FIGURE 6

Pseudomyxoma peritonei. Strips of epithelium may be present in the mucin. Low-grade mucinous epithelium is present in this example.

MATURE CYSTIC TERATOMA: NORMAL NEURAL DIFFERENTIATION

Definition—Germinal matrix or cerebellar differentiation in a mature teratoma; mimics immature neuroepithelium.

Clinical Features

Epidemiology

- Occurs in typical benign cystic teratoma.

Presentation

- Cerebellar or germinal matrix differentiation is uncommon, but benign cystic teratomas are the most common tumor in general in reproductive-age women.

Prognosis and Treatment

- The prognosis is excellent.

Pathology

Histology

- A key feature is the organized neural tissue with discrete layers.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Neuroblastoma arising in a teratoma—these are composed of disorganized poorly differentiated neuroblastic growth.
- Immature neuroepithelium—these form rosette-like arrangements, again without the multiple layers of differentiation.

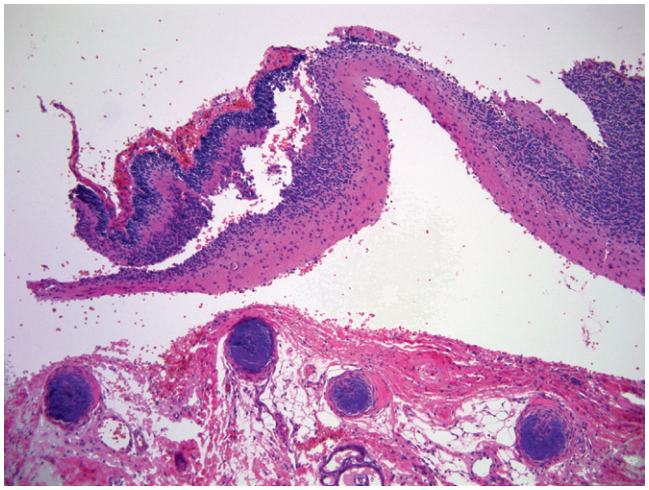

FIGURE 1

Cerebellar differentiation in a mature cystic teratoma. Hair shafts are in the lower aspect of the field.

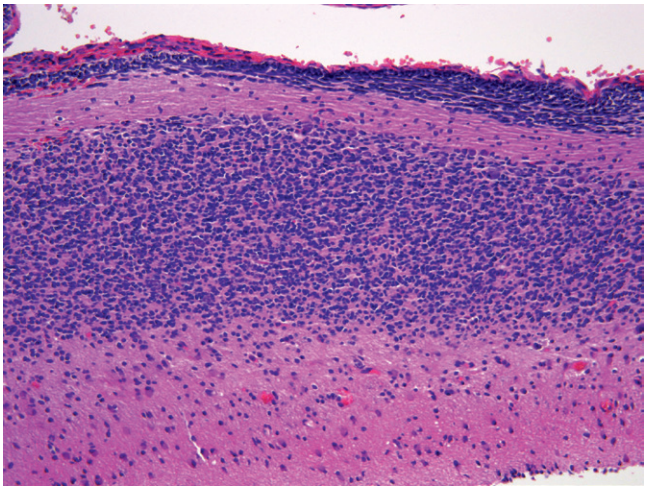

FIGURE 2

Cerebellar differentiation in a mature cystic teratoma. Note the orderly layering of neurons.

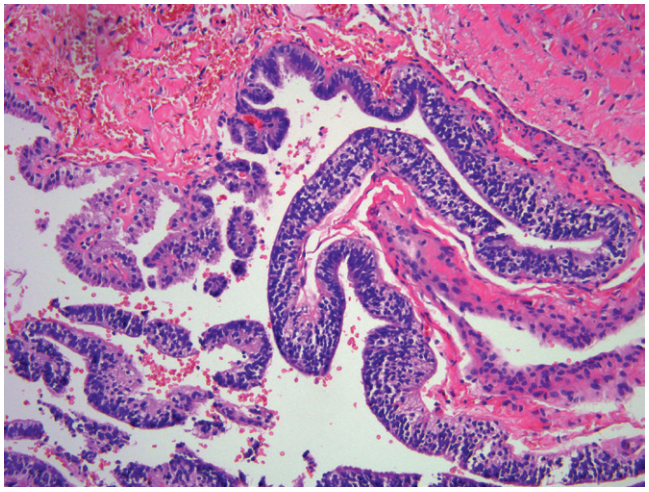

FIGURE 3

Germinal matrix in a mature cystic teratoma.

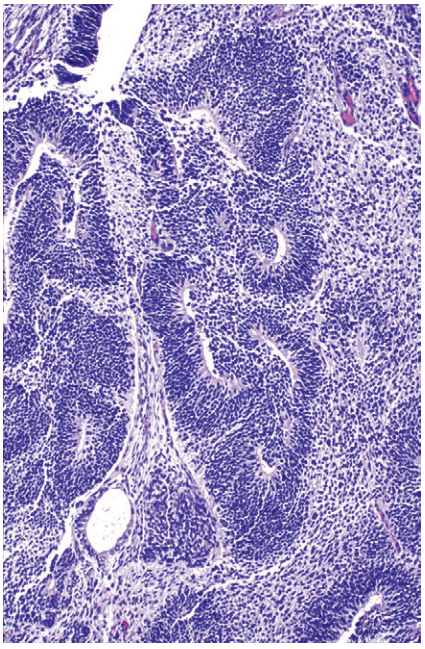

FIGURE 4

Immature neuroepithelium in an immature teratoma for comparison.

FETIFORM TERATOMA

Odise Cenaj, MD, PhD ■ Jelena Mirkovic, MD, PhD

Definition—A teratoma recapitulating human form.

Clinical Features

Epidemiology

- Exceedingly rare, reproductive-age group.

Presentation

- Ovarian mass.
- These tumors exhibit extremities, head and trunk, including phallus.

Prognosis and Treatment

- The prognosis is excellent. These tumors are not malignant.

Pathology

Histology

- When differentiation is extreme, tissues are oriented along both the anterior-posterior, dorsal-ventral, and left-right axes.
- Virtually any germ cell layer can be found in the appropriate region including brain, eye, viscera phallus, endocrine, and blood vessels.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Fetus in fetu—this is a monozygotic twin that becomes incorporated into the abdomen of the fetus. It would not be confused with a fetiform teratoma.
- Ectopic pregnancy—a fully formed embryo with an umbilical cord present.

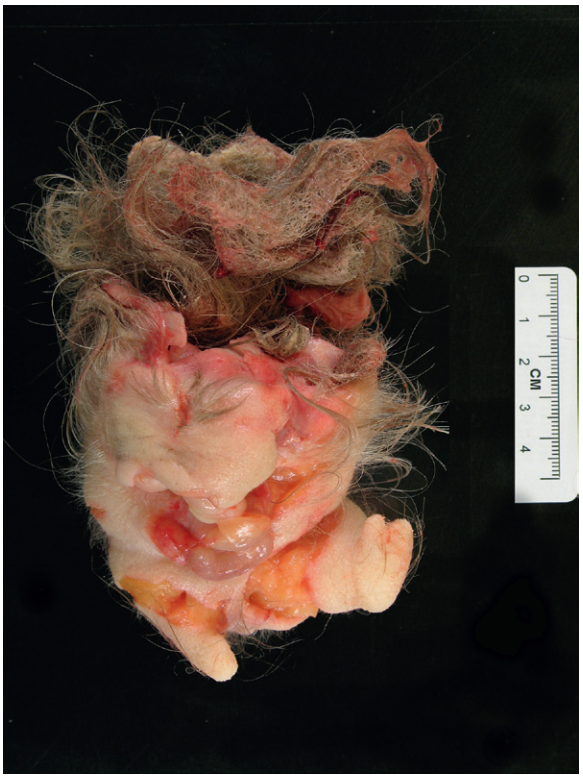

FIGURE 1

Fetiform teratoma. Note the vague resemblance to a fetus.

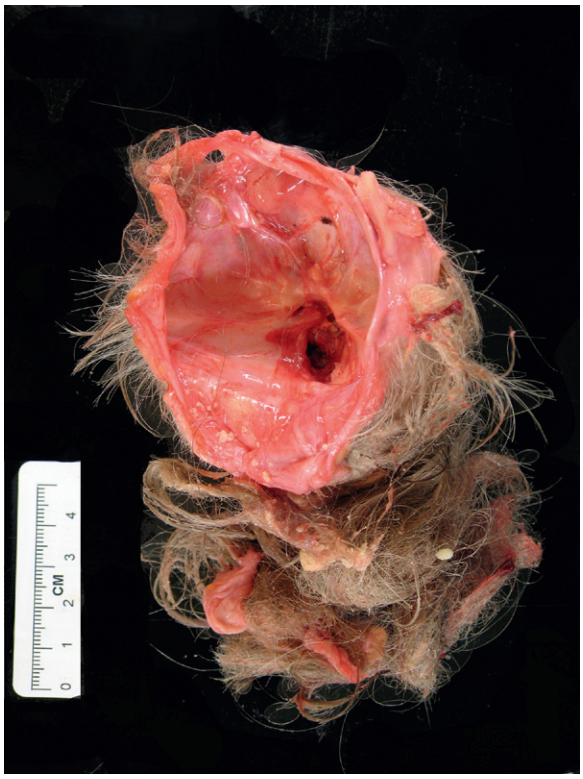

FIGURE 2

Fetiform teratoma. The "head" is opened to reveal a semblance of a cranial vault with some brain tissue.

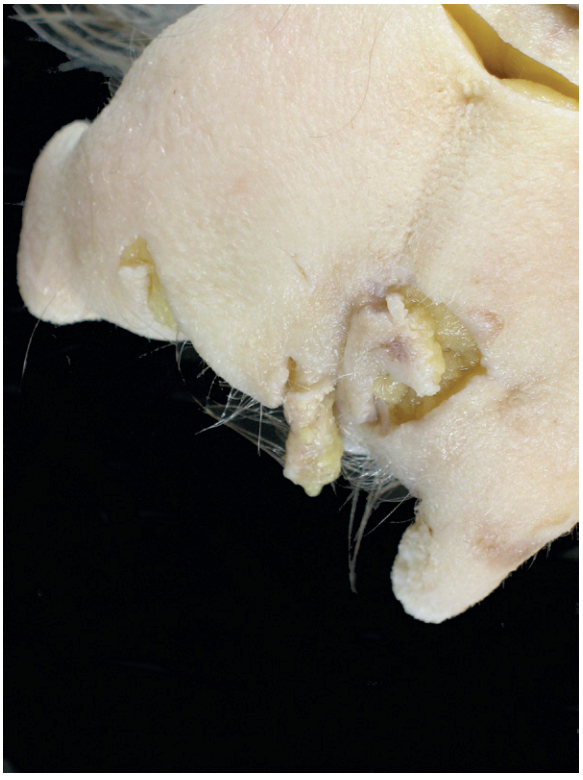

FIGURE 3

Fetiform teratoma. The lower torso exhibits limblike structures and a central phallic appendage.

FIGURE 4

Another example of a fetiform teratoma.

STRUMA OVARII

Definition—A teratoma composed principally of thyroid tissue.

Clinical Features

Epidemiology

- Struma ovarii is a monodermal ovarian teratoma predominantly composed of thyroid tissue.
- Seen most commonly in the fifth decade of life.
- Virtually always unilateral.
- Contralateral cystic teratoma in 10% to 15% of cases (we have seen one case of struma with contralateral carcinoid).

Presentation

- May appear complex on ultrasound (a clinical pitfall).
- Hyperthyroidism uncommon, pseudo-Meigs' syndrome and hyperemesis gravidarum–like symptoms rarely occur.
- Characteristic brown to greenish-brown color on gross exam.

Prognosis and Treatment

- Prognosis is excellent in the absence of peritoneal deposits, which rarely occur in benign-appearing struma but merit careful assessment.

Pathology

Histology

- Appearance ranges from an arrangement of prominent macrofollicles and microfollicles with abundant colloid to a fibrotic cyst with inconspicuous small tubules.
- Solid patterns lacking colloid with oxyphilic or clear cells may also be present.
- Trabecular patterns may be confused with or merge with carcinoid.
- If there is fibromatous stroma, the epithelial cells may form cords or microacini lacking colloid and may be confused with benign or malignant tumors, including Brenner tumor.

Immunopathology (Including Immunohistochemistry)

- TTF-1 or thyroglobulin will distinguish struma from most mimics. If carcinoid is suspected, staining for TTF-1 plus chromogranin or synaptophysin will delineate the different components.

Main Differential Diagnosis

- Sex cord–stromal neoplasms—inhibin positive.
- Carcinoid—TTF-1 and neuroendocrine stains will distinguish.
- Epithelial tumors—particularly if there is cordlike or trabecular growth in a fibrous stroma. Key here is an index of suspicion and resolution with special stains.

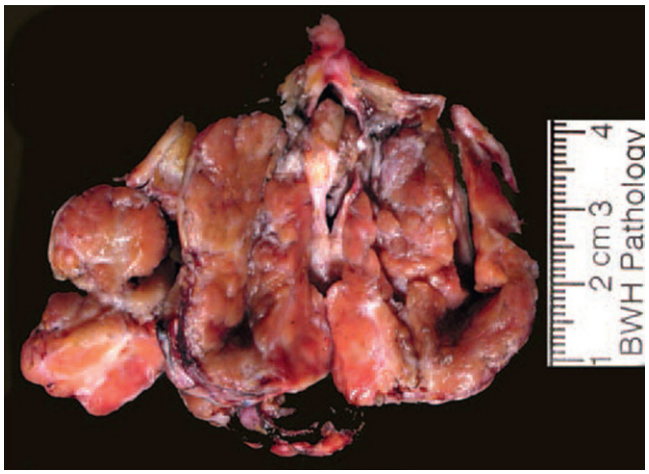

FIGURE 1

Gross photo of struma ovarii with the characteristic brown-green fleshy appearance.

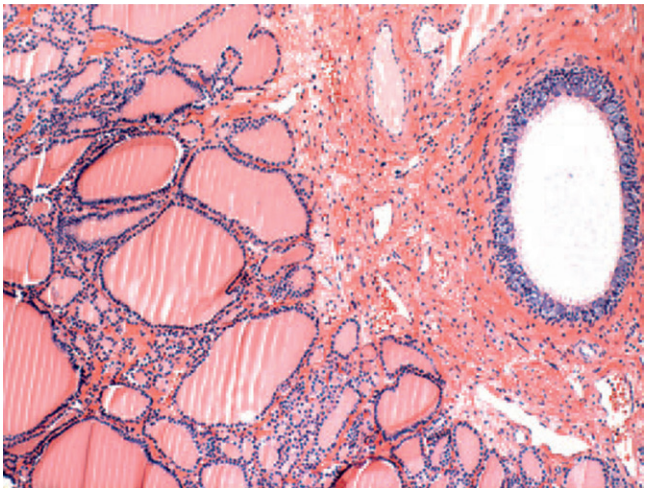

FIGURE 2

Struma ovarii. Characteristic thyroid follicles on the left and a cyst lined by respiratory epithelium on the right.

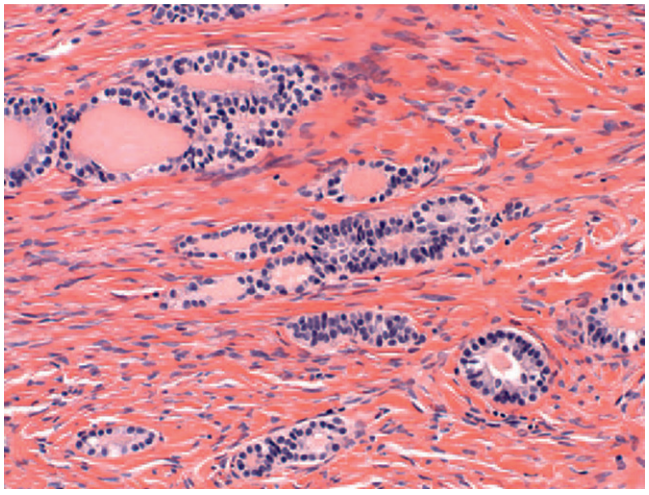

FIGURE 3

Struma ovarii. Smaller colloid-filled tubules.

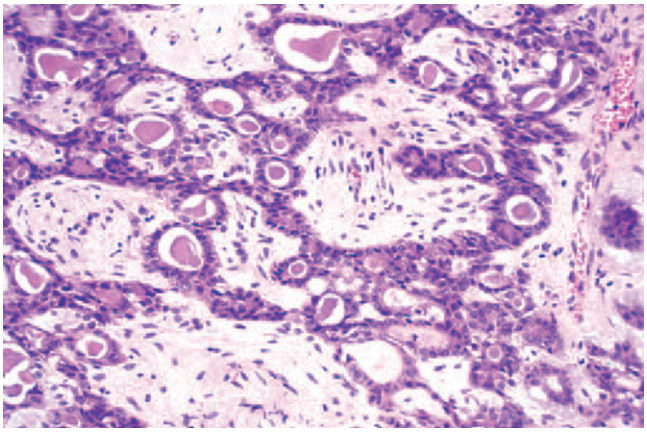

FIGURE 4

Admixtures of small follicles and cordlike or trabecular growth patterns.

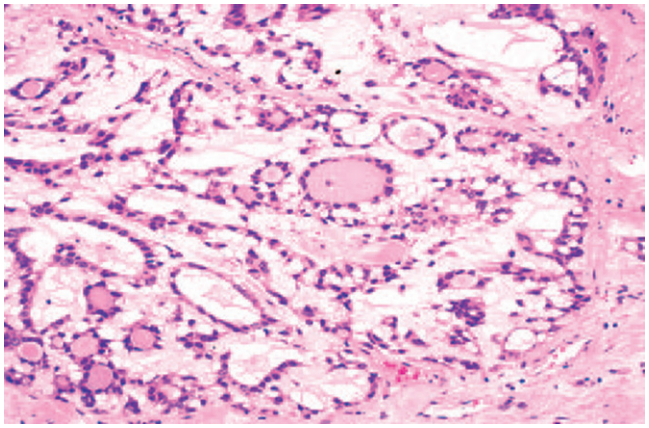

FIGURE 5

Follicles suspended in a loose matrix.

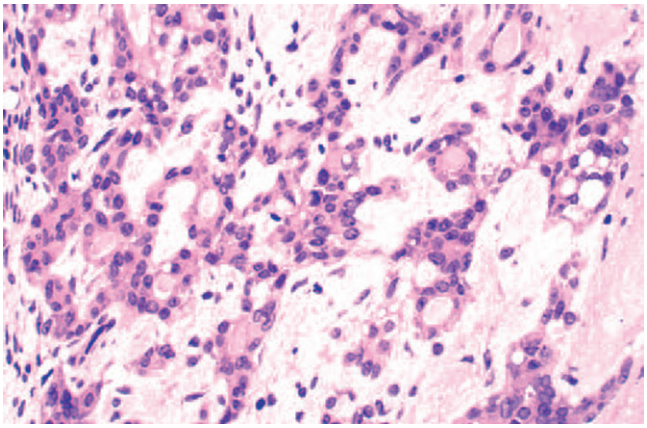

FIGURE 6

Follicles are less obvious here.

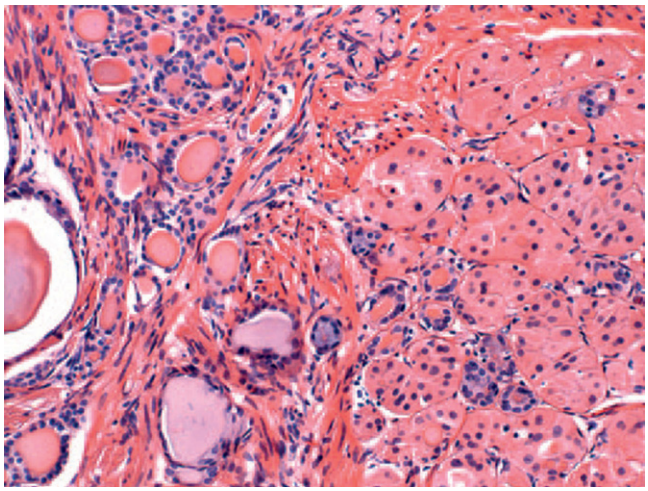

FIGURE 7
Oxyphilic change (right) in struma ovarii.

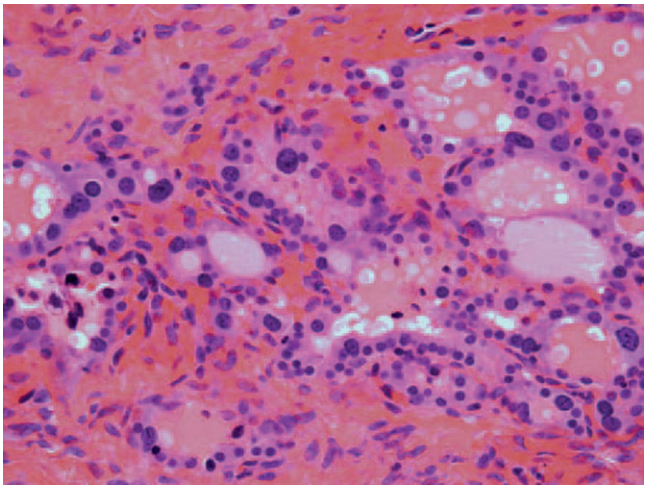

FIGURE 8
Focal atypia in struma ovarii.

MALIGNANT STRUMA

Definition—Malignant teratomatous thyroid tissue (carcinoma).

Clinical Features

Epidemiology

- Association with mature cystic teratomas and struma ovarii. Mean age is approximately 43 years.
- Approximately 5% of struma are malignant, at least focally. Some estimates are higher and this may depend on the stringency of the criteria for the diagnosis based on nuclear features.

Presentation

- Struma ovarii is defined as thyroid tissue composing over 50% of the teratoma. Approximately 5% of struma ovarii contain a malignant component. Many malignant strumas are found incidentally, but some patients are symptomatic, presenting with findings including pelvic/abdominal pain (~40%), abnormal uterine bleeding (~20%), or rarely hyperthyroidism (~5%). Fifteen to twenty percent have associated ascites. A contralateral cystic teratoma is found in 10% to 15% (with bilateral struma occurring in 7%).

Prognosis and Treatment

- The risk of concurrent spread or recurrence for papillary thyroid cancer (PTC) is 5% to 10% and 20% to 25% for follicular carcinoma.
- Rare benign and occasional proliferative strumas recur.
- Benign struma is treated with surgery and monitoring of thyroid levels.
- Malignant struma is often treated with thyroidectomy and I131.
- Most recurrences are seen in untreated patients.

Pathology

Histology

- The diagnosis of PTC is based primarily on nuclear features including
  Nuclear enlargement
  Nuclear contour irregularities
  Nuclear grooves
  Pseudoinclusions
  Clearing of the nucleus
  Nuclear crowding and overlapping
- Other findings that are less specific: psammomatous calcifications, uniformity of color of colloid, and scalloping of colloid.

Immunopathology (Including Immunohistochemistry)

- Three antibodies have been proposed to aid in distinguishing benign from malignant struma, including galectin-3, HBME-1, and cytokeratin 19. These antibodies stain most papillary carcinomas but with some overlap with follicular adenoma and benign thyroid. In comparative studies, a tumor that stains with all three biomarkers is *statistically* more likely to be a carcinoma; however, the pathologist cannot rely on these markers alone to make a diagnosis of malignant struma.

Main Differential Diagnosis

- Benign or proliferative struma—careful attention to the nuclear features is important. The distinction from papillary carcinoma may be difficult.
- Strumal carcinoid—the carcinoid component will stain with neuroendocrine markers (chromogranin, synaptophysin).
- Reactive epithelial changes—these can produce pale nuclei, mimicking carcinoma.

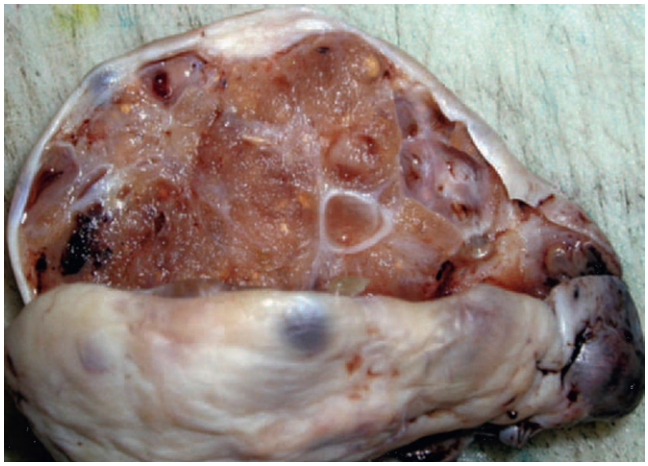

FIGURE 1

Malignant struma ovarii. A large mass-forming tumor distends the ovarian capsule. *(Courtesy Dr. Michael Roh.)*

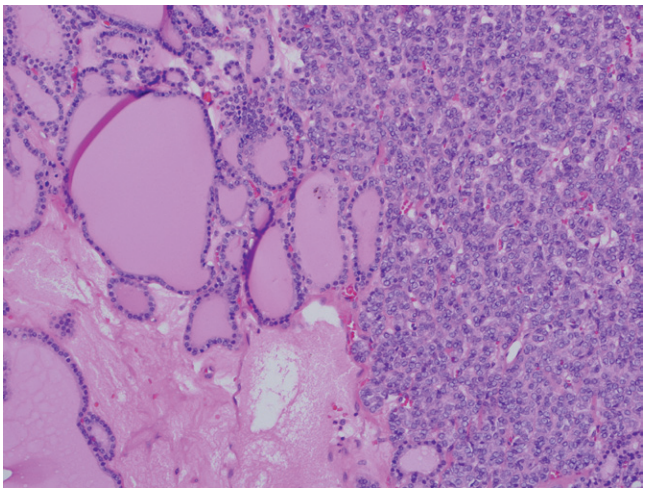

FIGURE 2

Interface of benign *(left)* and malignant (follicular variant of papillary carcinoma) *(right)*.

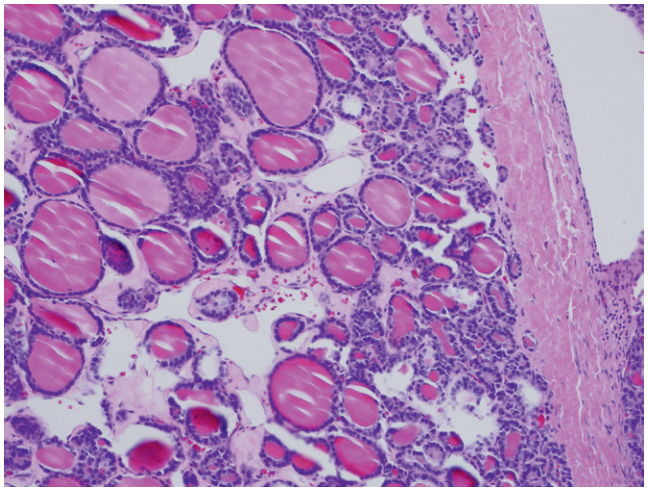

FIGURE 3

Benign strumal component at higher magnification.

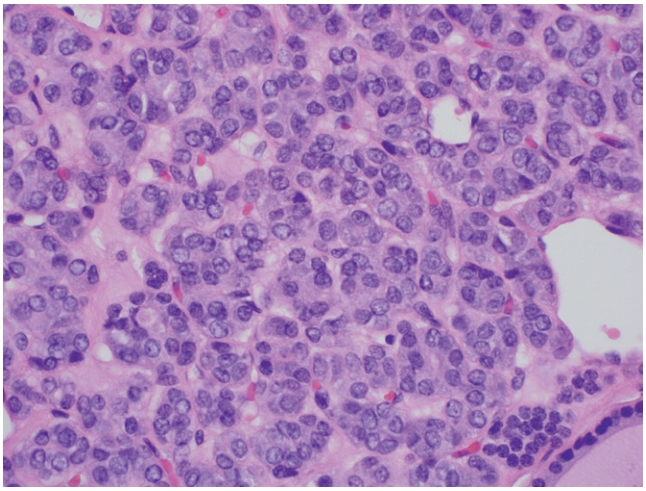

FIGURE 4

Malignant strumal component. There is nuclear enlargement, some nuclear contour irregularities, and nuclear clearing.

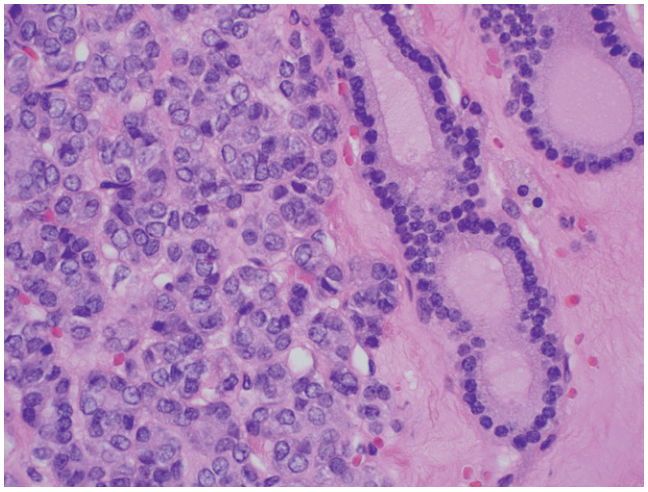

FIGURE 5

Benign thyroid follicles *(right)* are contrasted with carcinoma *(left)*.

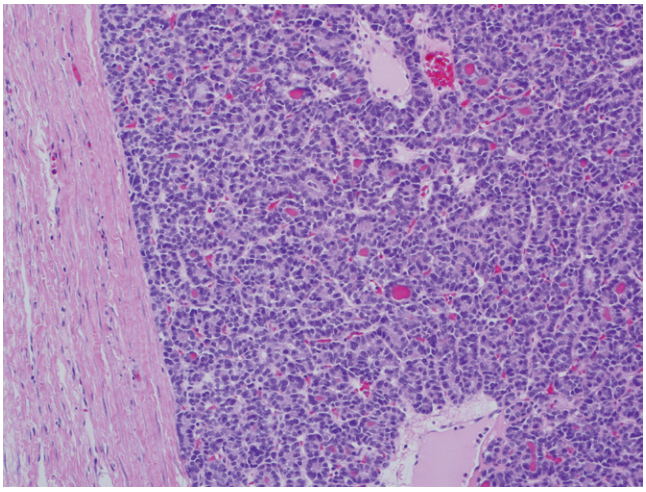

FIGURE 6

A more difficult nodule of thyroid tissue in a struma ovarii that is not conclusive for malignant struma.

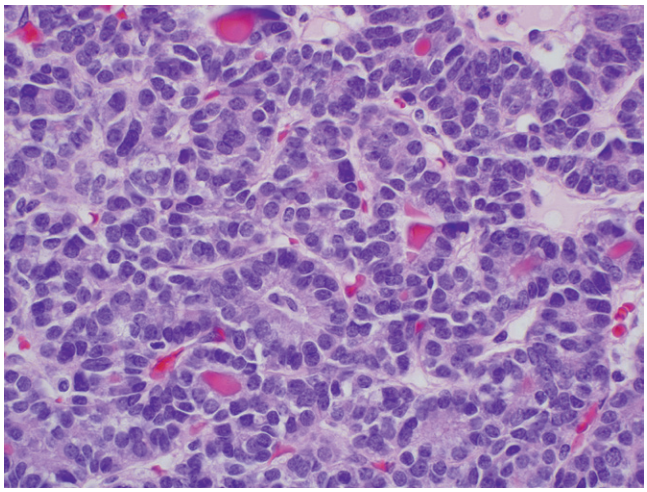

FIGURE 7
Higher power view of the focus in Figure 6 showing less pronounced nuclear abnormalities.

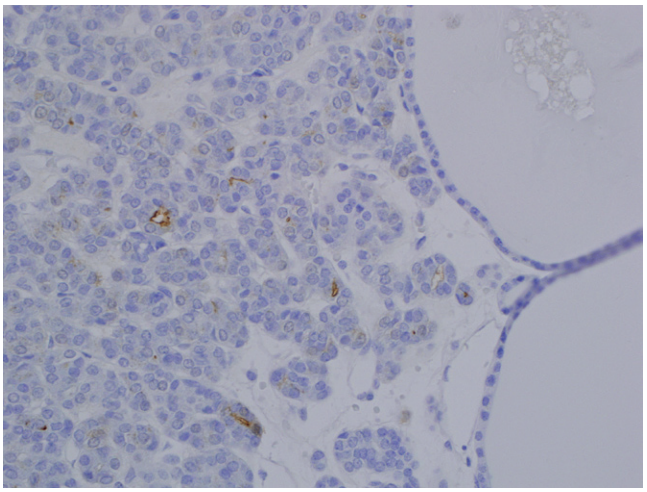

FIGURE 8
Immunostains may be helpful but are still under study. In this case (depicted in Figures 4 and 5) the malignant component stains for Galectin in contrast to the adjacent benign tissue on the right.

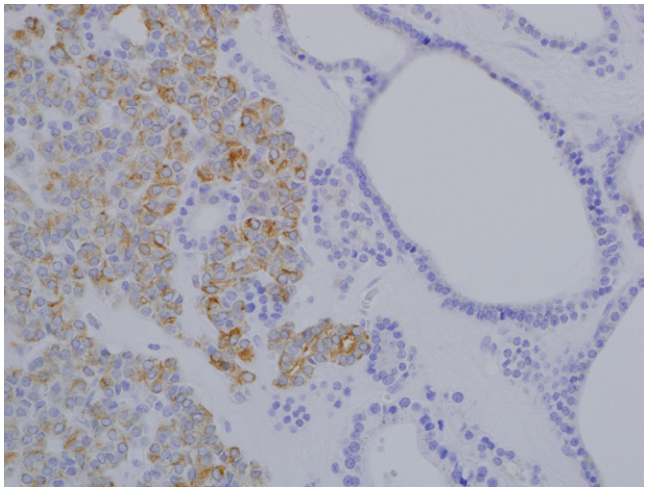

FIGURE 9
A stain for CK19 is diffusely positive.

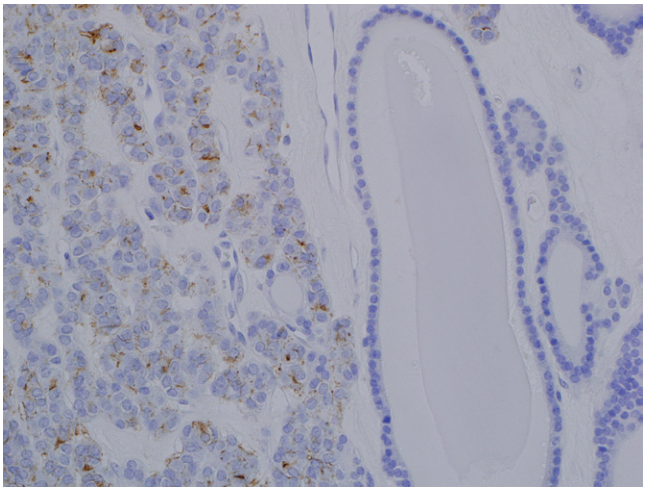

FIGURE 10
Staining for HBME-1 is also positive. Figures 8 to 10 show the "best case scenario" for immunostaining but the pathologist must use caution in their interpretation from case to case.

STRUMAL CARCINOID

Definition—A monodermal teratoma composed of both struma (thyroid) and a trabecular carcinoid.

Clinical Features

Epidemiology

- Strumal carcinoids are rare tumors with bidirectional differentiation, resulting in both thyroid and neuroendocrine differentiation.
- Seen over a wide age range, from the third to the eighth decades.
- Sixty percent are associated with dermoid cysts or solid teratomas.
- Always unilateral.
- Contralateral cystic teratoma in 10% to 15% of cases.

Presentation

- May appear complex on ultrasound (a clinical pitfall) like many teratomatous lesions.
- Functioning thyroid tissue is present in less than 10%.
- Carcinoid syndrome is not reported.
- Grossly composed of solid components in a cystic teratoma.

Prognosis and Treatment

- Prognosis is excellent. Rare cases with coexisting thyroid carcinoma have been reported. The carcinoid component typically behaves in a benign fashion.

Pathology

Histology

- Histologically the trabeculae of the carcinoid often merge abruptly with the thyroid follicles.
- In many cases hematoxylin and eosin staining will not distinguish the two elements. More subtle transitions, in which small colloid-producing lumina emerge within the trabeculae, are common.

Immunopathology (Including Immunohistochemistry)

- TTF-1 or thyroglobulin will distinguish struma from the carcinoid component, which is appreciated with staining for chromogranin or synaptophysin.

Main Differential Diagnosis

- Sex cord–stromal neoplasms—inhibin positive.
- Pure carcinoid or struma with trabecular features—TTF-1 and neuroendocrine stains will distinguish.
- Epithelial tumors—particularly if there is cordlike or trabecular growth in a fibrous stroma. Key here is an index of suspicion and resolution with special stains.

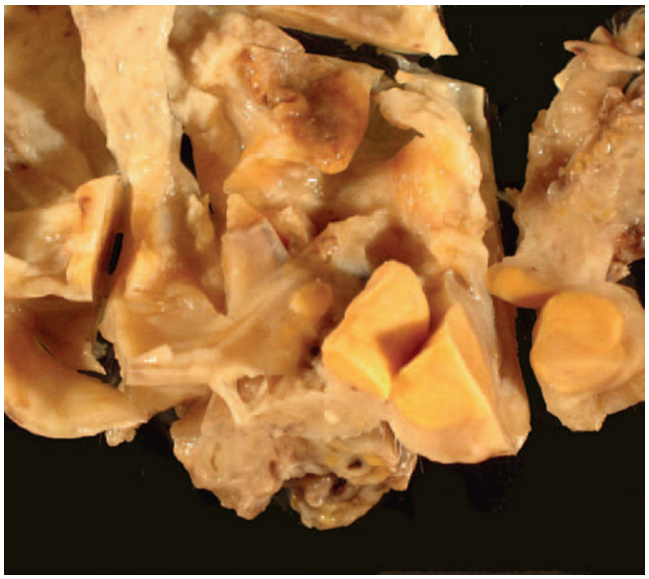

FIGURE 1

Gross photo of strumal carcinoid; a sectioned yellow mass within a multiloculated cyst.

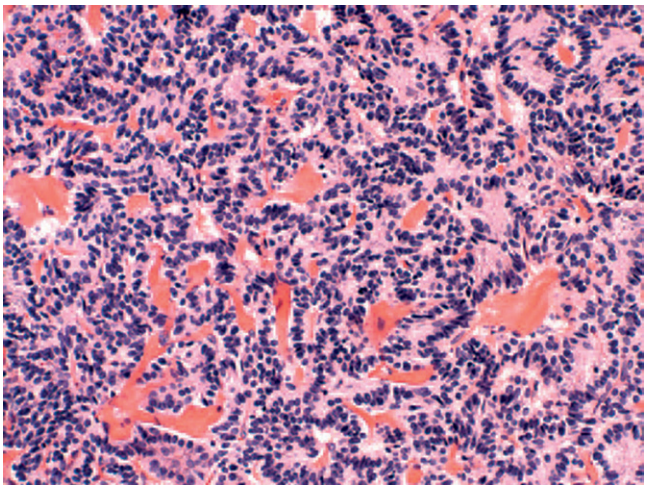

FIGURE 2

Strumal carcinoid. Thyroid component.

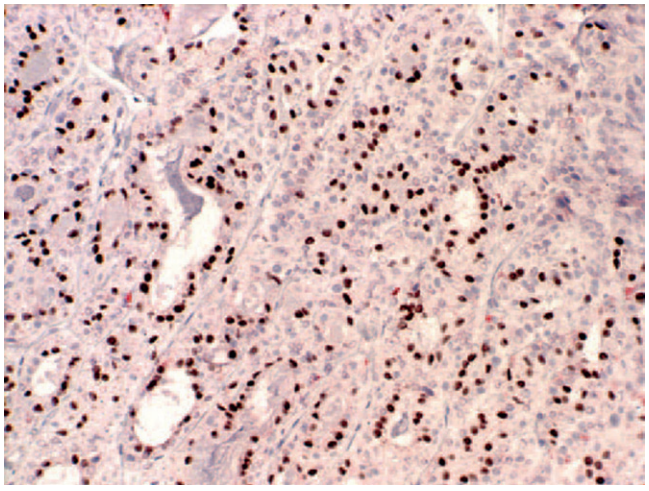

FIGURE 3

Strumal carcinoid. Thyroid component following immunostaining for TTF-1.

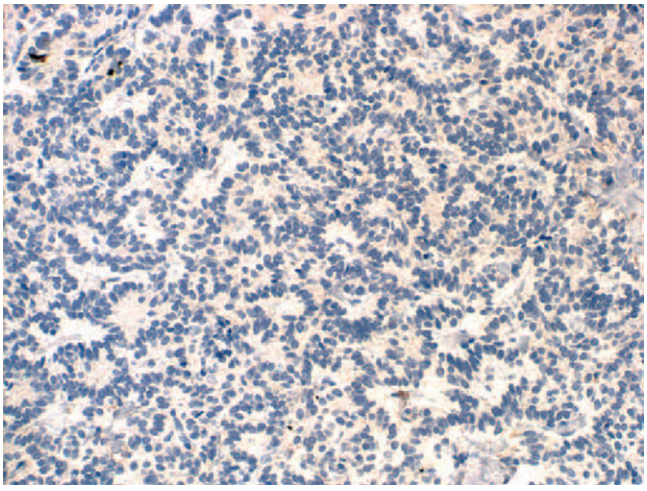

FIGURE 4

Strumal carcinoid. Thyroid component; there is absent immunostaining for chromogranin.

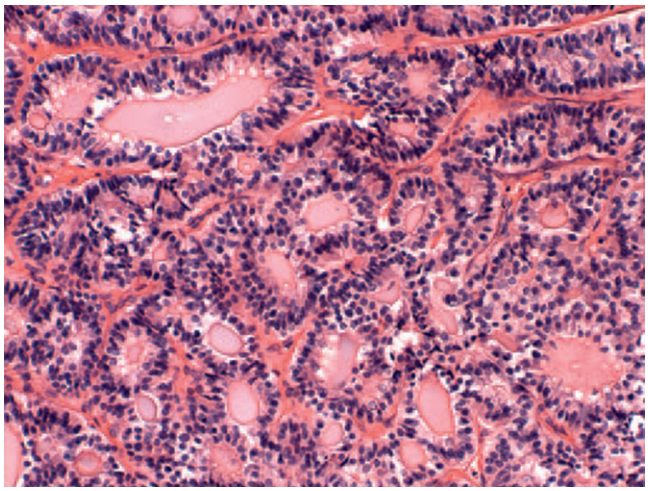

FIGURE 5

A focus of mixed differentiation in a strumal carcinoid.

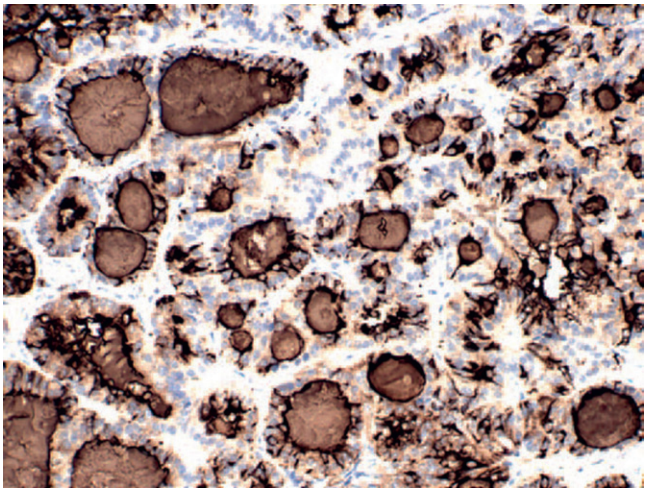

FIGURE 6

Mixed differentiation following staining for thyroglobulin.

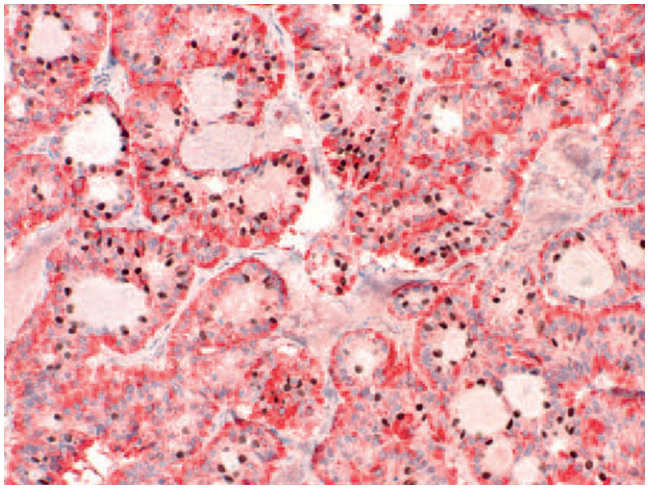

FIGURE 7

Mixed differentiation following double staining for TTF-1 (nuclear) and chromogranin (cytoplasm). This illustrates the common cell of origin for these tumors and the immunophenotypic overlap in these tumors.

METASTATIC CARCINOID

Definition—Metastatic carcinoid, usually from the gastrointestinal tract.

Clinical Features

Epidemiology

- The majority of metastatic carcinoids are of distal ileal origin.
- Have a wide age range, but most will be postmenopausal.

Presentation

- Bilateral in up to 90%.
- Urinary uptake of hydroxyindoleacetic acid (HIAA) is increased in 90%.
- Hepatic and peritoneal involvement common.
- Solid tan to yellow tumor masses, often multinodular.

Prognosis and Treatment

- Despite the metastatic nature of this disease, some reports note a 5-year survival exceeding 80% due to favorable response to therapy and the generally low level of malignancy. We have seen occasional patients survive for decades after resection of their ovarian tumor.

Pathology

Histology

- The most common pattern is an insular pattern.
- Formation of acini is common, with salt and pepper chromatin.
- Small cordlike patterns or linear arrays of tumor cells are not uncommon.
- Mucin production may also be seen, including gastrointestinal differentiation.
- Multifocal distribution, with frequent involvement of both ovaries.

Immunopathology (Including Immunohistochemistry)

- Synaptophysin and chromogranin stains should be positive.
- CDX2 stains often positive but not specific for metastatic carcinoid.

Main Differential Diagnosis

- Sex cord–stromal neoplasms—inhibin positive.
- Struma or strumal carcinoid—TTF-1 and neuroendocrine stains will distinguish.
- Epithelial tumors—particularly if there is cordlike or trabecular growth in a fibrous stroma. Key here is an index of suspicion and resolution with special stains. Glandlike patterns will closely resemble endometrioid and other epithelial tumors.

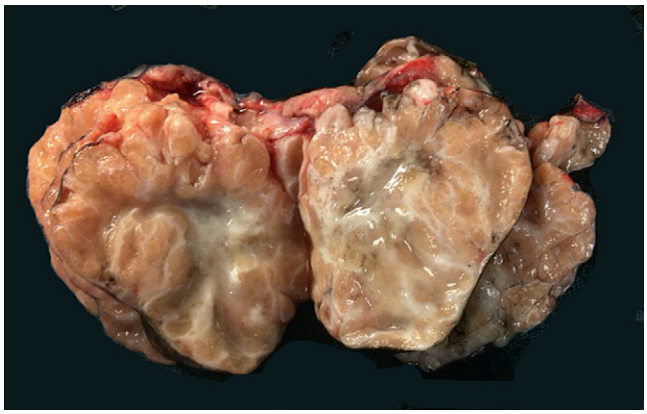

FIGURE 1

Metastatic carcinoid from the small bowel displays a brown-tan appearance.

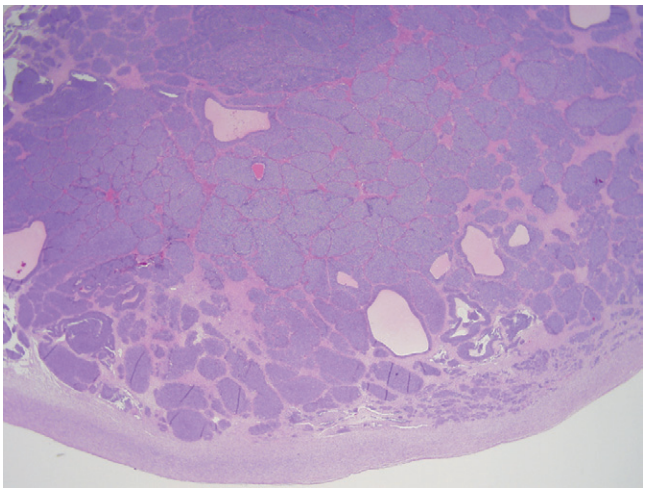

FIGURE 2

Metastatic carcinoid. Multiple confluent islands of tumor in the ovarian cortex.

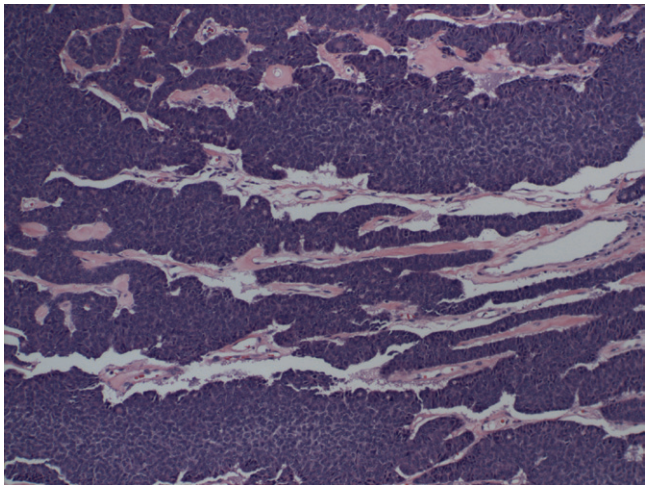

FIGURE 3

Metastatic insular carcinoid showing large cohesive sheets of tumor cells.

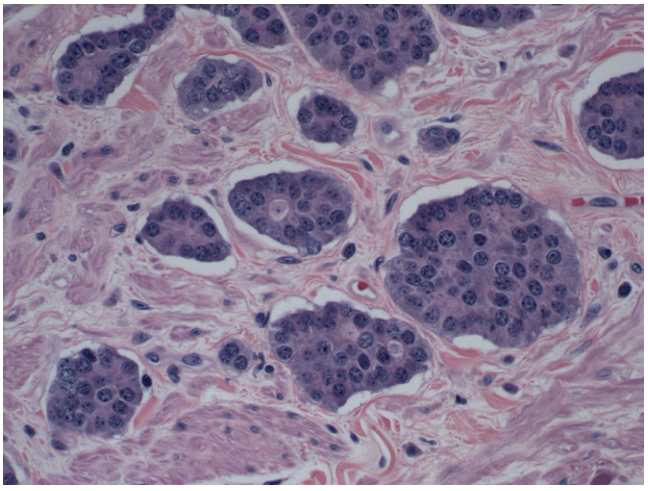

FIGURE 4

Metastatic insular carcinoid showing a range of patterns from predominantly solid nests to glandlike pattern. Key here are the nuclear features, which can be deceptive depending on fixation.

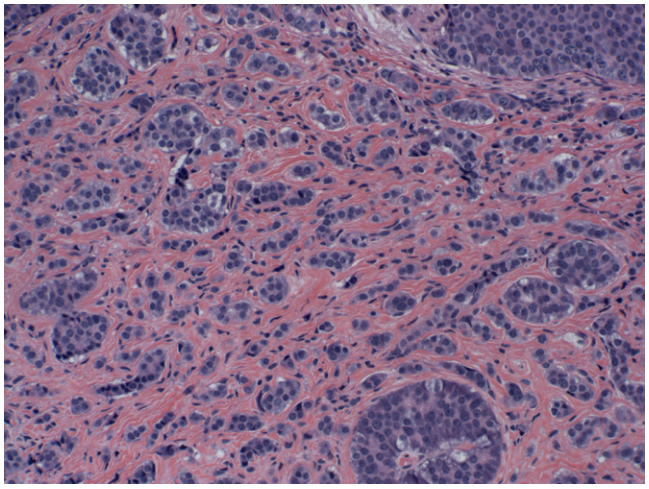

FIGURE 5

Metastatic insular carcinoid showing a range of patterns from predominantly solid nests to glandlike pattern. Key here are the nuclear features, which can be deceptive depending on fixation.

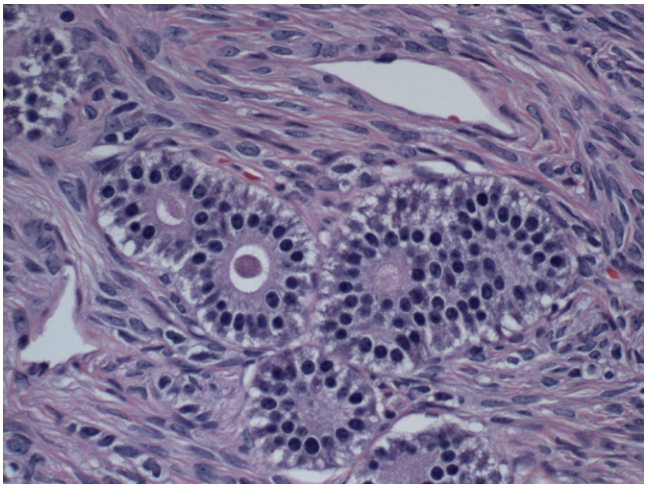

FIGURE 6

Metastatic insular carcinoid showing a range of patterns from predominantly solid nests to glandlike pattern. Key here are the nuclear features, which can be deceptive depending on fixation.

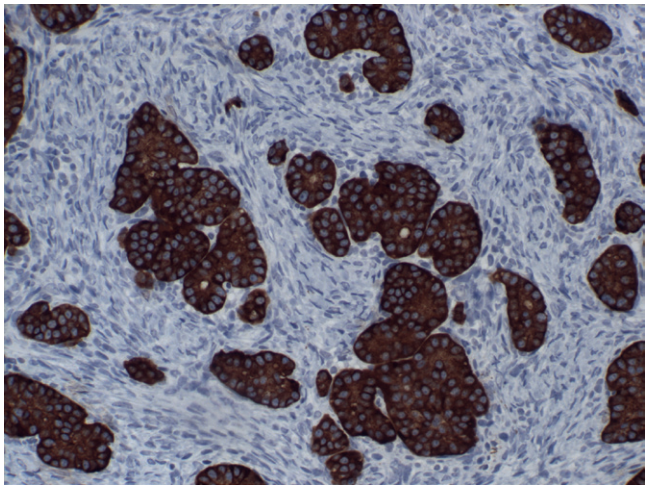

FIGURE 7

Synaptophysin staining of a metastatic carcinoma.

MALIGNANCY ARISING IN TERATOMAS

Definition—A malignant tumor of somatic tissues arising from an element of mature teratoma.

Clinical Features

Epidemiology

- Rare, occurring in 1% of mature cystic teratomas.
- Approximately 90% are epithelial, 80% of which are squamous carcinomas.
- Mean age is approximately 20 years older than that of benign teratomas.

Presentation

- Usually discovered incidentally following removal of the teratoma (pelvic mass).
- More commonly associated with tumors of 10 cm or greater in diameter.

Prognosis and Treatment

- One half are advanced stage (II or greater at diagnosis).
- The prognosis varies with tumor type and stage.
- Squamous carcinomas have the worst prognosis, influenced by stage, tumor size, and older age.
- Ten-year survival is 60% for stage I and less than 25% for more advanced stages.
- Carcinoids, malignant struma, and primitive neuroectodermal tumor (PNET) are discussed separately.

Pathology

Histology

- Most of these tumors are well-differentiated squamous carcinomas, befitting tumors of a non–human papillomavirus (HPV) pathogenesis.

Immunopathology (Including Immunohistochemistry)

- Noncontributory, although p16 should be negative or weakly positive in contrast to metastatic squamous carcinomas of the cervix.

Main Differential Diagnosis

- Metastatic squamous carcinoma from other sites—this can usually be excluded by the presence of other teratomatous elements. Rarely we have seen metastatic squamous carcinomas from the cervix in the region of the ovary. The latter should be excluded with a p16 immunostain (positive) and appropriate history.

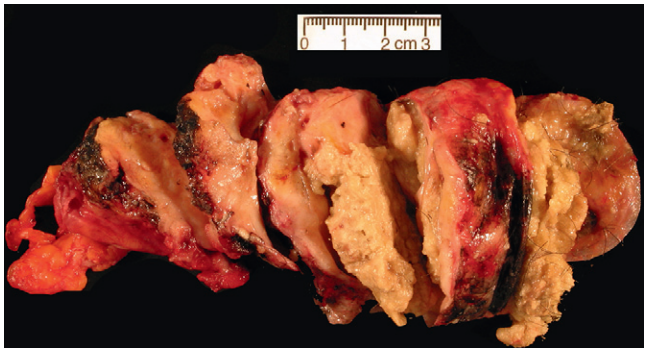

FIGURE 1

Squamous carcinoma arising in a teratoma. Note the presence of hair, coupled with a solid necrotic carcinoma.

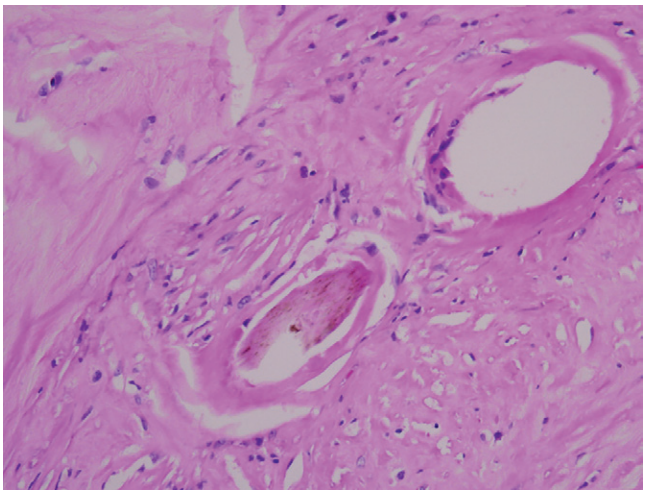

FIGURE 2

Squamous carcinoma arising in a teratoma. A portion of the normal parenchyma with hair shafts is histologic confirmation of a teratoma.

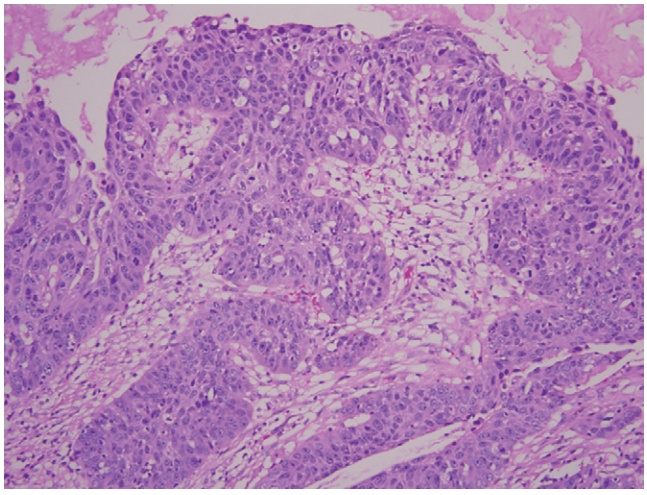

FIGURE 3

Squamous carcinoma lining a cyst.

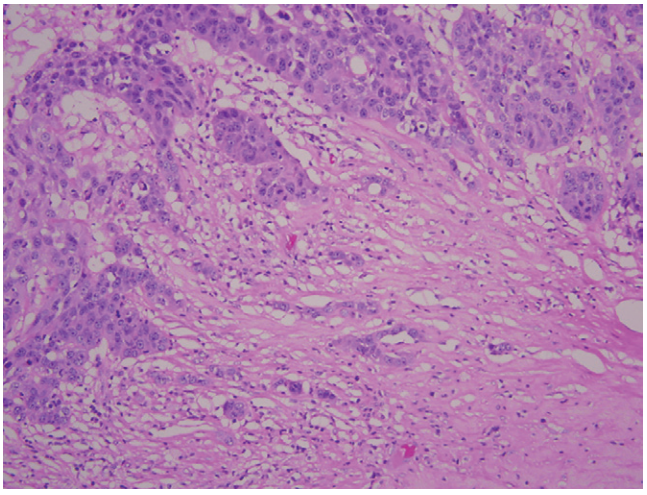

FIGURE 4

Invasive carcinoma penetrating the cyst wall.

DYSGERMINOMA

Definition—A malignant, primitive germ cell tumor of the ovary that is the counterpart to testicular seminoma.

Clinical Features

Epidemiology

- Rare; represents only 1% of all ovarian germ cell tumors but is the most common malignant germ cell tumor.
- Most cases arise in women in their teens or twenties with a mean age of 19 years.
- The most common malignant germ cell tumor identified in young persons.

Presentation

- Rapidly growing ovarian mass with 10% to 20% showing macroscopic or microscopic involvement of the contralateral ovary.
- Elevated serum lactate dehydrogenase in at least 95% of patients.
- Incidental finding in patients with gonadal dysgenesis (rare).

Prognosis and Treatment

- More than half of all cases are still confined to the ovary at the time of diagnosis; metastasis to the contralateral ovary is common and can be microscopic.
- Most recurrences occur in the first 2 years after initial diagnosis.
- Metastatic spread is to lymph nodes (iliac, mediastinal, supraclavicular) and later to solid organs (liver, lungs, bone).
- With treatment, survival is over 95%.
- For tumors limited to one ovary, patients are followed with the expectation of almost 100% salvage with chemotherapy for those that relapse.
- These tumors are highly sensitive to radiation, but chemotherapy has almost completely replaced radiation therapy in their management. Some authors still recommend BEP but others feel carboplatin, with or without etoposide, is sufficient.

Pathology

Histology

- Gross examination of the ovary is notable for a firm, solid mass that may be gray or tan-pink with or without hemorrhage and necrosis; true cystic structures should not be seen.
- The low-power appearance is characterized by large tumor cells arranged in nests or cords; occasional cases have cells arranged in thin, nearly single cell cords.
- The tumor cells have large, round to oval, vesicular nuclei with eosinophilic nucleoli and abundant pale to eosinophilic cytoplasm; cytoplasmic borders are often prominent.
- There is a moderate degree of variability in nuclear size; occasional giant cells or syncytiotrophoblastic cells may be seen, and this finding alone is not sufficient to warrant a diagnosis of mixed germ cell tumor.
- A delicate loose stroma is most commonly present; but in some cases, the stroma may be hyalinized or luteinized.
- Infiltrating inflammatory cells are variably present and usually consist of T-cells; in some cases even germinal center formation is present.
- A careful search for other germ cell elements should be undertaken, especially for yolk sac tumor.

Immunopathology (Including Immunohistochemistry)

- Positive for PLAP (membranous), CD117, OCT-4, LDH (usually), and desmin.
- Negative for CD30, EMA, and AFP.
- Variable for keratins (usually weak) and HCG (usually only in syncytiotrophoblasts, but rarely in the cytoplasm of dysgerminoma).

Main Differential Diagnosis

- Mixed germ cell tumor; teratoma, yolk sac tumor, embryonal carcinoma, and choriocarcinoma.
- Clear-cell carcinoma. Usually forms discrete acinar or papillary structures while dysgerminoma may show a nested pattern; positive for epithelial markers; usually (but not necessarily) older age group.
- Granulosa cell tumor. These lack the nuclear characteristics; inhibin positive.

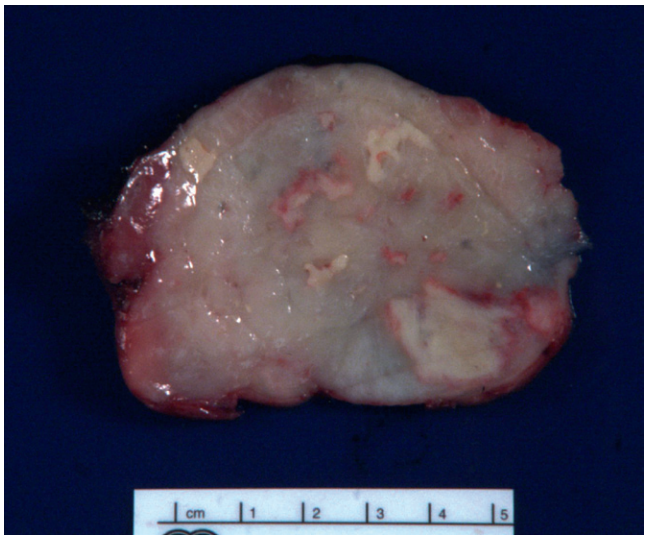

FIGURE 1

Dysgerminoma. Gross photograph demonstrating a tan, fleshy surface with foci of necrosis. Hemorrhage is also common.

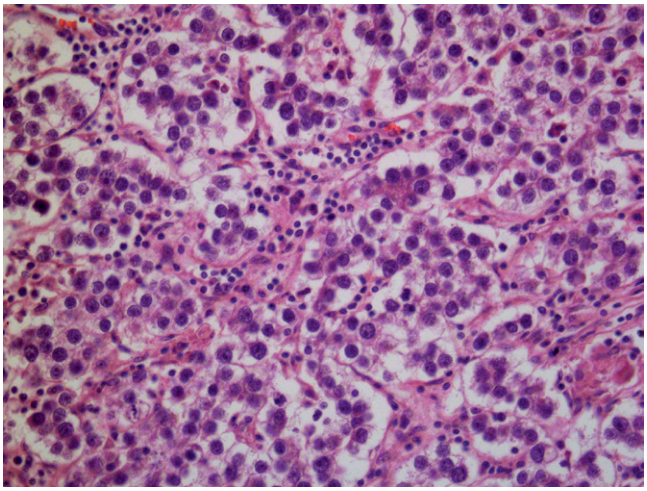

FIGURE 3

Dysgerminoma. At medium power this example is composed of small- to medium-sized nests of cells surrounded by delicate fibrovascular stroma.

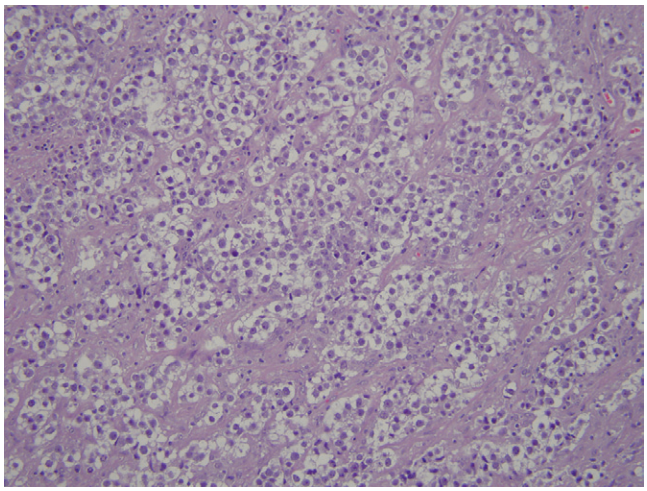

FIGURE 2

Dysgerminoma. At low power this tumor is composed of large cords of round, epithelioid neoplastic cells.

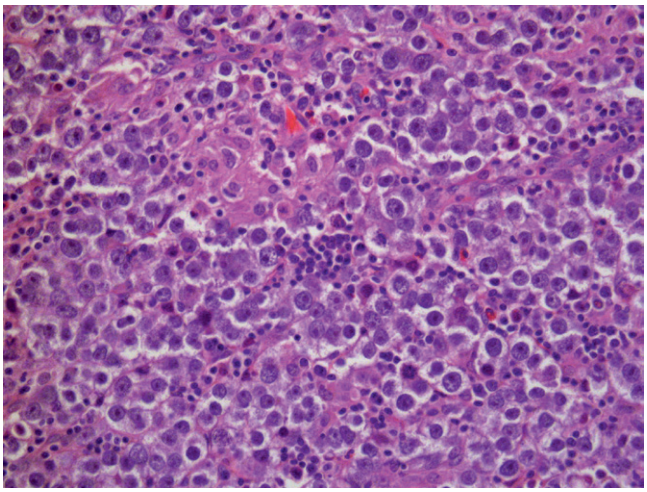

FIGURE 4

Dysgerminoma. An example of a more sheetlike architecture.

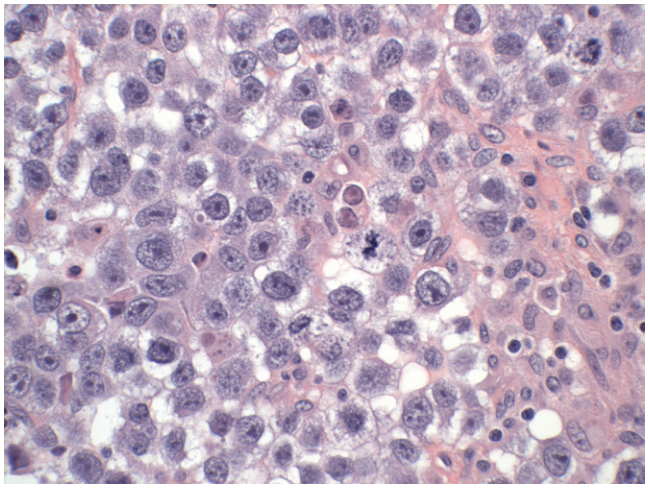

FIGURE 5

Dysgerminoma. At high power the cells have abundant clear to eosinophilic cytoplasm and round to oval nuclei. There are prominent violaceous nucleoli, and mitoses are common.

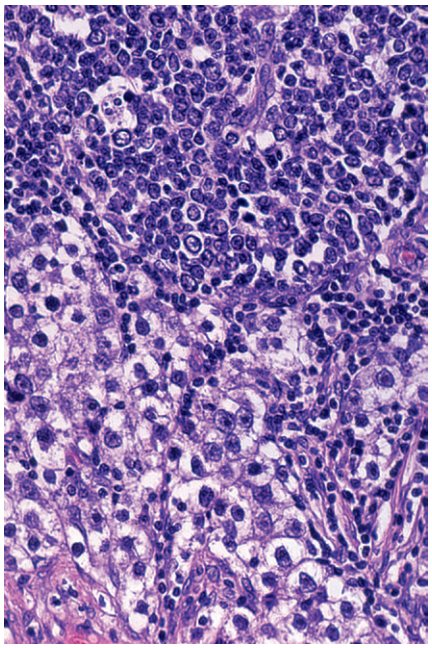

FIGURE 6

Dysgerminoma. Tumor-infiltrating lymphocytes are commonly seen.

YOLK SAC TUMOR

Definition—A malignant germ cell tumor with endodermal sinus or vitelline differentiation.

Clinical Features

Epidemiology

- The majority of patients are in their teens or twenties, although cases commonly occur in the first and fourth decades of life as well. The mean age is 19 years.
- Yolk sac tumors are the second most common malignant germ cell tumor (dysgerminoma is the most common) but are relatively rare overall.

Presentation

- Most patients present with abdominal pain and enlargement.
- If measured before surgery, alpha fetoprotein (AFP) levels are usually elevated.
- Imaging studies often reveal a unilateral, large, and solid to partially cystic mass.

Prognosis and Treatment

- The overall prognosis is good, with around 80% of all cases cured after surgery (unilateral salpingo-oophorectomy) and modern chemotherapy regimens (cisplatinum, etoposide, bleomycin).
- Pure hepatoid or glandular variants have been reported to be slightly less responsive to chemotherapy and thus have a more guarded prognosis.
- AFP levels are monitored after surgery to detect metastasis or recurrence.

Pathology

Histology

- The most common pattern is the microcystic pattern admixed with the endodermal sinus pattern, although any pattern may be seen in a tumor.
- Intensely eosinophilic hyaline droplets may be seen in any of the aforementioned patterns.
- Numerous histologic patterns of yolk sac tumor have been identified:
  - Microcystic/macrocystic: A lacelike network of small to large cystic spaces that tends to form a honeycomb-like pattern. The cysts are lined by flattened cells with hyperchromatic and pleomorphic nuclei.
  - Myxomatous: Abundant myxoid matrix with scattered cells forming strands and occasional glandlike structures.
  - Solid: Sheetlike arrangement of cells with clear cytoplasm and large nuclei. Occasional microcyst formation may be present but is typically focal.
  - Endodermal sinus: This pattern contains the classic Schiller-Duval body, which is composed of a vascular structure lined by a layer of cuboidal to columnar epithelial-like cells. The presence of these structures is diagnostic of yolk sac tumor; however, they may not be seen in every case.
  - Polyvesicular: Vesicle or cysticlike spaces that are lined by flattened cells. The vesicles may align and form a soap bubble–like pattern with intervening constrictions.
  - Alveolar-glandular: Glandlike or alveoli-like spaces lined by flat, cuboidal or columnar cells set in a myxoid stroma.
  - Papillary: True papillary structures with fibrous cores that are lined by markedly pleomorphic cells.
  - Hepatoid: Nest and cords of large eosinophilic cells with granular cytoplasm and well-defined cellular borders. Collections of these cells bear a remarkable resemblance to liver parenchyma.
  - Glandular (intestinal): Primitive cells in a glandular or nested pattern that are separated by stroma. The glands may be sparse and seen in varying levels of differentiation. Occasionally the glands may be well differentiated and resemble endometrial or colonic glandular epithelium. Be aware that there are rare examples of hybrid endometrioid/clear-cell and yolk sac tumors, seen in older women.

Immunopathology (Including Immunohistochemistry)

- Yolk sac tumors are often positive for AFP, alpha-1-antitrypsin, and keratins. The tumors are negative for CD30 and vascular markers, differentiating them from embryonal carcinomas and vascular tumors, respectively.
- Embryonal carcinoma—more pronounced nuclear atypia, syncytiotrophoblastic differentiation.
- Vascular tumors—positive for vascular markers.
- Retiform Sertoli-Leydig cell tumors—inhibin positive.
- Juvenile granulosa cell tumors—inhibin positive.
- Metastatic hepatocellular carcinoma (hepatoid variant)—consider if monomorphic and bilateral.

Main Differential Diagnosis

- Clear-cell carcinoma.
- Dysgerminoma.

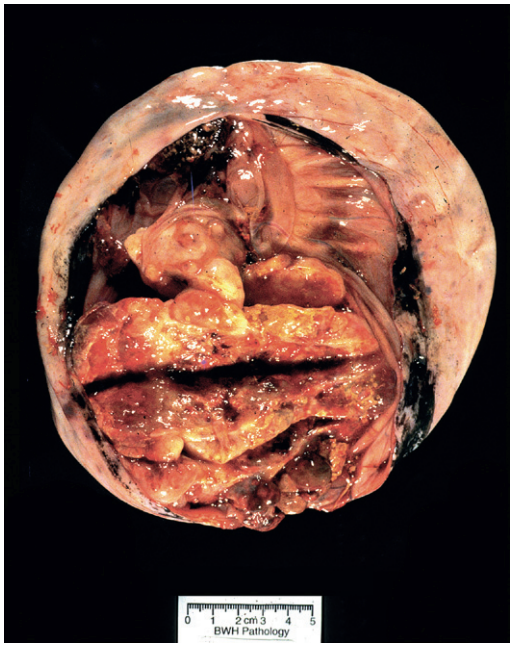

FIGURE 1
Yolk sac tumor with a solid and cystic cut surface.

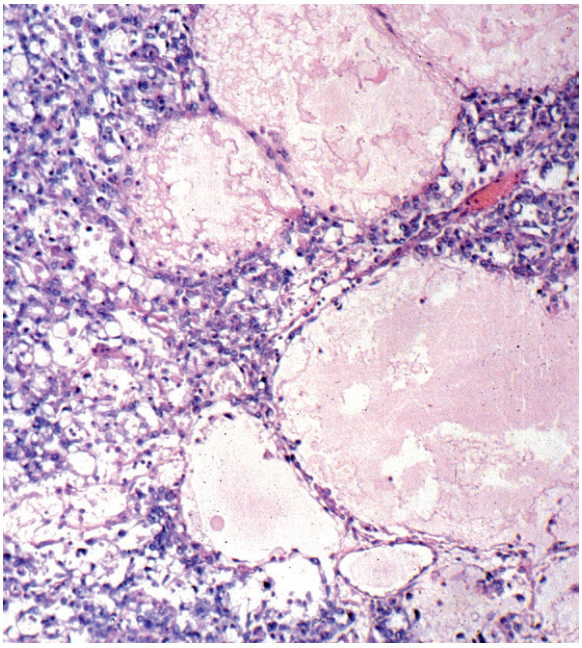

FIGURE 2
Yolk sac tumor. The polyvesicular pattern consisting of cystic spaces arranged in a soap bubble–like configuration.

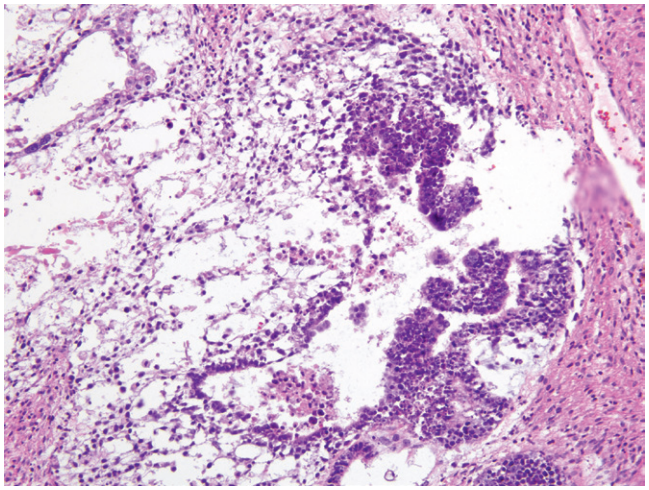

FIGURE 3

Yolk sac tumor. The microcystic pattern composed of a lacelike arrangement of primitive malignant cells.

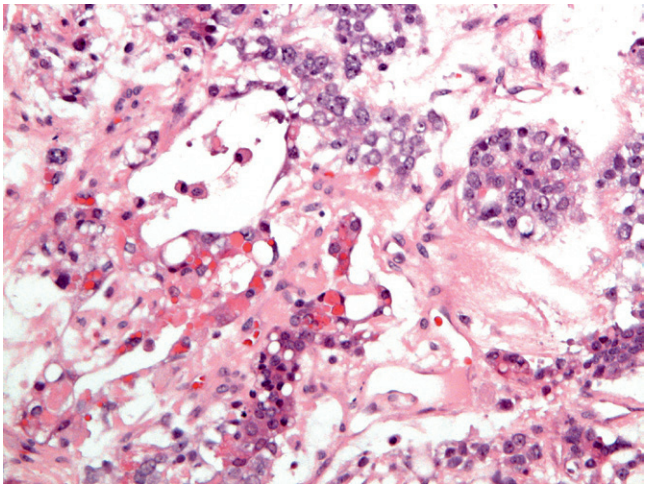

FIGURE 4

Yolk sac tumor. Numerous round, brightly eosinophilic hyaline bodies may be seen.

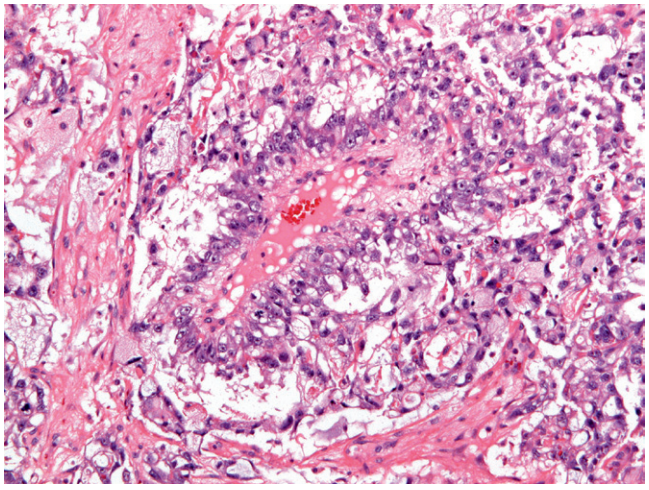

FIGURE 5

Yolk sac tumor. The endodermal sinus pattern composed of small to large Schiller-Duval bodies.

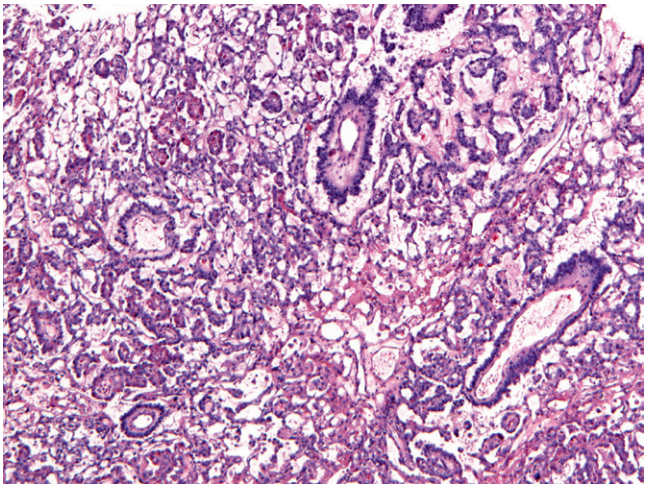

FIGURE 6

Yolk sac tumor. Numerous Schiller-Duval bodies can be seen.

EMBRYONAL CARCINOMA

Definition—A malignant, primitive germ cell tumor of the ovary with embryonic differentiation.

Clinical Features

Epidemiology

- Rare; represents less than 5% of all malignant ovarian germ cell tumors.
- Most cases arise in patients in their teens or twenties with a median age in the mid-teens.

Presentation

- Rapidly growing ovarian mass.
- Most are stage I when diagnosed.
- Elevated serum levels of alpha fetoprotein (AFP) and, in many cases, human chorionic gonadotropin (HCG).

Prognosis and Treatment

- High relapse rate by surgery alone.
- Highly sensitive to chemotherapy (bleomycin, etoposide, and cisplatin).
- Cure rate exceeds 95% even with bulky metastatic disease.
- Prognostic data is limited because of small number of cases in the literature, but long-term remissions are seen with chemotherapy.

Pathology

Histology

- Gross examination of the ovary will reveal a solid gray to tan with variable hemorrhage and necrosis.
- The low-power appearance is characterized by aggregates of primitive tumor cells that resemble malignant germ cells (dysgerminoma) but are arranged in glandlike structures, papillae with unpolarized cells and sheets.
- The tumor cells have large, variably shaped, vesicular nuclei with eosinophilic nucleoli, and very large nuclei may be seen as well as indistinct cell borders.
- There can be marked variability in nuclear size; giant cells or syncytiotrophoblastic cells may be seen, but cytotrophoblasts are absent except in true mixed germ cell tumors with choriocarcinoma.

Immunopathology (Including Immunohistochemistry)

- Positive for SOX2, NANOG, OCT-3/4, and CAM5.2.
- Negative for D2-40.

Main Differential Diagnosis

- Yolk sac carcinoma—less atypia; growth patterns will distinguish from embryonal carcinoma.
- Clear-cell carcinoma or poorly differentiated carcinoma—older age in general and negative for SOX2, NANOG, and OCT-3/4.

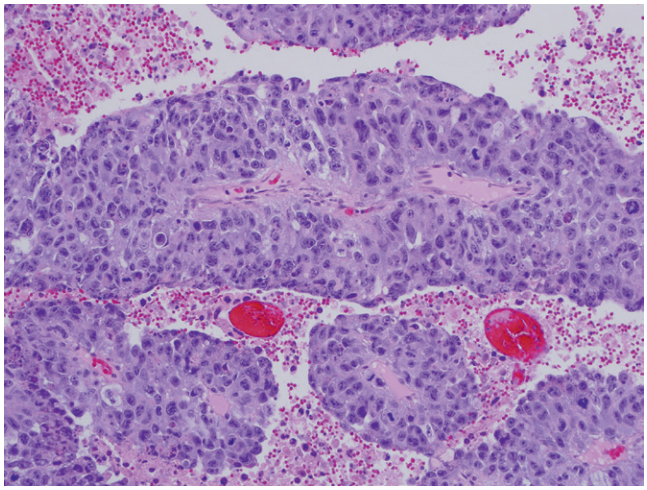

FIGURE 1

Embryonal carcinoma of the ovary. Note the papillary architecture and mildly polarized epithelioid cells with nuclear pleomorphism and nucleoli.

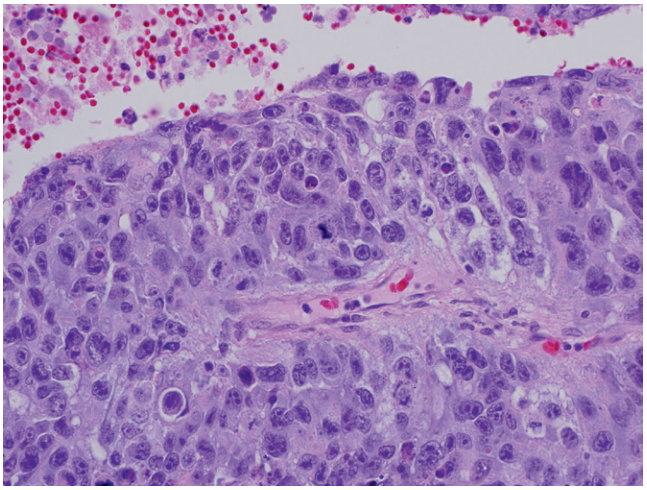

FIGURE 2

At higher power the cells exhibit nuclear enlargement with prominent nuclei. Note the more irregular nuclear spacing, a feature contrasting with conventional dysgerminoma.

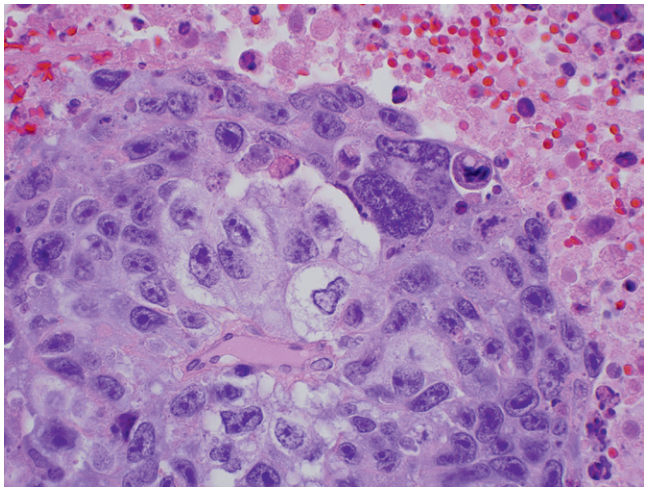

FIGURE 3

Very large nuclei can be seen in these tumors.

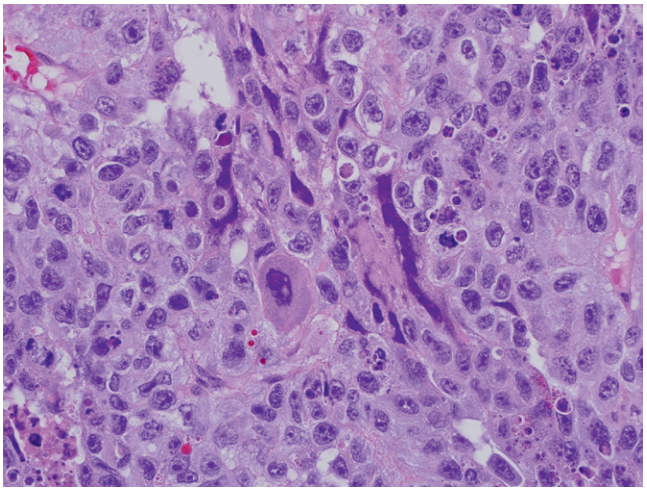

FIGURE 4

Syncytial giant cells *(center)* in an embryonal carcinoma can be associated with an elevated level of HCG.

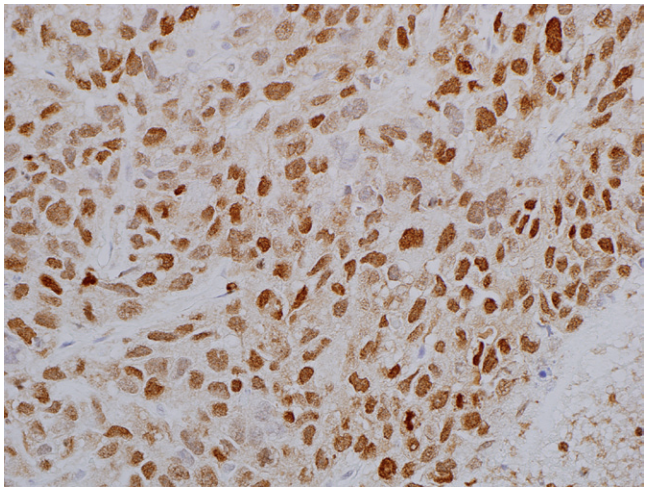

FIGURE 5

Staining for SOX2 highlights tumor cell nuclei.

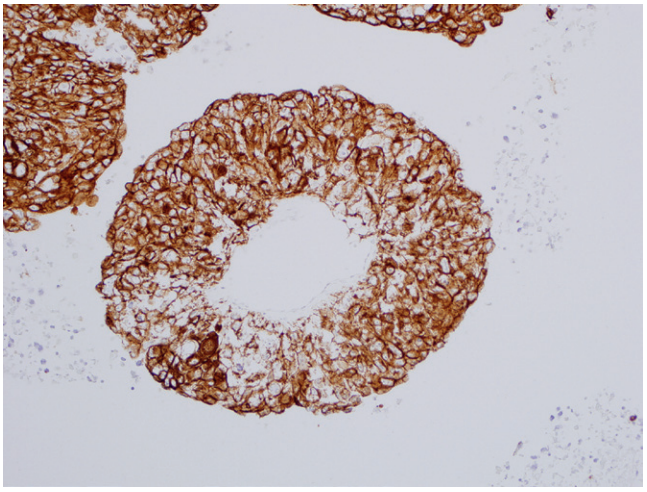

FIGURE 6

Strong staining for CAM5.2 will distinguish this tumor from a pleomorphic dysgerminoma.

IMMATURE TERATOMA

Definition—A malignant germ cell tumor recapitulating fetal somatic differentiation.

Clinical Features

Epidemiology

- Rare, comprising less than 1% of all germ cell tumors but third most common malignant germ cell tumor in young women.
- Mean age of 19 years; 75% are under age 35.

Presentation

- Pelvic mass.
- Always unilateral, although some (about 15%) will have a contralateral mature cystic teratoma.

Prognosis and Treatment

There are five categories of management.

- Stage I grade I immature teratomas require no more therapy (95% cure rate).
- Stage I grade II or III teratomas will require chemotherapy (bleomycin, ~75% cure rate). There is no evidence that contralateral oophorectomy or radiation therapy will improve survival.
- Gliomatosis peritonei is a concurrent or subsequent condition where glial tissue is of a different origin and does not affect outcome.
- Enlarging teratoma syndrome is an expanding terminally differentiated teratoma post chemotherapy. Curable with complete excision.

Pathology

Histology

- These tumors have a mixture of somatic elements in various stages of immaturity.
- Rarely, tumors may have only mild immaturity, and such neoplasms behave in a benign fashion.
- Grading is based principally on the amount of immature neuroepithelium, either as tubules or other primitive neuroectodermal differentiation.
  - Grade I—immature neural tissue is seen in less than a single 40× field per slide.
  - Grade II—immature neural tissue exceeds grade I but not more than three 40× fields per slide.
  - Grade III—primitive neural tissue exceeds three 40× fields per slide.
- One pitfall is overinterpreting germinal matrix or cerebellum as immature neuroepithelium.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Primitive neuroblastic tumors (PNET) in mature teratomas—these tumors are monomorphic and lack other immature elements.
- Germinal matrix differentiation in mature cystic teratomas.
- Rarely mature solid teratomas will be encountered and must be sampled carefully to exclude immature elements.

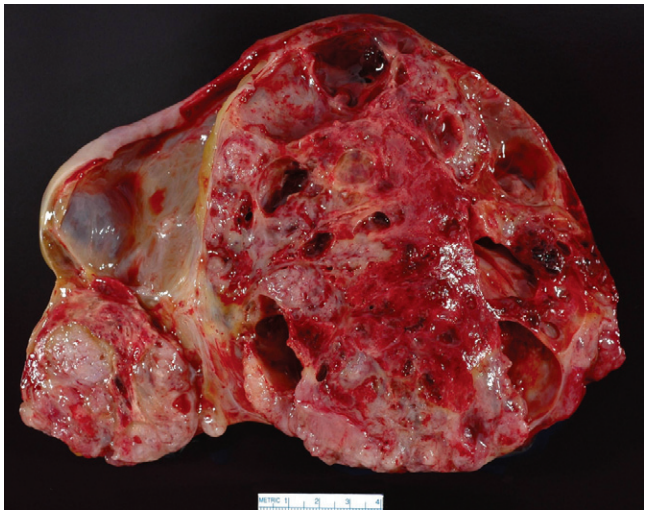

FIGURE 1

Immature teratoma. The tumor is a large encapsulated mass containing tissues of different consistency, some of which resemble cartilage.

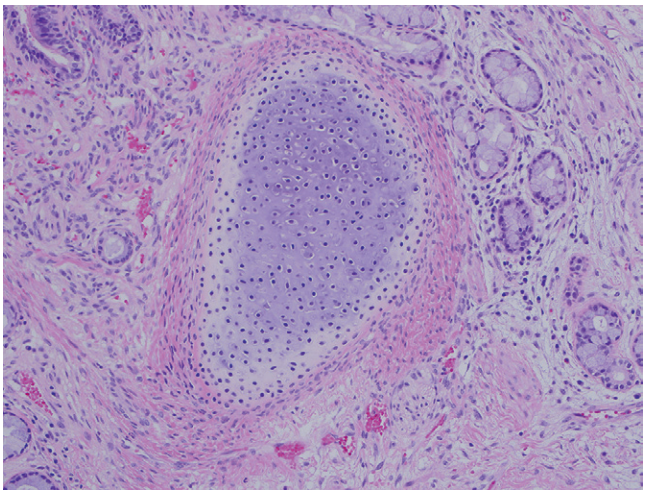

FIGURE 2

Immature cartilage in an immature teratoma. This is not used for the purposes of grading.

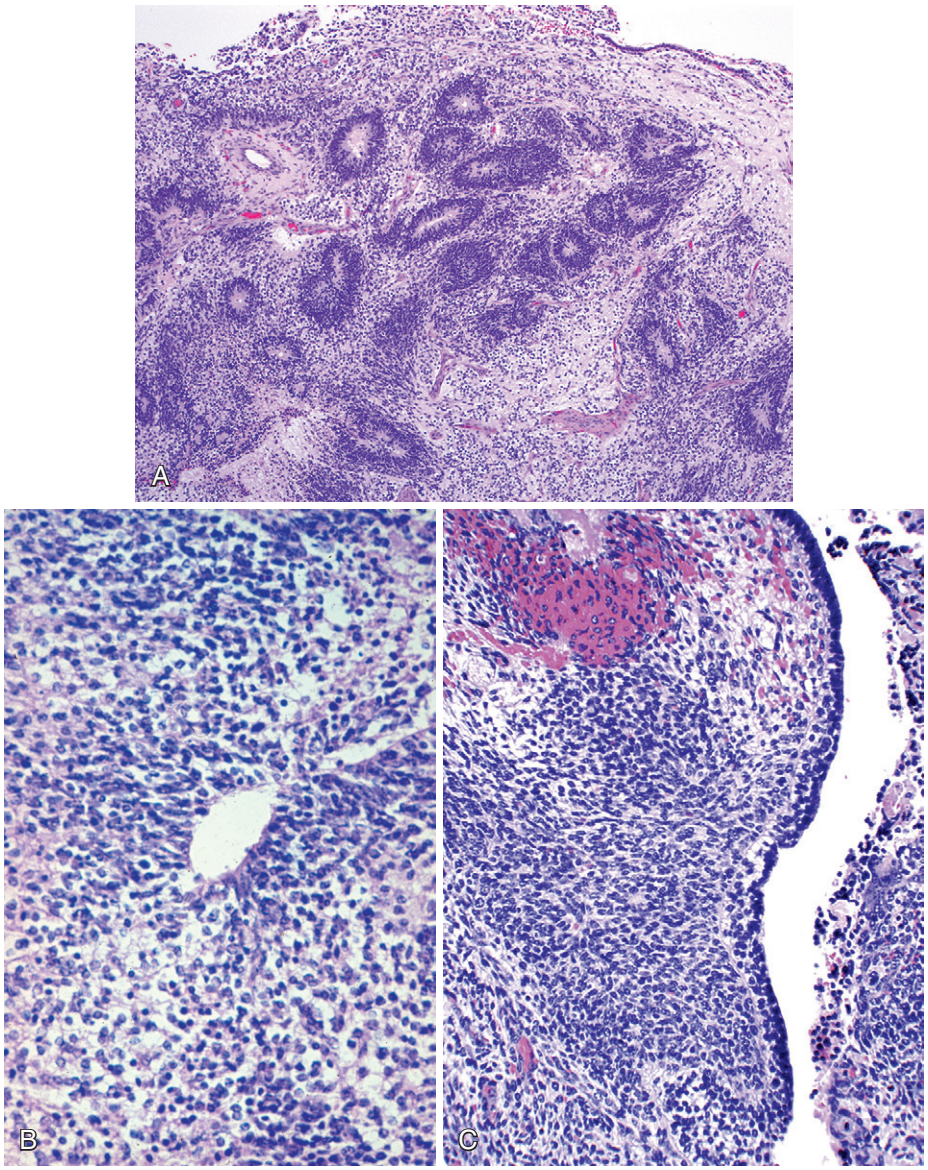

FIGURE 3

Grading of immature teratoma is based on the quantity of immature neuroepithelium, present as organized tubules **(A)** or disorganized primitive neuroectodermal cells **(B)**. Immature mesenchyme **(C)** for comparison.

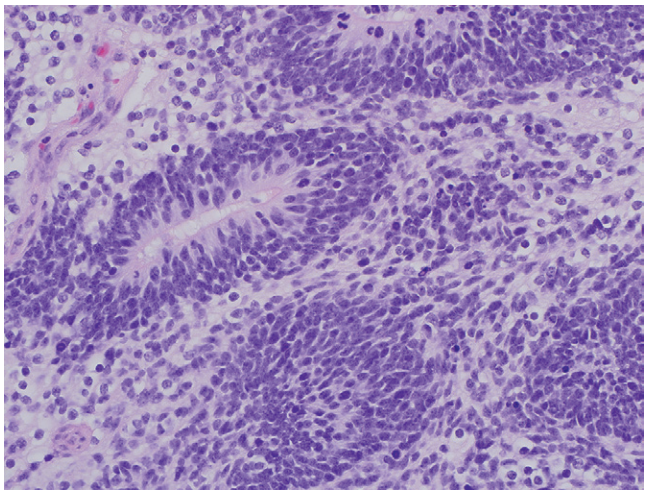

FIGURE 4

Higher magnification of immature neuroepithelium.

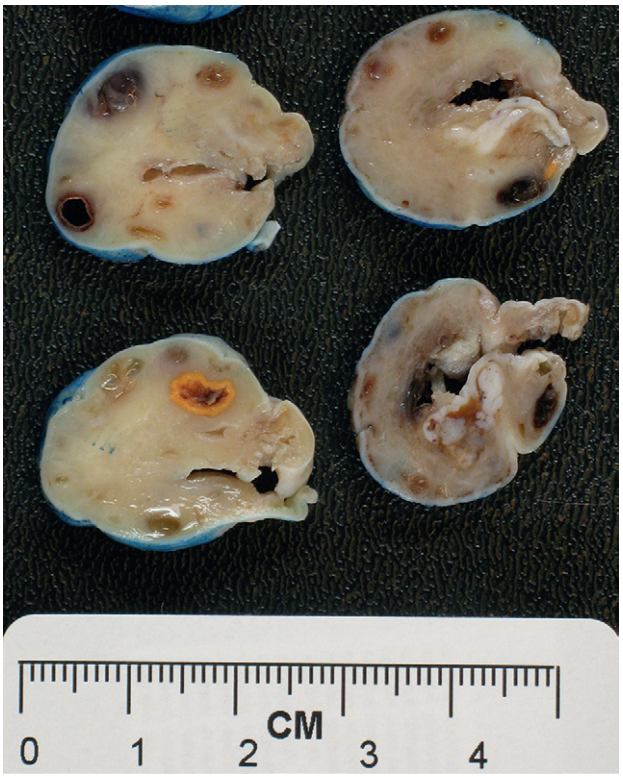

FIGURE 5

Unusual recurrent teratoma after therapy. This ovary is replaced by entirely mature teratomatous tissue.

MIXED GERM CELL TUMOR

Definition—A malignant germ cell tumor of the ovary with two or more germ cell elements.

Clinical Features

Epidemiology

- Rare; represents less than 5% of all ovarian germ cell tumors.
- Most cases arise in patients in their teens or twenties.

Presentation

- Rapidly growing ovarian mass, irregular bleeding, and isosexual precocity.
- Elevated serum lactate dehydrogenase in at least 95% of patients.

Prognosis and Treatment

- More than half of all cases are still confined to the ovary at the time of diagnosis.
- Most recurrences occur in the first 2 years after initial diagnosis.
- Metastatic spread is to lymph nodes (iliac, mediastinal, supraclavicular) and later to solid organs (liver, lungs, bone). Lymphadenectomy is typically performed given the increased risk of nodal involvement.
- With treatment, survival rates for stage I disease are over 90%. Some greater risk of recurrence for tumors with choriocarcinomatous or grade III immature teratoma.
- For tumors limited to one ovary, patients are followed with the expectation of almost 100% salvage, with chemotherapy for those that relapse.
- These tumors are highly sensitive to radiation, but chemotherapy has almost completely replaced radiation therapy in their management.

Pathology

Histology

- Typically large (15 to 20 cm) tumors with variable hemorrhage and necrosis depending on the germ cell elements.
- Any combination of germ cell features can be seen, including yolk sac carcinoma, choriocarcinoma, dysgerminoma, embryonal carcinoma, and immature teratoma.

Immunopathology (Including Immunohistochemistry)

- Positive for PLAP (membranous), CD117, OCT-4, LDH (usually), and desmin.
- Negative for CD30, EMA, and AFP.
- Results are variable for keratins (usually weak) and HCG (usually only in syncytiotrophoblasts, but rarely in the cytoplasm of dysgerminoma).

Main Differential Diagnosis

- Dysgerminoma or embryonal carcinoma with syncytial cells alone—this is not sufficient for a diagnosis of mixed germ cell tumor.
- Granulosa cell or Sertoli cell tumors with heterologous elements—these mixed patterns may be misinterpreted but should be distinguished from germ cell elements.
- Epithelial tumors with yolk sac carcinoma—these typically occur in older women; the clear-cell component may mimic embryonal carcinoma but is SOX2 negative.

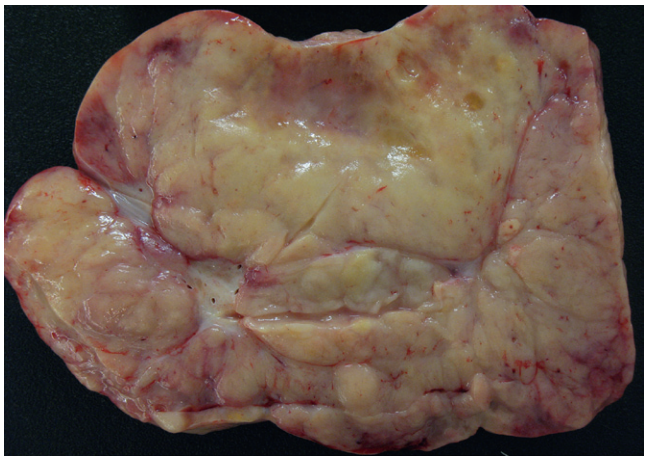

FIGURE 1

Mixed embryonal carcinoma and dysgerminoma. This tumor is predominantly dysgerminoma, and hence there is relatively little necrosis or hemorrhage.

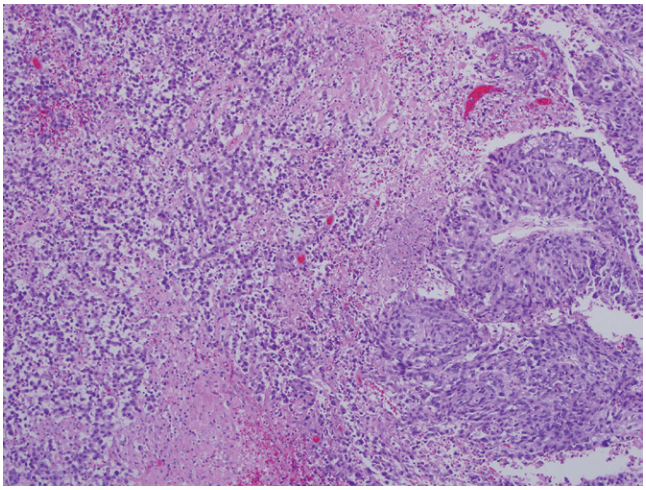

FIGURE 2

Embryonal carcinoma on the right versus dysgerminoma on the left.

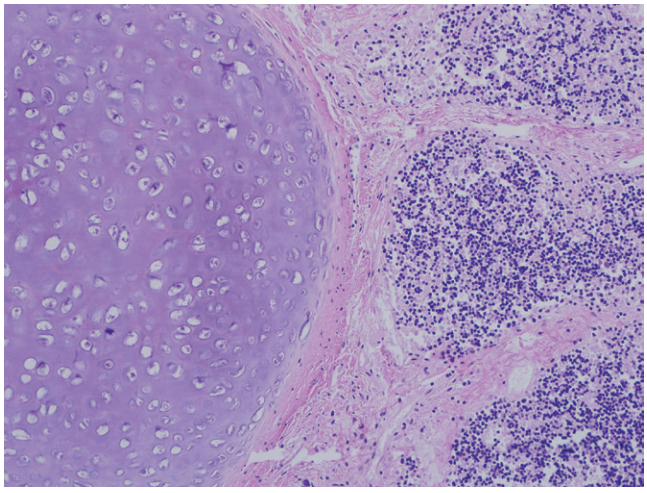

FIGURE 3

Mixed teratoma and yolk sac tumor. This focus contains immature cartilage and poorly preserved stroma.

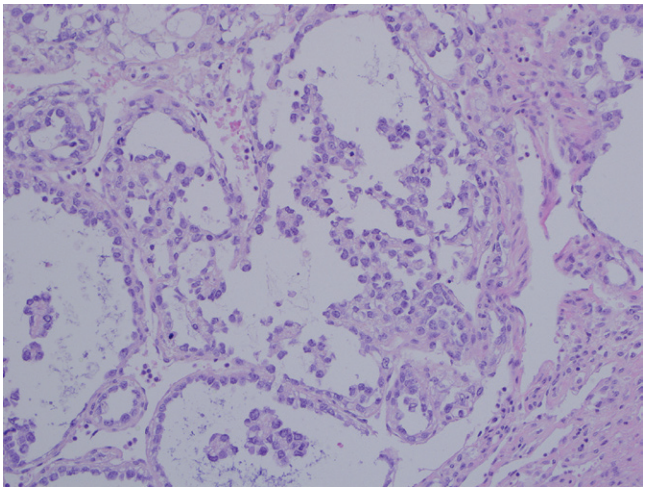

FIGURE 4

Mixed teratoma and yolk sac tumor. This focus contains yolk sac carcinoma.

THECOMA-FIBROMA

Definition—A benign ovarian stromal tumor composed of cells resembling ovarian stroma with variable theca cell differentiation.

Clinical Features

Epidemiology

- Fibromas are common, typically solitary, and found most commonly after menopause.
- Pure thecomas are rare and account for less than 1% of all ovarian tumors.
- Multiple fibromas can be encountered in Gorlin's syndrome, specifically in younger women.

Presentation

- Unilateral ovarian mass (less than 5% are bilateral).
- Postmenopausal women; about a decade older than women with fibromas.
- Mean age is 59 years.
- Fibromas usually are not associated with endocrine manifestations but hyperestrinism is present in about half of patients with thecomas and usually present as abnormal uterine bleeding.
- Thecomas are associated with endometrial hyperplasia or low-grade endometrioid carcinomas.
- Luteinized thecomas present with androgenic manifestations in 10% of patients.
- Luteinized thecomas are rarely associated with sclerosing peritonitis.

Prognosis and Treatment

- Excellent; these are benign tumors.
- Excision is curative.

Pathology

Histology

- *Thecoma:*
  - Grossly, thecomas are solid, smooth-surfaced masses with tan to yellow cut surfaces.
  - At low power thecomas are composed of nodules, sheets, and fascicles of plump spindled cells.
  - The tumor cells are fusiform, with vesicular oval nuclei, delicate nuclear membranes, and moderate to abundant amounts of palely eosinophilic cytoplasm.
  - Cytologic atypia is minimal, if present at all.
  - The stroma is composed of brightly eosinophilic collagen, and calcifications can be seen.
- *Luteinized thecoma:*
  - This type of thecoma is notable for the presence of either single luteinized cells or small clusters of luteinized cells.
  - The luteinized cells are small and round, with abundant clear cytoplasm.
- *Fibroma and Fibroma-thecoma:*
  - There is a significant degree of morphologic overlap between fibromas and thecomas; if there is a significant component of both, then the tumor should be termed "fibroma-thecoma" (the term thecoma should be reserved for tumors composed purely of thecoma cells).

Immunopathology and Special Stains (Including Immunohistochemistry)

- Positive for inhibin (diffuse) and CD10.
- Negative for keratin.
- Reticulin demonstrates positivity around each individual cell.

Main Differential Diagnosis

- Adult-type granulosa cell tumor—spindled variants will exhibit nested cell groups by reticulin staining.
- Fibrosarcoma—a rare tumor with atypia and high mitotic index.
- Smooth muscle tumor—look for classic smooth muscle fascicles.
- Sclerosing stromal tumor—these tumors exhibit a classic regional pattern of fibrosis.

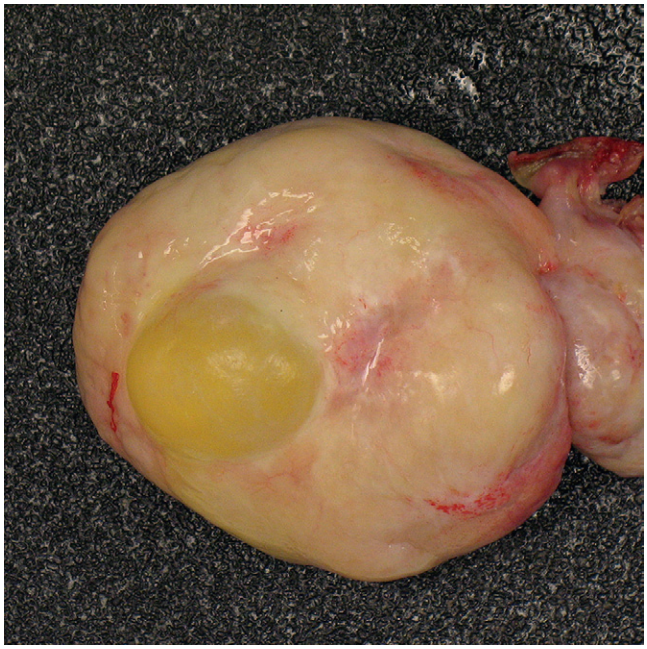

FIGURE 1

Thecoma gross image. Note the solid, vaguely nodular cut surface.

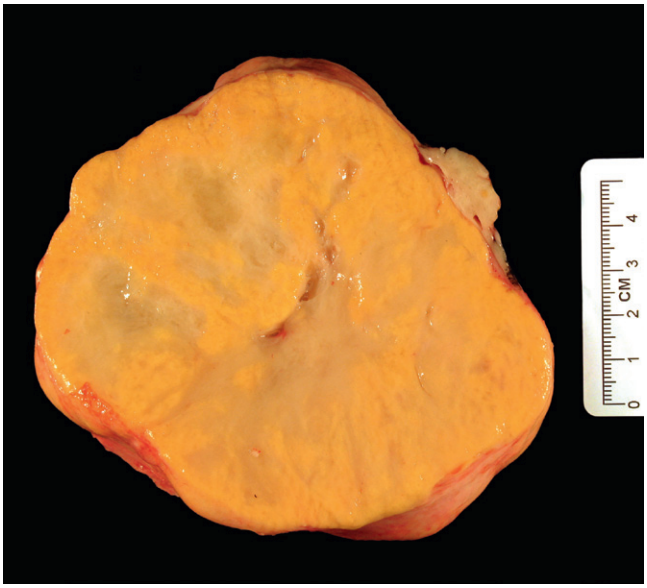

FIGURE 3

Luteinized thecoma. Note the yellow appearance in this gross image.

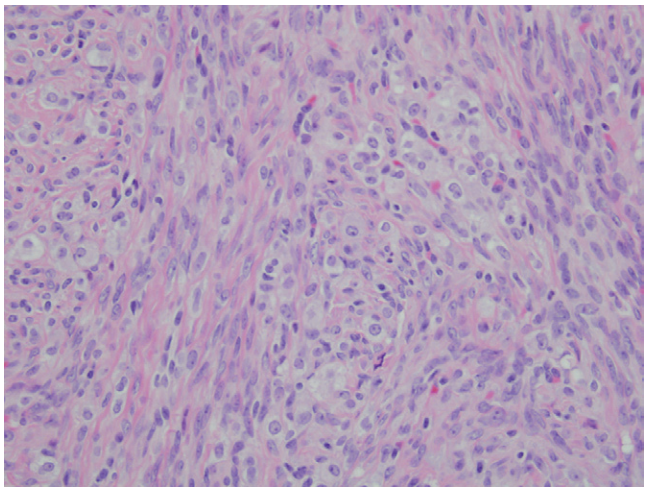

FIGURE 2

Thecoma-fibroma. Note the monotonous, somewhat fascicular population of bland cells. The nuclei are round to oval and have moderate amounts of cytoplasm.

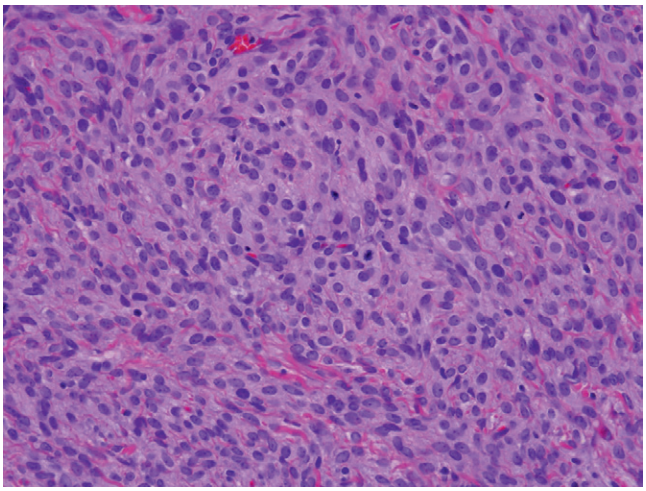

FIGURE 4

Luteinized thecoma. Note the plump-appearing cells with a vague spindled appearance.

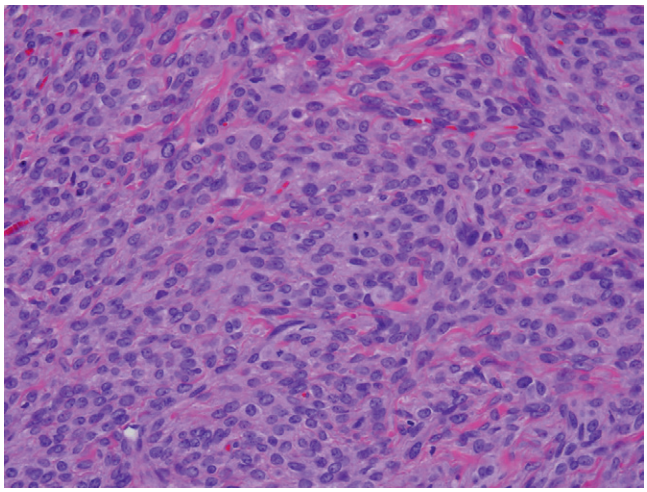

FIGURE 5

Luteinized thecoma. Note the plump-appearing cells with a vague spindled appearance.

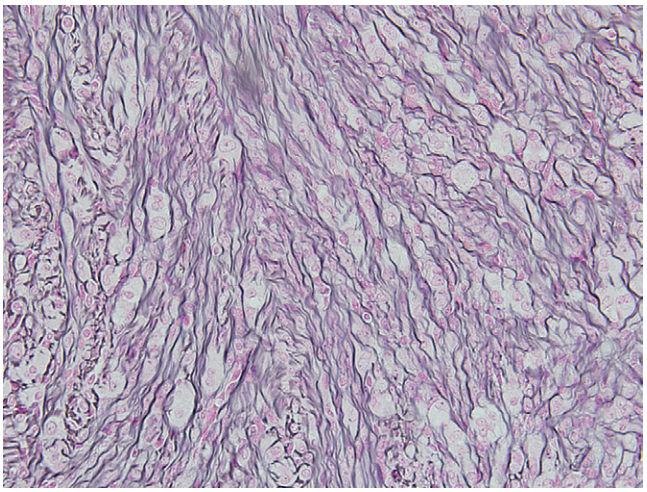

FIGURE 6

Thecoma-fibroma. A reticulin stain highlights individual cells. This is important for distinguishing this entity from a spindled granulosa cell tumor.

FIBROMA WITH MINOR SEX CORD ELEMENTS

Definition—A benign ovarian fibroma with nests or cords of sex cord elements.

Clinical Features

Epidemiology

- Rare.

Presentation

- Incidental.
- Presentation is the same as that for typical fibroma.

Prognosis and Treatment

- Excellent; these are benign tumors.
- Excision is curative.

Pathology

Histology

- At low power the majority of the tumor is identical to typical fibroma.
- The spindle cells are arranged in a storiform pattern with variable amounts of eosinophilic stroma.
- Scattered about the typical fibroma (accounting for less than 10% of the total tumor volume) are small tubules and/or cords of sex cord elements.
- The sex cord elements are composed of relatively large, epithelioid cells with abundant clear cytoplasm.

Immunopathology (Including Immunohistochemistry)

- Positive (sex cord elements) for inhibin.
- Negative (sex cord elements) for keratin and EMA.

Main Differential Diagnosis

- Granulosa cell tumor—these typically appear as cellular fibromas or fibro-thecomas with nested spindled areas as opposed to discrete sex cord elements. A recticulin stain will distinguish these areas of spindled granulosa cell tumor from the fibroma.
- Sertoli cell tumor—this tumor exhibits a broader distribution of tubules or blends a more poorly differentiated spindle cell component with the tubules (as in an intermediate-grade tumor). Leydig cells will also be seen in many instances.

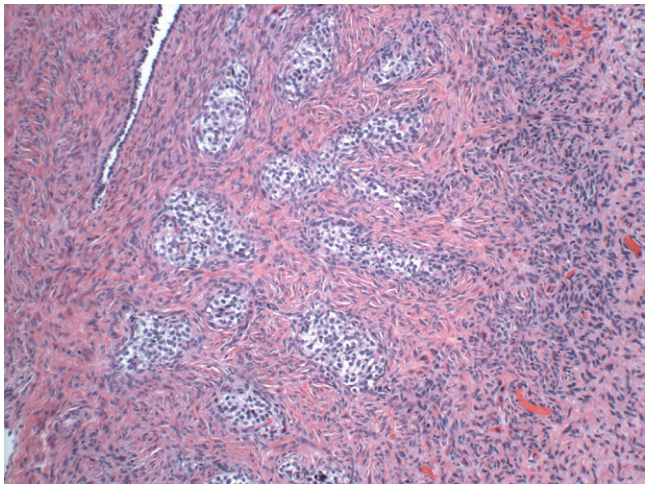

FIGURE 1

Fibroma with minor sex cord elements. At low power the background is that of a typical fibroma, but there is a second population of larger cells with abundant cytoplasm.

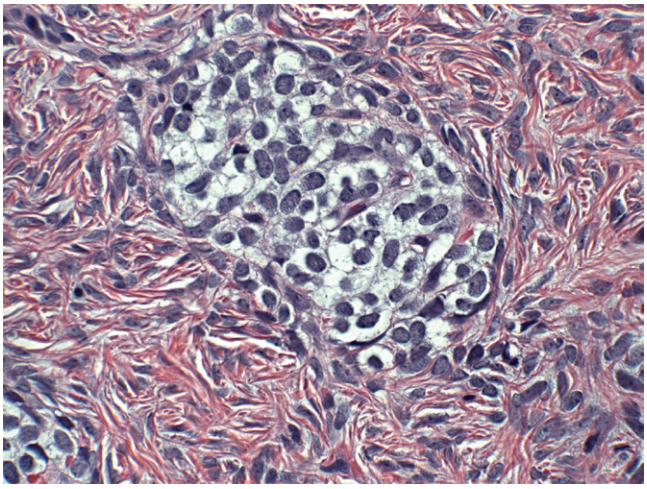

FIGURE 2

Fibroma with minor sex cord elements. At high power the sex cord elements are notable for their epithelioid appearance and nested growth pattern.

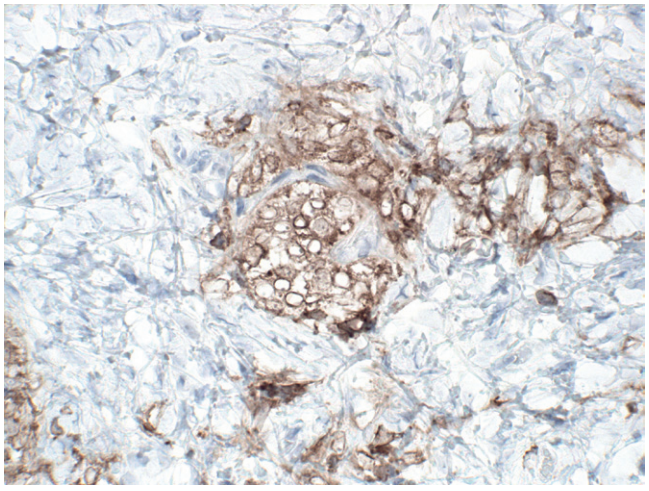

FIGURE 3

Fibroma with minor sex cord elements, inhibin stain. The sex cord elements are inhibin positive.

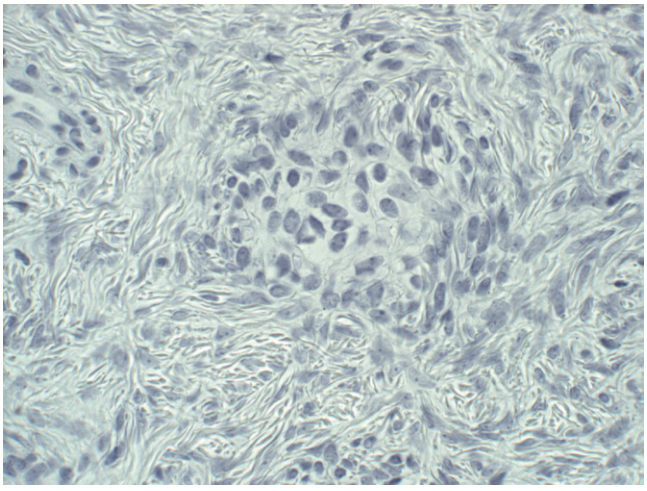

FIGURE 4

Fibroma with minor sex cord elements, keratin stain. The sex cord elements are keratin negative.

SCLEROSING PERITONITIS

Definition—A rare, potentially fatal process of thickening of the peritoneum/mesentery that has been rarely associated with luteinized thecomas.

Clinical Features

Epidemiology

- Sclerosing peritonitis is an uncommon entity that occurs most commonly in the seventh decade of life.
- There is no gender predilection, and cases have been associated with prior abdominal surgery or trauma; seen historically in association with dialysis and transplantation and in a few small series it has been associated with luteinized thecomas.

Presentation

- Most commonly patients present with abdominal pain or gastrointestinal symptoms including diarrhea or weight loss.
- Clinically, advanced lesions may simulate a malignant process or a mass.

Prognosis and Treatment

- The majority of patients are treated by excision of the mass.
- In lesions that cannot be surgically resected, medical treatment with thalidomide, tamoxifen, and prednisone has been helpful.
- Although this is a nonneoplastic process and the prognosis is good, death may result in advanced or refractory cases. Outcome was more favorable in some series with coexisting luteinized thecoma.

Pathology

Histology

- The histologic picture can be variable.
- The lesion is typically comprised of variable amounts of fat, fibrous tissue, and fat necrosis.
- A lymphohistiocytic infiltrate may be present and may be mild to extensive.
- Scattered calcifications may be present.
- Sclerosing peritonitis is a diagnosis of exclusion, and therefore other lesions in the differential should be ruled out (see Main Differential Diagnosis section).

Immunopathology (Including Immunohistochemistry)

- Noncontributory in diagnosis, but may be helpful to rule out lesions in the differential diagnosis.

Main Differential Diagnosis

- Desmoid fibromatosis.
- Inflammatory myofibroblastic tumor.
- Lymphoma.
- Gastrointestinal perforation (diverticulosis).
- Metastatic carcinoma.
- Well-differentiated liposarcoma.

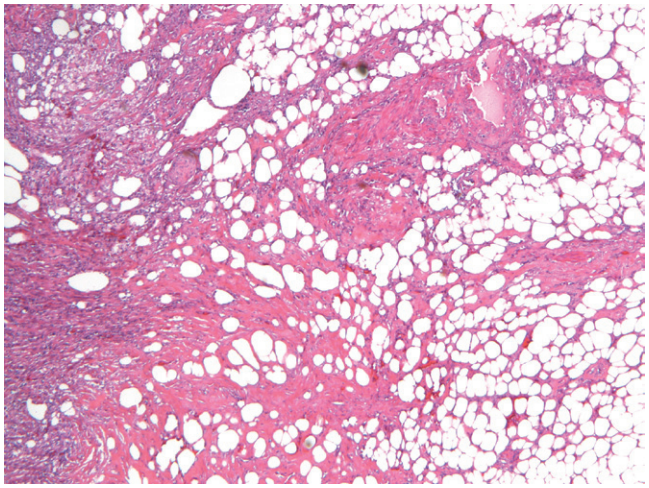

FIGURE 1

Sclerosing peritonitis. Fat necrosis, adipose cells, and fibrous tissue.

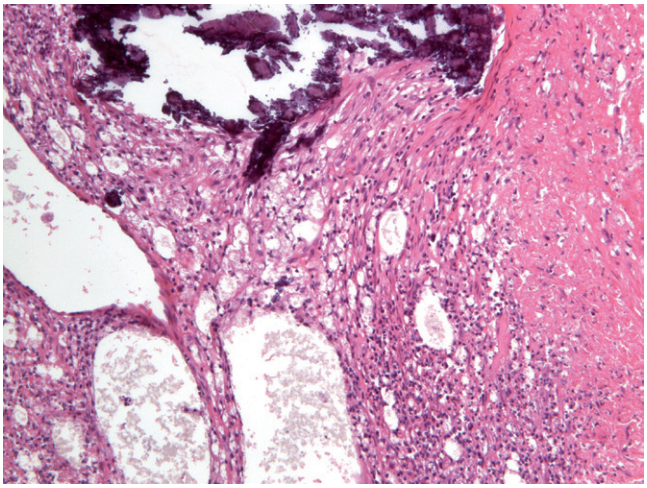

FIGURE 2

Sclerosing peritonitis. Fat necrosis with a chronic and histiocytic inflammatory infiltrate. Dystrophic calcification is present.

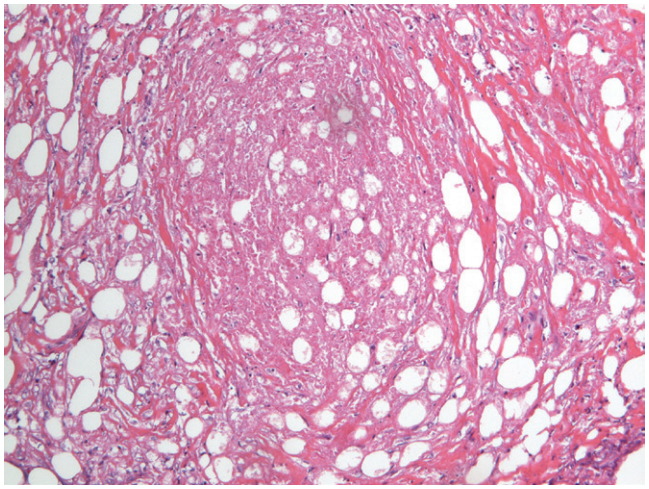

FIGURE 3

Sclerosing peritonitis. A nodule of fat necrosis with surrounding fibrous tissue and mature adipocytes.

GRANULOSA CELL TUMOR

Definition—An ovarian steroid-producing sex cord–stromal tumor composed of cells resembling the granulosa cells of the developing follicle.

Clinical Features

Epidemiology

- Uncommon.
- Perimenopausal or postmenopausal women.
- Mean age at presentation is in the mid-50s.

Presentation

- Androgenic or estrogenic symptoms; anovulatory pattern endometrium on endometrial biopsy is typical.
- The most common ovarian malignancy to present with spontaneous rupture.
- Unilateral ovarian mass (less than 10% are bilateral).

Prognosis and Treatment

- Most (more than 90%) of the patients present with stage I disease, and the 5- and 10-year survival is +90%.
- Five-year survival for patients who present with more advanced disease (stage 2 and above) is about 40%.
- Late recurrence (up to 20 years) is common. Recurrence is often managed with surgical re-excision.
- Although often employed for advanced or recurrent tumors, the benefit of chemotherapy or radiotherapy is unclear.
- Favorable prognostic indicators are Stage I, less than 15 cm in diameter, and an intact tumor capsule.

Pathology

Histology

- Gross examination is variable; these tumors can be solid or cystic, and hemorrhage is not uncommon.
- The cut surface is often yellow, owing to the steroid-producing cells.
- The low-power appearance and architectural patterns of adult-type granulosa cell tumor (GCT) are quite variable.
- The low-power appearance ranges from predominantly cystic with few identifiable tumor cells to solid sheet-like growth and can resemble a carcinoma or sarcoma.
- The classic description is of the microfollicular architectural pattern with frequent Call-Exner bodies and eosinophilic luminal secretions.
- Other patterns include diffuse, macrofollicular, insular, trabecular, and the so-called "watered silk."
- The tumor cells themselves are characteristic; they are monotonous uniform blue nuclei with delicate nuclear membranes and prominent grooves and folds ("coffee-bean" nuclei).
- Nuclear atypia can be seen and does not portend a worse prognosis. Some reports link increased recurrence risk with elevated mitotic index (> 4 per 10 400× fields) but this association with prognosis is not observed in all reports.
- The cytoplasm is usually minimal to moderate in quantity and slightly eosinophilic, but this too is highly variable.

Immunopathology (Including Immunohistochemistry)

- Positive for calretinin, inhibin, and CD99.
- Negative for keratins (including CK7), EMA, and neuroendocrine markers.
- Reticulin staining will reveal nests of cells rather than outlining individual cells.

Main Differential Diagnosis

- The differential diagnosis varies tremendously with the histologic pattern encountered.

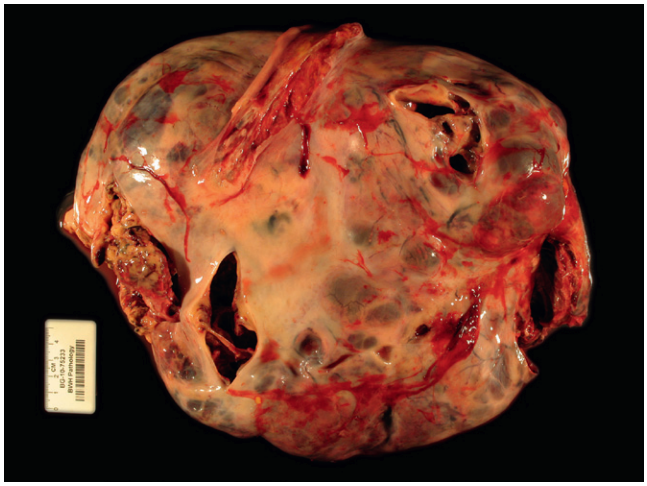

FIGURE 1

Adult-type GCT. Gross image. Note the multifocal hemorrhage and solid and cystic composition of the tumor on sectioning.

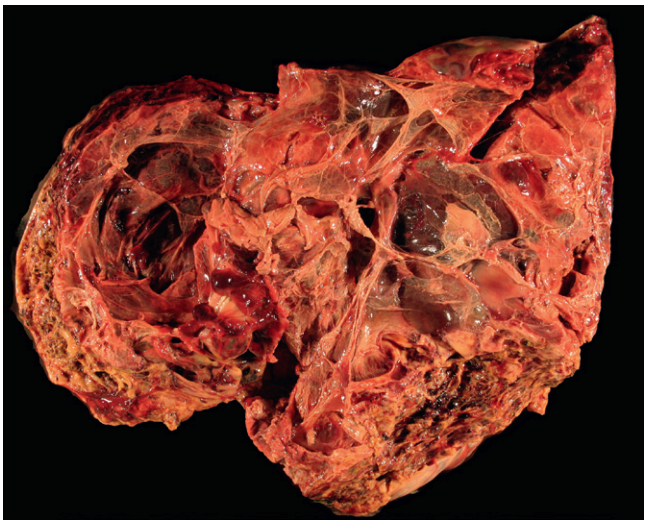

FIGURE 2

Cystic adult-type GCT. Gross image. Note that the tumor is predominantly cystic, but the cyst walls are thickened.

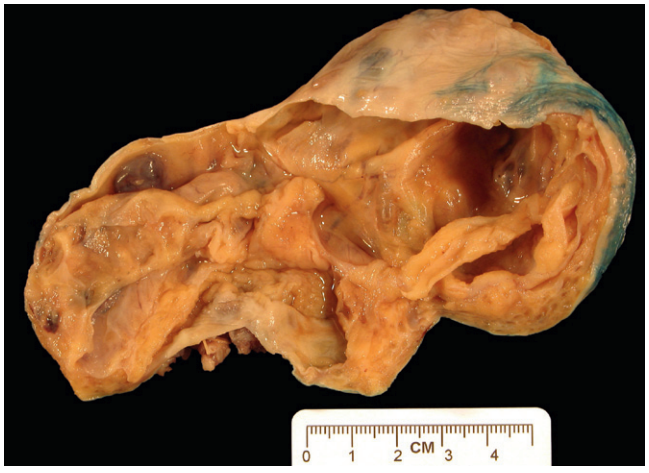

FIGURE 3

Another cystic GCT.

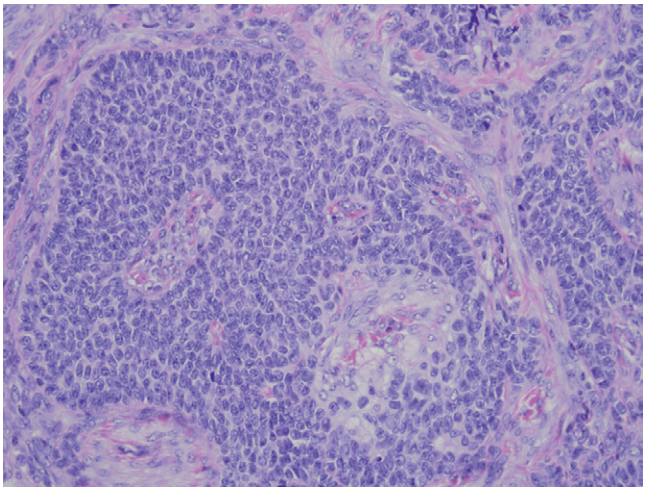

FIGURE 4

Adult-type GCT. Note the solid sheets of uniform cells with unremarkable nuclear features.

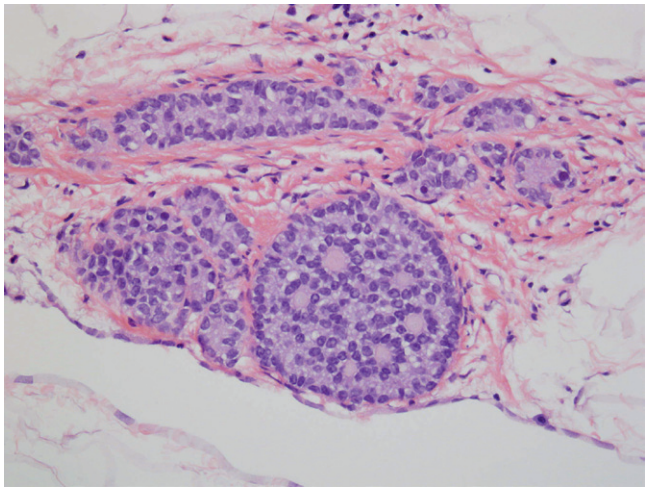

FIGURE 5

This focus of GCT in the omentum highlights the microfollicular pattern with Call-Exner bodies.

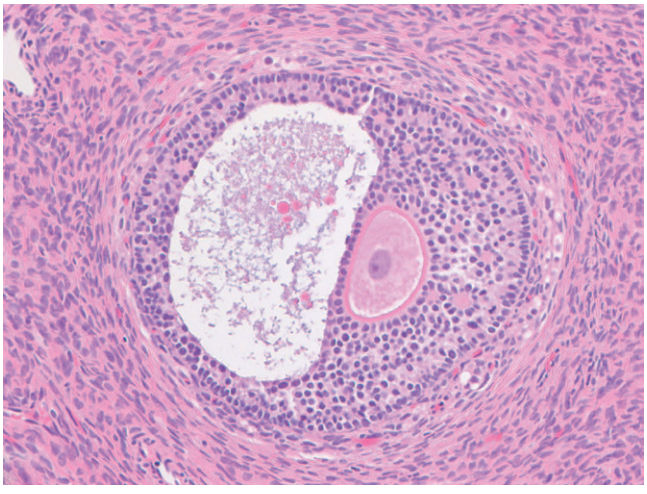

FIGURE 6

A normal follicle with granulosa cells for reference.

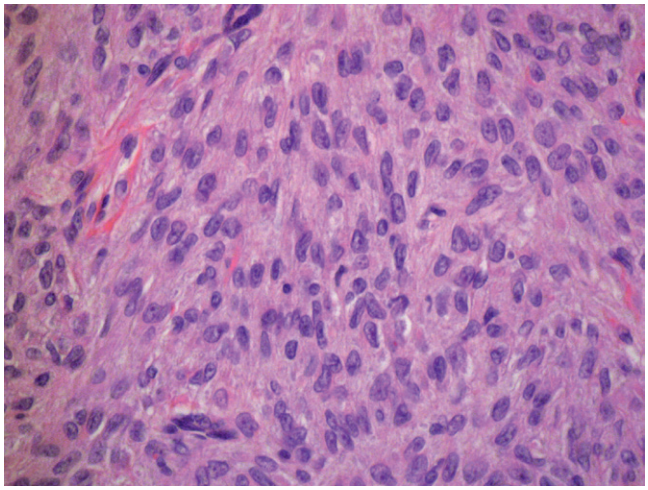

FIGURE 7
Adult-type GCT. Note the "coffee bean" nuclei.

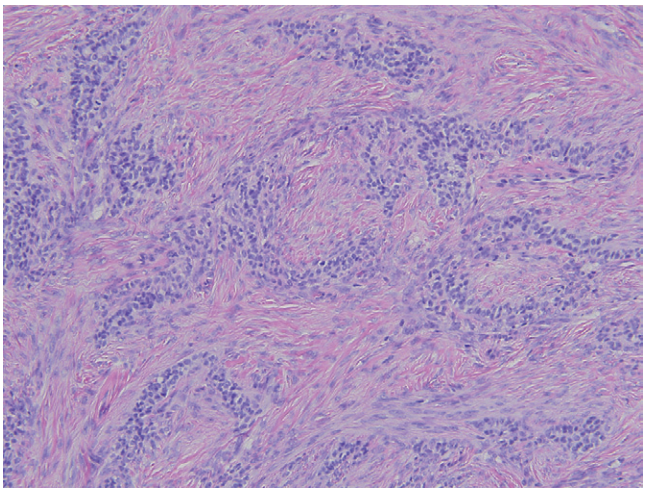

FIGURE 8
Adult-type GCT. The alternating tumor cell aggregates and fibrous stroma create a wavelet pattern (watered silk).

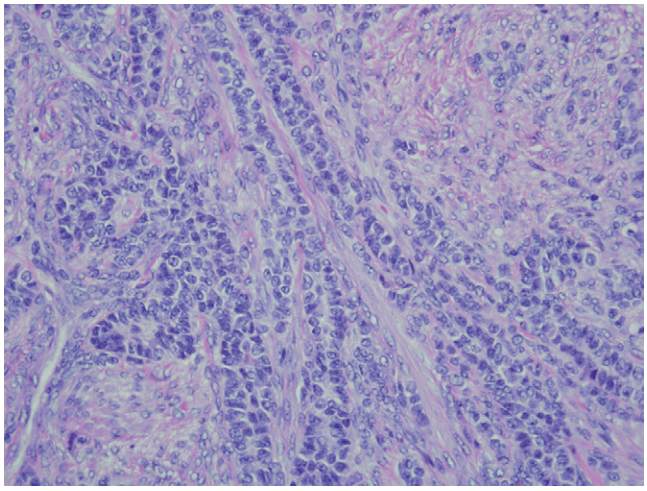

FIGURE 9
Adult-type GCT with a prominent trabecular pattern.

GRANULOSA CELL TUMOR VARIANTS

PITFALL

Definition—Diagnostically challenging variant patterns include those with nuclear atypia, cystic architecture, thecoma-like, luteinized, and sertoliform.

Clinical Features

Epidemiology

- Uncommon. The granulosa cell tumor (GCT) comprises less than 2% of ovarian tumors. Over 90% will be adult type (versus juvenile GCT).
- Perimenopausal or postmenopausal women.
- Mean age at presentation is in the mid-50s.

Presentation

- Androgenic or estrogenic symptoms; anovulatory pattern endometrium on endometrial biopsy is typical.
- Unilateral ovarian mass (less than 10% are bilateral).

Prognosis and Treatment

- Most (more than 90%) of patients present with stage I disease, and the 10-year survival is at least 85%.
- Five-year survival for patients who present with more advanced disease (stage 2 and above) is less than 50%.
- Recurrence occurs within the first 5 years after diagnosis.

Pathology

Histology

- Thecoma-like pattern is predominantly spindle cells. The important features of GCT are more rounded nuclei and focal loss of the spindle cell morphology. A reticulin stain is key to identifying the nests of tumor granulosa cells.
- Cystic GCTs may mimic cystic follicles. The number of neoplastic granulosa cells in the cyst lining may vary, and multiple sections may be needed to reveal these cells.
- Nuclear atypia can be profound in both adult and juvenile GCTs. By itself it does not portend a worse outcome.
- The sertoliform variant may demonstrate ribbons or multiple acinar structures. The characteristic coffee bean nuclei and older age are helpful parameters for distinguishing this from a Sertoli-Leydig cell tumor.

Immunopathology (Including Immunohistochemistry)

- Positive for calretinin, inhibin, and CD99.
- Negative for keratins (including CK7), EMA, and neuroendocrine markers.
- Reticulin staining will reveal nests of cells in the spindled variant.

Main Differential Diagnosis

- Spindle cell pattern—fibroma-thecoma, leiomyoma, and leiomyosarcoma.
- Cystic pattern: large follicle cyst.
- GCT with atypical nuclei—mesenchymal tumors and carcinosarcoma.
- Sertoliform—Sertoli cell tumor, trabecular carcinoid, and struma or strumal carcinoid.
- Luteinized—stromal luteoma and luteinized thecoma-fibroma.

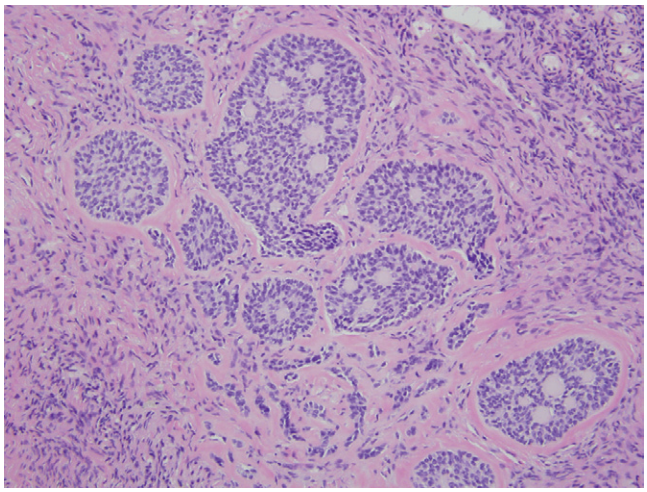

FIGURE 1
Microscopic GCT in the ovary.

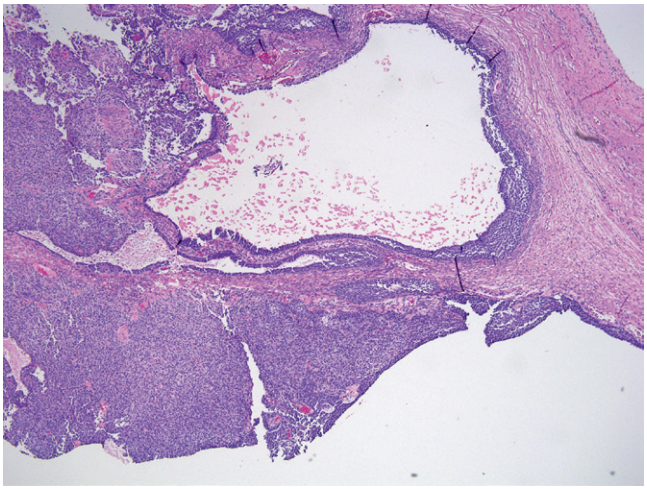

FIGURE 2
Cystic adult-type GCT.

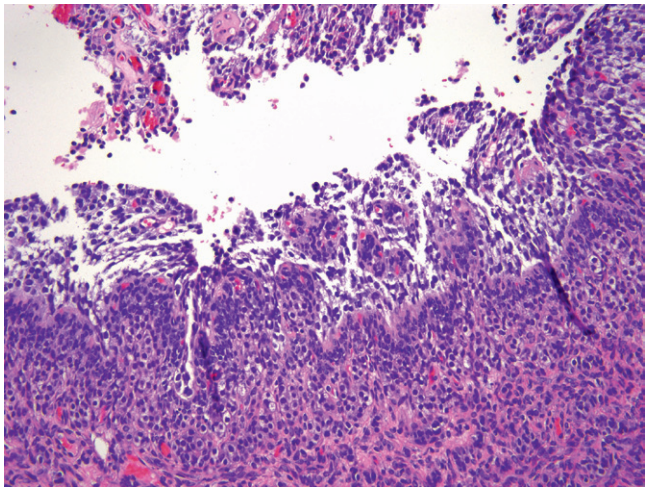

FIGURE 3
Cystic adult-type GCT. Note theca cells at the base of the granulosa cell–lined cyst.

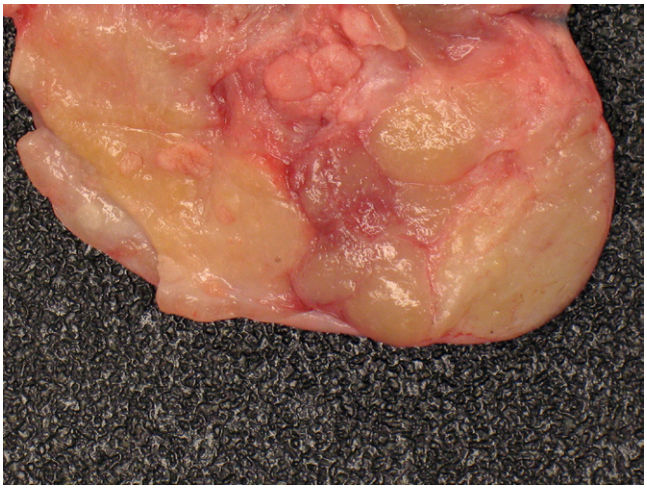

FIGURE 4
Luteinized adult-type GCT. Gross image. This luteinized example is solid and fleshy on cut section. Note the tan/white to yellow appearance.

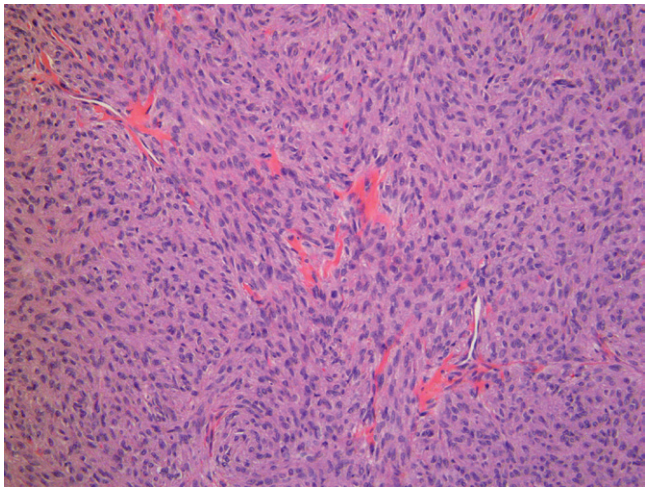

FIGURE 5
Luteinized GCT.

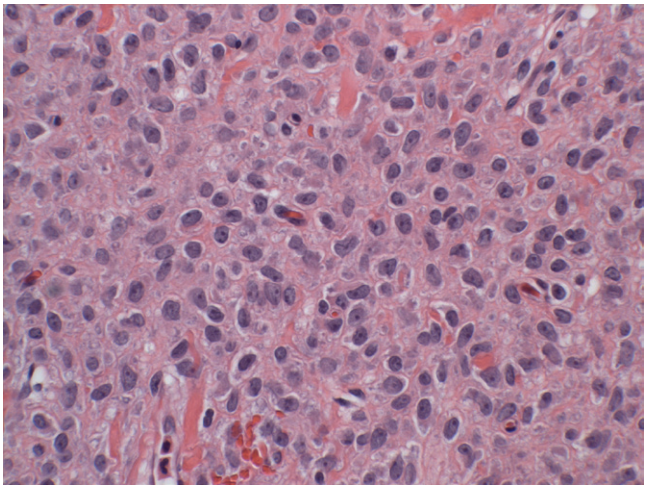

FIGURE 6
Luteinized GCT at higher power. Note the abundant cytoplasm and spaced nuclei.

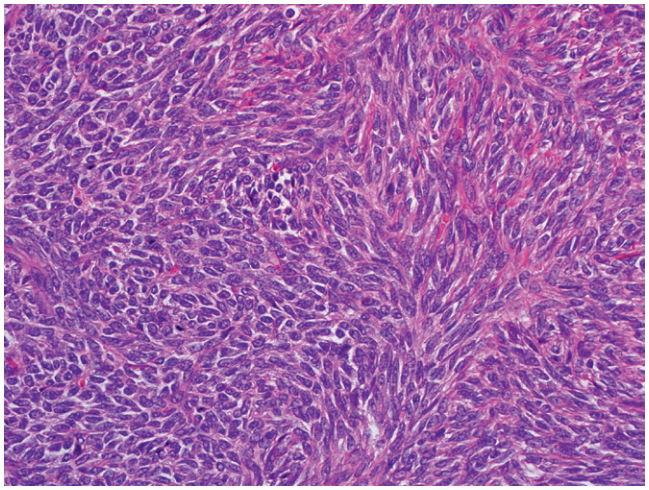

FIGURE 7

GCT with spindle features. The field at left has a faint nesting pattern in contrast to the more spindled appearance at upper right.

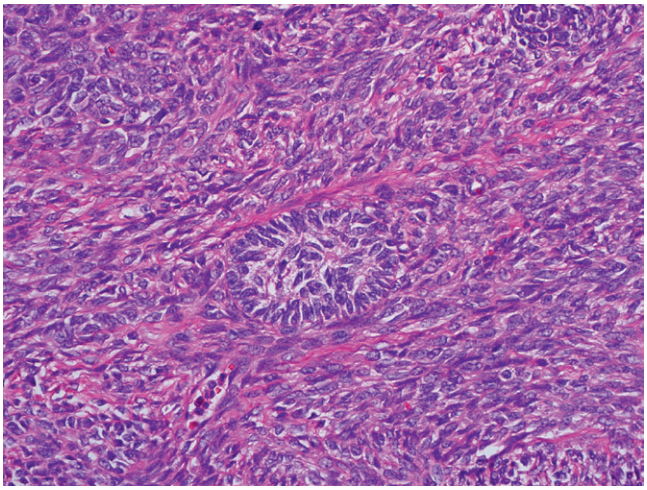

FIGURE 8

GCT with spindle features. Note the single sertoliform nest in the center.

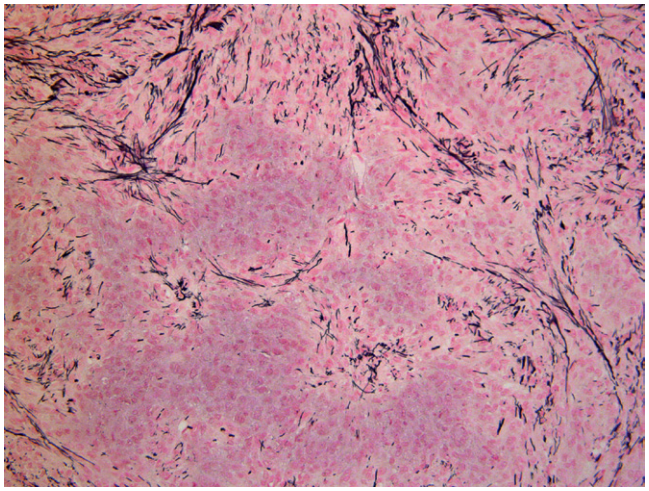

FIGURE 9

A reticulin stain highlights granulosa cell nests in a spindle cell GCT.

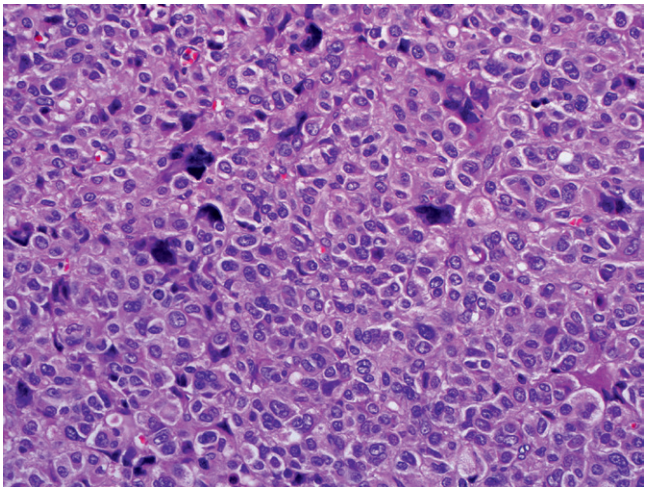

FIGURE 10

Adult-type GCT with marked atypia.

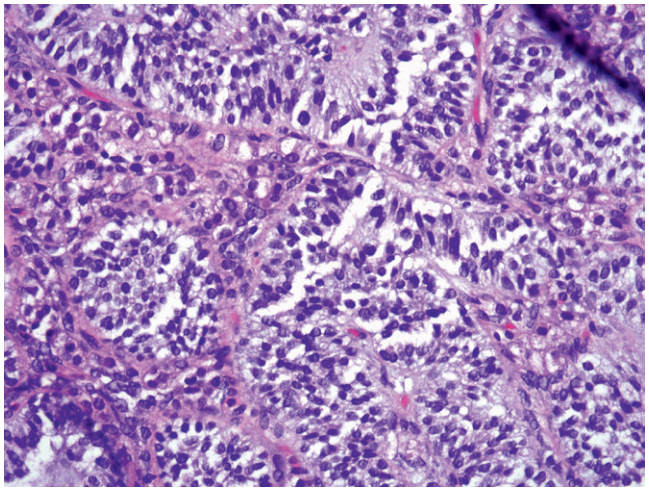

FIGURE 11

Adult-type GCT with tubules mimicking Sertoli cell tumor.

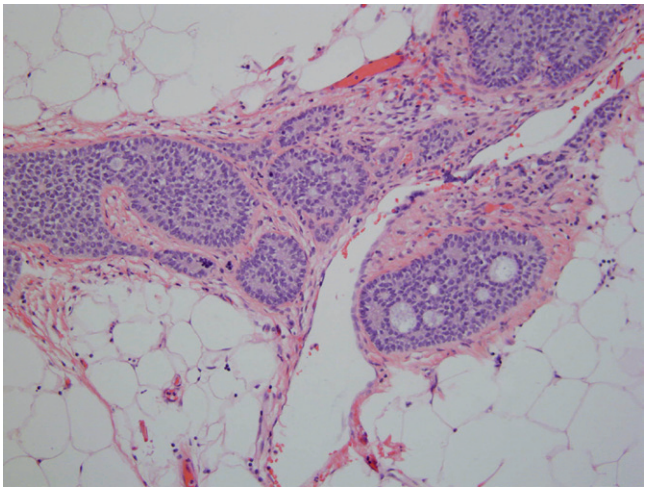

FIGURE 12

Metastatic GCT to the peritoneum.

JUVENILE GRANULOSA CELL TUMOR

PITFALL

Definition—A sex cord–stromal tumor seen in the first decades of life that closely resembles the developing follicle.

Clinical Features

Epidemiology

- Granulosa cell tumors (GCTs) comprise less than 2% of ovarian tumors.
- Juvenile GCTs comprise less than 10% of all GCTs.
- Accounts for only 10% of ovarian tumors in patients younger than age 20.
- Nearly all (more than 95%) occur before age 30, and 40% occur before age 10.

Presentation

- Unilateral ovarian mass; less than 2% are bilateral.
- Isosexual pseudoprecocity is not uncommon in young patients, owing to estrogens produced by the tumor.
- In postpubertal patients, abdominal pain, swelling, and abnormal uterine bleeding are common presenting symptoms.

Prognosis and Treatment

- Prognosis and outcomes are closely linked to stage.
- More than 95% of patients present at stage Ia, and the 10-year survival approaches 90%.
- Surgical excision (unilateral salpingo-oophorectomy) is the treatment for early-stage tumors.
- Debulking and combination chemotherapy are reserved for advanced or metastatic disease.
- Less than 10% of patients experience disease recurrence.

Pathology

Histology

- In contrast to the varied patterns of adult-type GCT, the juvenile-type GCT is characterized by a nodular and diffuse pattern of tumor cell growth.
- The cells are set in a myxoid or edematous matrix rather than the fibrothecomatous background of an adult-type GCT; in some cases, the background may be extensively hyalinized.
- Call-Exner bodies are rarely seen, but follicle-like spaces of various size and shape are prominently scattered throughout the tumor.
- The cells lining the cystic follicle-like spaces can exhibit a hobnail appearance.
- The tumor cells themselves are large and hyperchromatic, without prominent nuclear grooves.
- Cytologic atypia can be prominent, and atypical mitoses may be seen.
- The cytoplasm is relatively abundant and may be palely eosinophilic to vacuolated.
- Spindled theca cells can be seen surrounding tumor cell nodules or admixed with the granulosa cells.
- Foci of adult-type GCT are not uncommon.

Immunopathology (Including Immunohistochemistry)

- Positive for inhibin and calretinin.
- Variably positive for WT1, EMA, keratin, S100, and SMA.

Main Differential Diagnosis

- Germ cell tumor—inhibin negative.
- Small cell carcinoma may be difficult given the presence of pseudofollicles; inhibin negative.
- Epithelial malignancy—rare cases of solid or undifferentiated epithelial growth; inhibin or calretinin negative.
- Adult-type GCT.

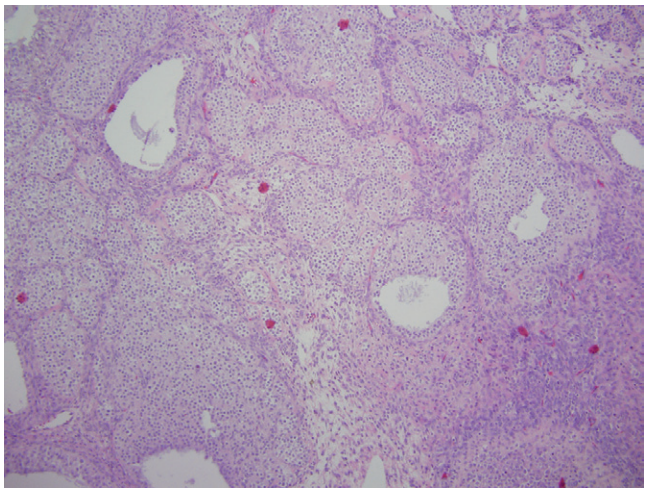

FIGURE 1

Juvenile-type GCT. The tumor is growing in a nodular pattern. Note the multiple follicle-like spaces.

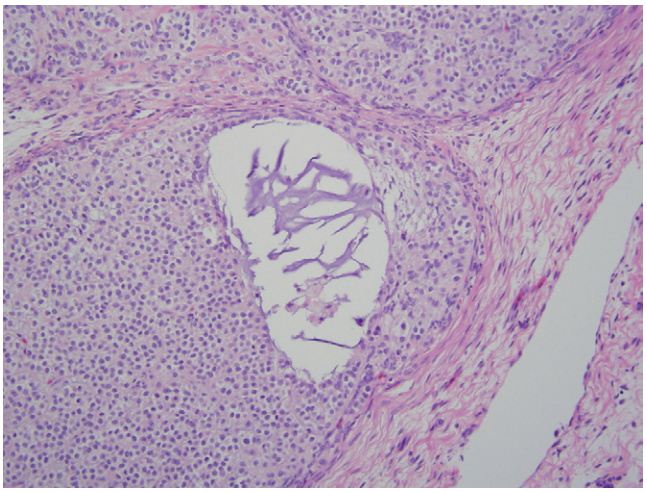

FIGURE 2

Juvenile-type GCT. Note the relatively abundant pale eosinophilic cytoplasm and the follicle-like spaces. Call-Exner bodies are absent.

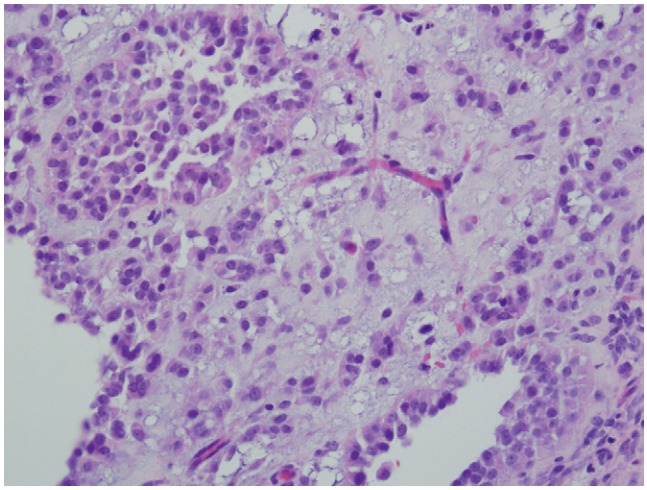

FIGURE 3

Juvenile-type GCT. At high power the myxoid background is apparent. Note the lack of nuclear grooves.

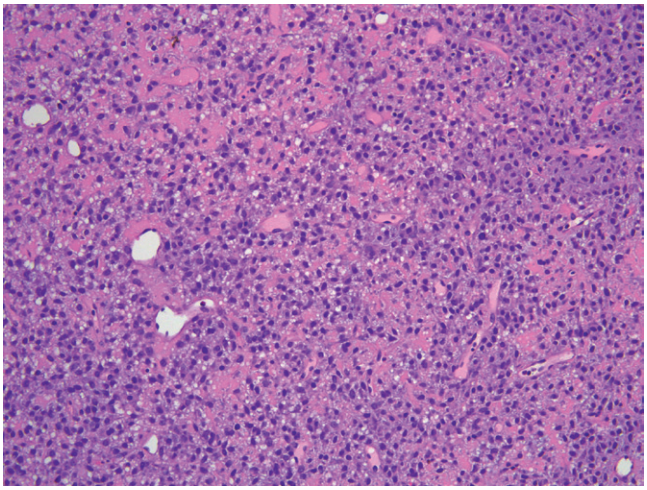

FIGURE 4

Juvenile-type GCT. In this image the background is alternately myxoid and hyalinized. The tumor cells are only mildly pleomorphic.

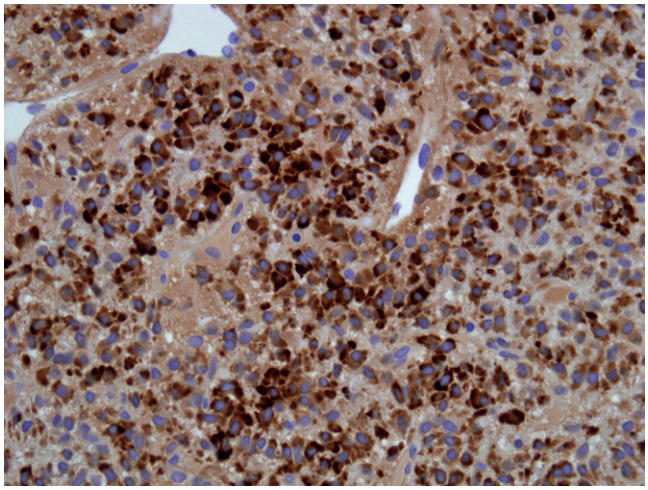

FIGURE 5

Juvenile-type GCT. Inhibin is strongly positive.

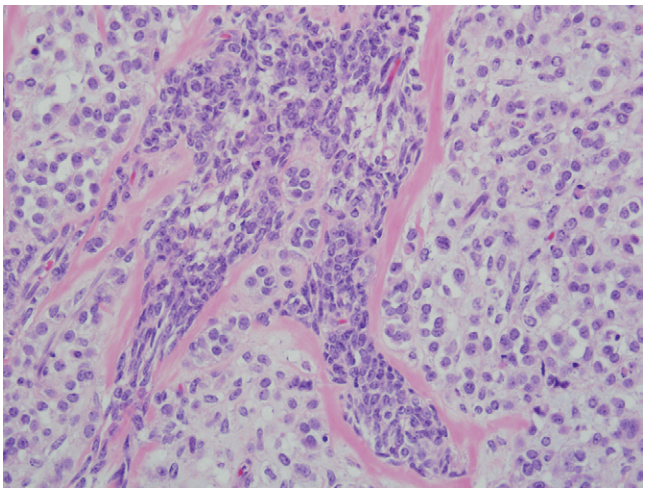

FIGURE 6

Juvenile-type GCT. A focus of adult-type GCT is present in the center of the image. Note the rounded cells with abundant cytoplasm (juvenile areas) on the edges of the image. In contrast, the adult-type focus had cells with minimal cytoplasm and darker nuclei and prominent grooves.

SERTOLI-LEYDIG CELL TUMOR

Definition—A sex cord–stromal tumor with testicular epithelial (Sertoli) and interstitial (Leydig) cell differentiation.

Clinical Features

Epidemiology

- These are rare tumors, comprising 1 : 2000 ovarian neoplasms.
- Usually seen in the second to fourth decades of life, but can occur after menopause. Well-differentiated tumor occurs in the 30s, whereas retiform variants are seen in teenagers.

Presentation

- Virtually always unilateral, as a mixed solid and cystic mass ranging from yellow to brown. If bilateral, most likely will not be a Sertoli-Leydig cell tumor (SLCT).
- Hemorrhage and necrosis are common.
- Fifty percent present with androgenic symptoms.

Prognosis and Treatment

- Prognosis is excellent in well-differentiated SLCTs.
- Odds of an adverse outcome increase with moderate and poorly differentiated SLCTs as well as the retiform variant.
- Poorly differentiated tumors can progress rapidly.

Pathology

Histology

- There are five variants: well, intermediate, poorly differentiated, retiform, and tumors with heterologous elements.
- Well-differentiated tumors exhibit prominent tubules lined by nonstratified rows of nuclei. May be cuboidal in appearance or more columnar and lipid rich. Leydig cells will be situated between tubules.
- Intermediate differentiation is characterized by less well-developed tubules, seen in the form of anastomosing cords in nodules of hypocellular edematous stroma. Leydig cells are situated at the periphery of the nodules.
- Poorly differentiated SLCTs demonstrate a spindle Sertoli cell morphology resembling primitive gonadal tissue, with scattered Leydig cell differentiation.
- Retiform histology is seen in 15% of intermediate and poorly differentiated SLCTs. Architectural patterns include poorly formed tubules and slit-forming glandlike structures in a stroma of variable cellularity, dilated spaces, and intraglandular micropapillary structures.
- SLCT with heterologous elements can be divided into two groups based on a limited amount of data. First, endodermal (gastrointestinal epithelium and carcinoid) elements: these are distinguished by the presence of typically benign-appearing mucinous epithelium including goblet cells or carcinoid tumor elements. Based on reports, these tumors have a favorable outcome. Second, SLCT with cartilage and skeletal muscle: in these tumors the poorly differentiated Sertoli cell component blends with areas of rhabdomyoblastic or cartilaginous differentiation. The outcome relative to SLCTs with endodermal differentiation is less favorable.

Immunopathology (Including Immunohistochemistry)

- Inhibin and calretinin staining are particularly helpful in excluding epithelial mimics and carcinoids.

Main Differential Diagnosis

- Well-differentiated tumors—include endometrioid tumors with sex cord–like differentiation, clear-cell carcinomas, Krukenberg tumors, strumal carcinoids, and tumors of wolffian origin.
- Intermediate and poorly differentiated tumors—carcinosarcomas.
- Retiform variants—low-grade serous tumors.

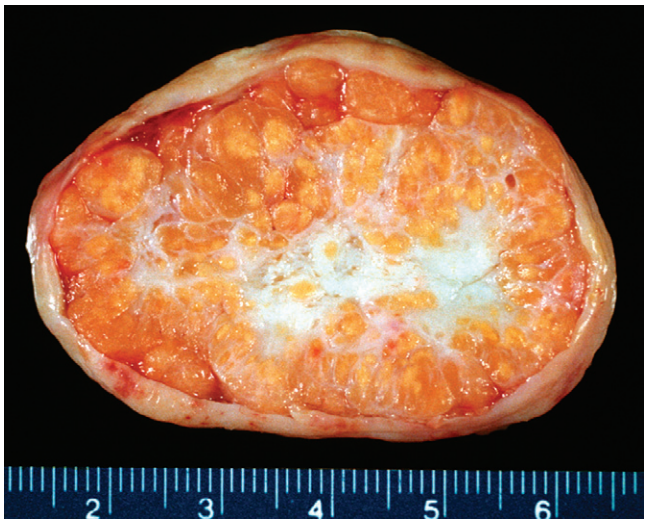

FIGURE 1

Sertoli-Leydig cell tumor (SLCT) with a characteristic golden brown appearance.

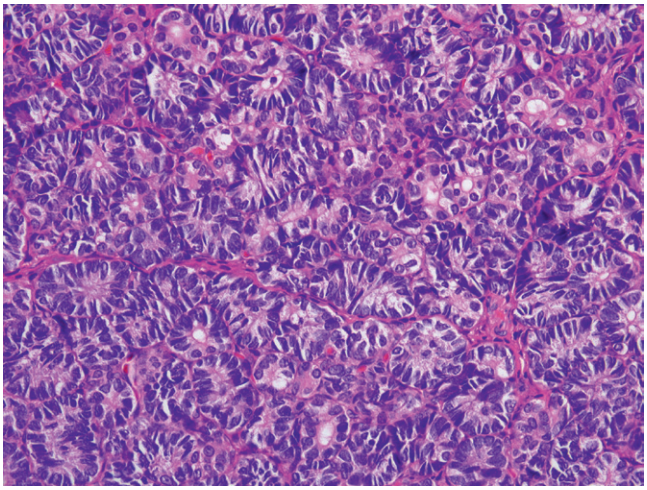

FIGURE 2

Well-differentiated SLCT with uniform tubules and interspersed Leydig cells.

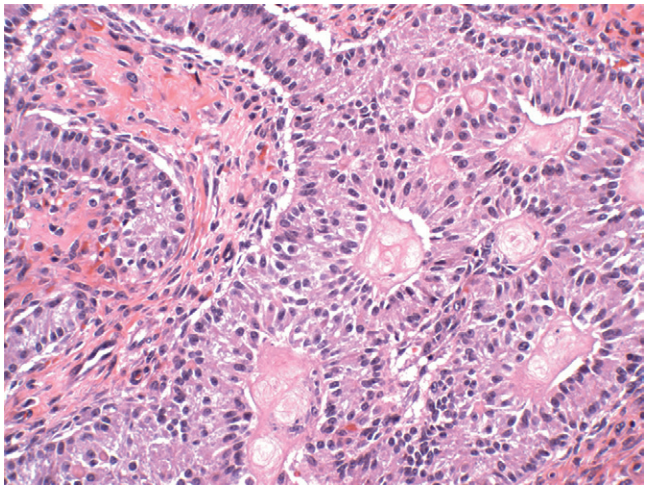

FIGURE 3

Well-differentiated SLCT with tall columnar cells lining tubules.

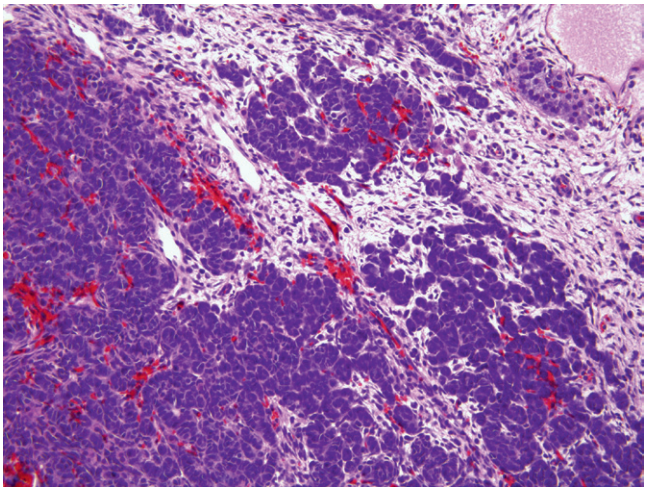

FIGURE 4

Intermediate SLCT with cordlike Sertoli cells in an edematous stroma.

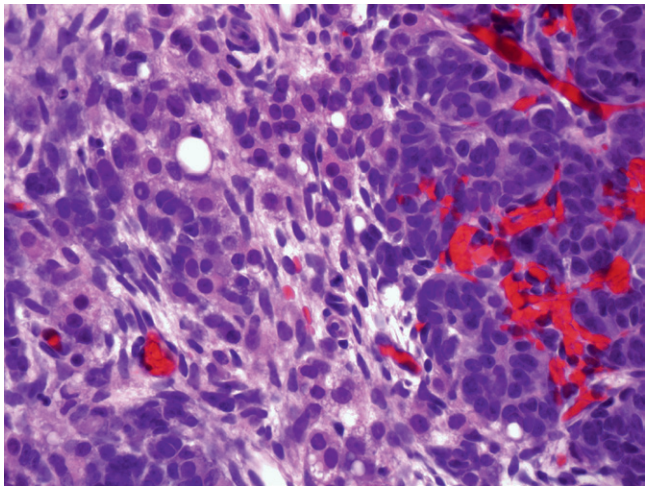

FIGURE 5
Intermediate SLCT with admixture of Sertoli cells and Leydig cells.

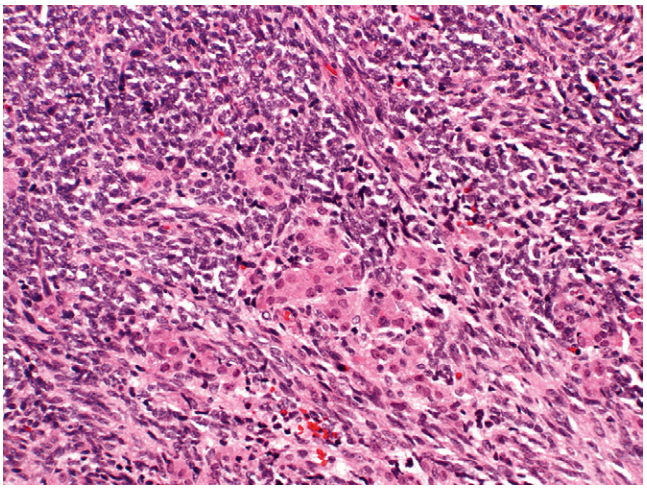

FIGURE 6
Poorly differentiated SLCT.

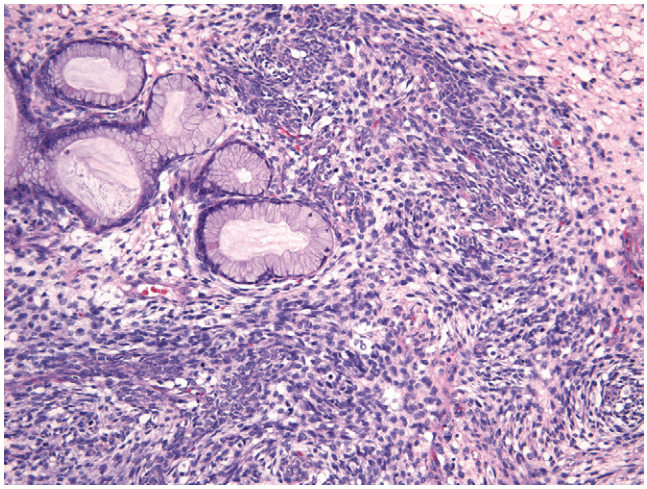

FIGURE 7
SLCT with heterologous elements.

RETIFORM SERTOLI-LEYDIG CELL TUMOR

PITFALL

Definition—A sex cord stromal tumor with testicular epithelial (Sertoli) and interstitial (Leydig) cell differentiation and a retiform architecture.

Clinical Features

Epidemiology

- These are rare variants of Sertoli-Leydig cell tumors (SLCTs), comprising less than 1:2000 ovarian neoplasms. Comprised about 10% of SLCTs in the study by Young and Scully.
- Usually seen in younger individuals (teenagers).

Presentation

- Virtually always unilateral, as a mixed solid and cystic mass ranging from yellow to brown. If bilateral, most likely will not be an SLCT.
- Abdominal mass, virilization, and amenorrhea (~25%) are common findings. Alpha-fetoprotein levels can be elevated if there is hepatic cell differentiation.

Prognosis and Treatment

- Prognosis for retiform SLCT is guarded, with a mortality of approximately 25%.

Pathology

Histology

- Most are intermediate differentiation, the rest are poorly differentiated.
- Architectural patterns include poorly formed tubules or sex cords, glandlike structures in a gonadal stroma of variable cellularity, cystic spaces, and intracystic papillae of mild complexity.
- Retiform SLCT typically displays heterologous elements including hepatocytes, mucin-producing epithelium, and skeletal muscle.

Immunopathology (Including Immunohistochemistry)

- Inhibin and calretinin stains are positive. Heterologous elements will stain with the appropriate immunomarkers.

Main Differential Diagnosis

- Low-grade serous tumors—these can be excluded with an index of suspicion for the retiform SLCT tumor variant and use of the appropriate immunostains.
- Carcinosarcoma—this might be suspected with the presence of heterologous elements but would be exceedingly unlikely in a young person.
- Yolk sac tumor—occasional retiform SLCTs were so misclassified in the study by Young and Scully.

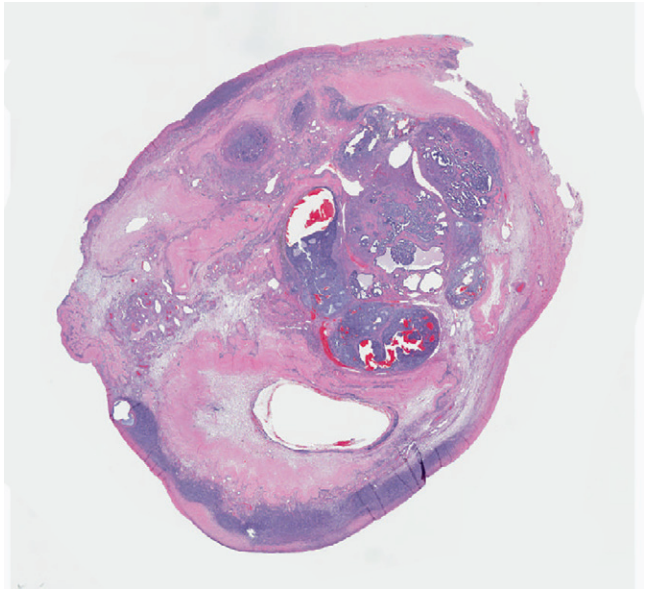

FIGURE 1

Retiform SLCT at scanning magnification, illustrating the combination of solid papillary and cystic features.

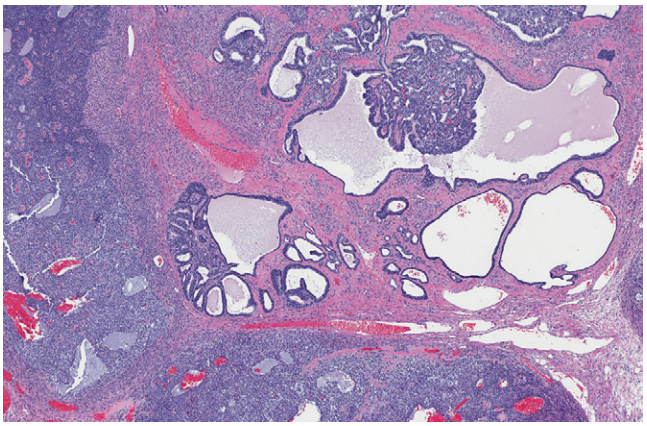

FIGURE 2

This field contains gonadal stroma on the periphery with zones resembling juvenile granulosa cell tumor.

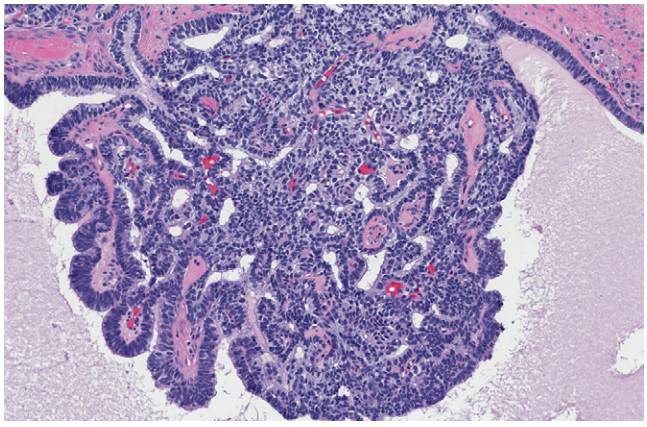

FIGURE 3

This small intracystic structure contains sertoliform tubules.

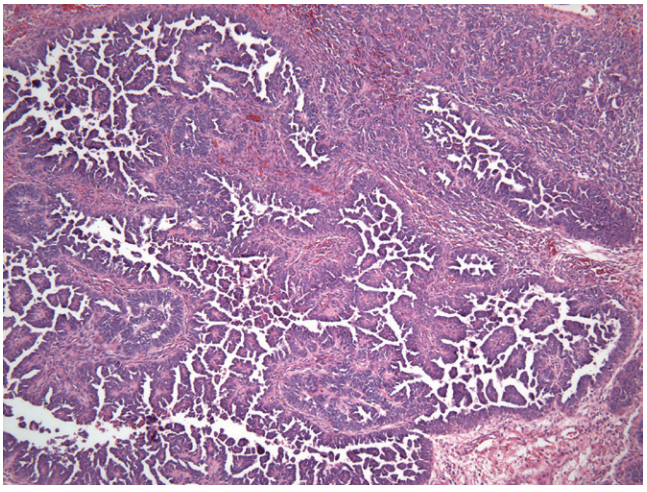

FIGURE 4

This field contains a prominent papillary architecture reminiscent of a borderline serous tumor. There is a hint of sertoliform differentiation, however, in the nonpapillary areas.

LEYDIG CELL (HILAR) TUMOR

Definition—A steroid cell tumor of the ovary arising in hilus cells and characterized by the presence of crystalloids of Reinke.

Clinical Features

Epidemiology

- Uncommon overall, but represents about one fifth of all ovarian steroid cell tumors.
- Patient age has a wide range, but the mean age at presentation is in the mid-50s.
- Most patients are in their sixth or seventh decade.

Presentation

- Androgenic symptoms, such as hirsutism or virilism, are common presenting concerns.
- Rare, estrogenic manifestations occur.
- Small, unilateral ovarian mass or enlargement.

Prognosis and Treatment

- Excellent in the majority of cases. Rare reports of malignant hilus cell tumors.
- Androgenic (or estrogenic) symptoms typically resolve after excision.
- Unilateral oophorectomy is curative.

Pathology

Histology

- Grossly, these tumors are characterized by a tan/brown to yellowish nodule in the ovarian hilum; if the nodule is based in the cortex, it is termed "Leydig cell tumor, nonhilar type" (these are extremely rare).
- Most tumors are less than 3 cm in size, although if they are smaller than 1 cm, they are usually diagnosed as hyperplasia rather than as a tumor.
- At low power the proliferation is either diffuse or multinodular.
- There are zones of hyaline material separating nests and aggregates of cells, with variable amounts of fibrous stroma.
- Tumor degeneration can produce areas with a pseudoglandular appearance.
- The tumor cell nuclei are generally small and round with a single nucleolus.
- As in other steroid cell tumors, larger bizarre tumor cells may be encountered, and this finding is not prognostically important.
- The tumor cells have abundant eosinophilic to vacuolated cytoplasm.
- In some cases, the classic Reinke crystals can be seen as polygonal, rod-shaped eosinophilic structures, but the presence of these bodies is not required for diagnosis.
- Blood vessel walls often exhibit fibrinoid necrosis.

Immunopathology (Including Immunohistochemistry)

- Positive for inhibin and calretinin.
- Variably positive for keratin.

Main Differential Diagnosis

- Stromal luteoma. These are seen in a non-hilar location and should not contain crystalloids of Reinke.
- Steroid cell tumor, not otherwise specified (NOS).

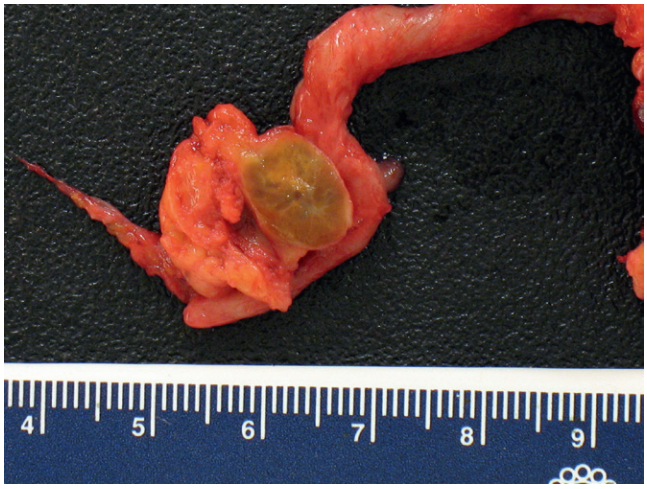

FIGURE 1

Hilus (Leydig) cell tumor. Gross image. A tan brown, well-circumscribed mass is present in the ovarian hilum.

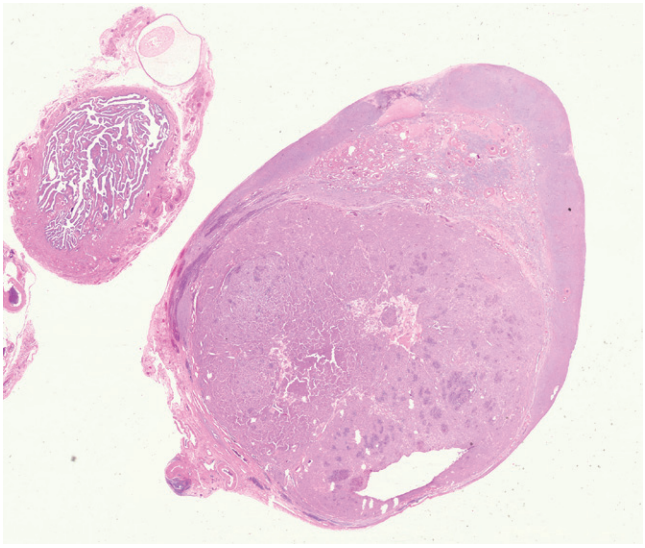

FIGURE 2

Hilus (Leydig) cell tumor. This very-low-power image shows a nodular mass replacing and expanding the ovarian hilum.

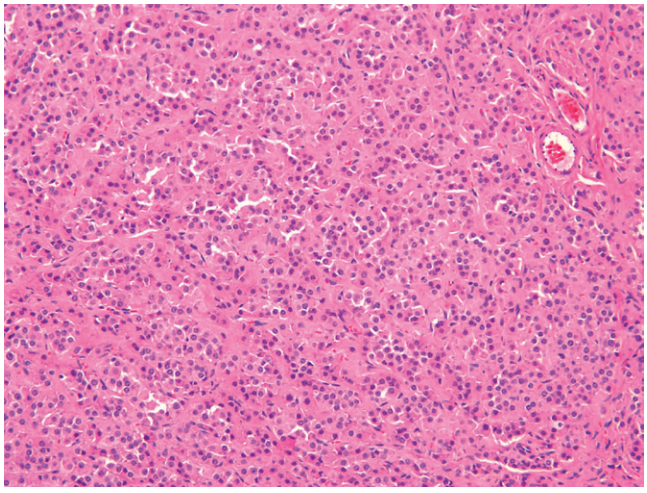

FIGURE 3

Hilus (Leydig) cell tumor. There are cords and nests of cells with brightly eosinophilic cytoplasm and small round nuclei.

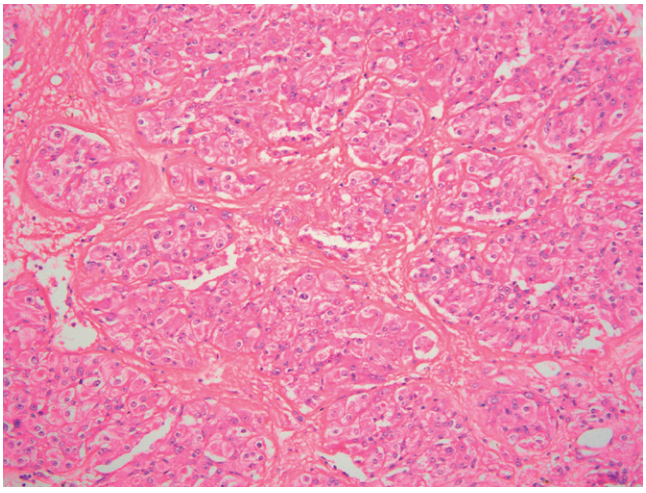

FIGURE 4

Hilus (Leydig) cell tumor. In this example the cells are arranged in small nests and surrounded by fibrous stroma.

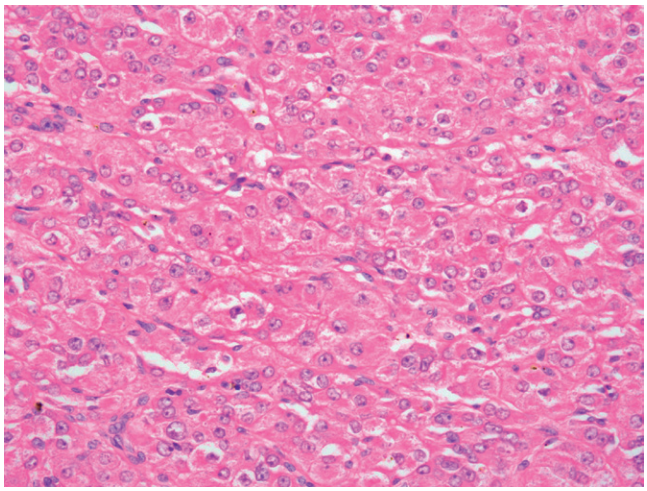

FIGURE 5

Hilus (Leydig) cell tumor. At high power the small round nuclei can be appreciated. Cytoplasmic borders are not well defined.

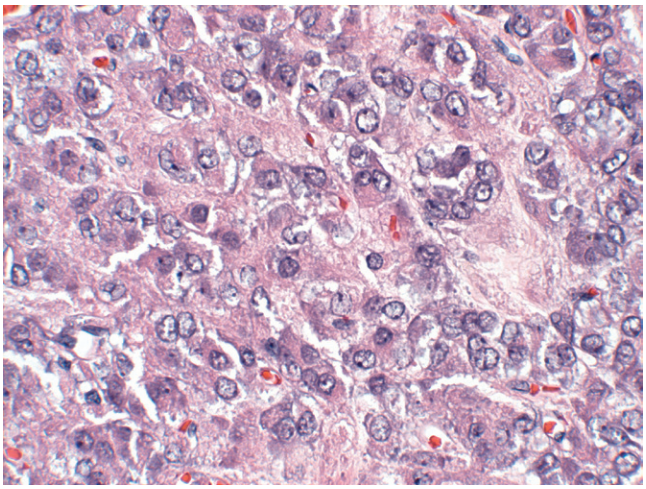

FIGURE 6

Hilus (Leydig) cell tumor. There is mild nuclear atypia in this example.

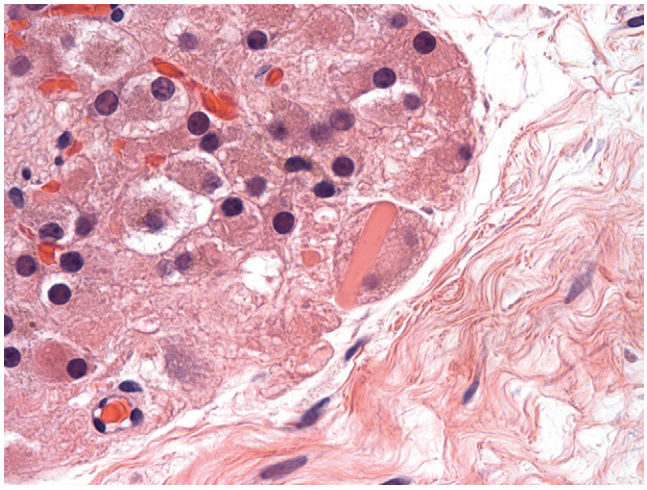

FIGURE 7

Crystalloids of Reinke *(center)* can be seen in both normal hilus cells *(seen here)* and in hilus cell tumors.

STROMAL LUTEOMA

Definition—A benign, steroid-producing tumor of the ovary.

Clinical Features

Epidemiology

- Rare overall, but accounts for about one fourth of ovarian steroid cell tumors.
- Occurs in women in their 50s and 60s, as with all ovarian steroid cell tumors.
- Most patients are postmenopausal.

Presentation

- Most patients present with estrogenic symptoms, such as vaginal bleeding.
- Androgenic symptoms (hirsutism, virilism) are less common and occur in about 12% of patients.
- Unilateral ovarian mass or enlargement.
- More than 95% of tumors are unilateral.
- Some tumors are incidentally identified.

Prognosis and Treatment

- Excellent; these are benign tumors.

Pathology

Histology

- The gross appearance is that of a well-circumscribed, tan to brown nodule centered in the ovarian parenchyma, usually less than 3 cm in size.
- The low-power microscopic appearance is also characterized by a well-demarcated proliferation of cells centered in the ovary and surrounded by a preserved ovarian cortex.
- The cells are polygonal and growing in nests and cords, and tumor degeneration can create pseudocystic or pseudoglandular spaces.
- The tumor cell proliferation is uniform and composed of cells with moderate to abundant amounts of finely granular eosinophilic or vacuolated cytoplasm.
- The cytoplasmic borders are typically prominent and well defined.
- The nuclei are round, with a single, centrally located nucleolus.
- Lipochrome pigment can be seen, but Reinke crystals are not present.
- Mitoses and nuclear atypia are not prominent.
- Stroma within the tumor itself is usually not prominent but can occasionally be hyalinized and striking.
- The uninvolved ovarian stroma is notable for the presence of stromal hyperthecosis in nearly all cases.

Immunopathology (Including Immunohistochemistry)

- Positive for inhibin and calretinin.
- Variably positive for keratin.

Main Differential Diagnosis

- Luteoma of pregnancy. These tumors are essentially identical.
- Luteinized granulosa-theca cell tumors.
- Luteinized thecoma.

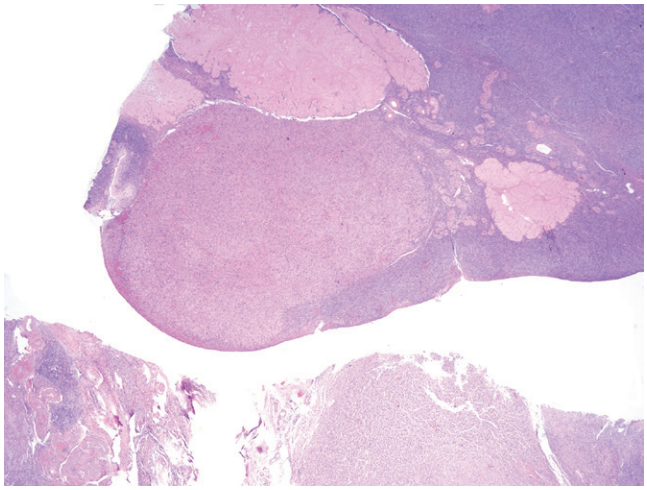

FIGURE 1

Stromal luteoma. At low power the nodule is centered in the ovarian cortex, but the surrounding cortex appears relatively undisturbed.

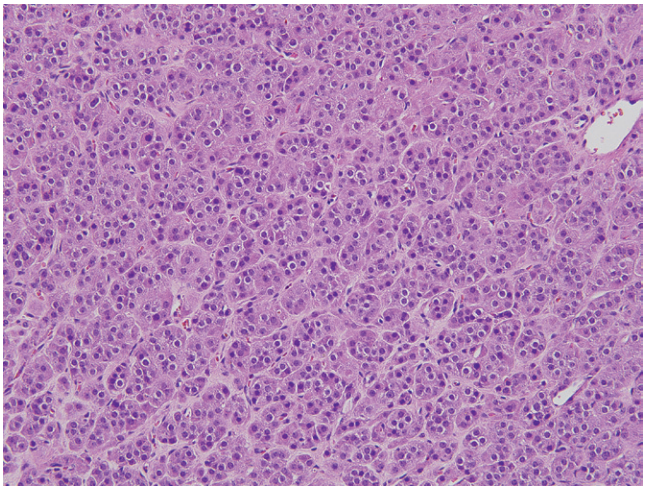

FIGURE 2

Stromal luteoma. In this case the predominant architecture is cords and nests of tumor cells.

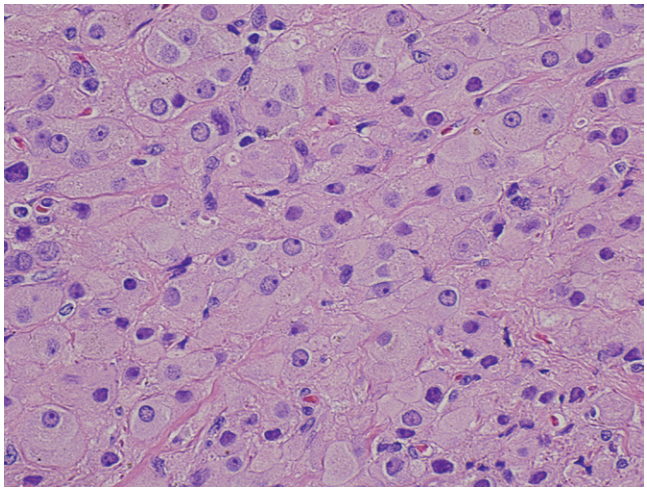

FIGURE 3

Stromal luteoma. At high power the uniform round nuclei, single nucleoli, and abundant finely granular cytoplasm are notable. Prominent cytoplasmic borders are also present.

PREGNANCY LUTEOMA

Definition—A benign steroid-producing tumor of the ovary seen in pregnancy.

Clinical Features

Epidemiology

- Rare.
- History of multiple pregnancies is common.
- More common in black women.

Presentation

- Most patients are asymptomatic.
- Androgenic symptoms (hirsutism, virilism) in the mother in some cases, and occasionally virilization of the neonate.
- Unilateral ovarian mass or enlargement is seen on ultrasound.
- More than 95% of tumors are unilateral.
- Some tumors are incidentally identified.

Prognosis and Treatment

- Excellent as these are benign tumors.
- Observation alone is appropriate, but most are removed.

Pathology

Histology

- The gross appearance is that of a well-circumscribed tan to brown nodule centered in the ovarian parenchyma, usually less than 3 cm in size.
- The low-power microscopic appearance is virtually identical to stromal luteoma and is characterized by a well-demarcated proliferation of cells centered in the ovary and surrounded by a preserved ovarian cortex.
- The cells are polygonal and growing in nests and cords, and tumor degeneration can create pseudocystic or pseudoglandular spaces.
- The tumor cell proliferation is uniform and composed of cells with moderate to abundant amounts of finely granular eosinophilic or vacuolated cytoplasm. The lobular architecture and delicate vascular network typical of a corpus luteum are not conspicuous.
- The cytoplasmic borders are typically prominent and well defined.
- The nuclei are round, with a single, centrally located nucleolus.
- Lipochrome pigment can be seen, but Reinke crystals are not present.
- Mitoses and nuclear atypia are not prominent.
- Stroma within the tumor itself is usually not prominent but can occasionally be hyalinized and striking.
- The uninvolved ovarian stroma is notable for the presence of stromal hyperthecosis in nearly all cases.

Immunopathology (Including Immunohistochemistry)

- Positive for inhibin and calretinin.
- Variably positive for keratin.

Main Differential Diagnosis

- Stromal luteoma—very similar in appearance, but seen in menopausal women.
- Luteinized granulosa-theca cell tumors. and luteinized thecomas—both typically more cellular with a less polygonal cell outline.

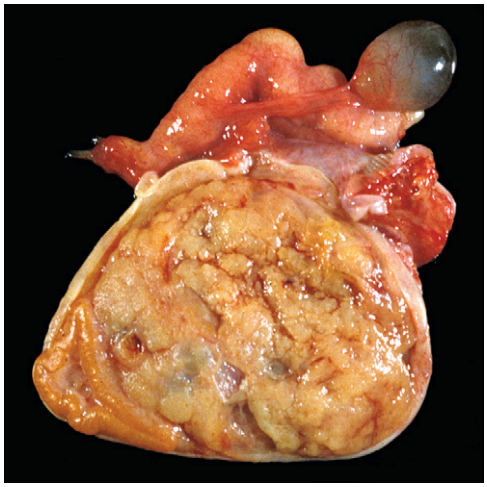

FIGURE 1

Pregnancy luteoma presenting as a solitary discrete brownish mass in the ovary.

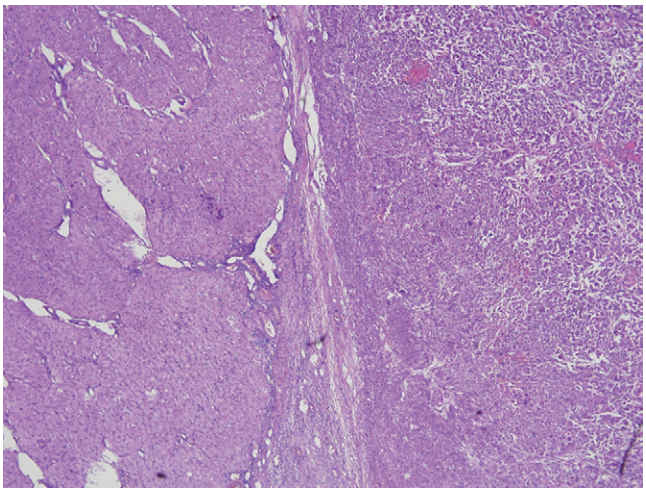

FIGURE 2

Pregnancy luteoma. At low power the monotonous array of tumor cells on the right contrasts with the architecture of a corpus luteum of pregnancy *(left)*.

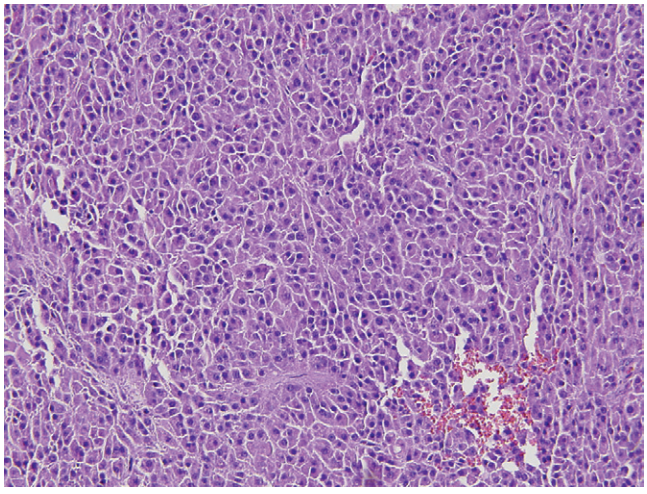

FIGURE 3

Pregnancy luteoma. A veritable sea of polyhedral cells with pink cytoplasm and centrally placed nuclei.

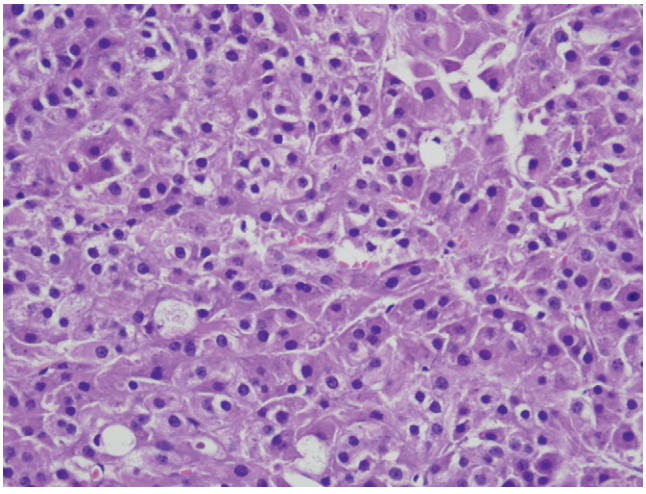

FIGURE 4

At higher magnification there is a lack of nuclear pleomorphism and a low nuclear-to-cytoplasmic (N/C) ratio.

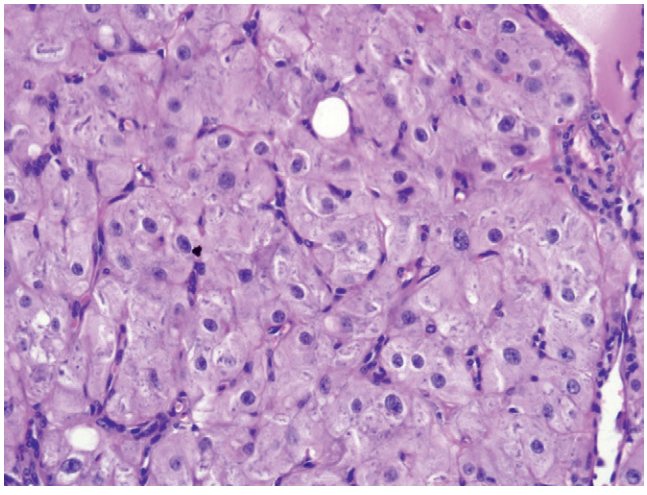

FIGURE 5

Note the larger luteinized granulosa cells of this corpus luteum of pregnancy and the characteristic interstitial vascular network.

SCLEROSING STROMAL TUMOR

Definition—Variant of sex cord–stromal tumor of the ovary.

Clinical Features

Epidemiology

- Uncommon; accounts for less than 2% of all sex cord–stromal tumors.
- Predominant in the second and third decades.

Presentation

- Most often presents with abnormal bleeding and an abdominal mass.
- Tumors tend to be large (over 10 cm), gray-white-yellow, lobular, and unilateral.

Prognosis and Treatment

- Limited data (small number of cases) indicate that this is a benign tumor.
- Surgical excision is curative.

Pathology

Histology

These tumors demonstrate three prominent features:

- A pseudolobular pattern with alternating hypocellular and hypercellular areas.
- Prominent vasculature resembling hemangiopericytoma.
- A heterogeneous cell population with both vacuolated or luteinized cells and spindled fibroblast-like cells with intervening collagenization or sclerosis.

Immunopathology (Including Immunohistochemistry)

- Positive for inhibin.

Main Differential Diagnosis

- Fibroma or fibroma-thecoma—can demonstrate luteinization or foci of sex chord differentiation, but lacks the pseudolobular appearance and the unusual mixture of collagenized areas with luteinized cells; also usually seen in older age group.

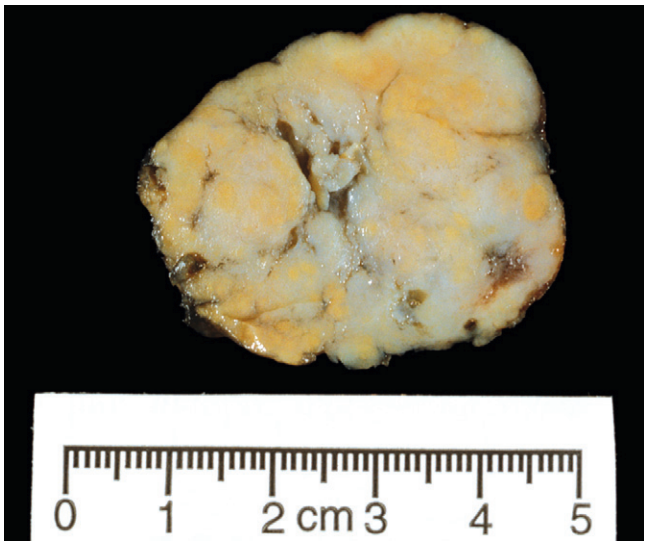

FIGURE 1

Sclerosing stromal tumor. The tumor shows a white to yellow appearance.

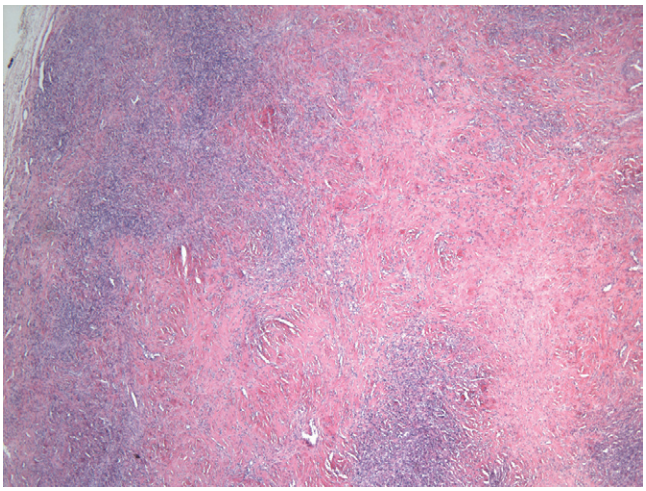

FIGURE 2

Sclerosing stromal tumor. Note the alternating cellular and more sparsely cellular collagenized zones.

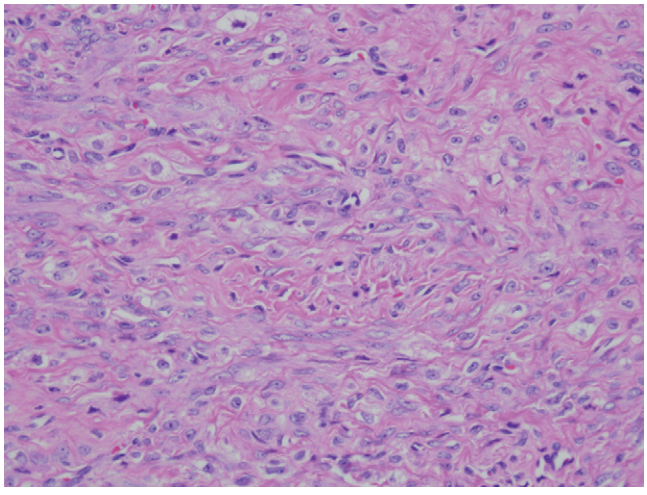

FIGURE 3

Sclerosing stromal tumor. Higher magnification depicts an area with prominent spindled fibroblasts and collagen deposition.

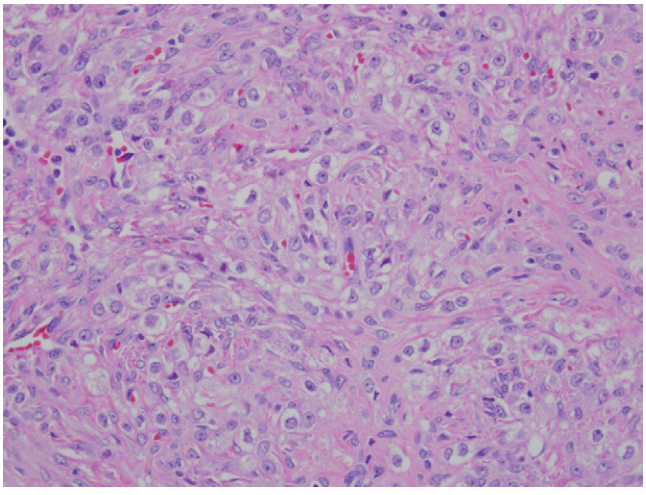

FIGURE 4

Sclerosing stromal tumor. In this area there are conspicuous luteinized cells within the collagen.

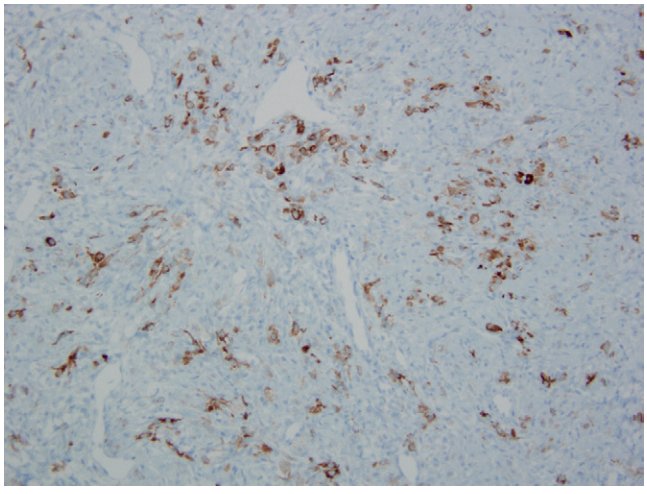

FIGURE 5

Sclerosing stromal tumor. The luteinized cells are strongly inhibin positive.

SMALL CELL CARCINOMA OF HYPERCALCEMIC TYPE

Definition—A malignant rhabdoid tumor associated with hypercalcemia and mutations and inactivation in the SMARCA4 gene.

Clinical Features

Epidemiology

- Presents between childhood and menopause, predominating in the late teens and early twenties.
- Rarely familial, but kindreds with mutations in the SMARCA4 gene have recently been described.

Presentation

- Unilateral.
- Elevated calcium level in nearly two thirds.
- Extraovarian spread in half.
- Solid, lobulated, and cream colored with necrosis and hemorrhage.

Prognosis and Treatment

- These tumors have a high mortality. One third of stage Ia cases survived in one study.
- Most with higher stage will not survive, although occasional extended survivors have been reported with combination radiotherapy and chemotherapy with platinum-based agents and etoposide.

Pathology

Histology

- Diffusely distributed, closely packed round tumor cells with a high nuclear-to-cytoplasmic (N/C) ratio and a high mitotic rate.
- Follicle-like structures, islets of cells, and cords or trabeculae.
- Variable cytoplasmic differentiation with large vesicular nuclei and prominent nucleoli. This can produce appearances of both small and large cell variants, particularly after chemotherapy.
- Occasionally other elements including mucin-producing epithelium.

Immunopathology (Including Immunohistochemistry)

- Stains for WT1, p53, CD10, and EMA are usually positive.
- Neuroendocrine markers are typically negative.
- Staining for SMARCA4 should be negative due to loss of gene function.

Main Differential Diagnosis

- Sex cord–stromal neoplasms—inhibin positive.
- Primitive neuroectodermal tumor—EMA negative.
- Rhabdomyosarcoma—desmin positive.
- Intraabdominal desmoplastic small round cell tumor.
- Neuroblastoma—EMA negative.
- Metastatic pulmonary small cell carcinoma—chromogranin positive and TTF-1 positive.
- Small cell carcinoma of the ovary (neuroendocrine type)—chromogranin positive and will often exhibit other epithelial components.

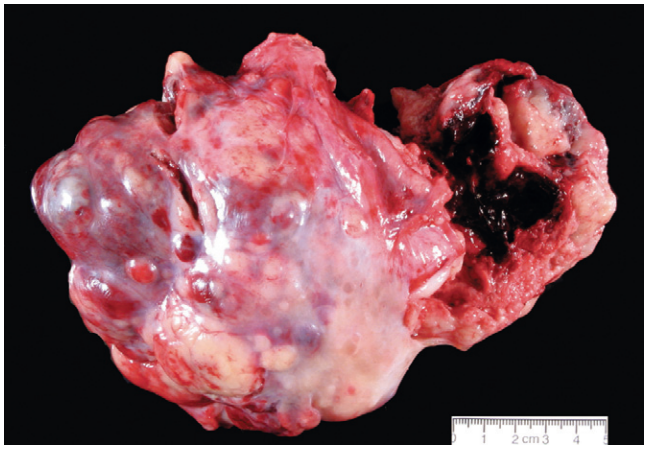

FIGURE 1

Small cell carcinoma, hypercalcemic type. Note the lobulated appearance, punctuated by hemorrhage and necrosis.

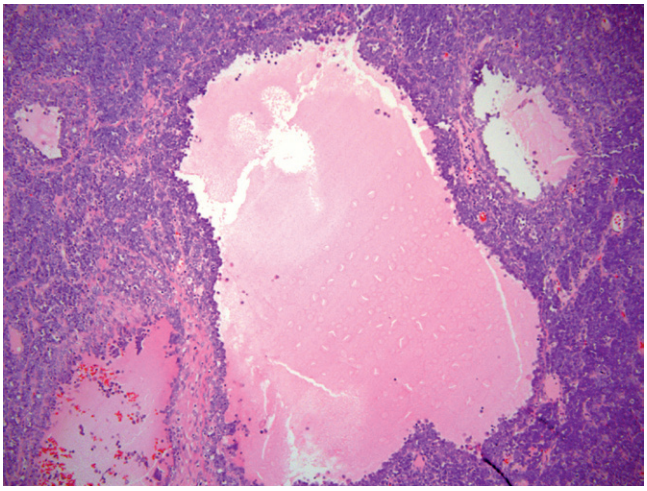

FIGURE 2

Small cell carcinoma, hypercalcemic type. At low magnification note the largely featureless landscape of blue cells punctuated by follicle-like spaces.

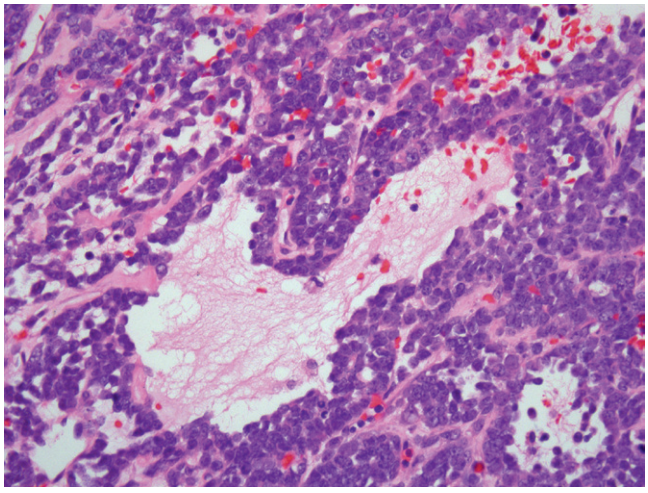

FIGURE 3

Small cell carcinoma, hypercalcemic type. At higher magnification another cystic space surrounded by small cells with a high N/C ratio.

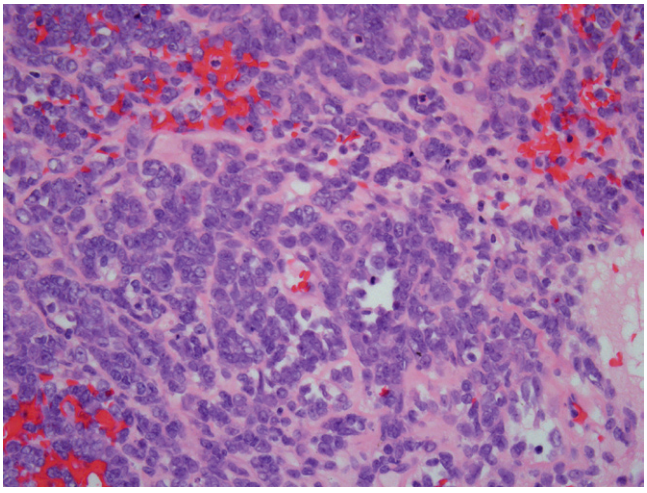

FIGURE 4

Small cell carcinoma, hypercalcemic type. Tumor cells are partially aligned in cordlike arrangements.

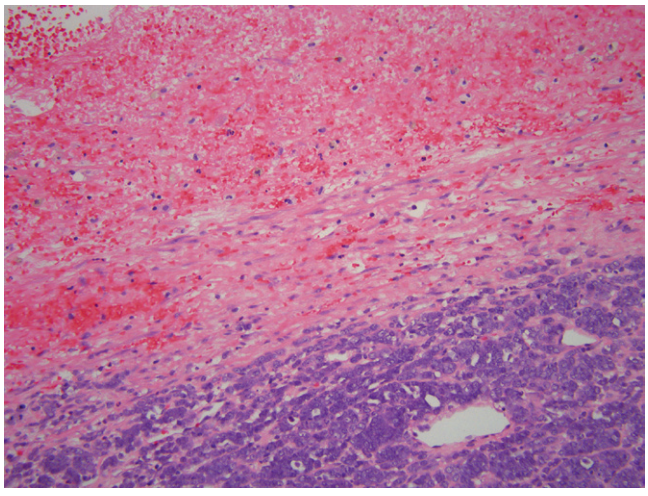

FIGURE 5

Small cell carcinoma, hypercalcemic type. An interface between viable tumor and necrosis with hemorrhage.

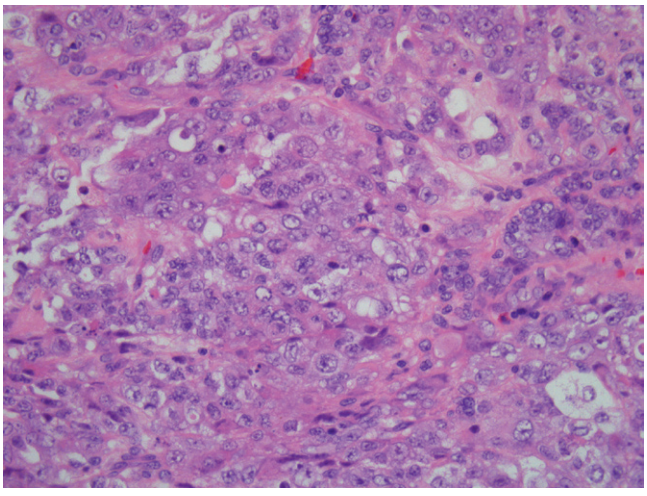

FIGURE 6

Small cell carcinoma, hypercalcemic type. Foci like this are seen in many tumors, with more abundant cytoplasm (large cell type), vesicular nuclei, and prominent nucleoli.

SMALL CELL CARCINOMA OF PULMONARY (NEUROENDOCRINE) TYPE

Definition—A malignant small cell ovarian tumor with features of pulmonary neuroendocrine carcinomas.

Clinical Features

Epidemiology

- Mean age of 48 years, which is over 20 years older than the small cell carcinoma of hypercalcemic type (SCCHT).
- *Not* associated with mutations in the SMARCA4 gene.

Presentation

- Unilateral.
- Abdominal pain, nausea, and pelvic mass.
- Average duration of symptoms of 4 months (vs. 1 month for SCCHT).
- Solid tumor with necrosis and hemorrhage.
- Over half are stage 2 or greater when diagnosed.
- Elevated Ca125 in over 80%.

Prognosis and Treatment

- These tumors have a high mortality similar to SCCHT.
- Ten-year survival of 20%.
- Management is based primarily on chemotherapy (e.g., platinum, taxol, etoposide).

Pathology

Histology

- Closely packed round tumor cells with a high nuclear-to-cytoplasmic (N/C) ratio and a high mitotic rate.
- Nuclear molding.
- Geographic necrosis.

Immunopathology (Including Immunohistochemistry)

- Stains for chromogranin and synaptophysin are usually positive.
- Stains for vimentin and WT1 should be negative.
- Staining for SMARCA4 gene should be positive due to preservation of gene function.

Main Differential Diagnosis

- Sex cord–stromal neoplasms—inhibin positive.
- Primitive neuroectodermal tumor—EMA negative.
- Rhabdomyosarcoma—desmin positive.
- Intraabdominal desmoplastic small round cell tumor—desmin positive (dotlike pattern), WT1 positive, and EWS-WT1 gene fusion.
- Neuroblastoma—EMA negative.
- Metastatic pulmonary small cell carcinoma—chromogranin positive and TTF-1 positive.

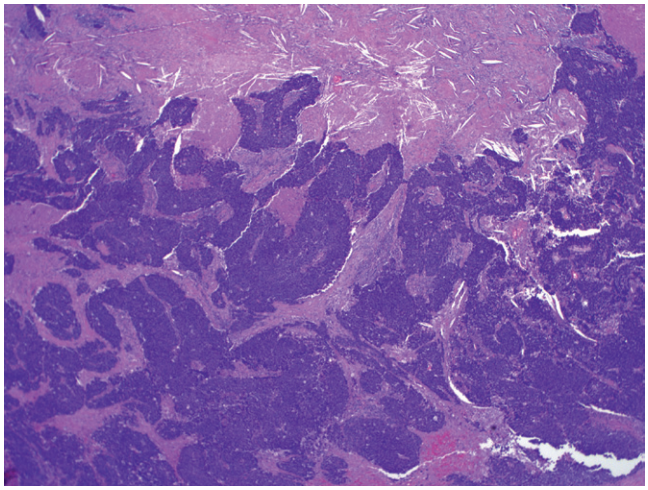

FIGURE 1

Small cell carcinoma, pulmonary type. At low magnification a featureless landscape of blue cells with necrosis.

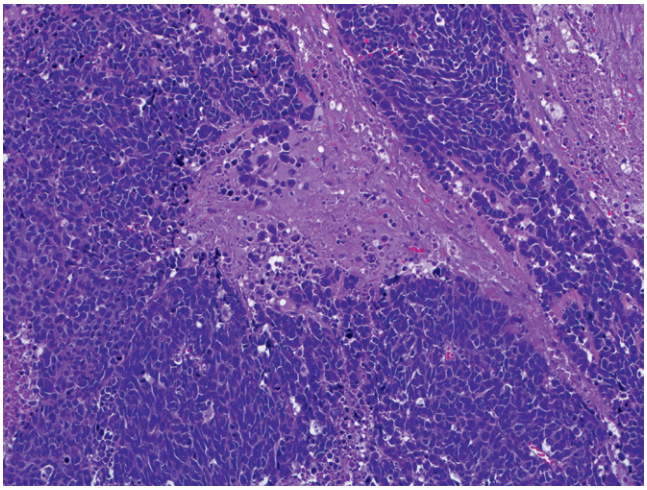

FIGURE 2

Small cell carcinoma, pulmonary type. At higher magnification, discohesive sheets of small tumor cells with necrosis.

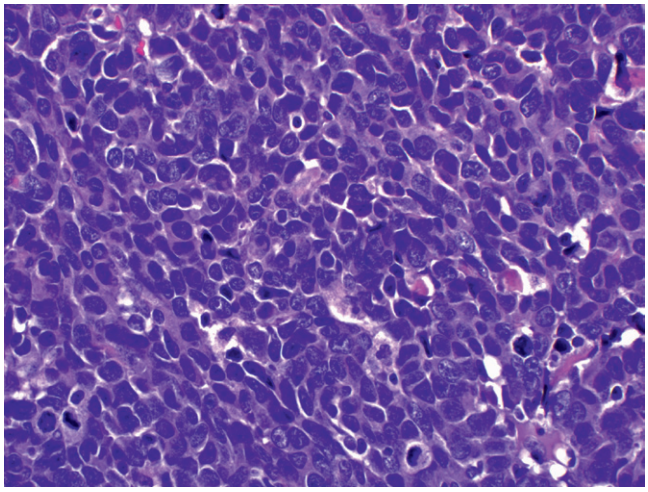

FIGURE 3

Small cell carcinoma, pulmonary type. At high magnification a nonuniform population of cells with dense nuclear chromatin and a high N/C ratio.

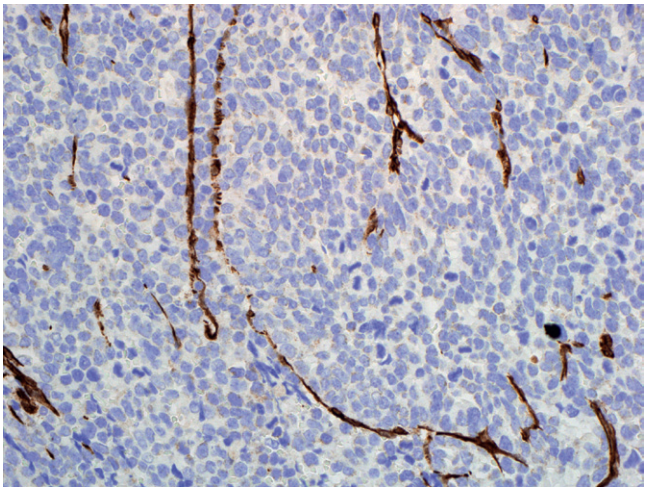

FIGURE 4

Small cell carcinoma, pulmonary type. A negative WT1 stain.

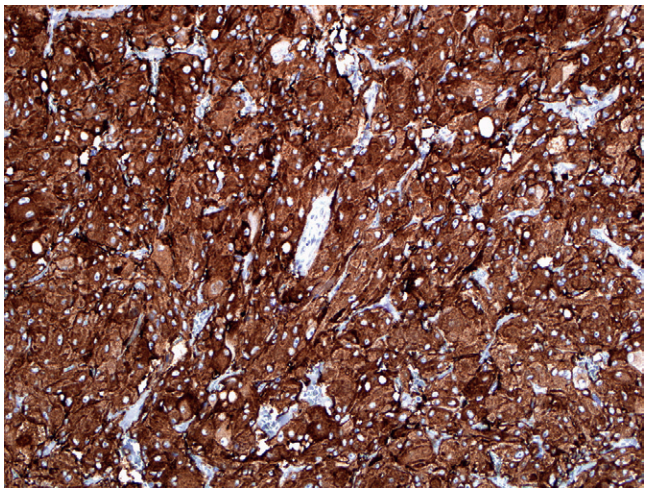

FIGURE 5

Small cell carcinoma, pulmonary type. Strong positivity for synaptophysin.

SEX CORD TUMOR WITH ANNULAR TUBULES

Definition—A sex cord stromal tumor with annular tubules and features of both granulosa and Sertoli cell tumors.

Clinical Features

Epidemiology

- These are rare tumors, comprising about 6% of sex cord stromal tumors and less than 1% of ovarian tumors.
- One third of cases are associated with Peutz-Jeghers syndrome.

Presentation

- Typically (if not invariably) unilateral, larger, cystic, and solid in nonsyndromic cases, with a median age of presentation in the third decade.
- Typically bilateral, smaller, multinodular, and calcified when associated with Peutz-Jeghers syndrome, with a median age in the fourth decade.
- Can present with sexual precocity and abnormal bleeding.

Prognosis and Treatment

- Typically behave benign with excellent prognosis in cases associated with Peutz-Jeghers syndrome.
- Nonsyndromic tumors are considered low-grade malignancies similar to granulosa cell tumors. Approximately 10% behave in a malignant fashion.
- Spread is typically via retroperitoneal lymph nodes; hence nodal dissection is often performed.
- Recurrences treated by combination of chemotherapy and radiation.
- Recurrences can be followed by extended periods of remission.

Pathology

Histology

- Multiple cystic and/or solid areas.
- Cysts or solid areas are punctuated by small annular tubules suspended in a matrix, surrounding eosinophilic hyaline bodies containing basement membrane material as seen on electron microscopy.
- Endometrium can exhibit hyperestrogenic features; in some cases even decidual change is seen with sexual precocity implying progesterone production as well.

Immunopathology (Including Immunohistochemistry)

- Positive for inhibin.

Main Differential Diagnosis

- Either Sertoli or granulosa cell tumors may share features with sex cord tumor with annular tubules (SCTAT), but the latter has the classic repetitive tubules.

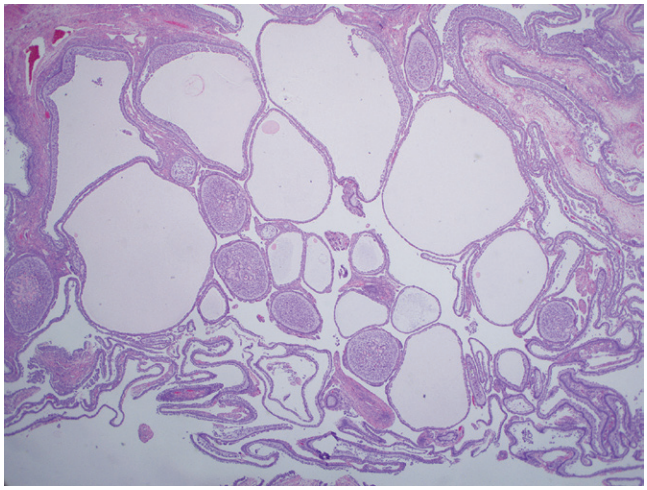

FIGURE 1

SCTAT from a 3 year old with sexual precocity. At low power, multiple cysts can be appreciated.

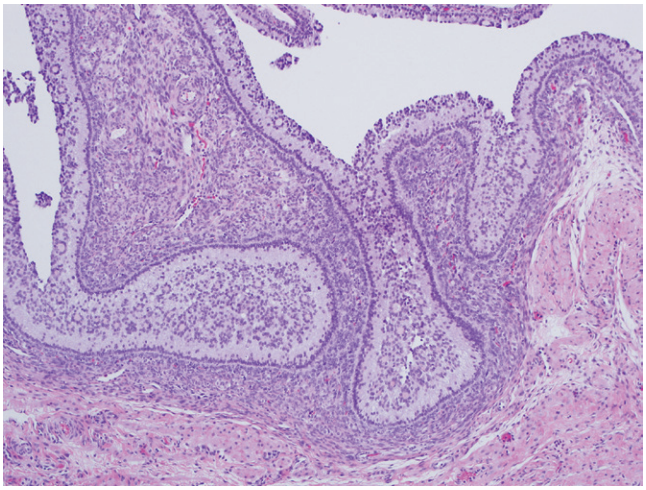

FIGURE 2

Lining of a cystic space of an SCTAT by annular tubules. Note the underlying mature-appearing ovarian stroma.

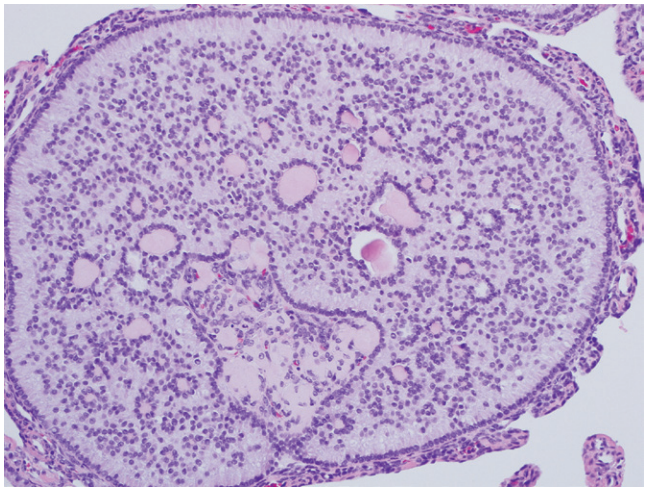

FIGURE 3

Numerous tubules suspended in an amphophilic matrix. Occasional eosinophilic materials are present in some lumens.

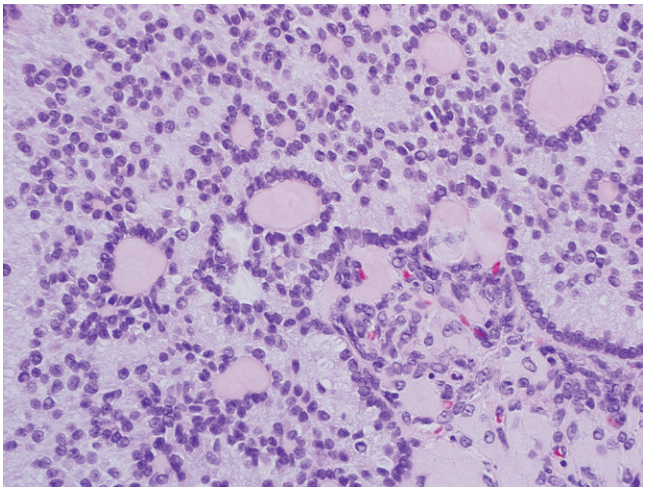

FIGURE 4

Higher magnification shows the intraluminal eosinophilic material *(center)*.

SOLITARY FIBROUS TUMOR

Definition—An uncommon spindled mesenchymal neoplasm of variable behavior with a NAB2-STAT6 fusion gene arising in the submesothelial mesenchyme.

Clinical Features

Epidemiology

- Uncommon; originally described in pleura, but now reported in multiple soft tissue sites including the pelvis.
- Afflicts adults over a wide age range.
- Usually benign; 10% to 20% are malignant.

Presentation

- Oval to lobulated mass averaging 11 cm in size, usually well circumscribed.
- On imaging, solid tumor with prominent vascularity.

Prognosis and Treatment

- Complete excision offers the best opportunity for cure.
- Late relapses, both local and distant, occurring beyond 10 years are not uncommon and can follow seemingly benign tumors.

Pathology

Histology

- Population of spindled to ovoid fibroblasts, variable cellularity, and prominent vascular network (hemangiopericytoma like).
- Unfavorable features are tumor necrosis and infiltrating margins.
- Dedifferentiation with heterologous elements is seen rarely.
- NAB2ex4-STAT6ex2/3 variant is associated with younger age group (MA 47 years), pleural location, fibrosis, and benign behavior.
- NAB2ex6-STAT6ex16/17 is associated with older (MA 69 years) age, deep soft tissue, and more aggressive behavior (Barthelmess et al. 2014).

Immunopathology (Including Immunohistochemistry)

- STAT6 expression is confined to the nucleus, usually strong but heterogeneous in 20%.
- Staining for vimentin, CD99, Bcl-2, and CD44 are positive.
- Staining for SMARCA4 should be positive due to preservation of gene function.

Main Differential Diagnosis

- Sex cord-stromal neoplasms—inhibin positive.
- Primitive neuroectodermal tumor—EMA negative.
- Rhabdomyosarcoma—desmin positive.
- Intraabdominal desmoplastic small round cell tumor—desmin (dotlike pattern) and WT1 positive. EWS-WT1 gene fusion.
- Neuroblastoma—EMA negative.
- Metastatic pulmonary small cell carcinoma—chromogranin and TTF-1 positive.

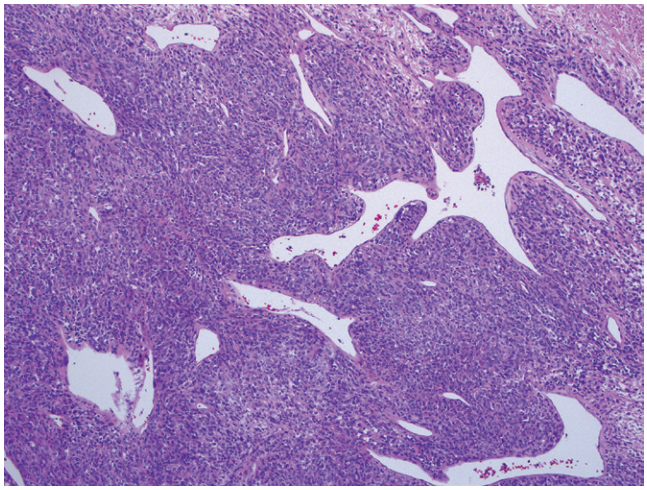

FIGURE 1
A cellular and presumably malignant solitary fibrous tumor (SFT).

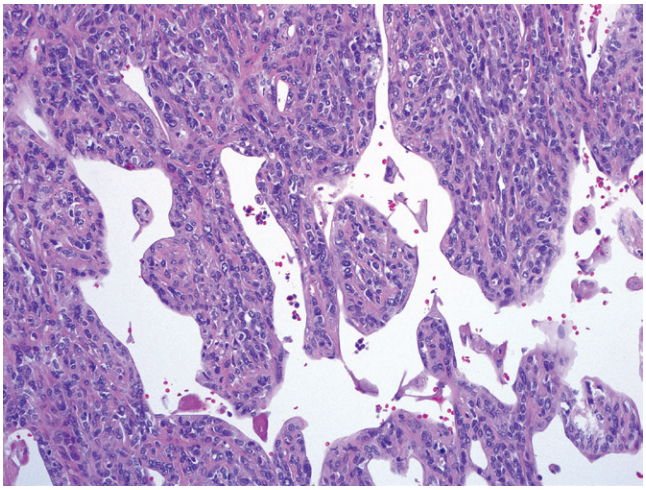

FIGURE 2
Note the arrangement around vessels (hemangiopericytoma like).

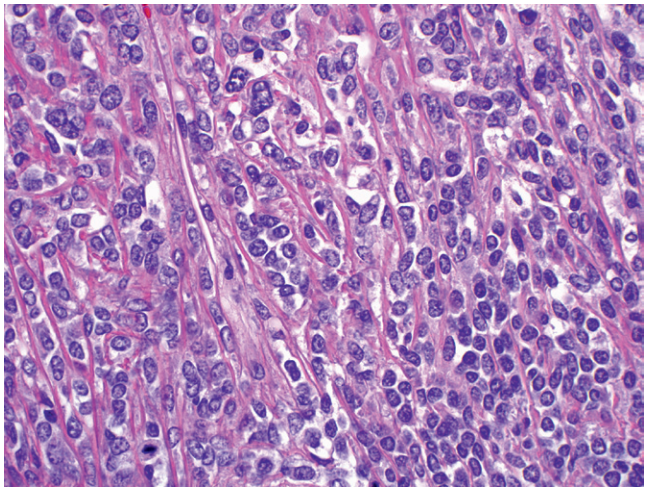

FIGURE 3
Cellular population of ovoid stromal cells.

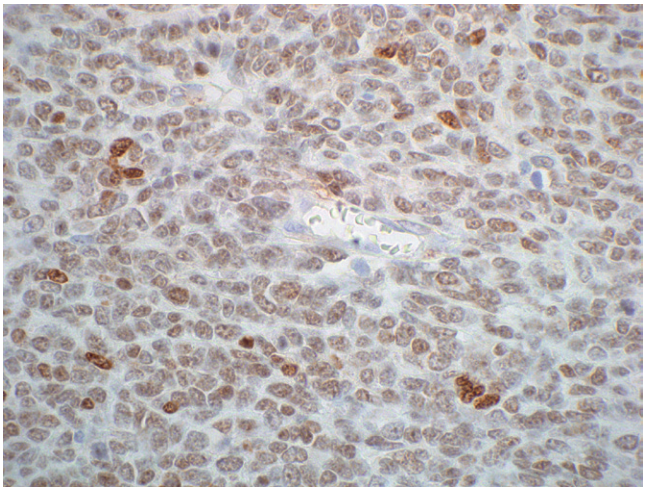

FIGURE 4
Positive STAT6 stain.

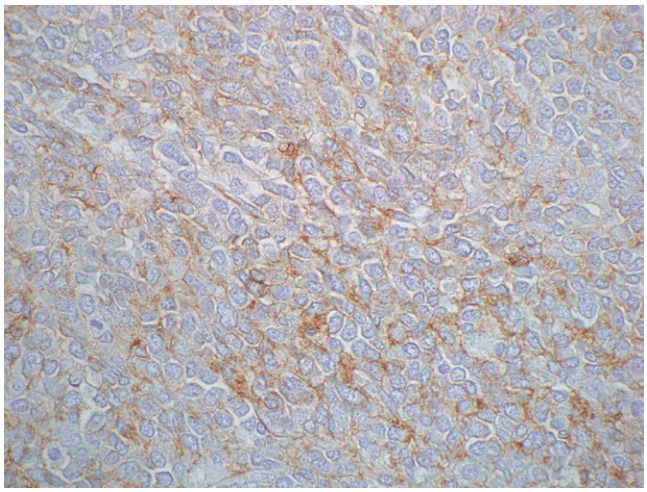

FIGURE 5
Positive CD44 stain.

GASTROINTESTINAL STROMAL TUMOR

Definition—Ovarian involvement is a rare metastatic presentation of this tumor.

Clinical Features

Epidemiology

- Most common mesenchymal tumor of the gastrointestinal tract.
- Driven by oncogenic KIT or PDGFRA mutations.
- Most common is an in-frame mutation of exon 11 in the c-KIT gene.

Presentation

- Tumors may present as an ovarian mass.
- Tumors are solid, tan, and lobulated in appearance.
- Most commonly originate in the stomach (~60%) and small intestine (~30%).

Prognosis and Treatment

- Twenty to thirty percent behave in a malignant fashion.
- Tumor size, mitotic index, and location influence outcome.
- Overall 5-year survival ranges from 35% to 65%, but mortality when ovary is involved exceeds 80% based on small studies.
- Imatinib (Gleevec) is an effective therapy, but resistance will occur in 50% of treated patients within 2 years; however, newly developed tyrosine kinase inhibitors have shown promise.

Pathology

Histology

- Monomorphic population of spindled and/or epithelioid cells.
- Shorter fascicles in contrast to the broader fascicles seen in leiomyoma or leiomyosarcoma.
- Bland cytologic appearance with ovoid to spindled nuclei, indistinct cell borders.
- Clear punched out perinuclear vacuoles are a hallmark.
- Nuclear pleomorphism is rare (less than 5%).

Immunopathology (Including Immunohistochemistry)

- Positive for c-KIT (CD117) (dotlike perinuclear) and dog-1.
- One half are positive for SMA.
- Less than 3% are desmin positive.

Main Differential Diagnosis

- Leiomyosarcoma—will manifest with higher histologic grade, longer fascicles; CD117 negative and usually desmin positive.
- Spindled granulosa cell tumor or fibrothecoma—CD117 negative and usually strongly inhibin positive.
- Schwannoma—shows a more tapered cytomorphology with Antoni A and Antoni B areas and diffusely positive for S100.

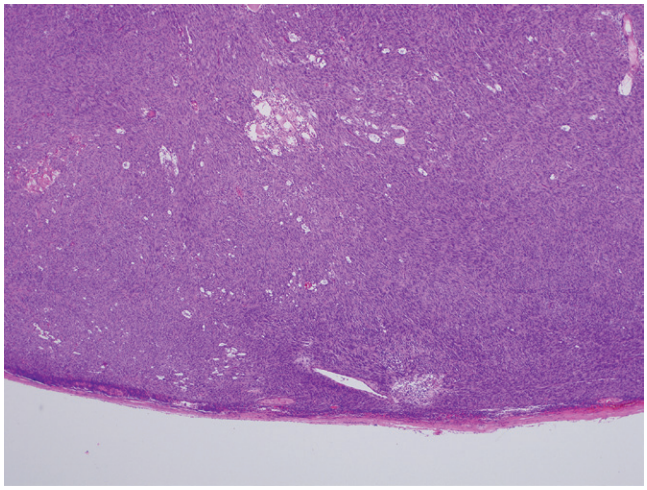

FIGURE 1

Gastrointestinal stromal tumor (GIST) involving the ovary and replacing the parenchyma.

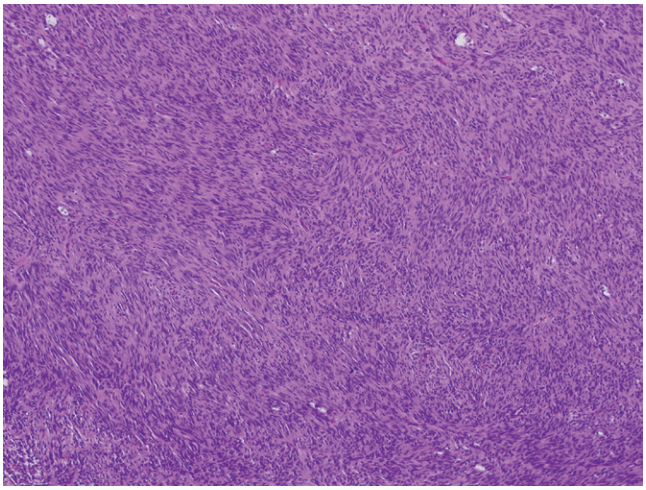

FIGURE 2

At higher power the spindle cell population is arranged in rather compact but less sharply defined fascicles.

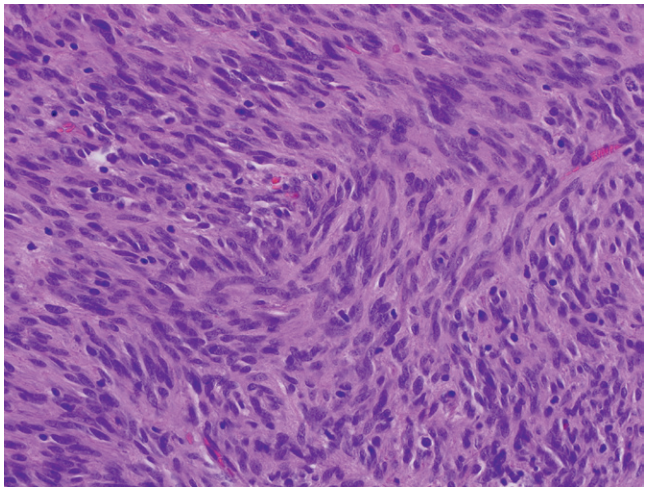

FIGURE 3

Fascicle formation in a GIST. Nuclei are elongated and show some palisading albeit less orderly than in a schwannoma.

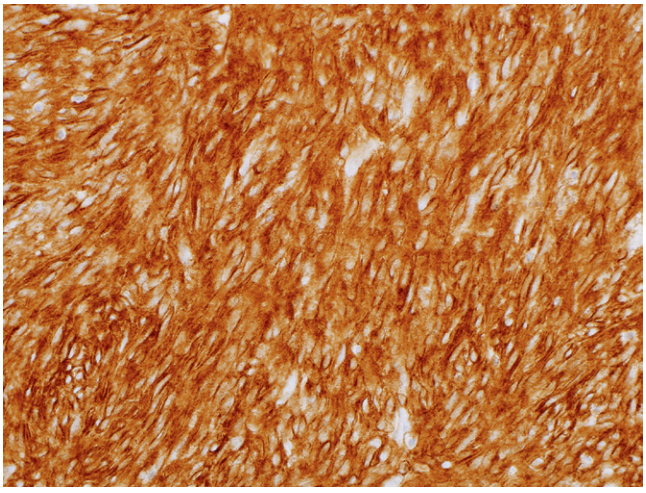

FIGURE 4

Staining for c-KIT is positive.

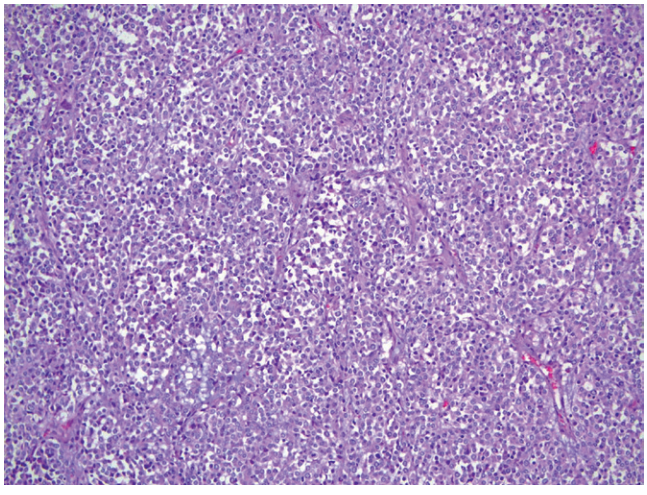

FIGURE 5

An epithelioid pattern in this GIST.

PRIMITIVE NEUROECTODERMAL TUMOR

Definition—A rare, poorly differentiated embryonal neuroectodermal tumor sometimes associated with a teratoma that mimics the central type of primitive neuroectodermal tumor (PNET).

Clinical Features

Epidemiology

- Extremely rare in the ovary.
- Belongs in the Ewing's family of tumors
- Ovarian tumors arise from neural tissue and are analogous to the "central" PNETs as opposed to the peripheral PNETs that contain a unique t(11:22)(q24;q12) translocation specific for the PNET/Ewing's sarcoma family.

Presentation

- In the ovary the tumor may be found incidentally or within an enlarging teratoma.

Prognosis and Treatment

- In small series the prognosis was a function of stage, with over 80% surviving if the tumor was limited to the ovary. Stage III and IV tumors have a poor prognosis irrespective of radiation and chemotherapy.

Pathology

Histology

- Monomorphic population arranged in sheets or nests with rosette-like structures in a fibrillar background (small, blue, round cell tumor).
- Often but not always associated with the primitive neuroepithelium of an existing immature teratoma.

Immunopathology (Including Immunohistochemistry) and Other Studies

- Strong CD99 staining characteristic of a central PNET.
- EWS/FLI-I chimeric RNA detected by reverse transcription polymerase chain reaction (RTPCR).

Main Differential Diagnosis

- In the ovary the main exclusion is an immature teratoma, which closely resembles embryonic neural tissue, whereas the PNET shows more anaplastic neural differentiation.

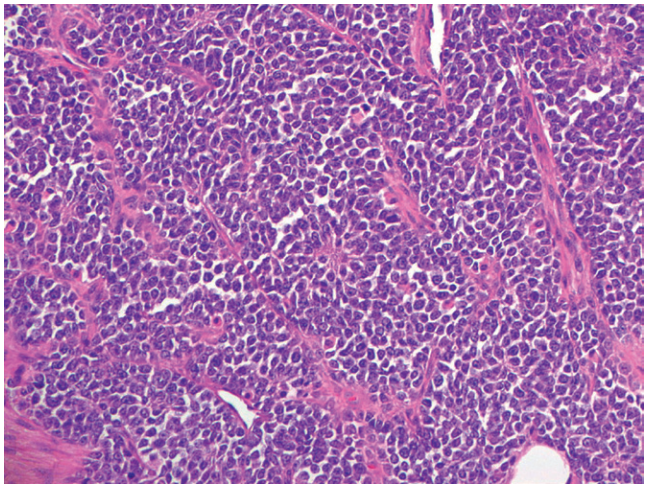

FIGURE 1

PNET. Note the monomorphic population of tumor cells with vague rosette-like formation.

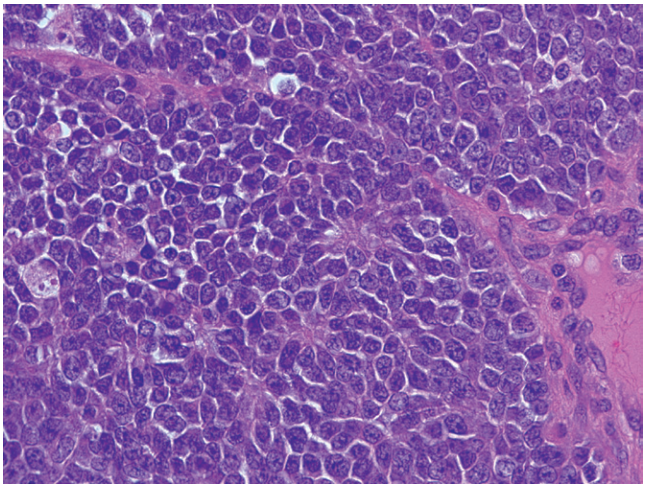

FIGURE 2

PNET. A uniform population condensing into rosette-like structures with a mesh of fine fibrillar material in the lumina.

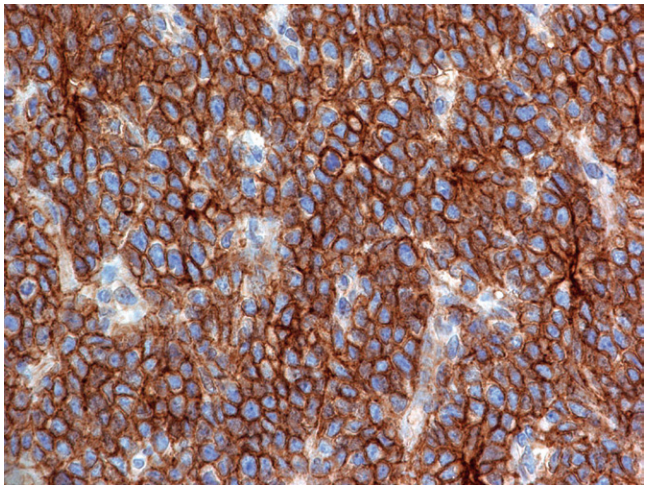

FIGURE 3

PNET with strong CD99 staining.

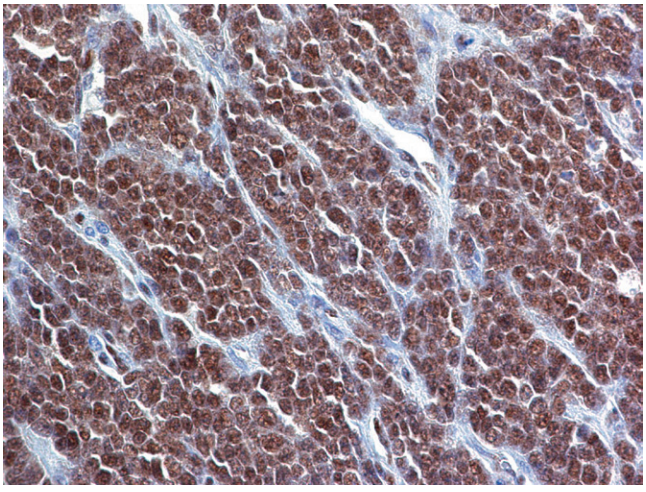

FIGURE 4

Strong staining for FLI-I in a PNET.

DESMOPLASTIC SMALL ROUND CELL TUMOR

Definition—A rare, predominantly intraabdominal tumor associated with a specific chromosomal translocation (t11;22)(p13:q12) that produces a fusion transcript EWS/WT1.

Clinical Features

Epidemiology

- Extremely rare, particularly in women.
- Typically seen in children and young adults.
- Specific cell of origin is unknown, but a primitive progenitor cell is suggested by some.

Presentation

- Rapidly enlarging abdominal mass in the first and second decades.
- When involving the ovary, the mean age is approximately 19 years.

Prognosis and Treatment

- Overall survival is less than 20%, because of rapid spread and chemoresistance. Most patients are dead within 3 years.
- Requires combined surgery, chemotherapy, and radiation therapy.

Pathology

Histology

- Another "small, round, blue cell tumor."
- Oval cells with high nuclear-to-cytoplasmic (N/C) ratio and nucleoli.
- Prominent desmoplastic stroma.

Immunopathology (Including Immunohistochemistry)

- Expresses cytokeratin, desmin, vimentin, and neuron-specific enolase.
- Adenosine transporter ENT4.

Main Differential Diagnosis

- Virtually any small, blue, round cell tumor can mimic this tumor including germ cell tumors, specifically dysgerminoma; embryonal rhabdomyosarcoma; neuroblastoma; Ewing's tumor; primitive neuroectodermal tumor; small cell carcinoma; and lymphoma.
- The diagnosis is best made by identifying the characteristic translocation (not always present) and the aforementioned immunoprofile.

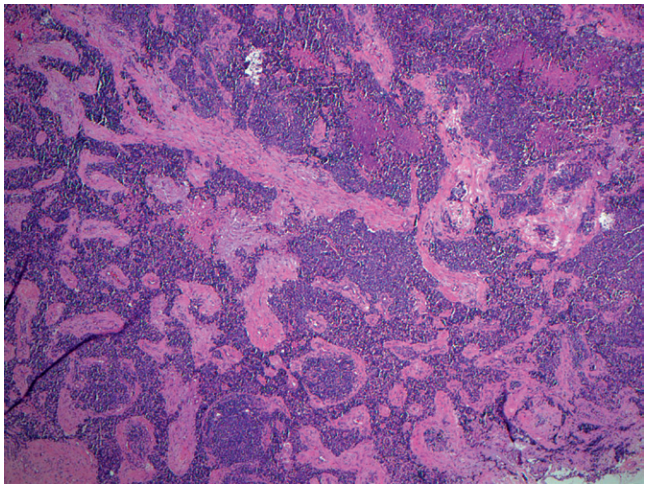

FIGURE 1

Desmoplastic small round cell tumor (DSRCT). A geographic arrangement of dense populations of oval cells in a desmoplastic stroma. Note the patchy necrosis.

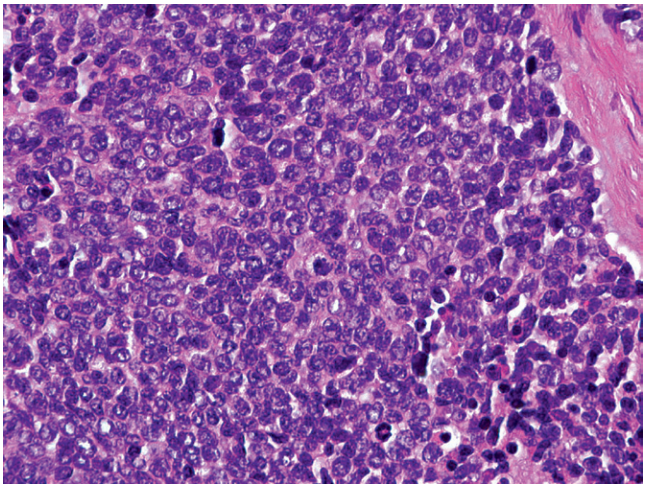

FIGURE 2

At high magnification the tumor cell displays a high N/C ratio, with crowding and nuclear overlap.

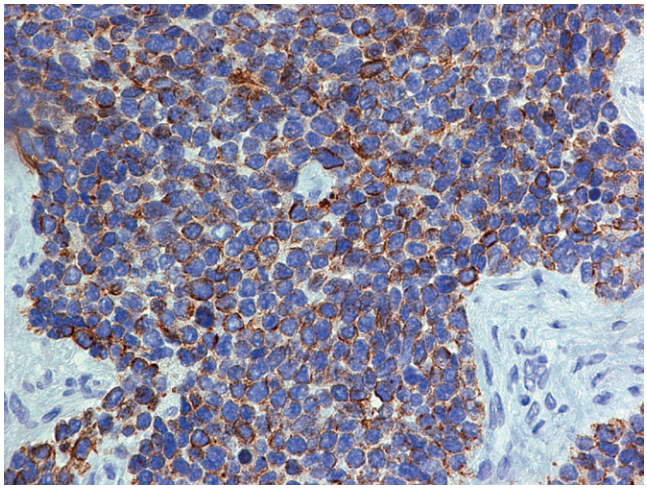

FIGURE 3

Cytokeratin staining in a DSRCT.

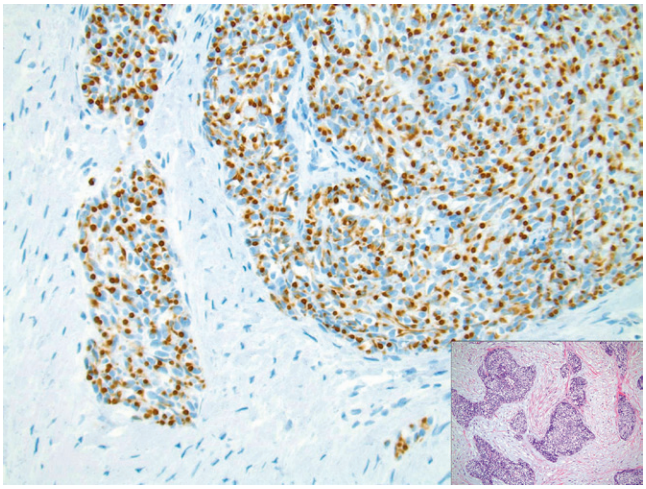

FIGURE 4

Dotlike desmin staining in this DSRCT (hematoxylin and eosin [H&E] in inset).

BENIGN CYSTIC MESOTHELIOMA

Definition—A rare benign disease consisting of multiloculated mesothelial-lined cysts in the peritoneum. Also termed "multiloculated peritoneal cyst."

Clinical Features

Epidemiology

- Rare.
- Reproductive-age women.
- History of a prior abdominal procedure or surgery is often noted.
- Controversy as to whether this is a neoplasm or reactive process.

Presentation

- Most patients present with abdominal pain.
- Imaging studies show a peritoneal mass.
- Intraoperatively the multicystic mass is found attached to the peritoneum and/or abdominal and pelvic organs.

Prognosis and Treatment

- Excellent; this is a benign condition.
- Occasional recurrences.

Pathology

Histology

- The gross appearance is that of a multicystic mass, with variably sized cysts.
- The cysts are filled by serous fluid.
- At low power the cysts have thin fibrous walls and are lined by a single layer of bland cuboidal cells.
- The lining cells are typically cuboidal to flattened, but occasionally hobnailing is apparent.
- Cilia are not present on the lining cells.
- Nuclear atypia can be seen, but mitoses are rarely identified.
- Solid growth of the mesothelial lining cells and/or invasion into adjacent stroma is not present.

Immunopathology (Including Immunohistochemistry)

- Positive for calretinin, WT1, and cytokeratin.

Main Differential Diagnosis

- Benign serous cyst—this will be lined by a ciliated epithelium.
- Malignant mesothelioma—greater proliferation of mesothelial cells with tubulopapillary architecture (see Papillary mesothelioma).
- Cystic adhesions—these typically have much more delicate fibrous septa, often lined by flattened, rather cuboidal mesothelial cells.

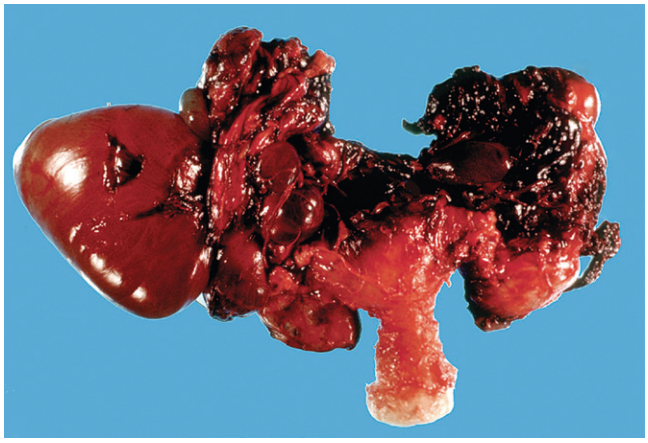

FIGURE 1

Benign cystic mesothelioma. This unusual lesion presents as multiple cysts on the surface of the ovaries and fallopian tubes.

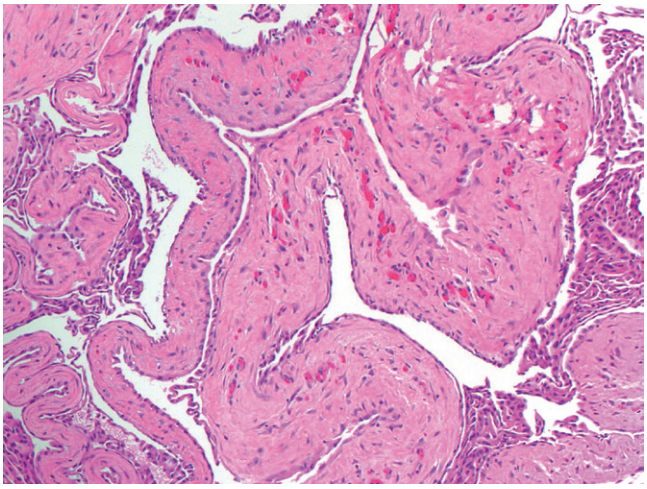

FIGURE 2

Benign cystic mesothelioma. At low power multiple collapsed cysts composed of relatively thin fibrous walls lined by flattened epithelium are apparent. Note the lack of solid or invasive growth.

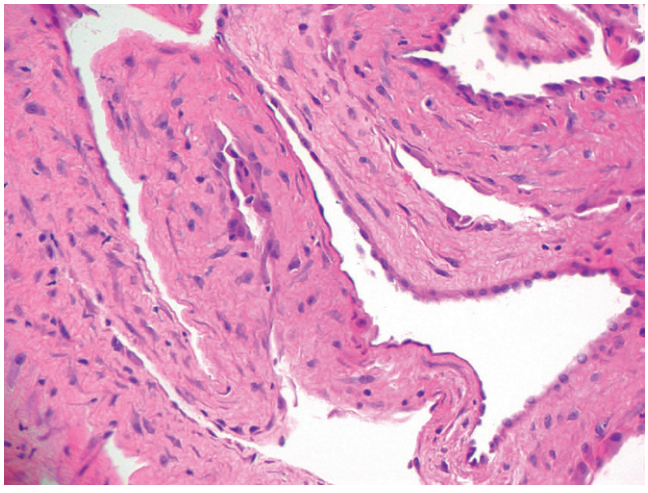

FIGURE 3

Benign cystic mesothelioma. At high power the lining cells are cuboidal and mesothelial to focally flattened and nondescript. Note the lack of cilia.

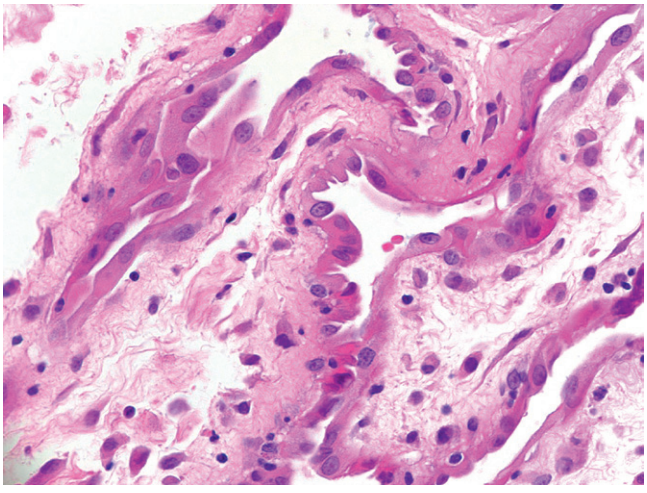

FIGURE 4

Benign cystic mesothelioma. In some foci, nuclear atypia is present. This is not indicative of a malignant process.

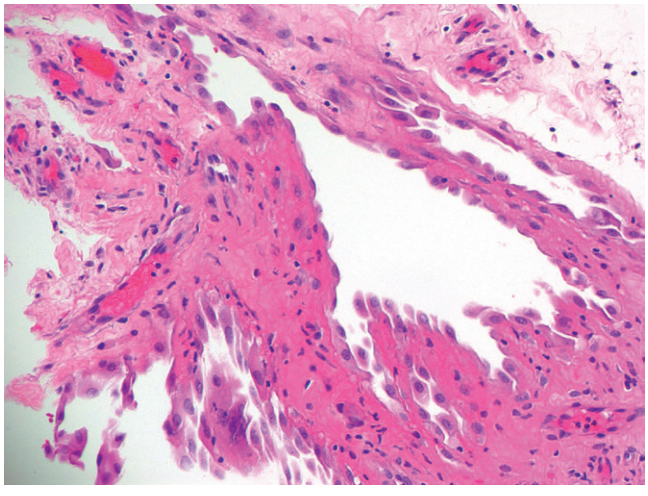

FIGURE 5

Benign cystic mesothelioma. Prominent hobnailing of the lining cells can sometimes be appreciated.

PAPILLARY MESOTHELIOMA

Definition—A well-differentiated tumor of mesothelial cells.

Clinical Features

Epidemiology

- An uncommon neoplasm occurring in women between 20 and 50 years of age.
- Some but not all have evidence of asbestos exposure.

Presentation

- Usually an incidental finding at time of surgery.
- Occasionally symptomatic with multiple nodular lesions on the peritoneal surfaces.

Prognosis and Treatment

- Indolent course. Not presumed to evolve into a malignant mesothelioma, but may require therapy, particularly if symptomatic on presentation.
- Treatment consists of removal and regular follow-up.

Pathology

Histology

- Papillary architecture with loosely arranged underlying stroma.
- Single layer of cuboidal lining cells similar to mesothelial hyperplasia.
- No nuclear atypia, and the mitotic index is very low.
- Psammoma bodies may be present.
- No evidence of invasion.

Immunopathology (Including Immunohistochemistry)

- Mesothelial cells are positive for keratins (CK5\6), calretinin, WT1, h-caldesmon, and D2-40 and should be negative for Ber-EP4, MOC31, and B72.3.

Main Differential Diagnosis

- Borderline serous tumor or low-grade serous carcinoma—both tumors can have a similar distribution. In virtually all cases this tumor will be PAX8 positive and calretinin negative or heterogeneous for PAX8.
- Malignant mesothelioma—some of these tumors have a papillary component but will demonstrate invasion.
- Mesothelial hyperplasia—focal and self-limited. More florid cases may be more difficult to distinguish from a low-grade mesothelioma.

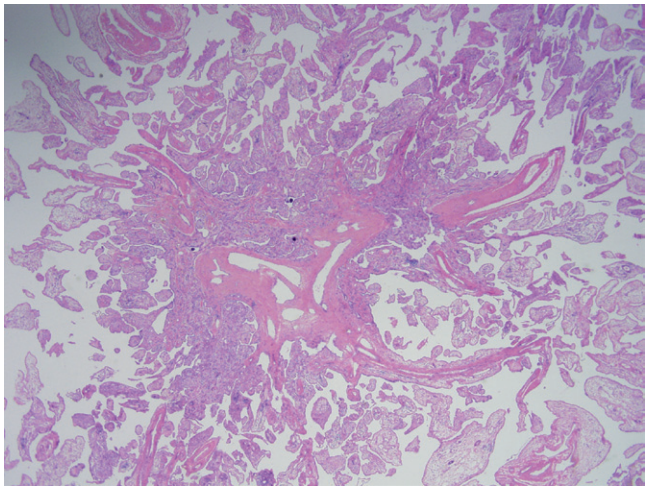

FIGURE 1

Well-differentiated papillary mesothelioma. This low-power microphotograph depicts the delicate papillae with mild stromal edema.

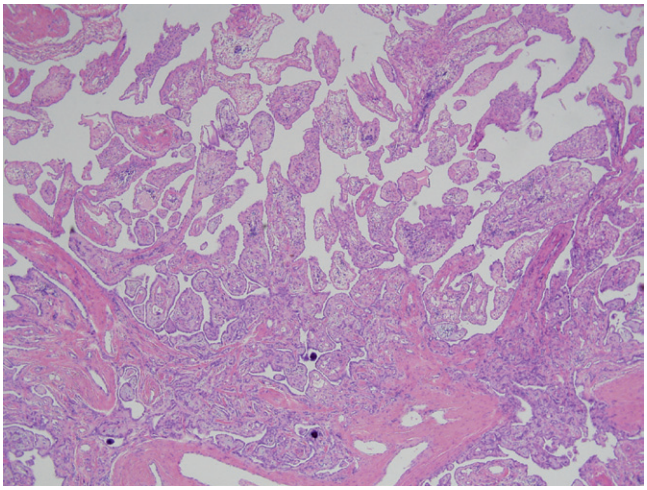

FIGURE 2

Well-differentiated papillary mesothelioma. Note the combination of papillary architecture and focal interdigitation with the underlying stroma *(bottom center)*.

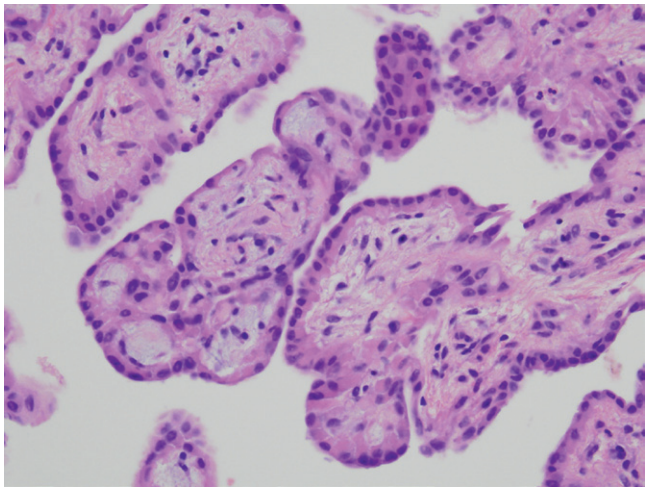

FIGURE 3

Well-differentiated papillary mesothelioma. Higher magnification showing a single layer of cuboidal lining cells without atypia.

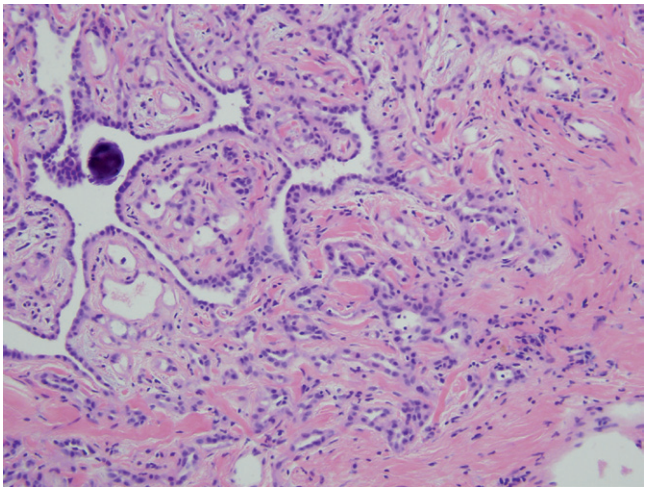

FIGURE 4

Interdigitation of small mesothelial cell-lined acini with stroma. This should not be confused with invasion (see Malignant Mesothelioma).

PAPILLARY MESOTHELIAL HYPERPLASIA

Definition—A benign, reactive condition consisting of hyperplastic mesothelial cells seen in association with acute and chronic irritation of the peritoneal surface.

Clinical Features

Epidemiology

- Papillary mesothelial hyperplasia is often found in cases of pelvic inflammatory disease, tubo-ovarian abscess, and upper genital tract tumors.
- Occasional cases may be associated with cardiac, renal, and hepatic insufficiency as well.

Presentation

- Commonly found incidentally at the time of surgery or pelvic washings.
- Patients should not present with an abdominal mass or symptoms.

Prognosis and Treatment

- The prognosis is dependent on the inciting event; however, as this is a reactive process, no treatment is warranted.

Pathology

Histology

- Mesothelial hyperplasia may present with a number of histologic patterns including solid, papillary, and tubulopapillary.
- The cells comprising the lesion are small with ample, eosinophilic cytoplasm; round nuclei; and variable (one to three) numbers of small, pinpoint nucleoli.
- Adjacent cells may display a cleft or "window" between them as a result of microvilli (seen ultrastructurally).
- Reactive mesothelial cells may be enlarged with more prominent nuclei and nucleoli.
- Mitotic figures are typically easily identifiable, and no necrosis should be present.

Immunopathology (Including Immunohistochemistry)

- Several reports state that EMA is negative in reactive, hyperplastic mesothelial conditions and positive in malignant mesothelial conditions; however, this is controversial.
- Mesothelial cells, both benign and malignant, are positive for keratins, calretinin, WT1, h-caldesmon, and D2-40.

Main Differential Diagnosis

- Malignant mesothelial processes—these will demonstrate invasion and atypia.
- Implants of serous borderline tumor or low-grade serous carcinoma—distinction may be difficult in small foci, in which case special stains will usually discriminate mesothelial from epithelial (PAX8-positive and calretinin-negative) cells. However, we have seen cases that straddle this divide, with both calretinin and PAX8 staining.

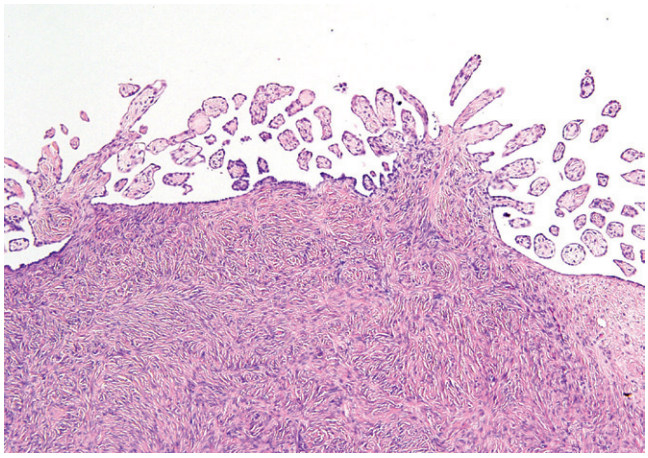

FIGURE 1

Papillary mesothelial hyperplasia. Papillary projections lined by mesothelial cells.

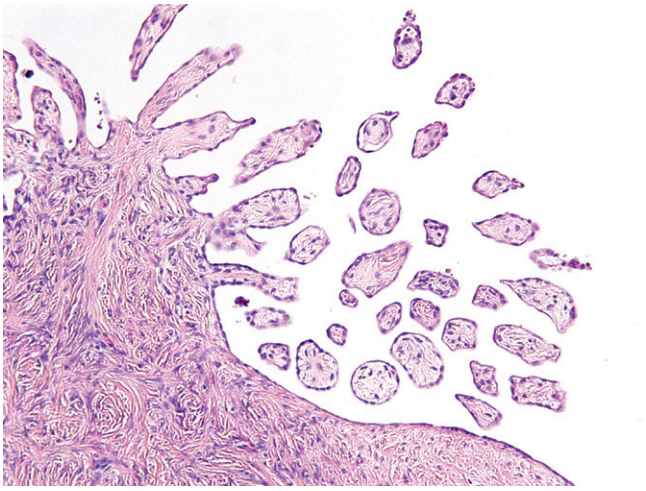

FIGURE 2

Papillary mesothelial hyperplasia. The lining cells are flattened; however, occasional cells with ample, eosinophilic cytoplasm can be seen in the upper right aspect.

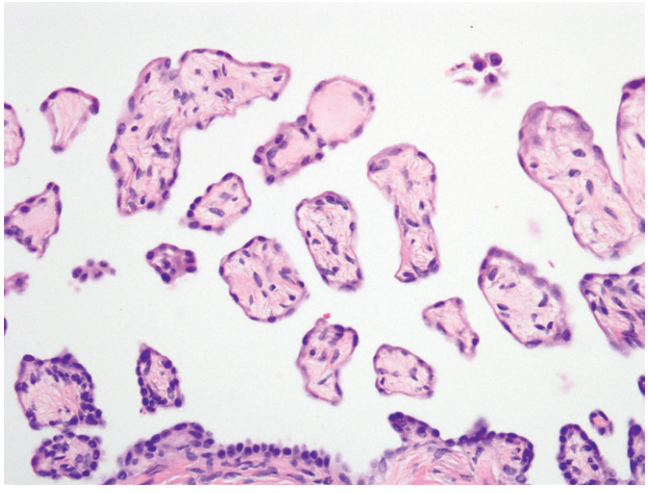

FIGURE 3

Papillary mesothelial hyperplasia. Indistinct cells with eosinophilic cytoplasm lining papillary structures.

MALIGNANT MESOTHELIOMA

Definition—Malignancy comprised of mesothelial cells.

Clinical Features

Epidemiology

- Malignant mesothelioma is an uncommon neoplasm that most often is found involving the pleura.
- Cases have been described within the abdomen; however, the majority of these cases have been described in men.
- The majority of cases occur later in life, between the sixth and ninth decades.
- Asbestos exposure is a risk factor for the development of mesothelioma, although some reports suggest that the association may not be as strong as in the pleural cavity.

Presentation

- Patients present with ascites, abdominal swelling, and pain.
- Large lesions may present with mass effect or vague gastrointestinal symptoms.

Prognosis and Treatment

- The prognosis in malignant mesothelioma is poor.
- Numerous clinical and morphologic features such as age, extent of disease, completeness of resection, nuclear atypia, and mitotic rate have all been associated with outcome.
- Therapy consists of aggressive debulking with interoperative and perioperative intraperitoneal chemotherapy; however, with these treatment modalities the prognosis is still grim.

Pathology

Histology

- Mesothelioma may have a strikingly heterogeneous growth pattern.
- The majority of tumors present with eosinophilic cells with an epithelioid cytology. Described patterns have included solid, papillary, tubular, and mixtures of all three.
- Tumors may appear well differentiated or very poorly differentiated, and frequently a sarcomatoid pattern may be focally present.
- The tumor cells are frequently round with moderate amounts of eosinophilic cytoplasm.
- The nuclei contain coarse, clumped chromatin and prominent nucleoli.
- Mitoses (including atypical forms), necrosis, and psammoma bodies are commonly identified.
- The tumor can be seen invading surrounding structures.

Immunopathology (Including Immunohistochemistry)

- Mesothelial cells, both benign and malignant, are positive for keratins (CK5\6), calretinin, WT1, h-caldesmon, and D2-40 and should be negative for Ber-EP4, MOC31, and B72.3.

Main Differential Diagnosis

- Papillary serous carcinoma—both tumors can have a similar distribution. In virtually all cases this tumor will be PAX8 positive and calretinin negative or heterogeneous. Rarely tumors will be encountered that have both müllerian and mesothelial differentiation.
- Papillary mesothelioma—this is a well-differentiated variant without invasion.
- Unspecified high-grade sarcoma or carcinoma—some tumors will be difficult to classify and will necessitate immunostains to resolve or narrow the diagnosis.

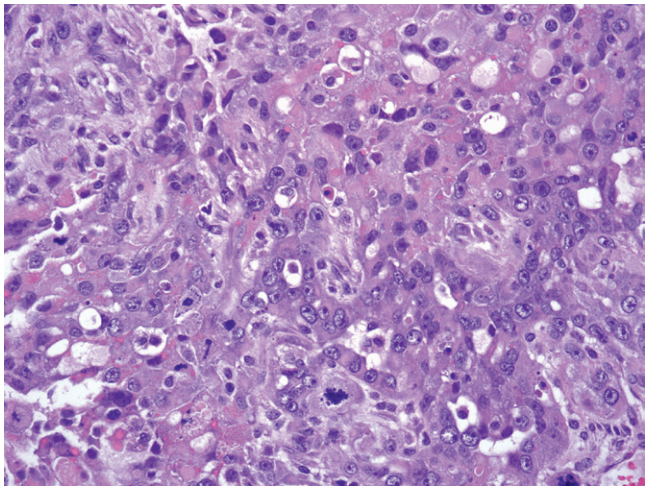

FIGURE 1

Malignant mesothelioma. Epithelioid malignant mesothelioma with marked atypia and prominent atypical mitotic figures.

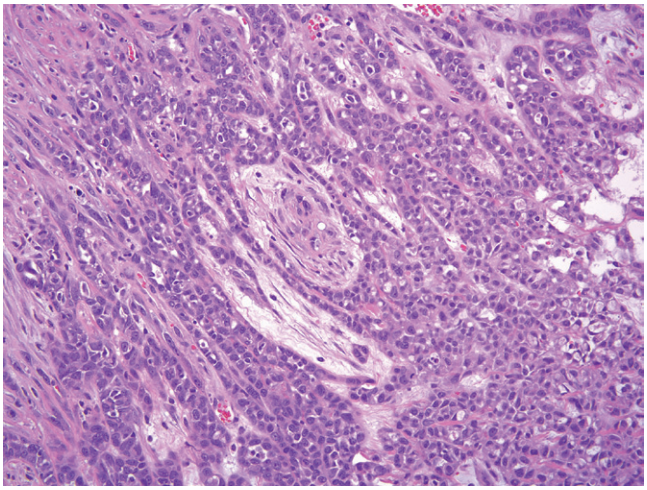

FIGURE 2

Malignant mesothelioma. Malignant cells arranged in a cordlike growth pattern. Note how the cells in this example are relatively monomorphic.

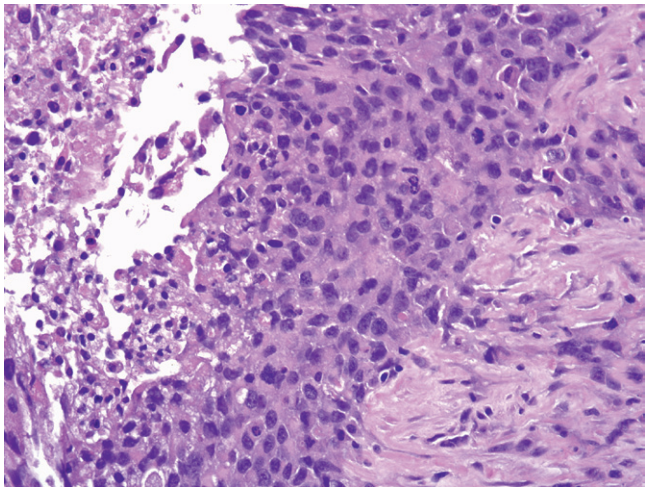

FIGURE 3

Malignant mesothelioma. Epithelioid malignant mesothelioma with large eosinophilic cells.

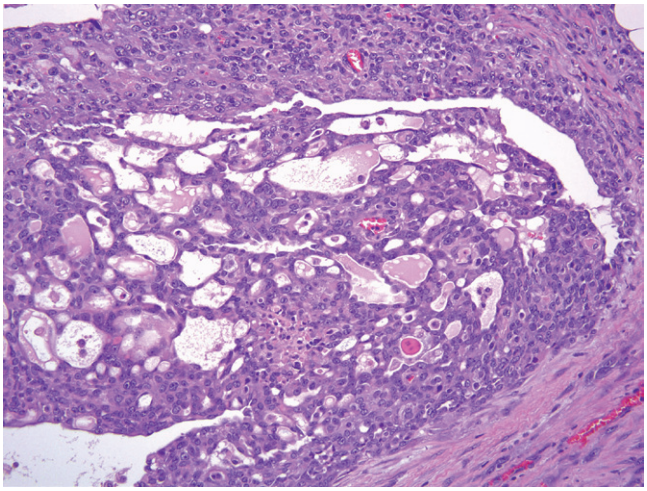

FIGURE 4

Malignant mesothelioma. Epithelioid malignant mesothelioma with pseudoglandular spaces.

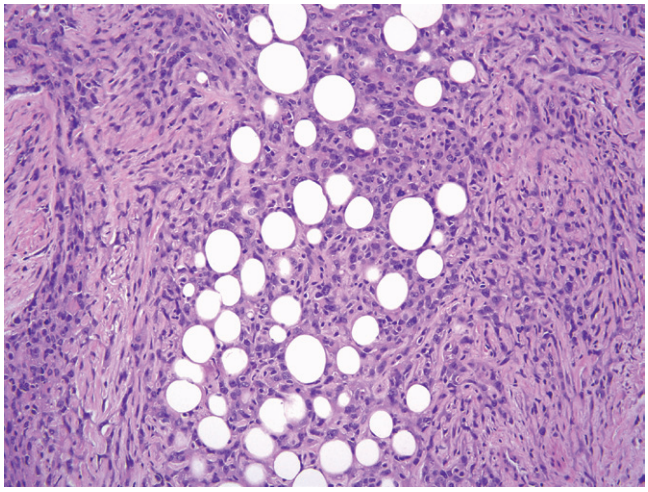

FIGURE 5

Malignant mesothelioma. Invasion of adipose tissue by malignant mesothelial cells.

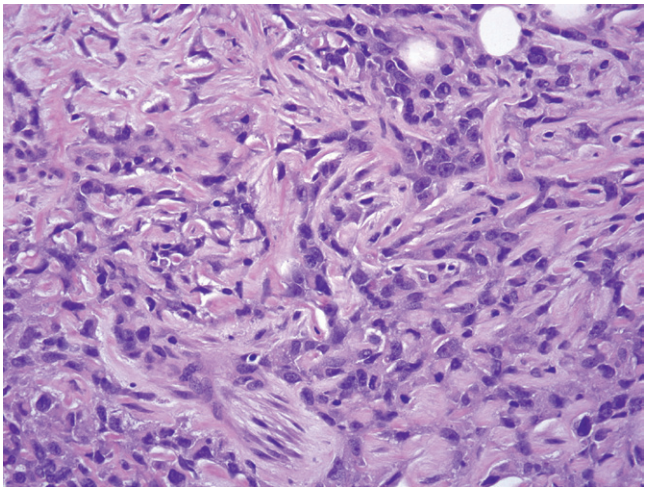

FIGURE 6

Malignant mesothelioma. Spindled (or sarcomatoid) growth in a malignant mesothelioma.

SECTION 6

Gestational

GESTATIONAL SAC

Definition—The membranous sac that envelops the developing embryo.

Clinical Features

Epidemiology

- The gestational sac can be identified in the majority of samples from previable pregnancies.
- The gestational sac confirms an intrauterine pregnancy, even in cases in which embryonic tissue cannot be identified.

Presentation

- In spontaneous abortions patients present with signs and symptoms of pregnancy loss, including cramping, vaginal bleeding, and passage of products of conception.
- In a missed abortion the patient has not yet passed the products of conception.
- The gestational sac can often be identified by the clinician at the time of dilation and curettage (D&C).

Prognosis and Treatment

- In a spontaneous or missed abortion, D&C is performed to ensure complete removal of the products of conception.
- If the ultrasound confirms no remaining products, treatment is not required.

Pathology

Histology

- The gestational sac consists of a single scantly cellular layer of stroma lined by trophoblasts.
- A large cavitation is often present.
- The cavitation occasionally resembles the central cavitations seen in a molar pregnancy; however, all other features of a molar gestation are absent.
- An empty gestational sac should be suspected whenever a single, large, villouslike structure is identified.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- May be confused with a hydropic villous with a cistern, and hence misinterpreted as a molar pregnancy.

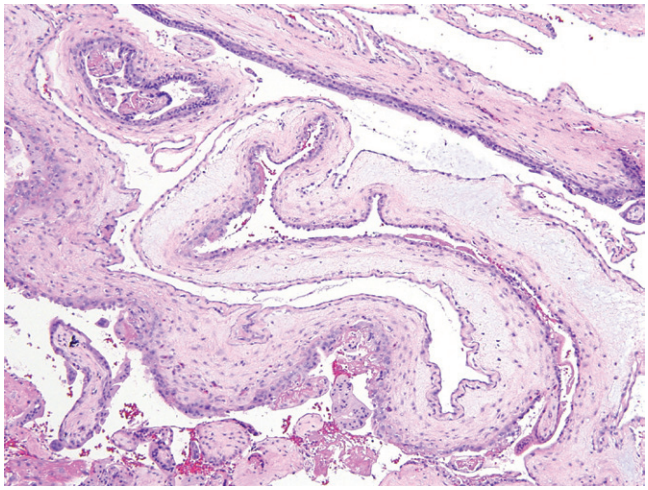

FIGURE 1
Gestational sac. Low power showing a minimally cellular stroma lined by a single layer of trophoblasts.

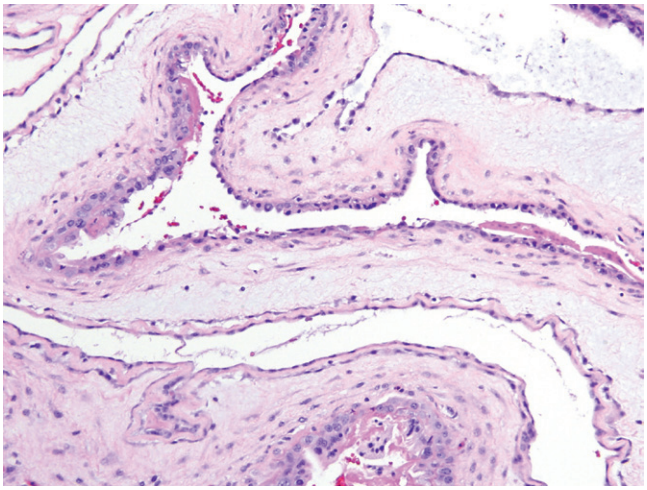

FIGURE 2
Gestational sac. The thin delicate lining is the amnion, and the shaggier side lined by large trophoblasts is the chorion.

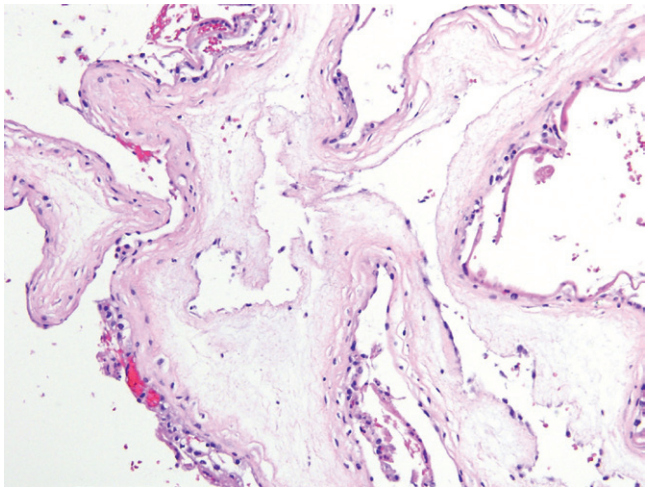

FIGURE 3
Gestational sac. A large central cavitation is present, but other features of a molar pregnancy are absent.

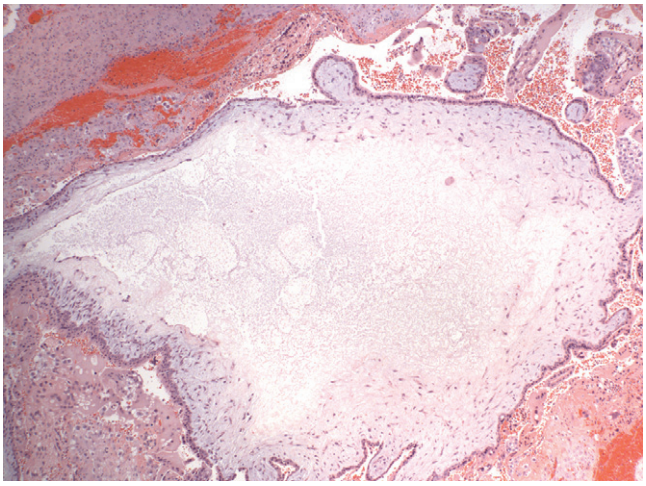

FIGURE 4
An empty gestational sac, resembling a hydropic villous.

FRESH IMPLANTATION SITE

PITFALL

Definition—The area adjacent to the gestational sac where intermediate trophoblasts and fibrinoid can be found permeating the decidua.

Clinical Features

Epidemiology

- Normal structure.

Presentation

- Implantation site (IS) is frequently identified on the maternal surface of the placenta.
- In previable pregnancies it can be identified admixed with other products of conception.
- Identification of fresh IS can confirm an intrauterine pregnancy.

Prognosis and Treatment

- In a spontaneous or missed abortion, dilation and curettage may be undertaken to ensure complete removal of the products of conception.
- If the ultrasound confirms no residual products of conception, treatment is not required.

Pathology

Histology

- IS is identified at scanning magnification by its brightly eosinophilic hue when compared with the background.
- The brightly eosinophilic material is known as Nitabuch's fibrin.
- Extravillous trophoblasts are identified migrating through the fibrinoid substance (Nitabuch's fibrin).
- The extravillous trophoblasts are dark and smudgy, with irregularly shaped nuclei and cytoplasm.
- There should not be significant trophoblastic atypia or mitotic activity in a normal IS.
- Mitoses are not identified.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Decidua—decidual cells may at times appear atypical, usually as a function of degeneration, and may mimic implantation. A keratin stain will make this distinction, particularly if when excluding ectopic pregnancy.
- Molar IS—the extravillous trophoblasts are "more atypical" than usual, with larger and more hyperchromatic nuclei.
- Placental site nodule or older IS—these are composed of epithelioid extravillous trophoblasts arranged in a more homogeneous aggregate intertwined with fibrin-like material.

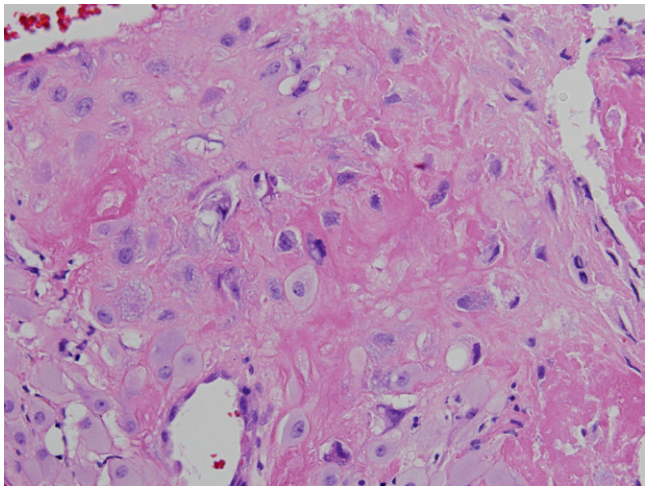

FIGURE 1

Fresh IS. Brightly eosinophilic fibrinoid material stands out from the background of decidualized endometrium. Dark, smudgy trophoblasts are scattered throughout Nitabuch's fibrin.

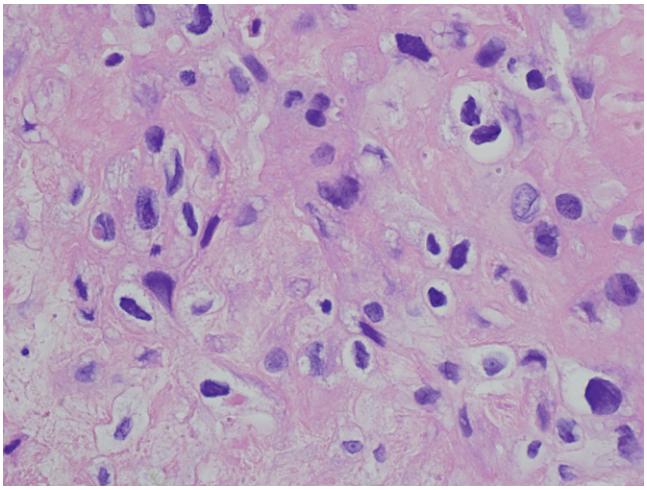

FIGURE 2

Fresh IS. The trophoblasts are irregularly shaped but not atypical. The chromatin is uniform and smudgy. The trophoblasts have abundant cytoplasm with indistinct cell borders. Mitoses are not present.

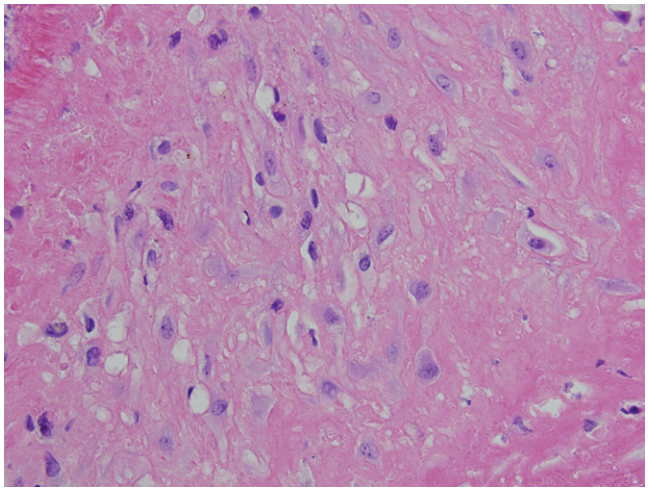

FIGURE 3

Fresh IS. In some areas the trophoblasts appear slightly spindled and also have prominent cell membranes in this focus.

IMPLANTATION SITE NODULE

Definition—A collection of extravillous trophoblasts within hyalinized stroma, indicative of a previous pregnancy.

Clinical Features

Epidemiology

- Implantation site nodules are common and typically have the same immunophenotype as epithelioid trophoblasts seen in the membranes, maternal surface, and intervillous fibrin.
- Can be identified in endometrial samples months to years following intrauterine pregnancies.

Presentation

- The vast majority are identified incidentally upon endometrial sampling (or hysterectomy) for other indications.

Prognosis and Treatment

- Implantation site nodules are benign and incidental.
- No further treatment is warranted.

Pathology

Histology

- Implantation site nodules are characterized by a collection of extravillous epithelioid trophoblasts set within hyalinized stroma.
- Fibrin is indicative of a recent implantation site and is by definition absent in placental site nodule (PSN).
- The trophoblasts show degenerative nuclear features.
- Nuclear atypia and mitotic activity are absent.

Immunopathology (Including Immunohistochemistry)

- Ki-67 immunostaining may be helpful in determining the level of proliferative activity.
- Immunostains are noncontributory in the vast majority of cases. However, the cells should be immunopositive for inhibin and p63. Mel-cam staining will highlight only a subset of these cells in contrast to early implantation site.

Main Differential Diagnosis

- Implantation site, recent. This is early implantation site, not epithelioid trophoblast. Look for Nitabuch's fibrin.
- Exaggerated implantation site. This is an exaggeration of the early implantation site trophoblast and is not arranged in nodules. There will often be some Nitabuch's fibrin present.
- Epithelioid trophoblastic tumor, especially in small samples. Look for cellular atypia, increased proliferative (greater than 10% Ki-67 positive nuclei) activity.

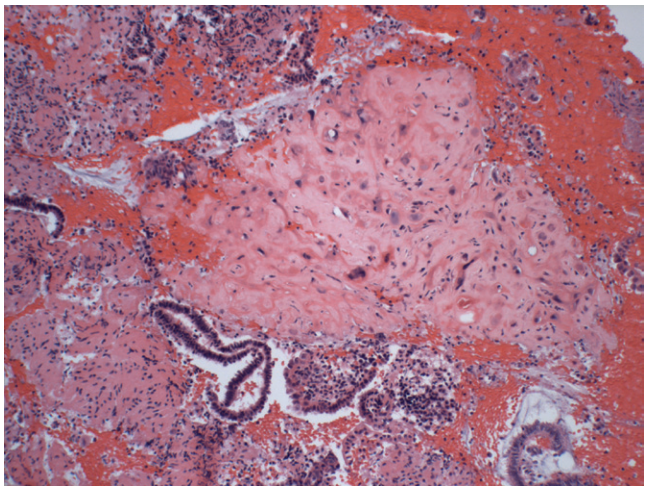

FIGURE 1

Implantation site nodule. At medium magnification a discrete fragment of hyalinized tissue is seen with a few hyperchromatic nuclei.

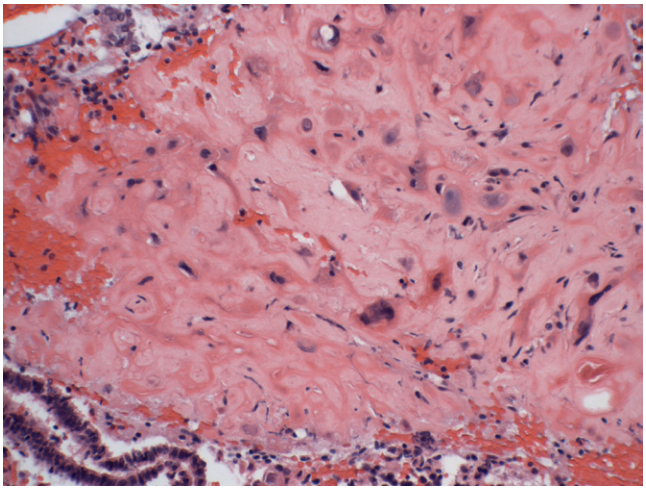

FIGURE 2

Implantation site nodule. At higher magnification a few hyperchromatic trophoblasts are seen in the hyalinized matrix. This matrix is composed of fibrinoid material elaborated by the extravillous trophoblast. A similar scenario plays out near the chorionic plate, within intervillous fibrin, and near the maternal surface of the placenta.

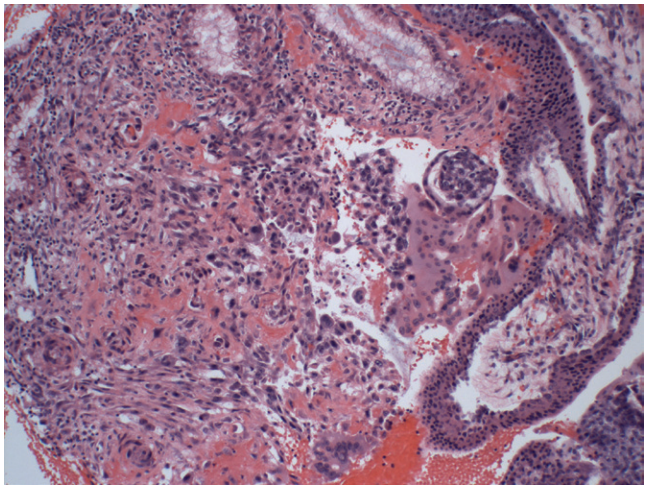

FIGURE 3

Implantation site in an early gestation. The origin of these cells is distinct from the implantation site nodule as they emanate from the trophoblastic columns during early gestation and invade the decidua and inner myometrium.

SPONTANEOUS ABORTION

Definition—Unavoidable loss of viability in the first 12 weeks.

Clinical Features

Epidemiology

- Approximately one third of clinically known pregnancies terminate in the first 12 weeks.
- Forty to fifty percent have a chromosomal anomaly.
- Twenty percent have trisomy aneuploidies, and 6% are triploid.
- The risk of a chromosomal abnormality increases with multiple losses.

Presentation

- Typically detected on ultrasound as the absence of a fetus or abnormal fetal growth.
- Vaginal bleeding.

Pathology

Histology

- Several important patterns should be appreciated that may cause confusion.
- Early previllous trophoblast may be confused with trophoblastic neoplasia.
- Villous enlargement and hydrops are common in early gestational loss. A key feature is the gradual differences in villous size that is typical of nonmolar pregnancies.
- Extravillous trophoblast may be exuberant; a key feature of benign trophoblastic changes is an eccentric orientation in the villi.
- Dysmorphic villi, scattered enlarged villi, and trophoblastic inclusions are features seen in aneuploidy gestations.
- Conspicuous cisterns in villi (a mimic is gestational sac) combined with prominent disparity in villous size are a feature of partial hydatidiform mole.

Immunopathology (Including Immunohistochemistry)

- Noncontributory with the exception of p57kip2, which will exclude about 99% of early complete moles by its expression in cytotrophoblast and stromal cells.

Main Differential Diagnosis

- Choriocarcinoma—marked trophoblastic atypias.
- Placental site trophoblastic tumor (PSTT)—implantation site trophoblast atypias with clear-cut myometrial invasion.
- Early complete mole—diffuse mild villous enlargement, basophilic villous stroma, apoptosis, mild or moderate thickening of the villous trophoblast, and dysmorphic villi with knucklelike projections.
- "Partial mole" conspicuously enlarged villi, cisterns, some villous irregularity, and/or increased trophoblast.

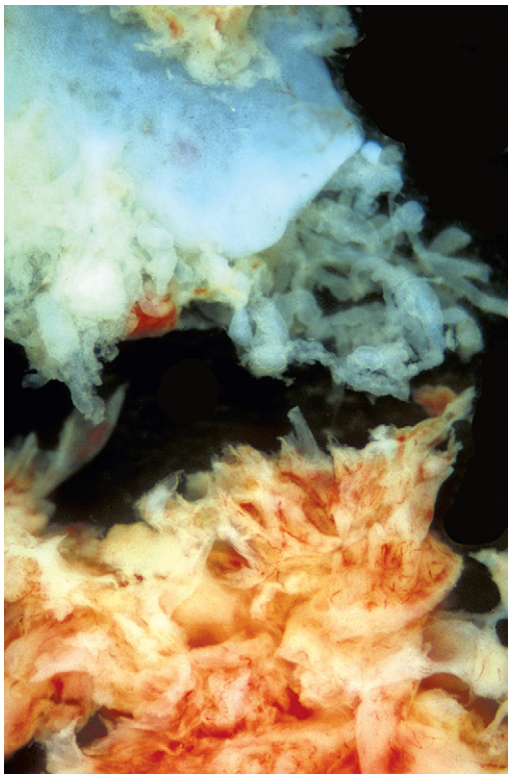

FIGURE 1
Dissecting microscopic image of early chorionic villi *(upper)*. Note the absence of vessels in contrast to the endometrial tissue *(lower)*.

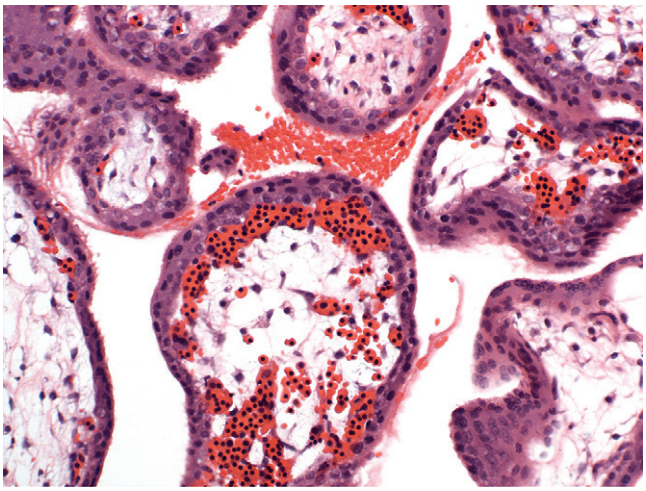

FIGURE 2
Immature chorionic villi at 6 weeks. Note the prominent nucleated red blood cells.

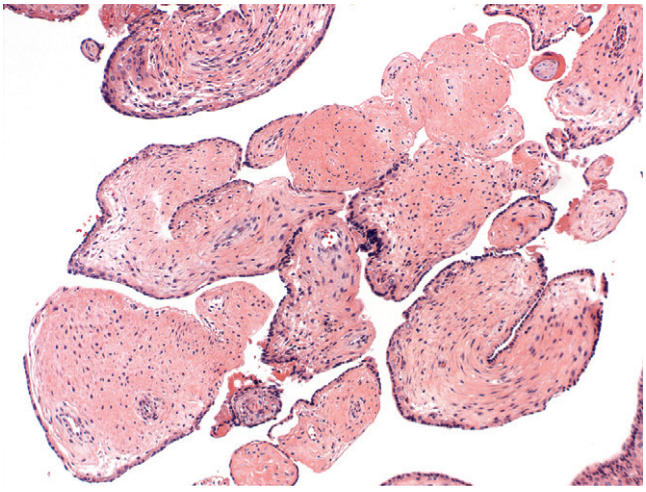

FIGURE 3
Villous sclerosis associated with embryonic death.

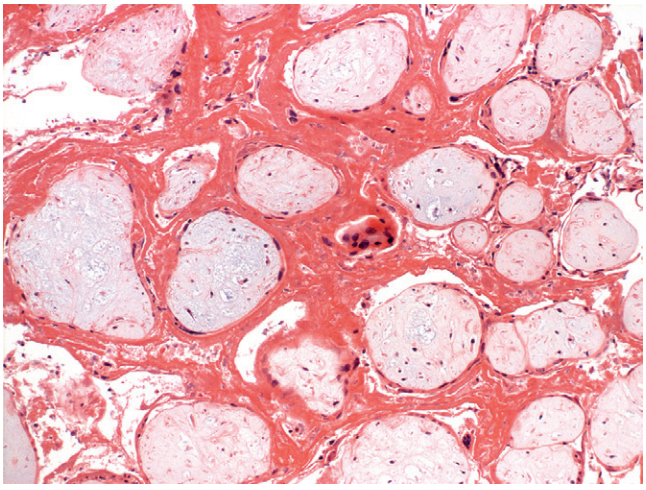

FIGURE 4
Villous edema with perivillous fibrin, commonly seen in early gestations.

ECTOPIC PREGNANCY

Definition—Implantation of the embryo that occurs outside the uterine cavity or in an abnormal location within the uterus.

Clinical Features

Epidemiology

- Ectopic pregnancies account for around 2% of all documented pregnancies in the United States.
- Ectopic pregnancy is associated with prior manipulation of the fallopian tube, infertility, and prior ectopic pregnancies. Ninety-five percent occur in the tube, 2.5% in the cornu, and the rest in the ovary.
- Inflammatory conditions, including pelvic inflammatory disease, affecting the fallopian tube are a major risk factor.

Presentation

- Patients classically present with pelvic or abdominal pain and vaginal bleeding.
- Sexual and reproductive history, beta-HCG levels, and transvaginal ultrasound are helpful.
- If a gestational sac is not identified, endometrial sampling may be undertaken to rule out ectopic pregnancy.

Prognosis and Treatment

- If identified early and treated appropriately, ectopic gestations have a low, though significant, risk of maternal morbidity and mortality.
- Maternal morbidity and mortality are due to rupture and intraabdominal hemorrhage.
- If an intrauterine pregnancy cannot be identified, several treatment options exist including watchful waiting and medical management (methotrexate).
- Surgical exploration may be indicated in medically unstable patients.

Pathology

Histology

- Endometrial samples from suspected ectopic pregnancies should be entirely submitted and carefully examined for evidence of uterine implantation.
- Structures that indicate the presence of a uterine pregnancy include embryonic tissue, placental villi, gestational sac, and fresh implantation site.
- Hormonally related endometrial changes, including Arias-Stella effect, are not sufficient to diagnose an intrauterine pregnancy and are often present in the setting of an ectopic pregnancy.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Previous pregnancy (implantation site nodule).
- Shed tissue from an ectopic pregnancy (scant villi).
- Molar pregnancy.
- Contamination (i.e., “floaters”) from another case.

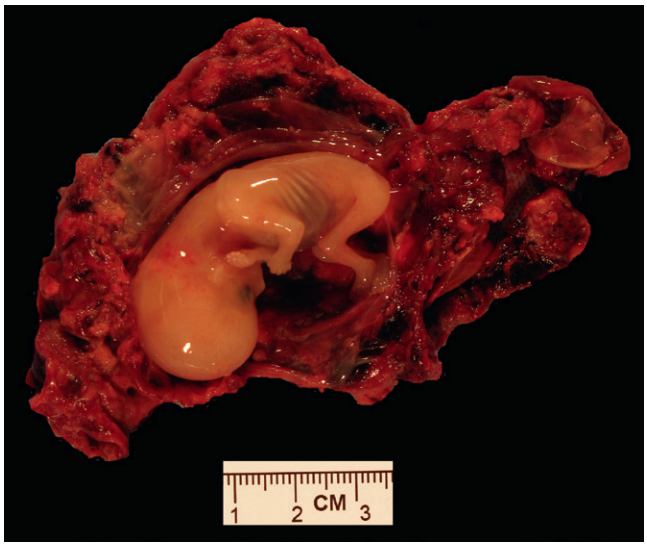

FIGURE 1

Tubal ectopic pregnancy. Gross example of an ectopic pregnancy discovered at a late stage in the fallopian tube.

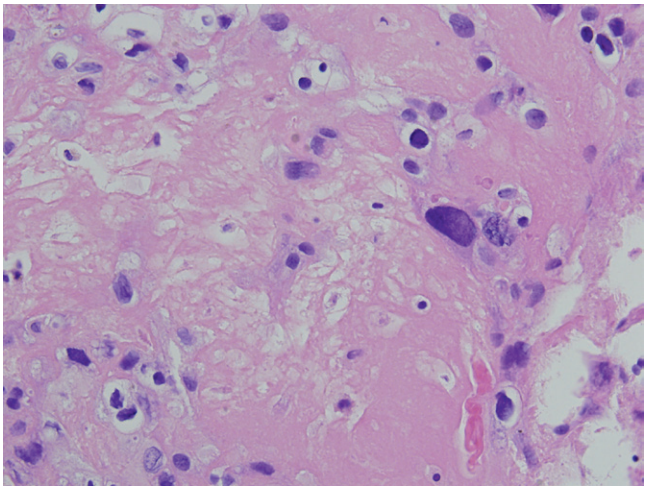

FIGURE 2

Example of fresh implantation site in an endometrial biopsy. This is indicative of an intrauterine pregnancy. However, be aware that a paired intrauterine and extrauterine gestation will occur in approximately one in 10,000 pregnancies.

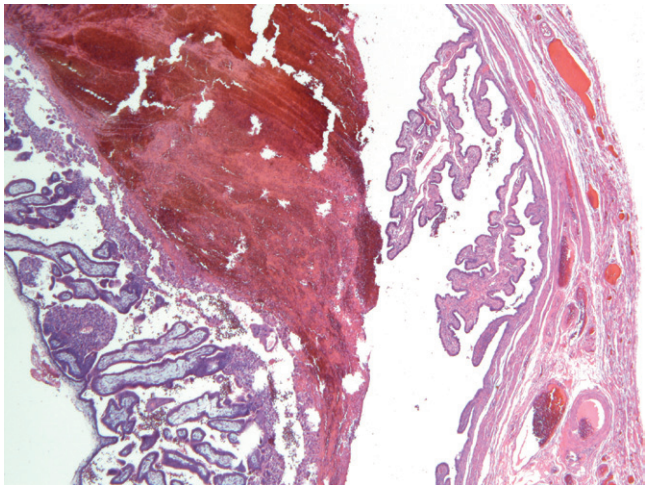

FIGURE 3

Ectopic pregnancy. Fallopian tube *(fimbria on right)* with immature placenta and implantation site with underlying hemorrhage.

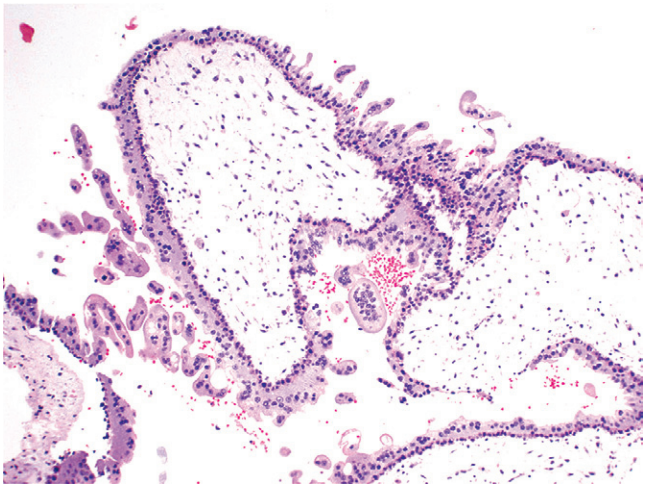

FIGURE 4

An ectopic molar pregnancy. This must always be excluded as it may often recur if unnoticed. High vascularity and elevated beta-HCG levels are common features but half are not suspected on ultrasound.

COMPLETE HYDATIDIFORM MOLE

PITFALL

Definition—An abnormal gestation in which all of the genetic material is paternally derived.

Clinical Features

Epidemiology

- Molar pregnancies have a biphasic age distribution, with increased incidence at the reproductive extremes: before age 20 and after age 40.
- Increased incidence has also been noted in women of Asian descent.
- Other risk factors include low socioeconomic status, prior molar pregnancies, and nulliparity.

Presentation

- In classic complete hydatidiform mole (CHM) patients present with vaginal bleeding, vomiting, thyrotoxicosis, and markedly elevated levels of beta-human chorionic gonadotropin (HCG).
- Ultrasonographic evaluation shows a "snowstorm" or "Swiss cheese" appearance, which corresponds to the swollen, hydropic villi (hydatidiform, meaning grapelike).
- Early CHMs typically do not exhibit the classic signs and may be detected clinically as a missed abortion.
- In early CHM, beta-HCG levels are only mildly elevated.
- The diagnosis of an early CHM may not be apparent until histologic examination of the products of conception.

Prognosis and Treatment

- CHM carries a risk of developing a postmolar tumor.
- Initial treatment is usually evacuation of the uterus by suction dilation and evacuation (D&E), but hysterectomy may be employed in patients who have completed childbearing.
- Following D&E or hysterectomy, patients are followed with weekly serum beta-HCG determinations until they are normal for 4 consecutive weeks, then monthly for an additional 5 months.
- Approximately 15% to 20% of patients with CHM go on to develop persistent gestational trophoblastic disease (GTD), including 2% to 3% who develop choriocarcinoma.
- There are no histologic features that can predict which patients will develop progressive disease.
- Factors that are associated with an increased risk of recurrence include patient age, length of time to diagnosis, uterine size, and beta-HCG levels.
- Almost 100% of patients should be cured if followed appropriately.

Pathology

Histology

Classic (late) CHM:

- Late CHMs, those identified after 12 weeks, are characterized by a uniform population of large, hydropic villi with frequent central cavitations (cisterns).
- Trophoblastic hyperplasia is concentric, has a lacy appearance, and is conspicuous.
- Concentric trophoblast hyperplasia is often described as having a Medusa head–like configuration.
- Mild to moderate trophoblastic atypia is present but not necessarily conspicuous.
- Embryonic tissue, including nucleated fetal red blood cells, is absent.
- Atypical implantation site is often seen; however, this feature is also present in partial molar pregnancies.

Early CHM:

- Early CHMs, those presenting at 8 to 12 weeks gestation, are often grossly indistinguishable from a missed abortion.
- Villous morphology is the most helpful feature.

- The villi in an early complete mole are hypercellular, with a blue myxoid matrix.
- Villi typically have scalloped or "knucklelike" contours.
- Karyorrhexis of the villous mesenchymal cells is often seen.
- The lack of fetal red blood cells can be a helpful feature.
- Villous edema may be minimal, and cistern formation is often inconspicuous or absent.
- Trophoblastic hyperplasia and atypia may only be focal.
- An atypical implantation site may be identified; however, this feature is also seen in partial hydatidiform moles.
- Extensive sampling of a suspected early CHM is critical to the diagnosis.

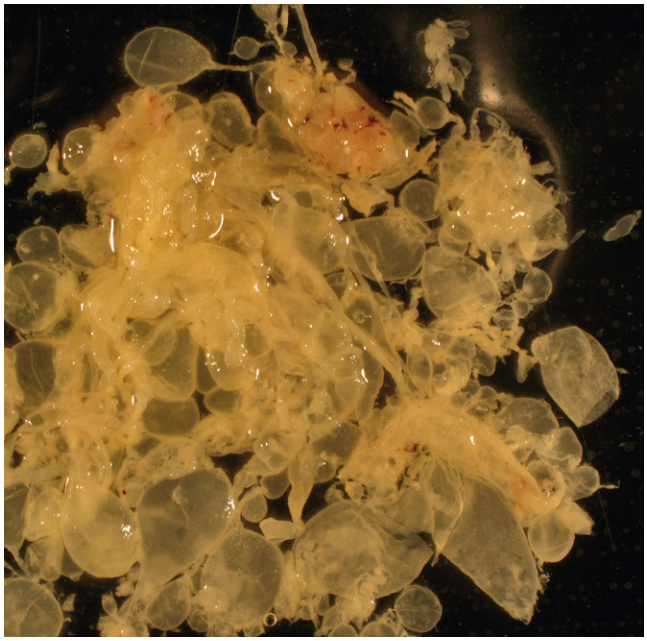

FIGURE 1
Early CHM. Villi floated in saline are uniformly enlarged.

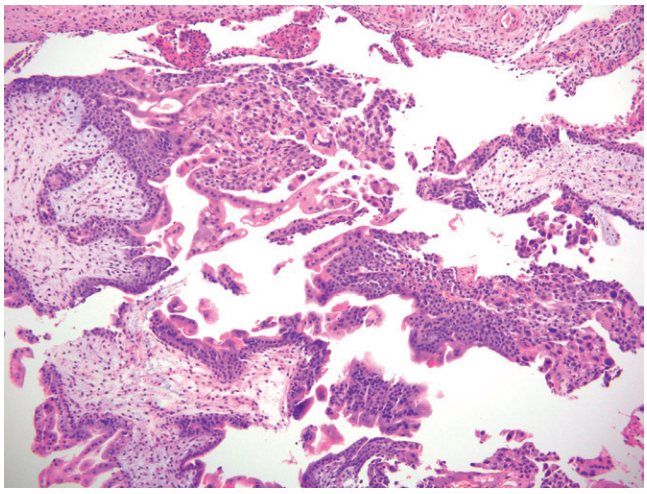

FIGURE 2
Early CHM. Note the irregular villous outlines and increased trophoblast.

Immunopathology (Including Immunohistochemistry)

- Immunostaining for p57 is negative.
- A negative result indicates that villous mesenchymal and cytotrophoblastic cells lack staining; extravillous trophoblasts may exhibit positive staining for p57 even in a CHM.

Main Differential Diagnosis

- Partial hydatidiform mole.
- Normal early gestation.
- Hydropic abortus.
- Empty gestational sac.

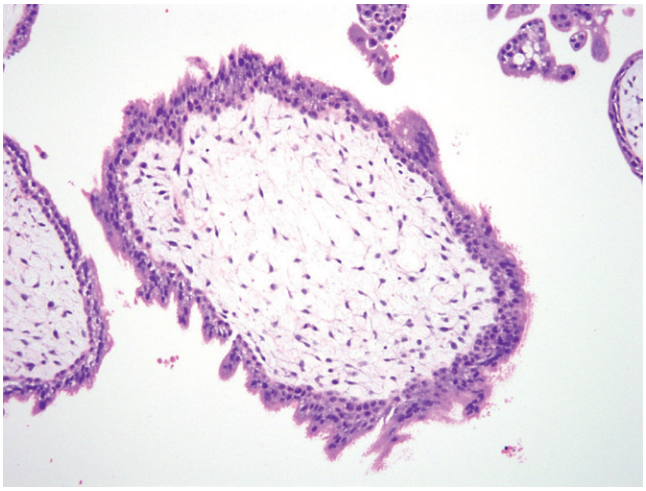

FIGURE 3
Early CHM. This villous is not conspicuously enlarged but note the absence of vessels or nucleated red blood cells.

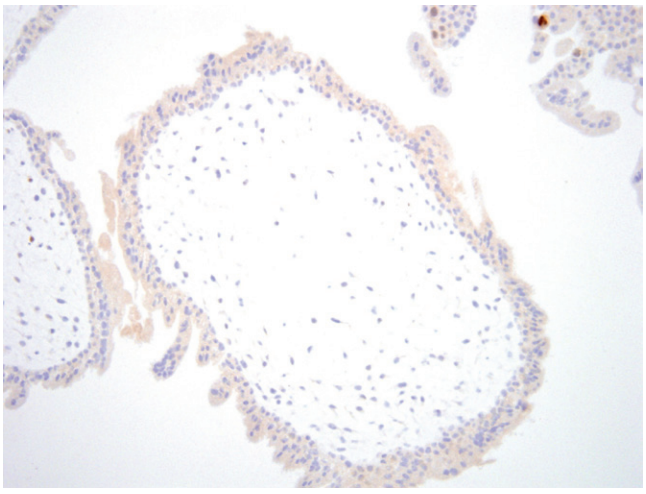

FIGURE 4
Note the absence of p57 staining.

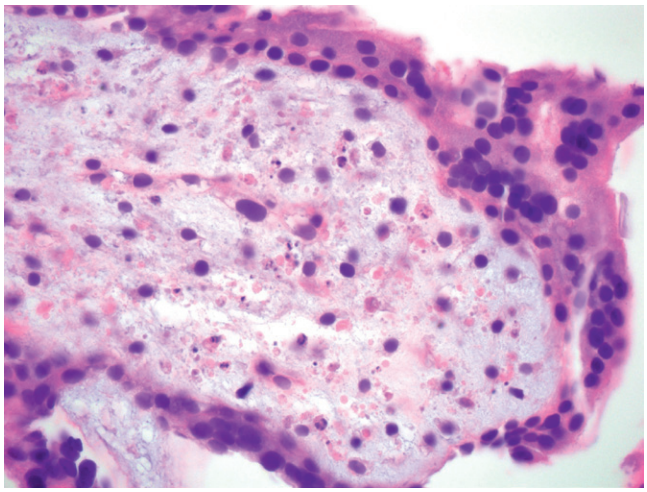

FIGURE 5

Early CHM. Note here the prominent karyorrhexis in the stromal cells and the faint blue stromal matrix.

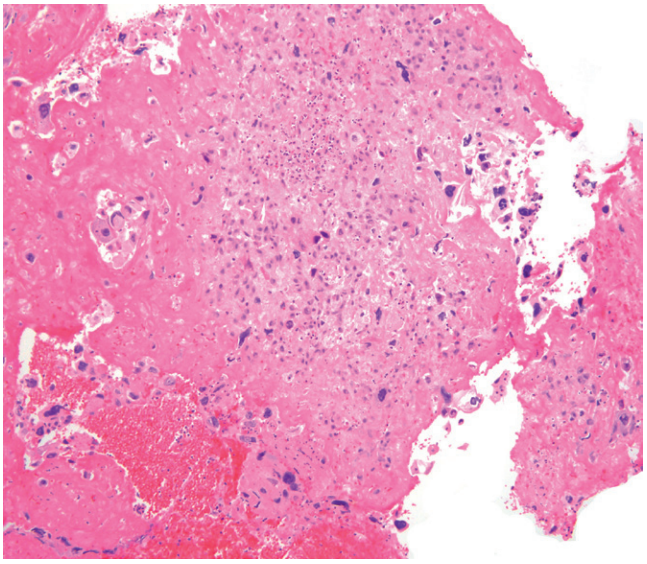

FIGURE 6

Molar implantation site. At moderate magnification the trophoblastic atypias can be appreciated.

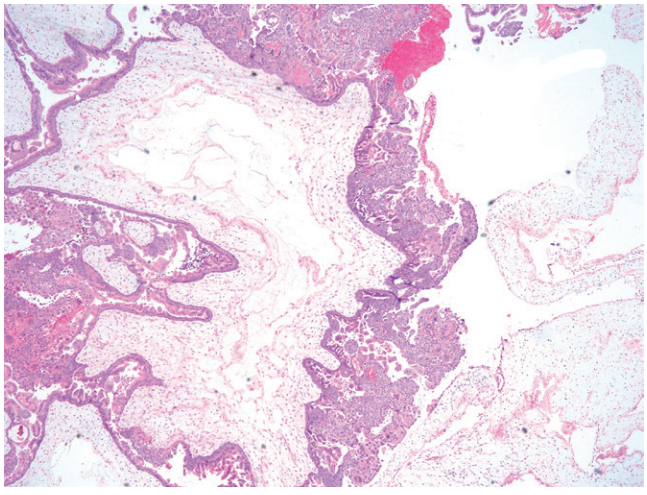

FIGURE 7

CHM. Somewhat more advanced mole with large villi and abundant cytotrophoblastic and syncytial trophoblastic proliferation.

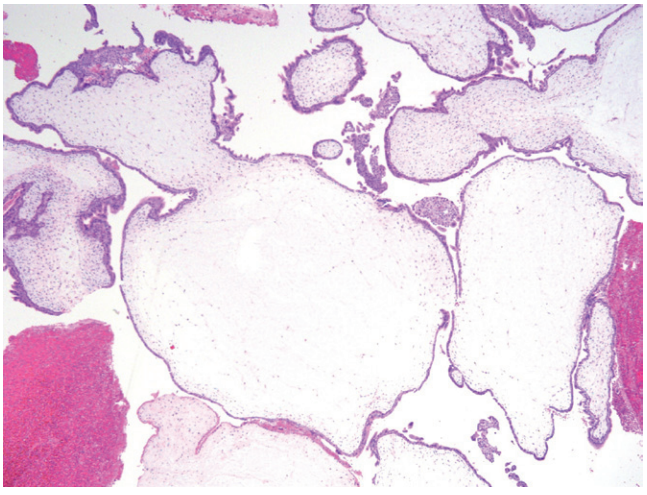

FIGURE 8

CHM. Somewhat more advanced mole with large villi and abundant cytotrophoblastic and syncytial trophoblastic proliferation.

INVASIVE HYDATIDIFORM MOLE

Definition—A complete mole that invades into the underlying myometrium.

Clinical Features

Epidemiology

- Is defined as an uncommon sequel to complete mole, occurring in less than 5% of complete moles.
- Increased incidence has been noted in women of Asian descent.

Presentation

- Patient typically has a recent history of a molar pregnancy but can present with invasive mole.
- Large uterus for gestational age after prior molar evacuation, with rising or plateaued HCG levels.
- Continued vaginal bleeding and abdominal pain.
- Confirmation of invasive mole is rarely possible on curettage alone, inasmuch as the diagnoses rest with the identification of molar tissue in the myometrium.

Prognosis and Treatment

- Management is typically hysterectomy.
- Overall, invasive moles have a favorable prognosis, with remission rate of over 98% in early-stage disease and up to 80% in the setting of recurrent lesions.

Pathology

Histology

- The classic finding is that of molar villi in the myometrium.

Immunopathology (Including Immunohistochemistry)

- Immunostaining for p57 is negative. This stain is rarely needed for the diagnosis given the presentation, but might be helpful in rare cases where the diagnosis is not clear-cut.

Main Differential Diagnosis

- Choriocarcinoma—this entity will be effectively excluded if chorionic villi are identified.
- PSTT or ETT—both of these trophoblastic neoplasms can penetrate through the uterine wall, but villi will be absent.

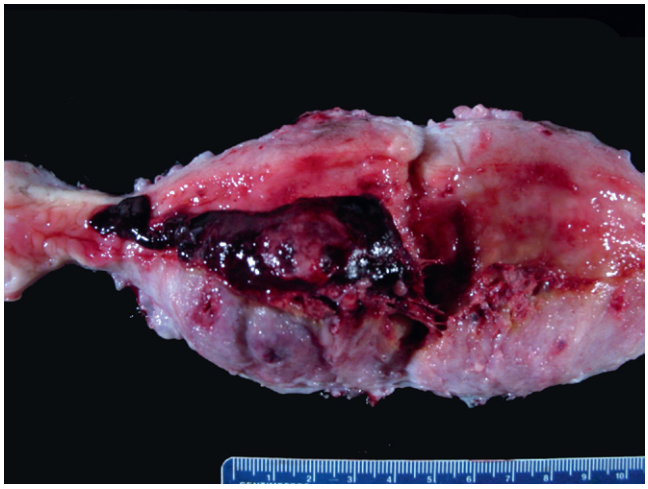

FIGURE 1

Invasive complete hydatidiform mole. On opening this uterus, there is a large amount of retained molar tissue.

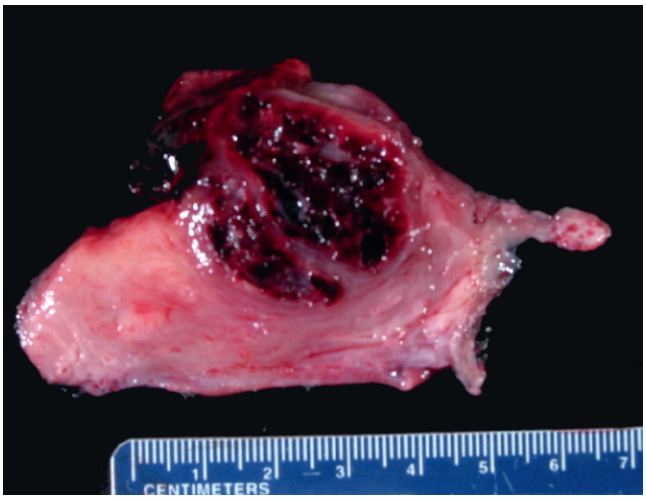

FIGURE 2

Invasive complete hydatidiform mole. This cross section of the endomyometrium reveals a hemorrhagic focus in the myometrium signifying ensconced molar tissue.

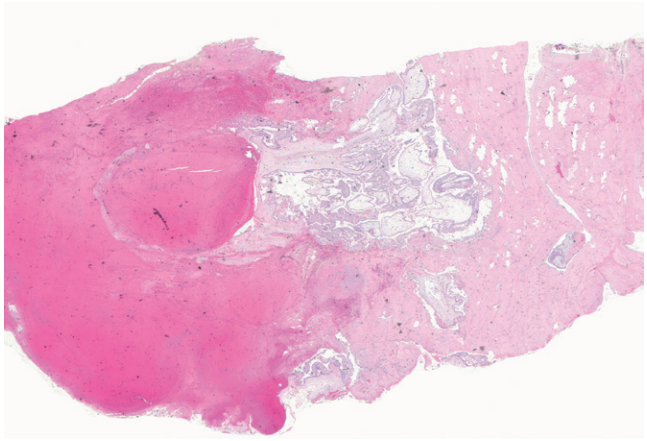

FIGURE 3

Invasive complete hydatidiform mole. At low power this section shows the blood clot on the cavity side (*left*), villi within the myometrium (*center*), and a villous in a vessel (*lower right*).

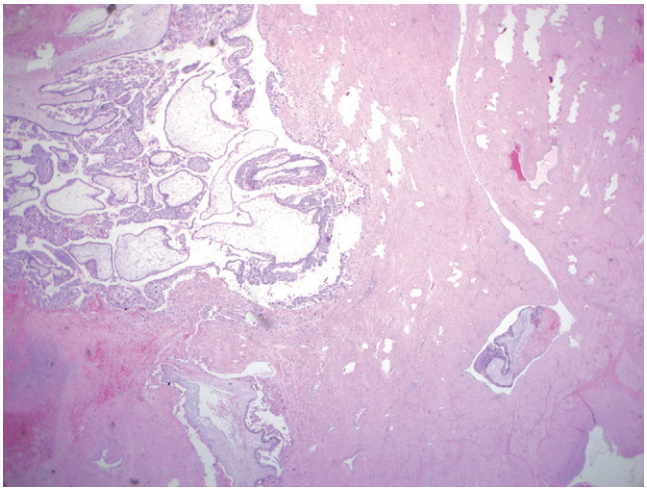

FIGURE 4

Invasive complete hydatidiform mole. Higher magnification of Figure 3 shows the invasive molar tissue at the center and below, and the intravascular villi at the lower right.

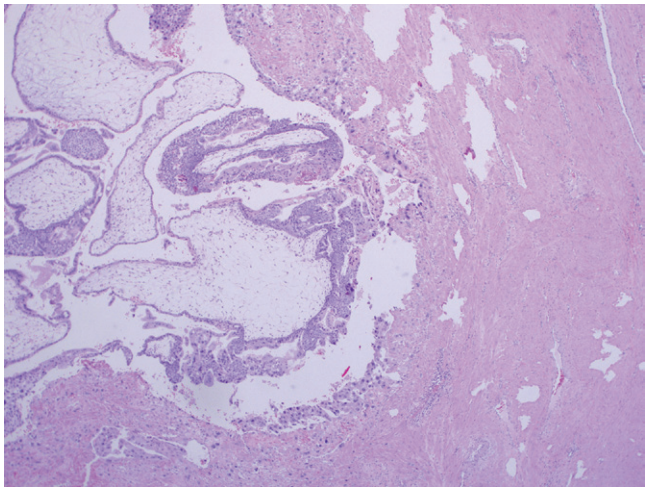

FIGURE 5

The interface between the villous and myometrium is composed of implantation site without decidua. This is very similar to placenta increta.

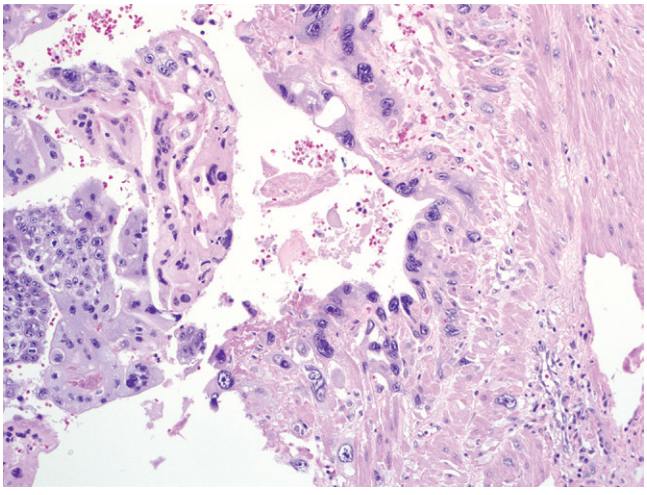

FIGURE 6

Invasive complete hydatidiform mole. At higher magnification, note the atypia of the extravillous trophoblast at the interface.

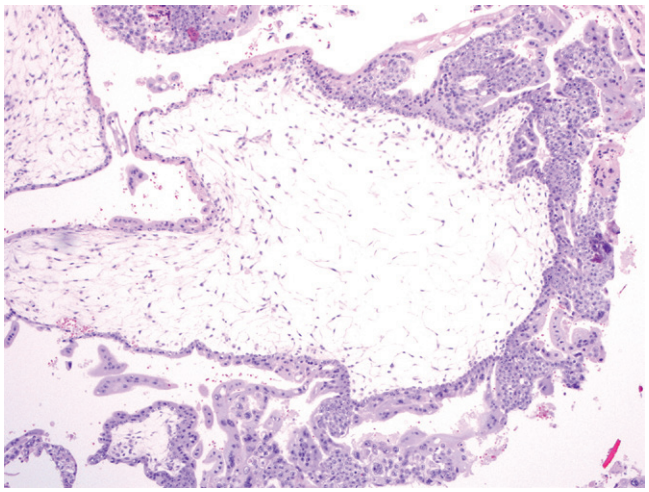

FIGURE 7

Invasive complete hydatidiform mole. A molar villous seen at higher magnification.

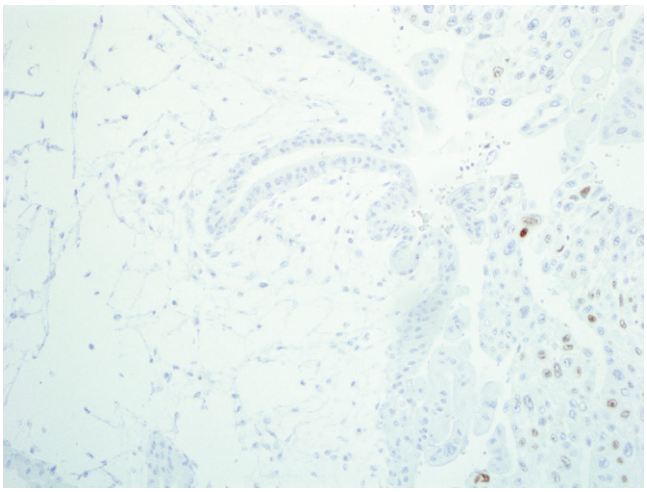

FIGURE 8

A negative p57kip2 stain confirms a complete mole.

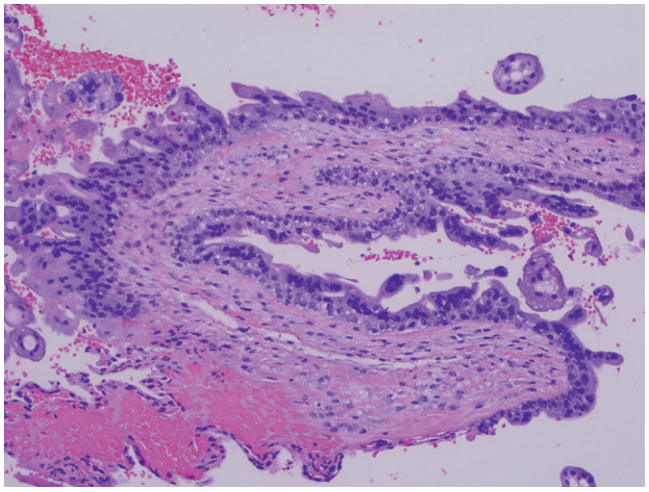

FIGURE 9

From a curetting from a patient with suspected invasive mole on imaging. The presence of molar villi supports this diagnosis.

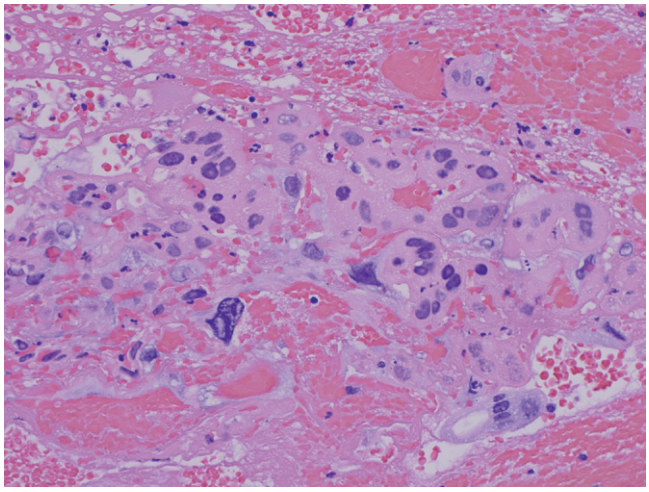

FIGURE 10

Atypical trophoblast in a curetting from a patient with a suspected invasive mole on imaging.

PARTIAL HYDATIDIFORM MOLE

Definition—Gestational trophoblastic disease in which the conceptus contains a triploid (3n) amount of genetic material (typically 1n maternal and 2n paternal).

Clinical Features

Epidemiology

- Partial moles are 10 times more common than complete moles.
- The risk factors for partial molar pregnancy are the same as for complete molar pregnancy and include age greater than 40 and less than 20, Asian descent, low socioeconomic status, prior molar pregnancies, and nulliparity.

Presentation

- The majority present as a missed abortion with vaginal bleeding and a small uterus.
- Beta-human chorionic gonadotropin (HCG) levels are only mildly elevated.
- Partial mole is not suspected clinically in most cases.

Prognosis and Treatment

- Partial hydatidiform moles are associated with low risk of developing postmolar persistent disease (less than 15%) and choriocarcinoma (less than 1%).
- Therapy consists of complete removal (suction curettage) of the products of conception.
- Serial beta-HCG levels are checked weekly until normal values are attained.
- Follow-up beta-HCG levels are then followed monthly for 6 months.
- In addition, patients complete a 6-month course of contraceptive therapy.

Pathology

Histology

- Partial moles consist of a biphasic population of small, fibrotic, normal villi and larger hydropic villi.
- The hydropic villi may display cistern formation and may have focal trophoblastic proliferation.
- The larger, dysmorphic villi will frequently have a scalloped contour resembling knuckles or fingers and toes.
- Trophoblastic "inclusions" are present within the villous stroma.
- These "inclusions" represent tangential sectioning of the irregular villous surface.
- Villous blood vessels, fetal nucleated red blood cells, membranes, and fetal parts may be identified and are a helpful finding in distinguishing from an early complete mole.
- Implantation site atypia may be present but is much less common that in complete moles.
- If fetal tissues are identified, they may contain malformations.
- The most common finding in association with partial moles is syndactyly (fusion) of the third and fourth or second and third fingers.

Immunopathology (Including Immunohistochemistry)

- The villous mesenchymal cells and cytotrophoblasts are positive for p57.

Main Differential Diagnosis

- Early complete mole. Look for dysmorphic villi, basophilic stroma, loss of p57kip2 staining in stromal cells, and cytotrophoblast.
- Hydropic abortus. The distinction from partial mole is not always possible but uniform swelling of villi and graduated variations in villous size with absence of cisterns is helpful.
- Nonmolar aneuploidy. Typically differences in villous size are not marked and cisterns are absent.
- Mesenchymal dysplasia. Seen as asymmetric enlargement of stem villi. Cisterns are absent as is trophoblastic proliferation.

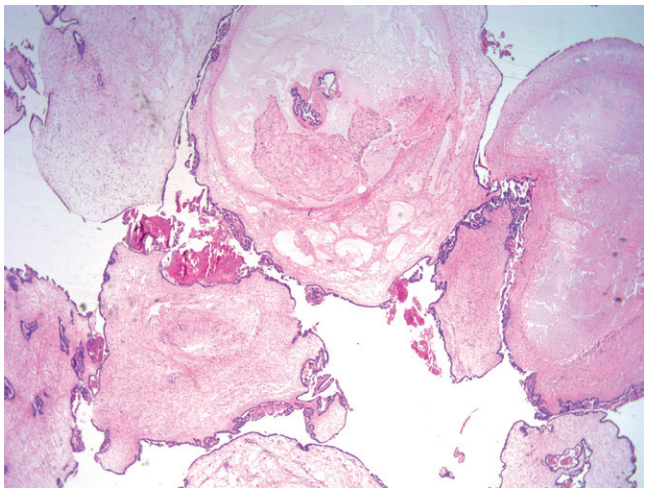

FIGURE 1

Partial hydatidiform mole. Low-power image showing a dual population of large edematous villi and smaller, more fibrotic-appearing villi.

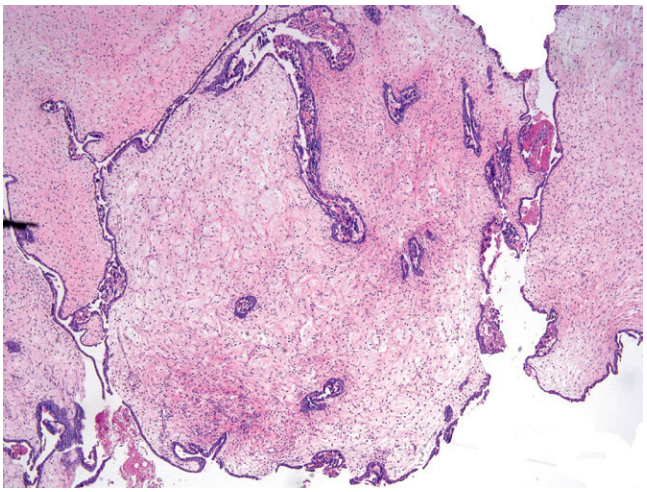

FIGURE 2

Partial hydatidiform mole. Large edematous villi with several so-called trophoblastic "inclusions." The villous contours are irregular. Concentric trophoblastic hyperplasia is not present.

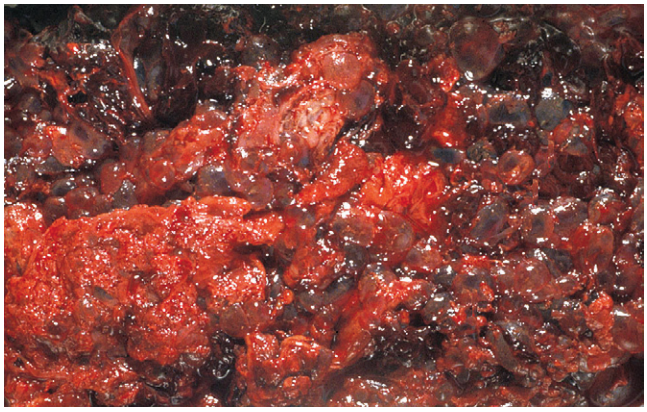

FIGURE 3

Immature placenta with focal villous hydrops suggesting partial mole.

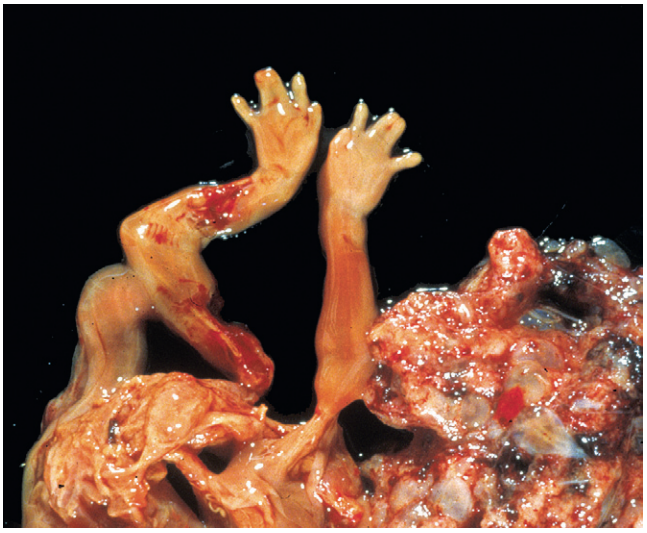

FIGURE 4

Characteristic 3-4 syndactyly in a triploid fetus associated with a partial mole.

MESENCHYMAL DYSPLASIA

PITFALL

Definition—An abnormally large placenta characterized by striking, cystically dilated stem villi, stromal overgrowth, and hypervascularity.

Clinical Features

Epidemiology

- Rare; case reports only.

Presentation

- Large (more than 1 kg) term placenta.
- Ultrasound may reveal a potential molar pregnancy.
- Associated with fetal Beckwith-Wiedemann syndrome and omphalocele.
- Frequently associated with preeclampsia.

Prognosis and Treatment

- Excellent.

Pathology

Histology

- Stromal overgrowth, cystic degeneration, and increased vascularity are seen in varying proportion and distribution throughout the placenta.
- Large, thick stem villi are hydropic and hypervascular.
- Smaller villi exhibit abnormal branching, dilation, and sinusoid formation.
- Terminal villi exhibit normal morphology.
- No trophoblastic hyperplasia is present.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- The clinical differential includes primarily partial mole. This entity will exhibit two discrete populations of villi but with some trophoblastic proliferation. The vascular changes seen in the villi in mesenchymal dysplasia will not be seen.

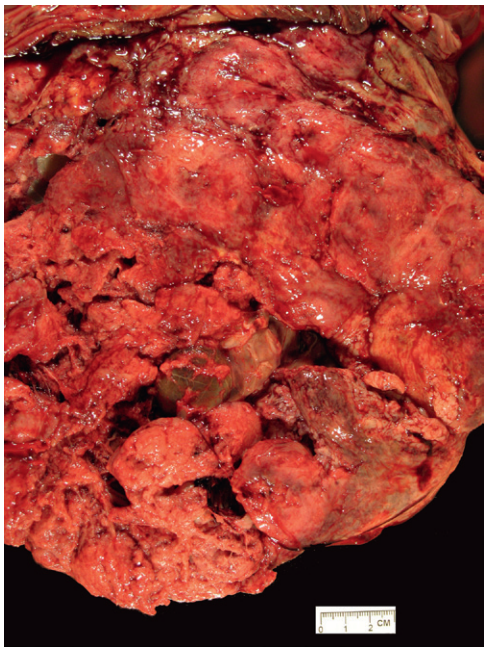

FIGURE 1

Placental mesenchymal dysplasia. Grossly, the placenta is large with abnormal, edematous appearing villi. Some foci show cystic change.

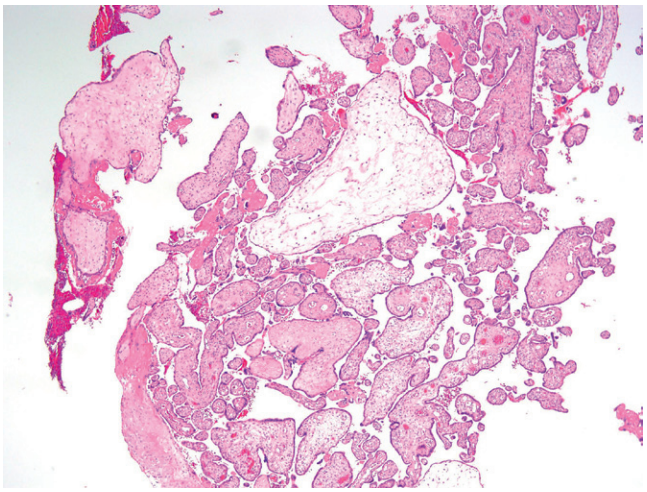

FIGURE 2

Placental mesenchymal dysplasia. At low power the stem villi are large, thick, and hypervascular. Hydropic change is prominent.

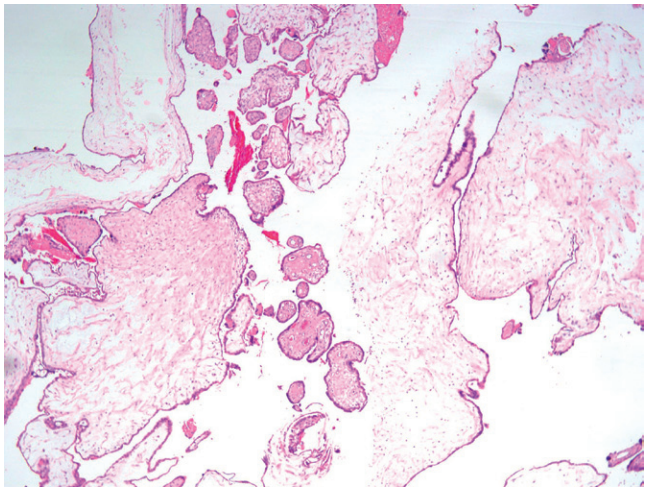

FIGURE 3

Placental mesenchymal dysplasia. At higher power there is a mixture of large and small villi. The villous contours are normal, and trophoblastic hyperplasia is absent.

CHORIOCARCINOMA

Definition—A trophoblastic malignancy composed of syncytiotrophoblasts and cytotrophoblasts, intermediate trophoblasts of both.

Clinical Features

Epidemiology

- At least half of choriocarcinomas follow a molar pregnancy, but only 2% to 3% of complete moles are followed by a diagnosis of choriocarcinoma.
- The remainder of choriocarcinomas follow a spontaneous abortion (25%), a normal gestation (20%), or an ectopic pregnancy (2.5%).
- Rare cases occurring more than a decade after the last gestation have been described.

Presentation

- Choriocarcinoma is typically detected several months after pregnancy.
- Elevated serum beta-human chorionic gonadotropin (HCG).
- Patients present with abnormal uterine bleeding, which is due to endomyometrial invasion by choriocarcinoma.
- A metastatic lesion involving (in decreasing order of frequency) the lungs, brain, or liver is a not uncommon presentation.
- Because most patients are treated with chemotherapy based on their beta-HCG levels and imaging studies, the histologic diagnosis is not made in many patients (i.e., invasive mole vs. choriocarcinoma).

Prognosis and Treatment

- Cases that are detected early and treated with appropriate chemotherapy have better outcomes than patients who present later in the course of their disease.
- Advanced disease may be fatal despite aggressive surgical and medical therapy.
- Choriocarcinoma occurring after a diagnosis of complete hydatidiform mole is thought to have a better prognosis, although this is likely due to close clinical follow-up of these patients.
- Even with appropriate therapy, choriocarcinoma is fatal in about 10% of cases.

Pathology

Histology

- Choriocarcinoma presents as a hemorrhagic, well-circumscribed nodule within the endomyometrium.
- Microscopic sections are characterized by a biphasic tumor composed of multinucleated syncytiotrophoblasts and either cytotrophoblasts or intermediate trophoblasts.
- Marked cytologic and nuclear atypia are common.
- In some cases only rare syncytiotrophoblasts can be identified.
- A background of abundant hemorrhage and necrosis is typical.
- In some cases only rare syncytiotrophoblasts can be identified.
- Placental villi should not be present.

Immunopathology (Including Immunohistochemistry)

- Both syncytiotrophoblasts and intermediate trophoblasts are for HCG and for hPL.
- Syncytiotrophoblasts are strongly positive for HCG whereas intermediate trophoblasts are only weakly positive.
- All of the trophoblastic tumor cells should stain strongly and diffusely for cytokeratin.
- Inhibin is negative.

Main Differential Diagnosis

- Residual benign trophoblasts from an early gestation.
- Persistent molar tissue—this will be seen as atypical implantation site. Presence of villi effectively excludes choriocarcinoma. Necrosis should be minimal.
- Invasive mole—defined as villi in the myometrium excluding choriocarcinoma.
- Placental site trophoblastic tumor—lacks the biphasic trophoblast of choriocarcinoma and the high serum b-HCG levels.
- Undifferentiated carcinoma, particularly in metastatic lesions—typically seen in older age groups. Serum HCG is low.

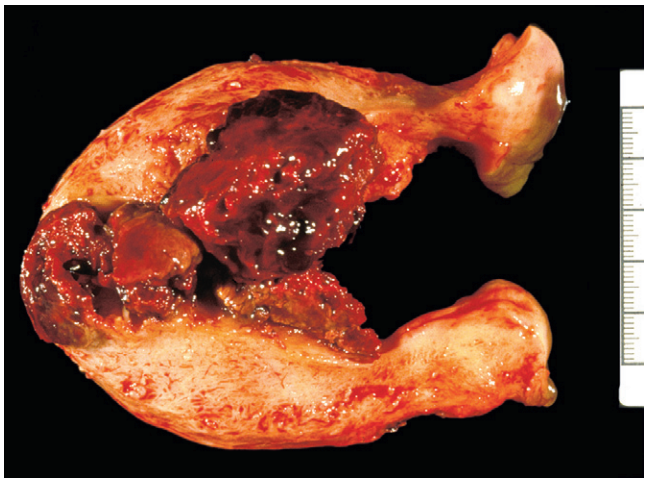

FIGURE 1

Gross appearance of choriocarcinoma, consisting of a hemorrhagic mass involving the endomyometrium.

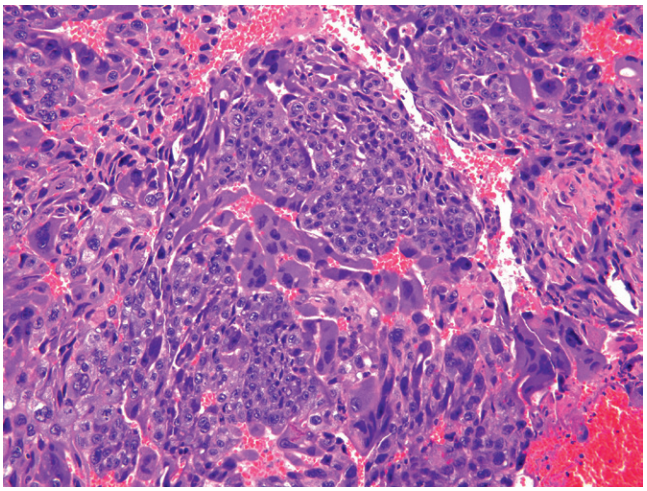

FIGURE 3

Choriocarcinoma. A biphasic carcinoma with characteristic wrapping by the syncytiotrophoblasts. Marked cytologic atypia is present in both populations of trophoblasts.

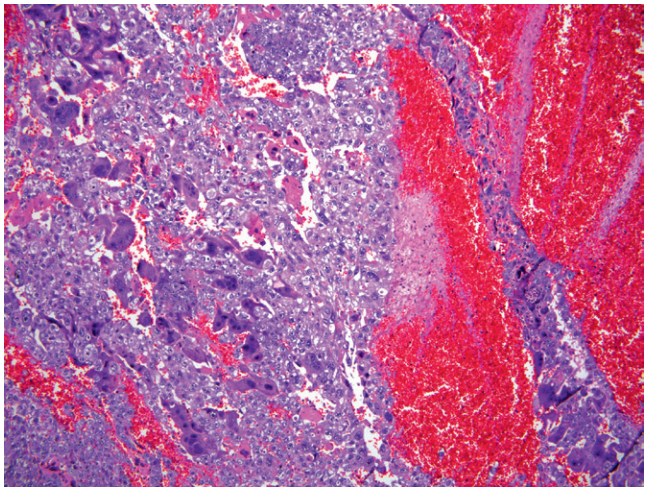

FIGURE 2

Choriocarcinoma. Low-power image shows a hemorrhagic and necrotic background. A clearly biphasic tumor is present.

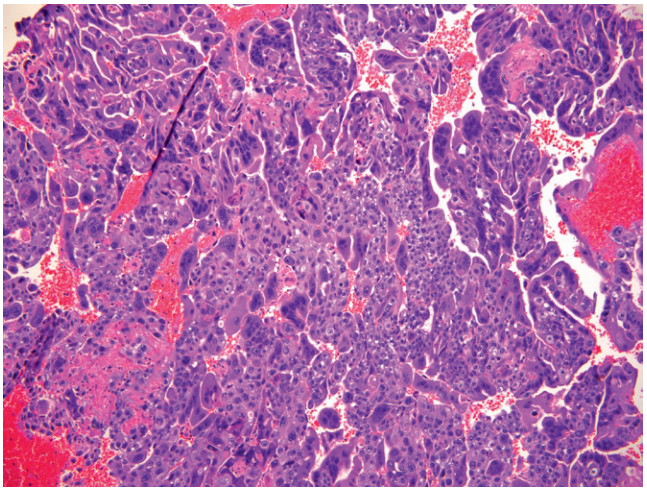

FIGURE 4

Choriocarcinoma. A biphasic carcinoma composed of an admixture of trophoblasts. Biphasic atypia is apparent.

INTRAPLACENTAL CHORIOCARCINOMA

PITFALL

Definition—Choriocarcinoma occurring concurrently with a normal pregnancy.

Clinical Features

Epidemiology

- Intraplacental choriocarcinoma is exceedingly rare.

Presentation

- Intraplacental choriocarcinoma is occasionally diagnosed before delivery when symptomatic metastasis occurs.
- In rare cases the disease is diagnosed when the infant presents in early life with metastatic disease.
- Disease is most often detected at the time of placental examination.

Prognosis and Treatment

- Patients with disease that is detected early and treated with appropriate chemotherapy have a better outcome than patients who present later in the course of their disease.
- Beta-human chorionic gonadotropin (HCG) can be followed in both the mother and the newborn to monitor for metastatic disease, which can be fatal.
- Systemic chemotherapy is the most common treatment modality.
- Hysterectomy is performed in some cases.

Pathology

Histology

- Grossly, intraplacental choriocarcinoma mimics placental infarction and appears as either single or multiple scattered tan nodules.
- Microscopic examination demonstrates a solid nodule composed of an admixture of atypical cytotrophoblastic and syncytiotrophoblastic cells.
- The tumor cells are present in the intervillous spaces and are histologically similar to choriocarcinoma seen in other settings.
- Both components are markedly atypical.

Immunopathology (Including Immunohistochemistry)

- Cytokeratins are diffusely positive in the tumor cells.
- Syncytiotrophoblasts are strongly positive for HCG and weakly positive for human placental lactogen (hPL).
- Intermediate trophoblasts are weakly positive for both HCG and hPL.

Main Differential Diagnosis

- Complete hydatidiform mole—this is not a problem in the mature placenta. It can be a difficult distinction in a postmolar curetting without villi.
- Intraplacental trophoblastic proliferation with admixed fibrin—these occasionally occur, but the trophoblasts are extravillous in nature.
- Chorangioma-associated trophoblastic proliferation—this can be striking at times, and there have been rare reports of so-called "chorangiocarcinoma." However, the trophoblastic proliferation in chorangiomas is typically adherent to the exterior of the tumor and is modest in degree without hemorrhage or necrosis.

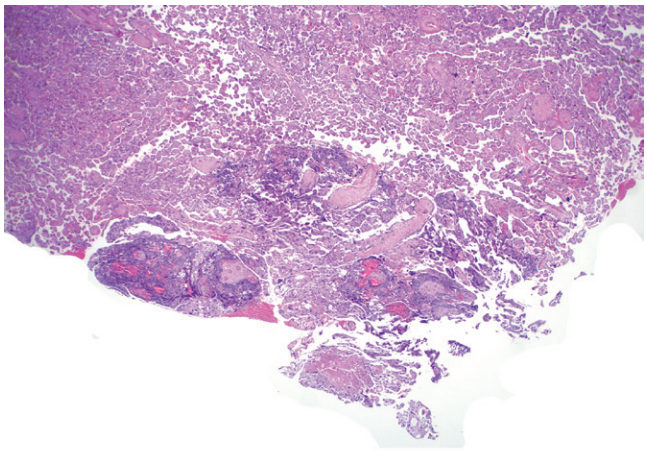

FIGURE 1

Intraplacental choriocarcinoma. Low-power image depicts a discrete proliferation of atypical epithelioid cells present in the intervillous spaces.

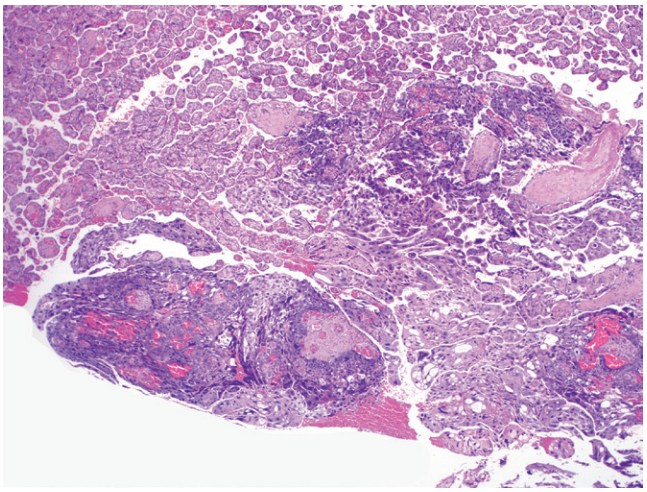

FIGURE 2

Intraplacental choriocarcinoma. Low-power image depicts a discrete proliferation of atypical epithelioid cells present in the intervillous spaces.

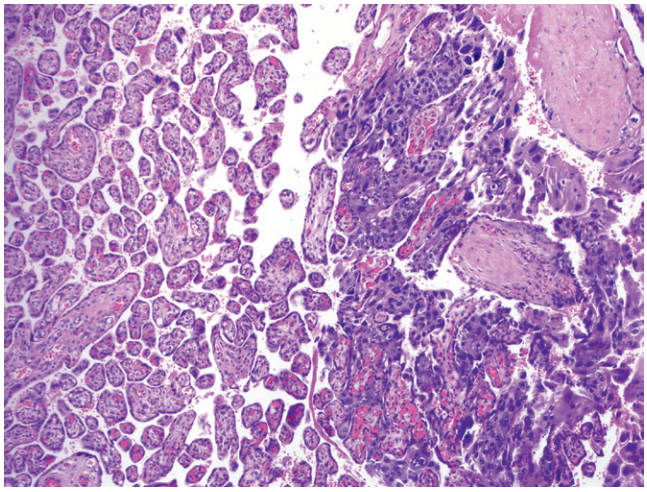

FIGURE 3

Intraplacental choriocarcinoma. Note the juxtaposed normal placental parenchyma and the highly atypical trophoblastic epithelium of the intraplacental choriocarcinoma. The neoplastic epithelium is associated with sclerotic villous remnants.

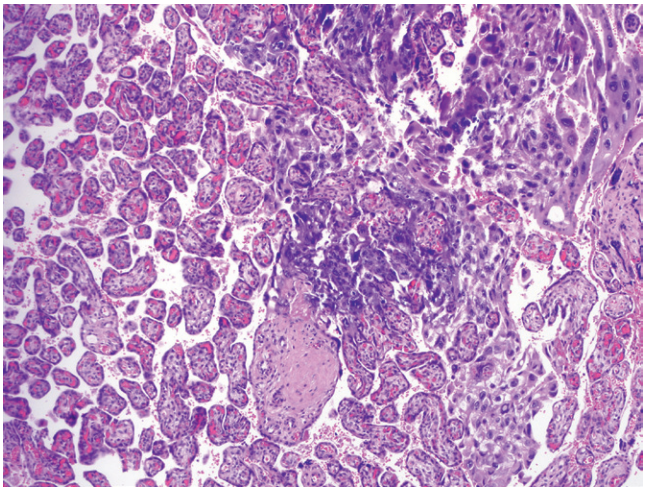

FIGURE 4

Intraplacental choriocarcinoma. Another field illustrating the marked disparity in trophoblastic density between tumor *(center)* and surrounding villi.

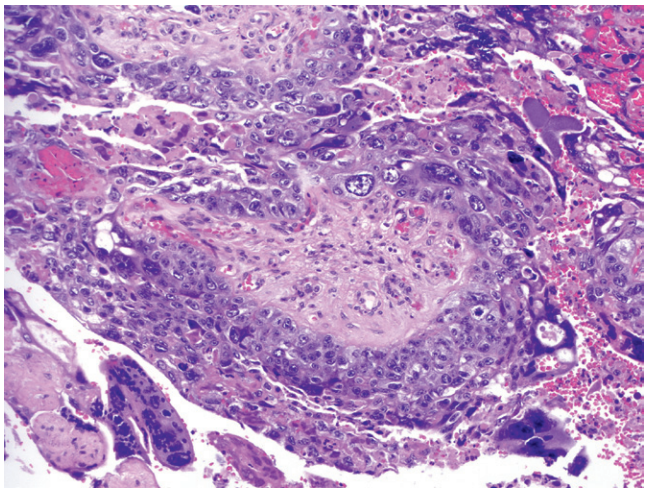

FIGURE 5

Intraplacental choriocarcinoma. Higher magnification highlights the malignant cytotrophoblast and syncytiotrophoblast surrounding the remnant of a villous.

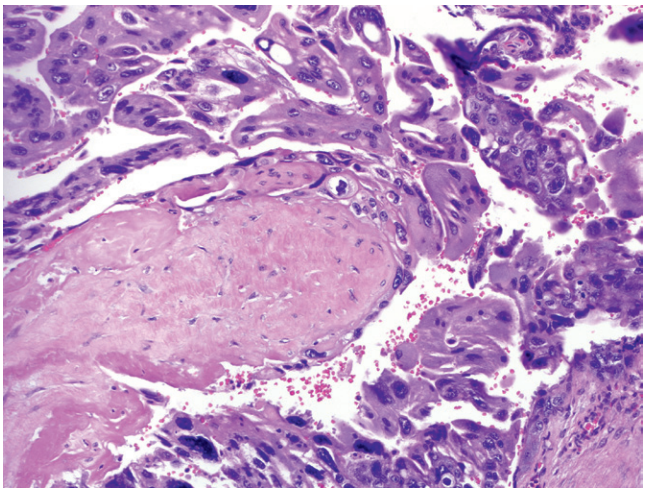

FIGURE 6

Intraplacental choriocarcinoma. Higher magnification highlights the malignant cytotrophoblast and syncytiotrophoblast surrounding the remnant of a villous.

PLACENTAL SITE TROPHOBLASTIC TUMOR

PITFALL

Definition—A malignancy that arises from the early implantation site extravillous trophoblasts.

Clinical Features

Epidemiology

- Placental site trophoblastic tumors (PSTT) are rare and were only recognized as a malignancy in 1981.
- PSTT are most commonly seen following a normal term delivery.
- Occasional cases follow spontaneous abortions, therapeutic abortions, and ectopic or molar pregnancies.
- Most cases are seen in reproductive-age women, although rare cases are reported in postmenopausal women.

Presentation

- Most patients present with vaginal bleeding months to years following a pregnancy.
- The clinical impression is usually that of a missed abortion.
- The beta-human chorionic gonadotropin (HCG) level is only mildly elevated and is not reflective of tumor burden.
- A complex intrauterine mass may be apparent on ultrasound.
- One third to one half of patients have metastatic disease at the time of diagnosis; the most common sites are lung, pelvis, and lymph nodes.
- Rarely patients present with nephrotic syndrome, which has been attributed to immune complexes stimulated by the PSTT.

Prognosis and Treatment

- The prognosis is highly variable, but at least 30% of patients develop recurrent disease.
- The more remote the antecedent pregnancy, the higher the risk of recurrence. A time frame of greater than 2 years is thought to be a useful cutoff.
- The treatment of choice is hysterectomy, although uterine preservation is attempted in young patients who have not completed their childbearing.
- Adjuvant chemotherapy is used in the setting of metastatic disease at presentation and/or if adverse histologic factors are present.

Pathology

Histology

- Grossly PSTT appears as a large, discrete, complex mass confined to the uterus.
- The mass may be exophytic and polypoid or have an endophytic growth pattern.
- The tumor cells are large polyhedral extravillous trophoblastic cells.
- The cells may be round or spindle shaped and have little to intervening stroma between the cells.
- The tumor cells can be seen dissecting between bundles and fibers of smooth muscle within the myometrium.
- Necrosis is common.
- The amount of mitotic activity is variable, and in most cases is 1 to 2 per 10 HPF, but up to 50 per 10 HPF can be seen.
- The mitotic rate is thought to be prognostically relevant; fewer than 5 per 10 HPF is associated with worse outcomes.

Immunopathology (Including Immunohistochemistry)

- Positive for MelCAM, human placental lactogen (hPL), and inhibin.
- Negative for p63.
- The Ki67 proliferative index should be greater than 10%.

Main Differential Diagnosis

- Placental site nodule—this is actually composed of epithelioid extravillous trophoblast and must be distinguished from an epithelioid trophoblastic tumor. The latter is distinguished from PSTT by strong nuclear staining for p63.
- Choriocarcinoma—usually distinguished by the presence of both cytotrophoblastic and syncytiotrophoblastic differentiation combined with a high serum beta-HCG level. However, we have seen PSTTs that stained quite strongly for beta-HCG.
- Molar pregnancy—this will enter into the differential diagnosis when villi are not evident and there is only implantation site present. However, the implantation site in a molar pregnancy, although atypical, is not hypercellular and does not split myofibers like a PSTT does.

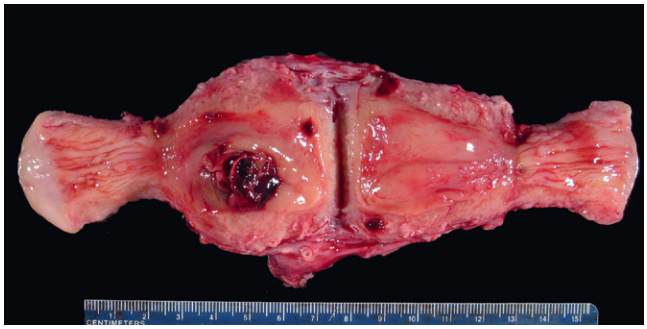

FIGURE 1

Placental site trophoblastic tumor. Large, polygonal, eosinophilic cells with irregular nuclei.

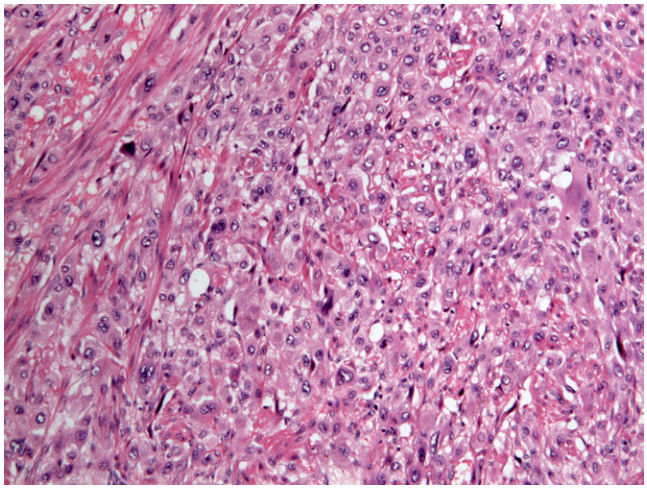

FIGURE 2

Placental site trophoblastic tumor. Trophoblasts dissecting between smooth muscle bundles.

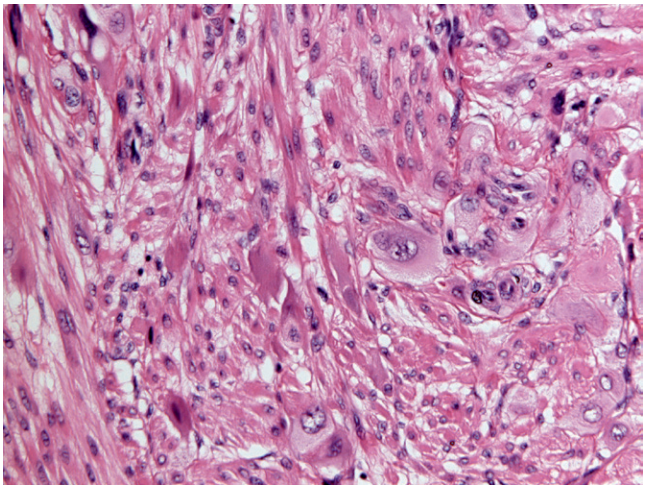

FIGURE 3

Placental site trophoblastic tumor. Trophoblasts remodeling the lining of a vascular space.

MOLAR IMPLANTATION SITE

Definition—An abnormal early implantation site (IS) that can be identified in the setting of a molar pregnancy.

Clinical Features

Epidemiology

- Atypical molar ISs may be seen in the setting of any molar pregnancy.
- They are much more common in the background of a complete hydatidiform mole, seen in at least two thirds of cases versus less than 20% of partial moles.

Presentation

- Molar IS is encountered at the time of histologic examination of the products of conception.

Prognosis and Treatment

- See sections on complete and partial hydatidiform moles for managing these entities.
- The principal management issue for the pathologist is the exclusion of normal or exaggerated IS and malignant (choriocarcinoma or placental-site trophoblastic tumor [PSTT]) trophoblasts.

Pathology

Histology

- ISs can be identified at scanning magnification by their brightly eosinophilic fibrinoid.
- Molar IS trophoblasts display conspicuous nuclear atypia, principally in the form of variable nuclear enlargement and most importantly hyperchromasia, especially in the case of a complete mole.
- Molar IS tends to be more densely cellular than typical IS.
- In small samples where no chorionic villi are visible, an atypical molar IS can be a helpful feature in reaching the diagnosis of or registering a suspicion for a molar pregnancy.

Immunopathology (Including Immunohistochemistry)

- Noncontributory when the differential diagnosis is normal implantation versus molar implantation. If a PSTT is suspected, MelCAM and MIB1 co-staining can exclude a neoplasm of extravillous IS trophoblast.

Main Differential Diagnosis

- Placental site trophoblastic tumor (in isolation)—distinguished by a confluent population of polyhedral cells with nuclear enlargement and penetration of the myometrium with splitting of the smooth muscle fibers.
- IS nodule—these have a distinctive lobular or well-circumscribed appearance with typically well-spaced vacuolated extravillous trophoblasts within a pink fibrinoid matrix.
- Choriocarcinoma (in isolation)—marked trophoblastic atypia and necrosis with cytotrophoblastic and syncytial trophoblastic phenotypes.
- IS in early pregnancy—this in particular may at times be difficult to separate from molar IS, particularly if partially degenerated with chromatin condensation. If there is no other gestation material present, a follow-up HCG to exclude persistence is in order.

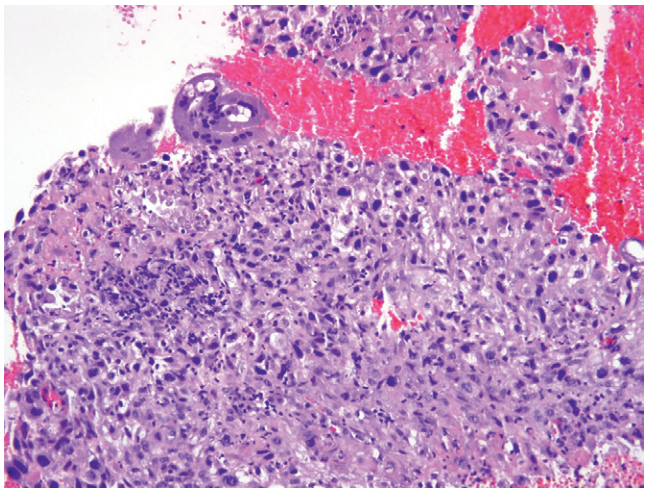

FIGURE 1

Molar IS. Brightly eosinophilic fibrinoid material is infiltrated by a population of atypical cells with dark, irregularly shaped nuclei. Compare to nonmolar IS.

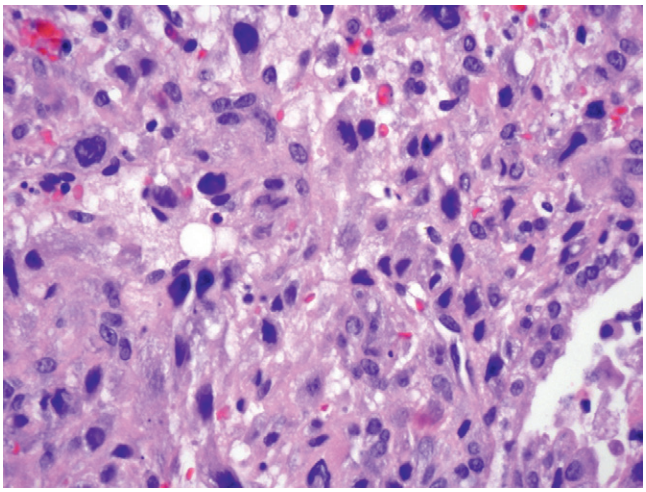

FIGURE 2

Molar IS. At higher magnification note that virtually all of the extravillous trophoblasts are hyperchromatic.

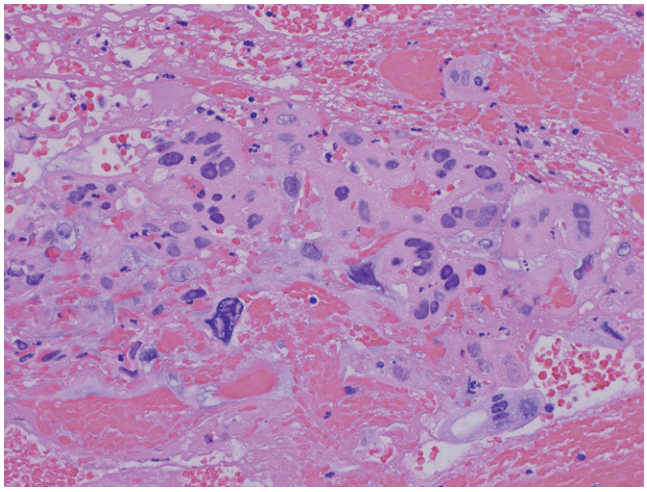

FIGURE 3

Molar IS. The trophoblasts are well spaced in the fibrinoid matrix but note the considerable variations in nuclear size and staining.

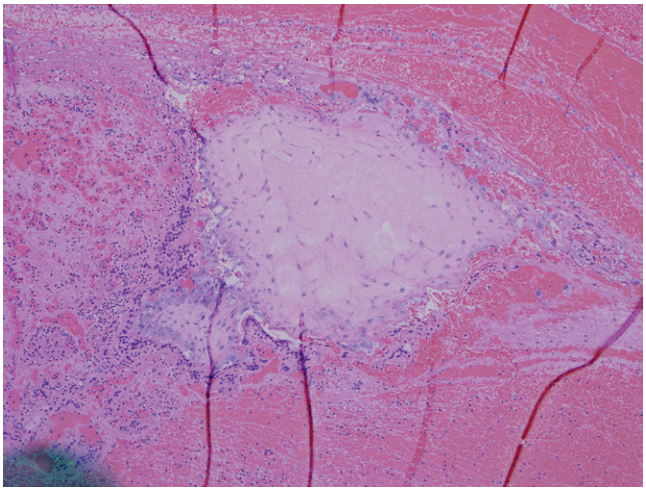

FIGURE 4

A rare degenerating molar villous was associated with the molar IS shown in Figure 3.

EPITHELIOID TROPHOBLASTIC TUMOR

Definition—A subset of extravillous trophoblastic tumor that is thought to arise from an extravillous (transitional) trophoblast that forms a transition from villous cytotrophoblast to mature extravillous trophoblast. These cells are found in the chorionic membrane, maternal surface of the placenta, and where intervillous fibrin is deposited.

Clinical Features

Epidemiology

- Rare.
- Occurs in reproductive-age women.
- Epithelioid trophoblastic tumors (ETTs) are an unusual type of extravillous trophoblastic tumor.
- Both ETTs and placental site trophoblastic tumors (PSTTs) are almost always seen following a term delivery.

Presentation

- Patients present with irregular vaginal bleeding.
- The preceding pregnancy may have been months or years earlier.
- The beta-human chorionic gonadotropin (HCG) level is only mildly increased.
- The clinical impression may be that of a missed abortion.
- Uterine enlargement or an intrauterine mass may be identified. Occasional cases are found outside the uterus, presumably from residual trophoblasts exposed to the peritoneal cavity following cesarean section.
- Patients may have metastatic disease at the time of diagnosis.

Prognosis and Treatment

- The prognosis is variable.
- Features associated with adverse clinical outcome include increased mitotic rate (>5 mitosis per 10 hpf) and presentation more than 2 to 4 years after previous pregnancy.
- The majority of patients undergo hysterectomy.
- Adjuvant chemotherapy may be appropriate in some cases.

Pathology

Histology

- Grossly, ETT appears as a solitary, circumscribed, solid and cystic hemorrhagic mass that invades into the myometrium or cervical stroma.
- Microscopically ETT is composed of medium-sized, relatively monomorphic epithelioid cells with prominent cell borders that resemble intermediate trophoblasts.
- The cells have abundant eosinophilic cytoplasm and are arranged in nests and cords which coalesce to form large expansile sheets and nodules of tumor.
- Occasional large or markedly atypical cells can be seen, but overall, ETT has a bland uniform appearance.
- A prominent hyalinized eosinophilic extracellular material is present and often associated with necrotic debris.
- In some cases ETT grows along the surface of the endometrium and cervix and can resemble an in situ cervical squamous lesion.

Immunopathology (Including Immunohistochemistry)

- Negative for human placental lactogen (hPL), and only focally positive for MelCAM.
- Positive for p63, inhibin, and cytokeratins (AE1/AE3).
- Ki-67 labeling indexes of less than 10% are consistent with an placental site nodule.

Main Differential Diagnosis

- Epithelioid placental site nodule—usually small and isolated, but can be prominent. A low MIB1 index and the absence of necrosis are helpful.
- Epithelioid leiomyosarcoma—this might be problematic in a small sample. A simple keratin stain will exclude this entity.
- Keratinizing squamous cell carcinoma—usually not going to be mistaken for ETT, but ETT might be mistaken for carcinoma. A positive inhibin stain will exclude this.
- PSTT—this tumor of early implantation site trophoblast is usually an easy exclusion (p63 negative, MelCAM positive), but we have seen rare examples of ETTs merging with PSTT-like areas in some tumors.

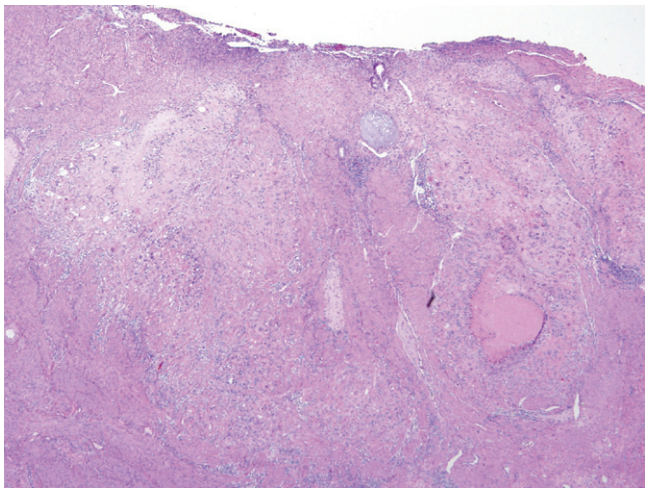

FIGURE 1

ETT. Low power of a hysterectomy specimen showing a nodular infiltration of the myometrium by an epithelioid neoplasm.

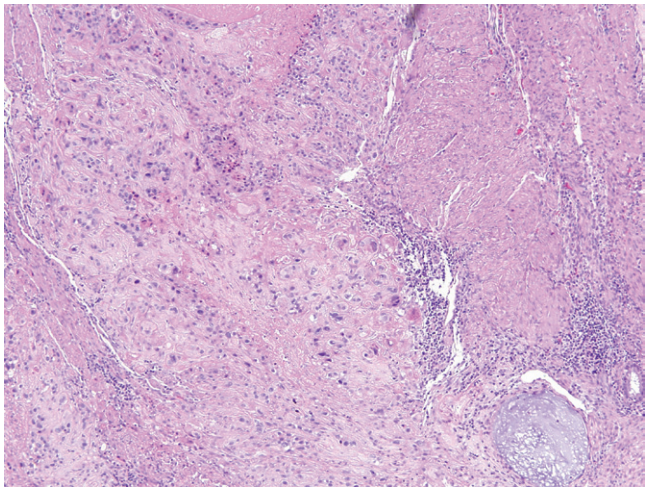

FIGURE 2

ETT. A relatively monomorphic population of cells with abundant eosinophilic cytoplasm form sheets and nodules that bluntly dissect through the surrounding myometrium. Foci of necrosis are present.

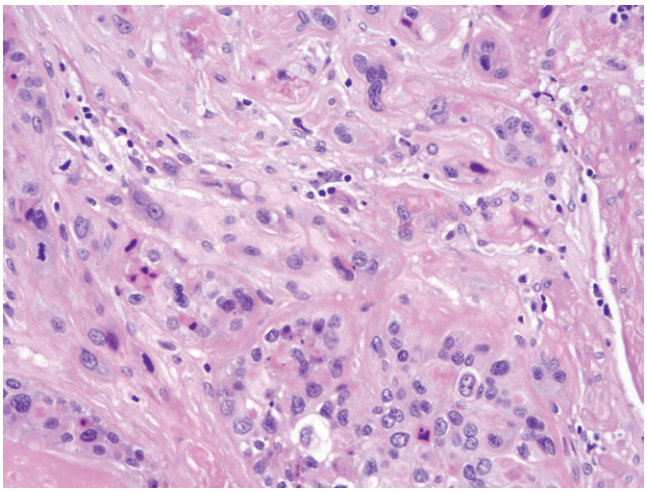

FIGURE 3

ETT. The cells are medium sized, with abundant extracellular hyaline material. Scattered lymphocytes are present.

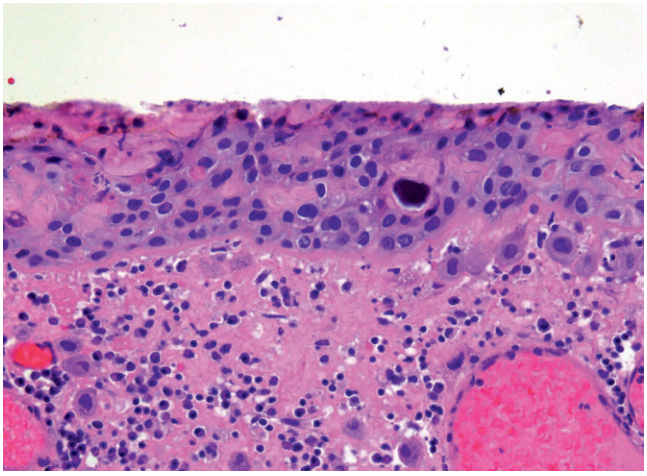

FIGURE 4

ETT. Tumor grows down from the endometrium to involve the surface of the endocervix. The tumor cells mimic a squamous intraepithelial lesion.

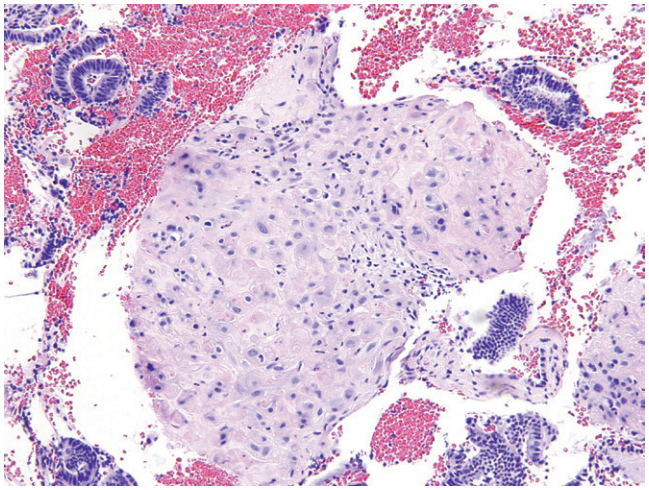

FIGURE 5

ETT. Tumor fragments in an endometrial biopsy. The monomorphic tumor cells have abundant eosinophilic cytoplasm and prominent cell borders.

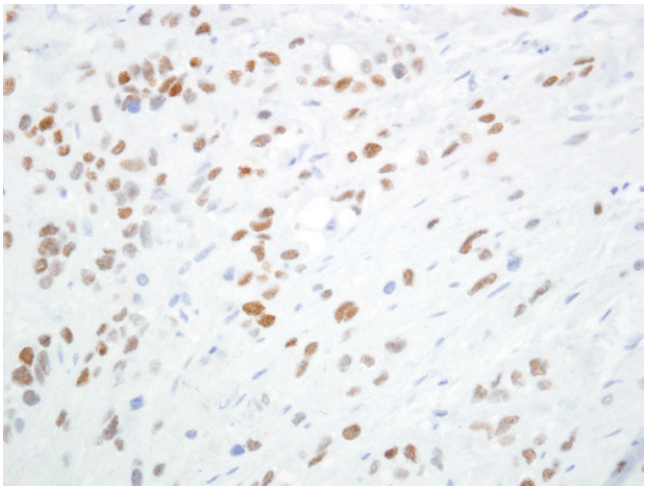

FIGURE 6

ETT. Immunostain for p63 shows diffuse nuclear positivity.

CHORANGIOMA

Definition—Benign expansile nodule of capillaries and stromal cells.

Clinical Features

Epidemiology

- Uncommon; this finding is seen in less than 0.5% of placentas.
- Associated with twin gestations and preeclampsia.

Presentation

- Term placenta.
- Incidental firm, tan nodule located at the disk edge or in the subchorion.

Prognosis and Treatment

- Varies with size; small lesions are nearly always incidental.
- Intermediate-sized lesions are associated with intrauterine growth restriction and may be noted on ultrasound examination.
- Large lesions (>9 cm) can cause arteriovenous shunting and subsequent polyhydramnios, hydrops, and even fetal death.
- Platelet sequestration within the chorangioma can rarely lead to disseminated intravascular coagulation in the fetus.

Pathology

Histology

- A circumscribed nodule of small capillary channels is apparent at low power.
- Within the nodule there are varying amounts of bland stromal cells and collagen separating vascular spaces.
- In localized chorangiosis the changes are isolated to a single-stem villous, with all of the smaller villi containing excess numbers of capillary channels.
- An area of distended villous capillary channels should not be mistaken for chorangiosis.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Intraplacental choriocarcinoma—the extravillous trophoblast at the periphery of a chorangioma will sometimes display some atypias that might be mistaken for a trophoblastic neoplasm. There have been rare reports of "chorangiocarcinomas" that might be an extreme example. However, the vast majority of trophoblastic proliferations on the perimeter of a chorangioma are benign.
- Diffuse chorangiosis—this will usually not be a problem, inasmuch as the process is not as discrete as a chorangioma.

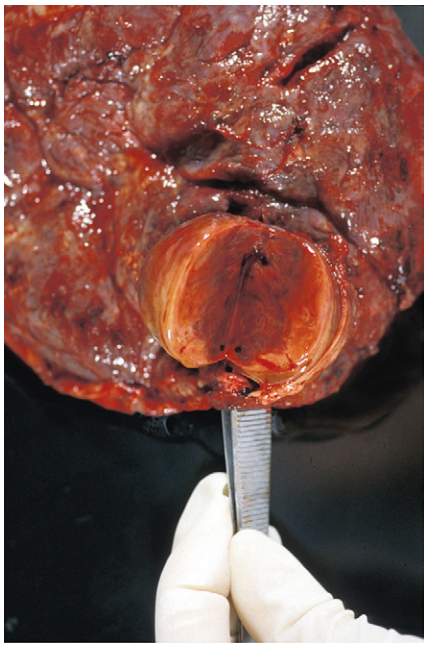

FIGURE 1

Chorangioma, shown here in the parenchyma as a discrete circumscribed red nodule with a pale rim.

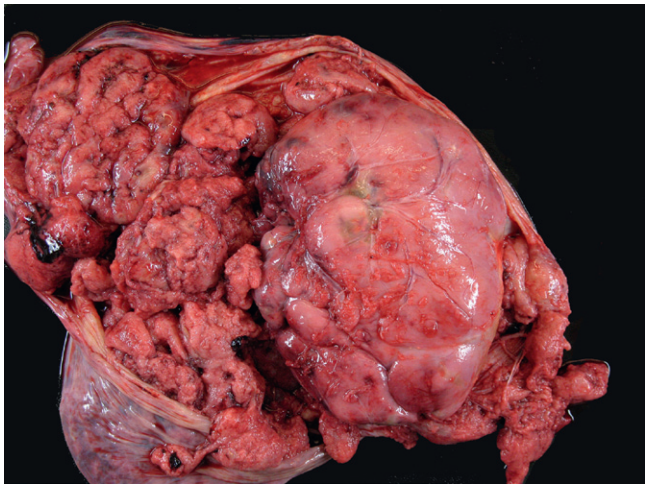

FIGURE 2

A very large chorangioma on the right side of the placental disk.

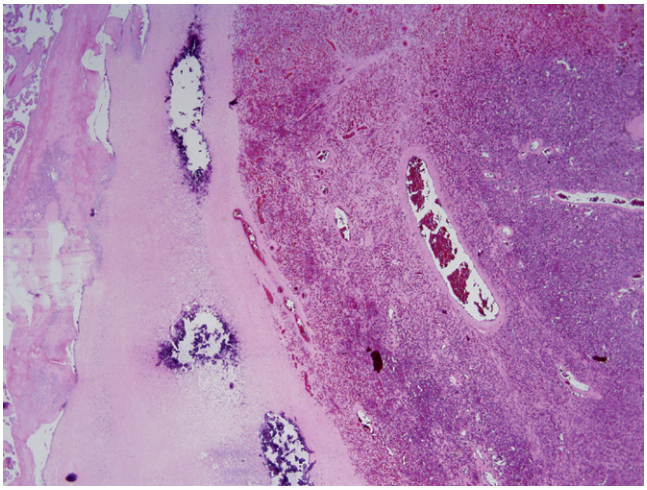

FIGURE 3

Chorangioma. Low-power image showing a circumscribed nodule within the placental parenchyma.

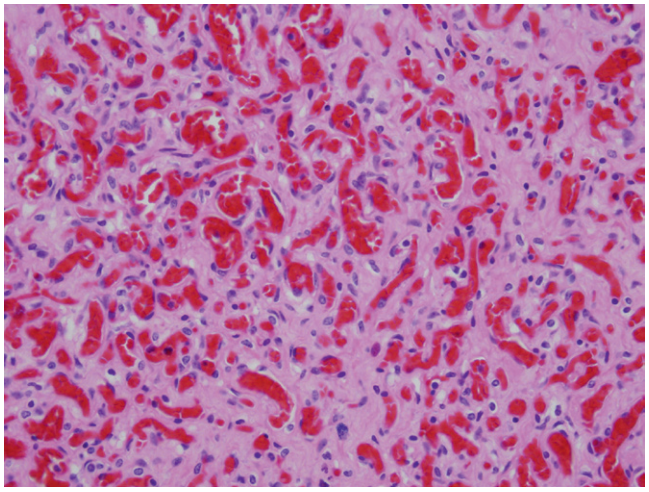

FIGURE 4

A proliferation of small, capillary-sized channels lined with a single layer of bland endothelial cells. The stroma is composed of dense eosinophilic material and scattered bland stromal cells.

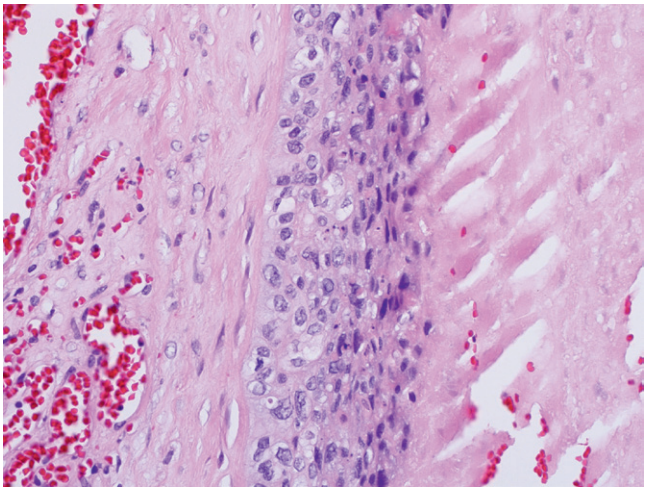

FIGURE 5

Extravillous trophoblast on the perimeter of the chorangioma might show some nuclear atypia.

KNOTS IN THE UMBILICAL CORD

Definition—True knots in the umbilical cord.

Clinical Features

Epidemiology

- Uncommon, occurring in 1% to 2% of pregnancies.
- Nuchal cord (around neck) is more common, in up to 25% of pregnancies.
- Constricting knots rarer, approximately 1:2000 pregnancies.
- Associated with large babies, long umbilical cords.

Presentation

- Most often an incidental finding when not constricting.
- Reduced fetal movement if constriction and hypoxia occur.
- Rarely a primary cause of fetal death.
- May be detected by ultrasound (e.g., hanging noose sign, four-leaf clover).

Prognosis and Treatment

- Outcome is typically uneventful, but risk of death is up to 10-fold greater than with unknotted cords.

Main Differential Diagnosis

- "False knots" in the cord are common, the consequence of vascular ectasia from varices.

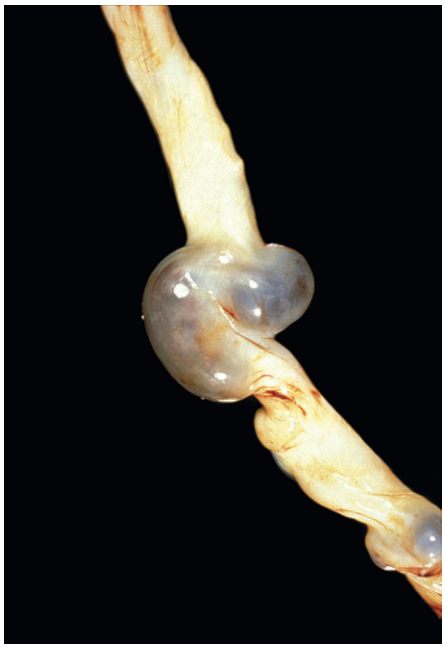

FIGURE 1

False knot created by a common vascular ectasia.

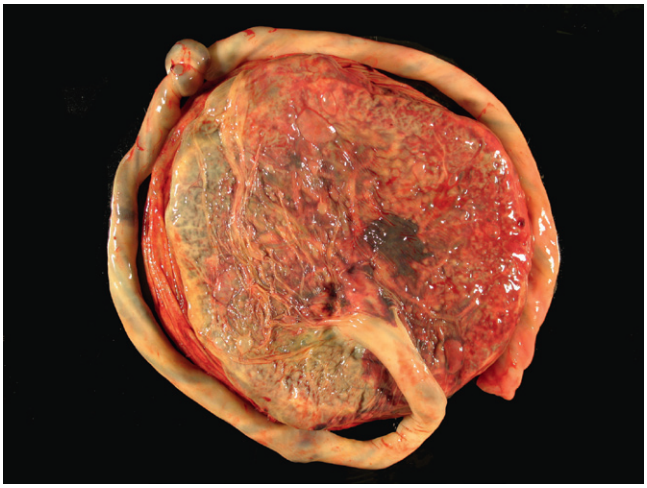

FIGURE 2

True knot in a case of fetal hypoxic demise.

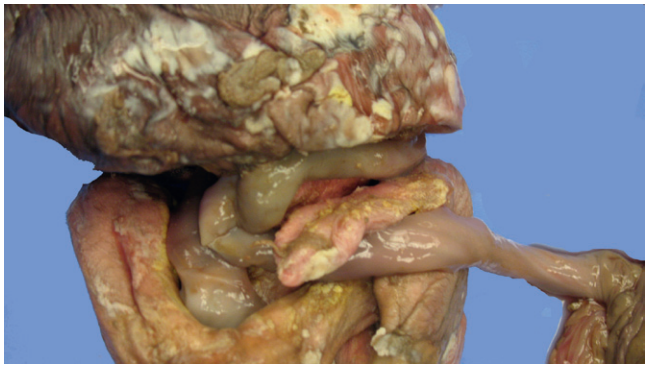

FIGURE 3

Constricting nuchal cord resulting in fetal death.

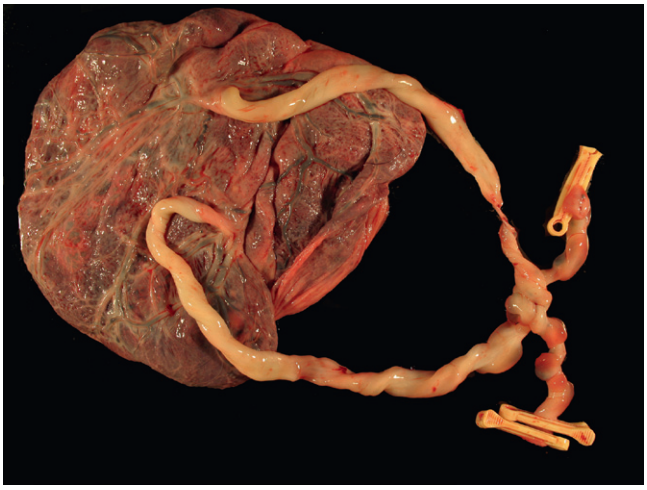

FIGURE 4

A dramatic case of cord entanglement of twin placentas. Both twins survived.

SINGLE UMBILICAL ARTERY (SUA)

DEFINITION—Umbilical cord with two vessels; one umbilical artery and one vein.

CLINICAL FEATURES

EPIDEMIOLOGY

- Common; noted in 1% to 3% of all gestations.
- More frequent in spontaneous abortions.
- More frequent in white women than black or Asian women.

PRESENTATION

- Commonly found with other anomalies.
- Sixteen percent of live-born infants with *isolated* SUA have a renal malformation, half of which are minor.

PROGNOSIS AND TREATMENT

- Excellent if not associated with other fetal anomalies.

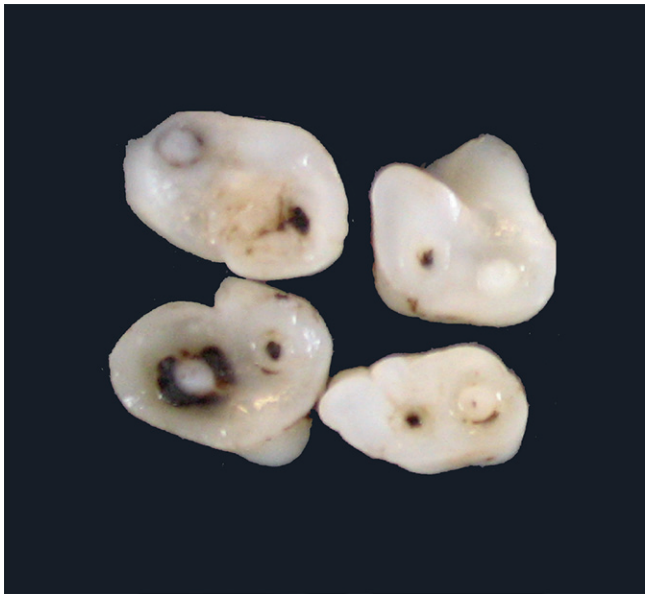

FIGURE 1

Two-vessel cord seen on cross section of several segments.

PATHOLOGY

HISTOLOGY

- Umbilical cord contains two vessels: one artery and one vein.
- The usual embryonic remnants can still be present in the cord.

IMMUNOPATHOLOGY (INCLUDING IMMUNOHISTOCHEMISTRY)

- Noncontributory.

MAIN DIFFERENTIAL DIAGNOSIS

- Incomplete sectioning of cord can give the illusion of a single umbilical artery. It is important to ensure that the entire segment is represented in the section.

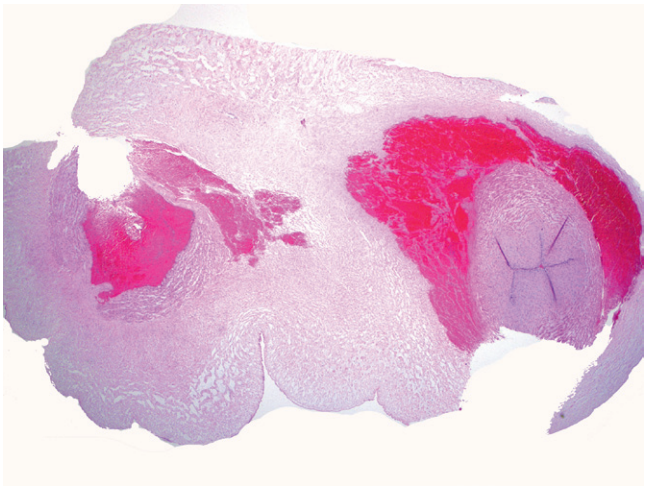

FIGURE 2

Single umbilical artery. Microscopic section shows a single umbilical artery *(right)* accompanied by the usual single umbilical vein *(left)*.

HYPERCOILED AND HYPOCOILED UMBILICAL CORD

■ **Kathleen Sirois, BA**

Definition

- Hypercoiled cord: Defined as an umbilical coiling index ([UCI] measured as 1/average distance between coils in cm) of greater than 0.3.
- Hypocoiled cord: Defined as a UCI of less than 0.1.

Clinical Features

Epidemiology

- Coiling of the cord is considered a function of the nature of the surrounding Wharton's jelly, genetic factors, and fetal movement.

Prognosis

- Hypocoiled cords have been associated with growth retardation, fetal distress, and even Trisomy 21. Cords with a UCI (measured as 1/average distance between coils in cm) of under 0.1.
- Hypercoiled cords have a wide range of frequencies, ranging from 1% to 18%. Believed by some to result from deep placenta implantation into the decidua.

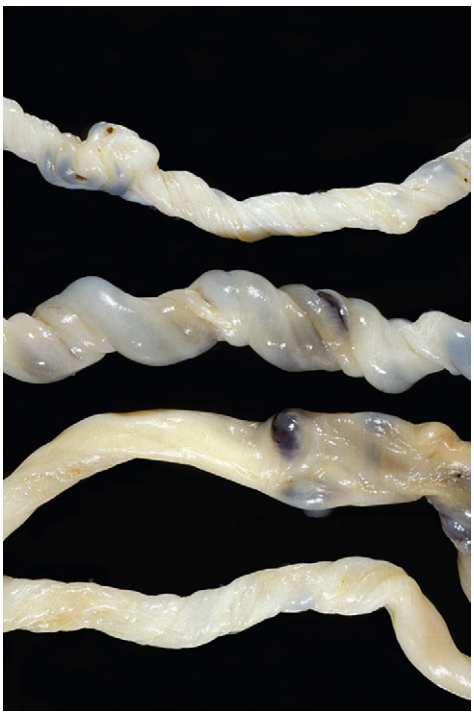

FIGURE 1

Examples of cord twist. The UCI is defined as 1 divided by the distance between coils in centimeters. On average there should be about one coil per 5 cm.

FIGURE 2

Hypercoiled umbilical cord.

VARIATIONS ON CORD INSERTION (MARGINAL, MEMBRANOUS, FURCATE)

■ **Kathleen Sirois, BA**

DEFINITION—Marginal cord insertion is defined as insertion within 2 cm of the periphery of the disk. With a membranous (velamentous) cord insertion, the cord vessels insert into the placental disk within the membranes, in the absence of Wharton's jelly. Furcate cord insertion appears as a forklike division of the cord prior to insertion into the placental disk.

CLINICAL FEATURES

EPIDEMIOLOGY AND PATHOGENESIS

- Marginal cord insertion occurs in less than 10% of single pregnancies but is more common in twin pregnancies, seen in up to one fourth. It is not significantly associated with any growth restriction or preterm delivery.
- Membranous (velamentous) cord insertion may occur as a function of asymmetric placental growth and involution during pregnancy, with the cord migrating from the center to the periphery. One percent of singleton gestations but 15% of monochorionic twin gestations.
- Furcate cord insertion.

PATHOLOGY

- In marginal cord insertion the cord emerges within 2 cm of the edge of the placenta.
- In membranous (velamentous) cord insertion vessels branch out into the membranes above the disk.
- Furcate cord insertion.

PROGNOSIS

- Membranous (velamentous) cord insertions have been associated with a wide range of complications including fetal growth restriction, death (this can occur with vasa previa, when the vessels are compressed by the fetus during delivery), low Apgar scores, and fetal distress; however, the risk in singleton pregnancies is considered very low. In contrast, it is associated with growth restriction of the affected fetus in monochorionic pregnancies. When detected on ultrasound, the pregnancy will be monitored more closely.
- In marginal cord insertion the cord emerges within 2 cm of the edge of the placenta.
- Furcate cord insertion.

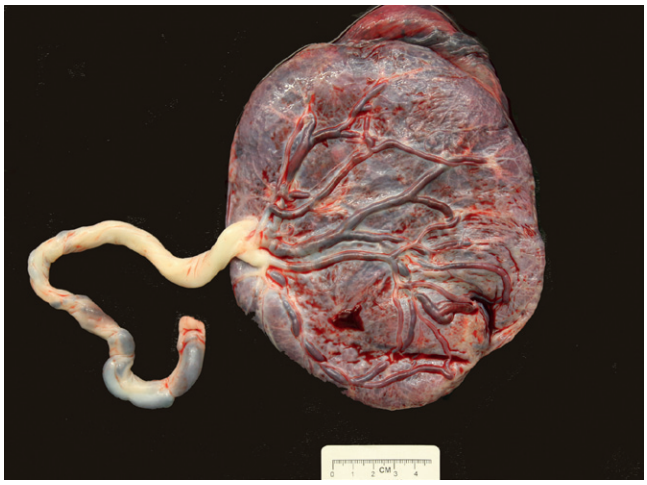

FIGURE 1

Marginal cord insertion. The cord emerges within 2 cm of the periphery of the disk.

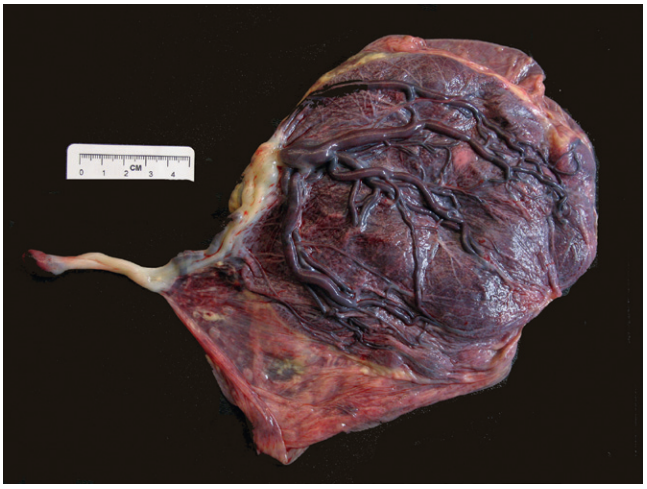

FIGURE 2

Membranous cord insertion. The cord enters the membrane prior to insertion into the disk.

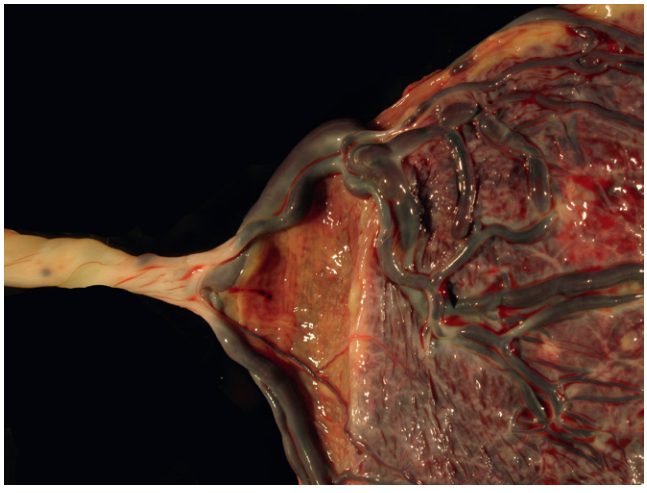

FIGURE 3

Membranous cord insertion. Note the branched cord vessels coursing through the membranes.

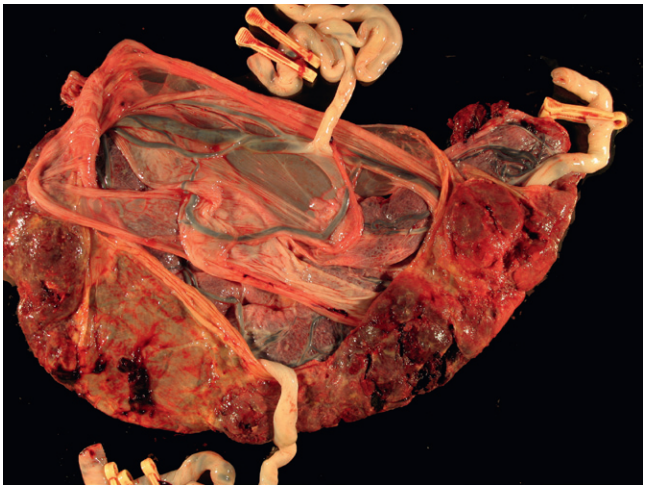

FIGURE 4

Another example of membranous cord insertion in this twin placenta.

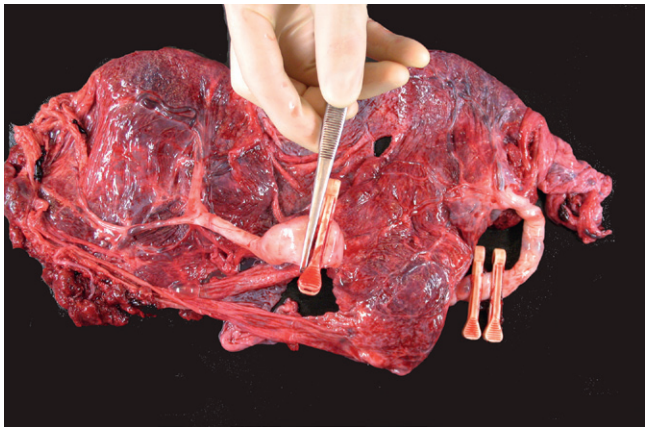

FIGURE 5

Furcate placenta. The cord bifurcates above the insertion with loss of Wharton's jelly.

CIRCUMMARGINATE AND CIRCUMVALLATE PLACENTAS

Kathleen Sirois, BA

Definition—Variations in membranous insertions on the placental disk.

Clinical Features

Epidemiology

- Circummarginate membranes are not strongly associated with any abnormality other than possibly fetal malformations in one study.
- Circumvallate membranes have a wide range of frequencies, ranging from 1% to 18%. Believed by some to result from deep placenta implantation into the decidua. Associated with abruption.

Presentation

- Circummarginate membranes: Rather than joining the disk at the margin, the membranes arise concentrically directly from the fetal surface inside the margin. The zone between the membrane edge and the periphery of the placenta is yellow in appearance.
- Circumvallate membranes: The membranes join the placenta at the margin, but a concentric, redundant, duplicated rim of membrane, like the whitewall of a tire, covers the periphery of the disk.

Prognosis and Treatment

- None.

Pathology

- Histologic examination of the placenta with circumvallate membranes should include careful exam of the membrane role and maternal surface for hemosiderin-laden macrophages, which could signify prior retroplacental bleeding.

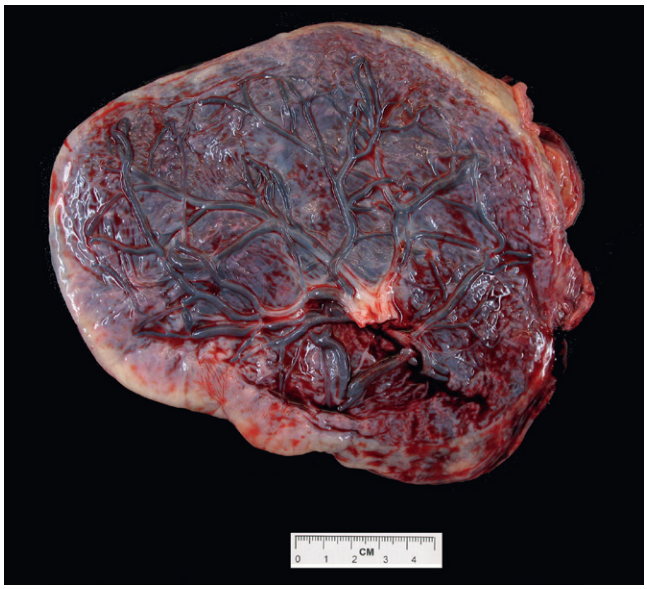

FIGURE 1

Circummarginate membranes. Note the insertion of the membranes is at the periphery of the disk.

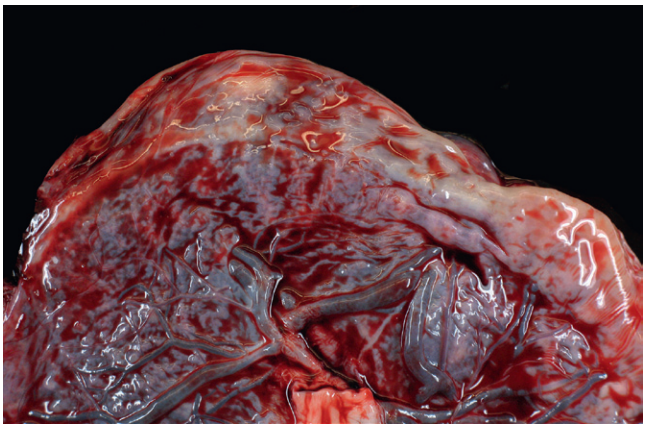

FIGURE 2

Circummarginate membranes.

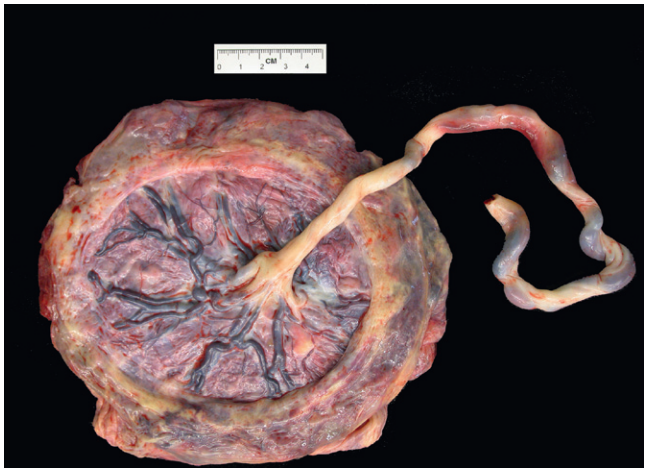

FIGURE 3

Circumvallate membranes. Note the duplicated membrane centrally, which is sharply demarcated.

FETAL VASCULAR THROMBOSIS

PITFALL

Definition—Thrombus formation within the umbilical cord, within its tributaries on the placental surface, or within stem villi.

Clinical Features

Epidemiology

- Common; seen in 3% to 10% of placentas.
- Increased incidence with maternal diabetes.

Presentation

- Very large or multifocal (40% to 60% of placental mass) thromboses can cause sudden intrauterine fetal demise.
- Small or localized fetal vascular thrombosis (FVT) is generally an incidental finding.
- If FVT occurs early in gestation or in a somatic vessel, the infant can present with cerebral infarcts or limb reductions.

Prognosis and Treatment

- Usually incidental.
- Rarely the presence of FVT can identify newborns with inherited coagulopathies or those at risk of somatic thrombi.
- Rarely associated with childhood stroke.

Pathology

Histology

- Microscopic examination shows wedge-shaped zones of infarction, with the base oriented toward the fetal surface, following the distribution of the thrombosed stem villous.
- An inflammatory infiltrate is absent.
- Downstream terminal villi exhibit ischemic change, with endothelial disruption, stromal karyorrhexis, and red blood cell extravasation.
- If the thrombus is remote, the terminal villi are collagenized and sclerotic (ghost villi).
- Thrombi are similar to those seen at other sites with attachment to the vessel wall, endothelial disruption, and expansion of the vessel lumen by a multilayered clot.
- Older thrombi show organization, with fibrosis and recanalization of the vessel lumen.
- Early fetal vascular thromboses can be confirmed by the presence of red cell extravasation into the vessel wall.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Placental infarcts of maternal origin may interrupt fetal blood supply to nearby villi, producing villous sclerosis.
- Chronic villitis, when moderate or severe, can lead to vascular obliteration. In some instances the villitis may not be conspicuous.

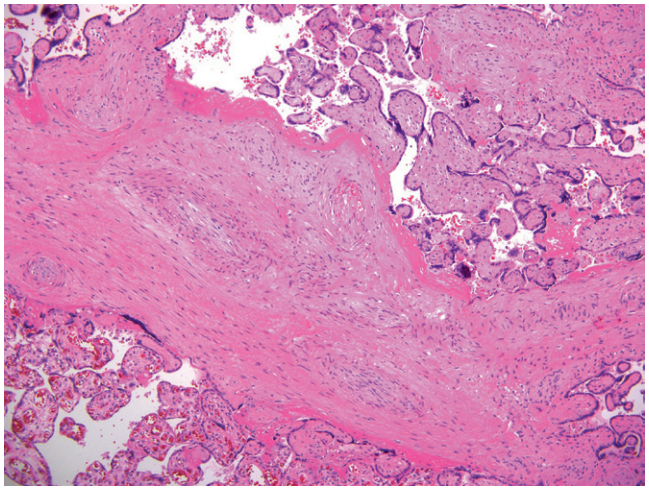

FIGURE 1

FVT. Thrombosed and nearly obliterated fetal vessels *(center)* are associated with sclerotic, avascular villi in the upper right. The avascular villi lack stromal inflammation or other features to suggest a chronic villitis.

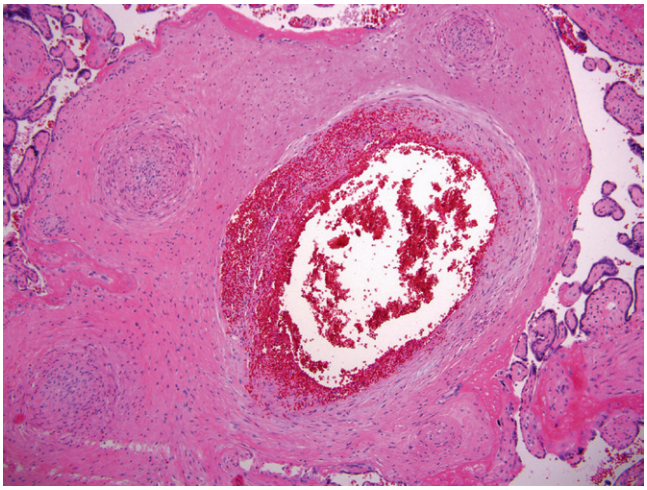

FIGURE 2

FVT. Fetal vessel with early thrombosis. Note the disruption of the vessel wall.

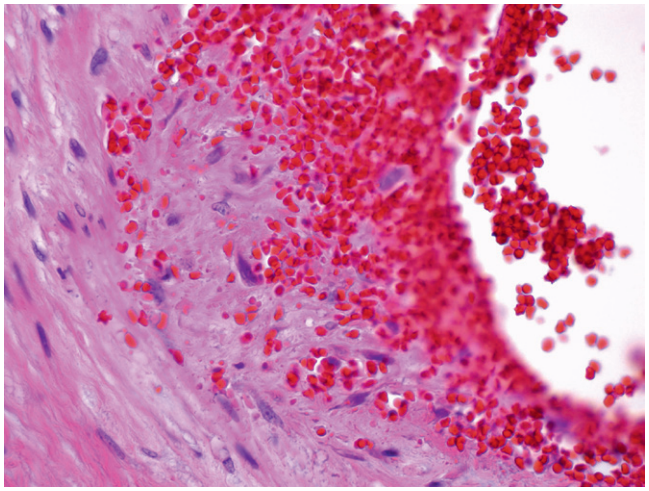

FIGURE 3

FVT. Higher power of an early vascular lesion shows extravasation of red blood cells into the vessel wall. Inflammation is absent.

AMNIOTIC BANDS

Definition—Detached strips of amniotic membrane that restrict fetal growth, resulting in asymmetric anomalies that do not follow a recognized developmental pattern.

Clinical Features

Epidemiology

- One in 2,500 to 10,000 deliveries.

Presentation

- Usually an isolated fetal anomaly (e.g., missing limb).
- Occasionally, severe or multiple anomalies are present, such as exposure of cranial, abdominal, or thoracic cavities.
- The pattern of anomalies does not follow the distribution of embryogenesis or that seen in any known syndrome.

Prognosis and Treatment

- Varies with resulting deformity.

Pathology

Histology

- Gross placental evaluation occasionally reveals residual entangled strips of amnion near the site of umbilical cord insertion, sometimes presenting as an amniotic "sleeve" around the base of the umbilical cord.
- The detached strips are histologically identical to the nondetached amniotic membrane.
- Gross examination of the fetus or infant reveals an isolated anomaly.
- In some cases the amnion may be totally stripped from the placental disk.
- If the amnion is missing from the placental surface, reactive changes in the chorion (presumably due to amniotic fluid exposure) can be identified and include the so-called chorion nodosum.
- The "chorion nodosum" consists of eosinophilic, proteinaceous debris and squames embedded in the chorionic surface.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Anomalies of another origin (e.g., genetic, toxic).

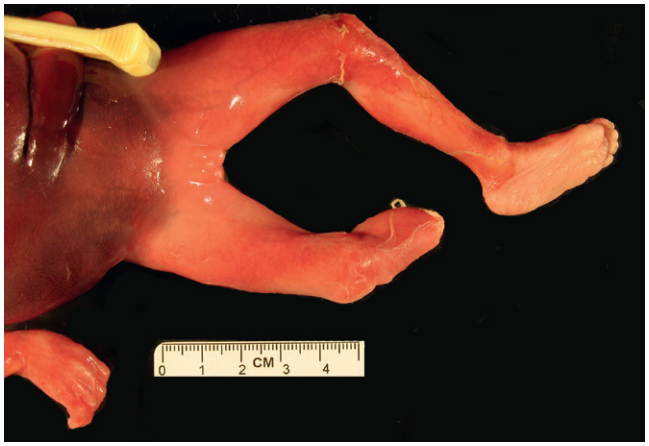

FIGURE 1

Amniotic band. Fetus with absent right lower leg, consistent with amniotic band.

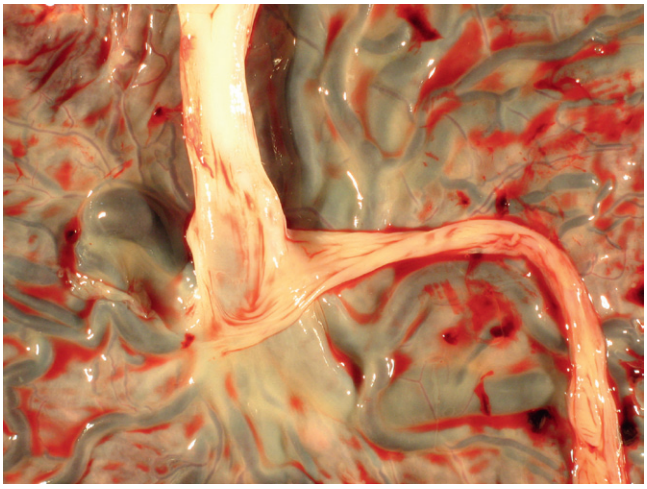

FIGURE 2

Amniotic band. Placenta with detached strip of amniotic membrane around the umbilical cord insertion site.

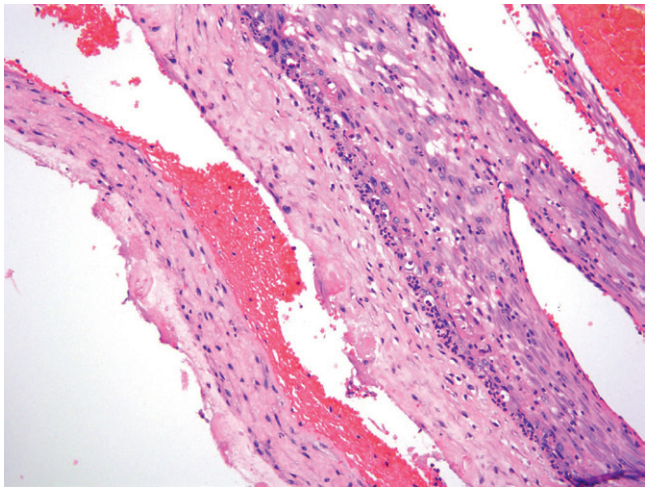

FIGURE 3

Amniotic band. Eosinophilic material and individual squames adherent to bare chorion, with reactive stromal changes.

MATERNAL FLOOR INFARCT/MASSIVE PERIVILLOUS FIBRIN DEPOSITION

Definition—Diffuse or multifocal fibrin deposition that fills and obliterates the intervillous space along a significant portion of the chorionic plate.

Clinical Features

Epidemiology

- Uncommon (less than 1% of placentas).
- Occasionally associated with abnormal maternal clotting (APhA, ATIII deficiency).

Presentation

- Sudden intrauterine fetal demise in the third trimester.
- Can present with recurrent spontaneous abortions.

Prognosis and Treatment

- Tends to recur in subsequent pregnancies.
- If fibrin deposition involves at least 40% to 50% of the parenchyma, it is uniformly fatal.
- Maternal floor infarction is also associated with intrauterine growth restriction.

Pathology

Histology

- Amorphous eosinophilic material (fibrin) surrounds individual villi or groups of villi.
- Mononuclear intermediate trophoblasts persist.
- Surrounded villi or groups of villi are widely separated from one another.
- The findings occupy a "significant" portion of the placenta.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Sampling from the placental margin only—this region typically exhibits abundant intervillous fibrin, but the remainder of the placenta should be unaffected.
- Placental infarct—early infarcts might not have collapse of villous structures, but the trophoblasts have the telltale dusky appearance of early degeneration. In contrast, although focal villous infarction often is present in maternal floor infarct, the majority of the syncytiotrophoblasts are still viable. Cytotrophoblasts will often abandon the villi to differentiate into vacuolated (p63 positive) and mature extravillous trophoblast.

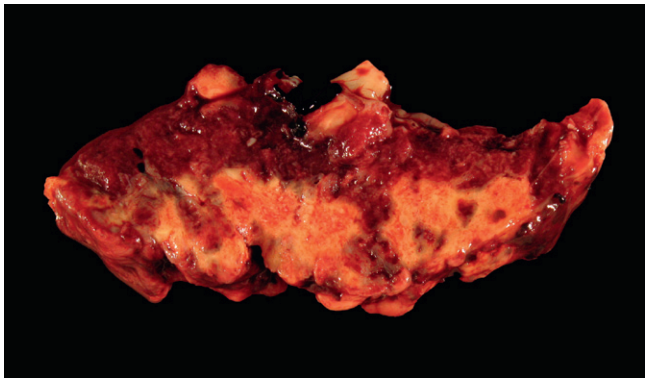

FIGURE 1

Massive perivillous fibrin. Gross example showing a diffuse process along the entirety of the maternal surface of the placenta, as seen on cut section.

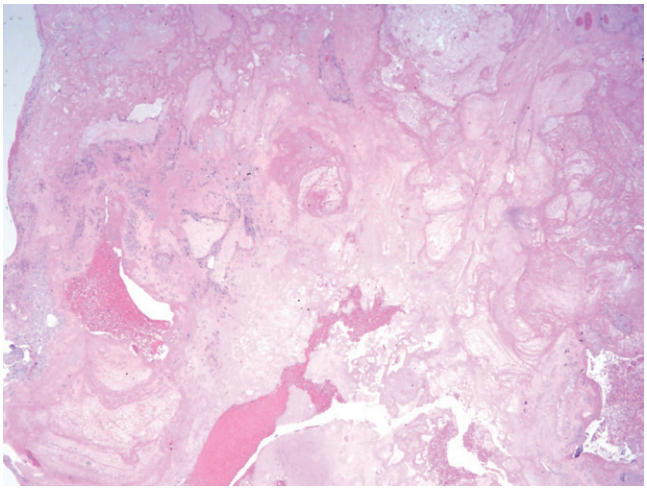

FIGURE 2

Massive perivillous fibrin. Widely separated groups of villi are apparent. There is abundant fibrin deposition along the maternal surface of the placenta. Note on the left clusters of extravillous trophoblast that have migrated from the villi into the fibrin. On the right there are a number of vague villous outlines signifying villous infarction. The key feature is the separation of villi, viable or dead, by abundant fibrin.

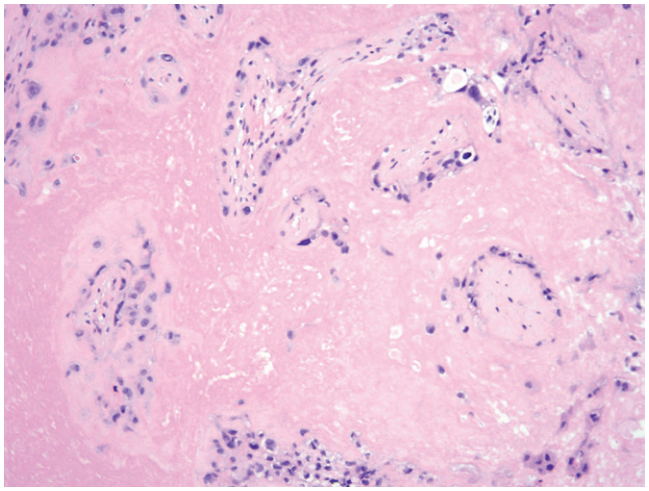

FIGURE 3

Massive perivillous fibrin. At high power the villi are viable. There is dense pink fibrin deposition completely surrounding the villi.

CHORIOAMNIONITIS

Definition—Ascending infection of the amniotic fluid leading to a fetal and maternal inflammatory response.

Clinical Features

Epidemiology

- Acute chorioamnionitis (ACA) is detected in approximately 25% of preterm deliveries, and gestational age of babies born with ACA is significantly younger than those born without ACA.
- Chorioamnionitis is a common end outcome of several infectious agents.
- May occur at any stage during pregnancy.
- Common cause of second-trimester inevitable abortion.
- Risk increased with cervical dilatation, premature rupture of membranes, or foreign bodies.

Presentation

- Preterm premature rupture of membranes, resulting in preterm labor.
- Signs and symptoms of infection including fever and malaise.
- Uterine pain and tenderness may be present.

Prognosis and Treatment

- The prognosis is variable and highly dependent on the infectious agent, gestational age, duration, and severity of infection.
- Delivery is the most common method of treatment, with intensive unit care for the infant.
- The principal adverse neonatal outcomes are death, sepsis, pneumonia or bronchopulmonary dysplasia, intraventricular hemorrhage, and ultimately cerebral palsy. To what degree these complications are directly related to the ACA versus premature delivery is unclear. Some have linked ACA to a higher frequency of preterm neonatal morbidity, and increasing severity of histologic chorioamnionitis has been associated with intraventricular neonatal hemorrhage. ACA has also been linked to a *lower risk* of respiratory distress syndrome (RDS) and neonatal death in premature infants.
- Corticosteroids or antibiotics are often used to counteract the inflammatory effects on the fetus, although controlled trials evaluating their effectiveness are needed.

Pathology

Histology

- The placenta displays opaque membranes and fetal surfaces in severe cases.
- A characteristic odor may be present in some specific infections, such as *Listeria*, *Fusobacterium*, or *Bacteroides*.
- Histologically the distinct fetal and maternal responses can be distinguished.
- The fetal neutrophilic response is seen in the umbilical cord and chorionic plate vessels.
- Nonspecific indicators of fetal distress, such as nucleated red blood cells, can also be seen.
- The maternal response consists of acute inflammation in the membranes, chorionic plate, and subchorion.
- Neutrophils present within the chorion and subchorion are not diagnostic of infection and should not be diagnosed as chorioamnionitis.
- Attempts have been made to categorize the extent of the inflammatory infiltrate (grade and stage) based on the distribution and extent of inflammation; however, these schemes do not correlate well with outcome.
- In general, a maternal response indicates an early infection, and the addition of an identifiable fetal response suggests a more chronic infection.
- Nonspecific, postmortem maternal inflammation may be seen that can mimic ascending infection; the presence of a fetal inflammatory response is helpful in ruling in infection in these cases.
- Amniotic fluid infection results in the presence of neutrophils within the alveolar spaces and gastrointestinal tract lumens, which can be a useful clue in cases of prolonged intrauterine fetal demise.

- In prolonged intrauterine demise of noninfectious causes, neutrophils should not be present within the alveolar spaces or along the gastrointestinal tract.
- Careful examination of the surface of the cord is important inasmuch as microabscesses on the surface could signify *Candida* infection and should prompt special stains to exclude this possibility.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Specific infections such as viral, fungal, or bacterial infections, including *Listeria* or beta-streptococcus, spread hematogenously and will also be associated with an acute intervillositis.
- Subchorionitis or other maternal-derived inflammatory responses may be found following intrauterine fetal death and prolonged rupture of membranes prior to delivery. This is not related to fetal death and is considered an incidental finding.

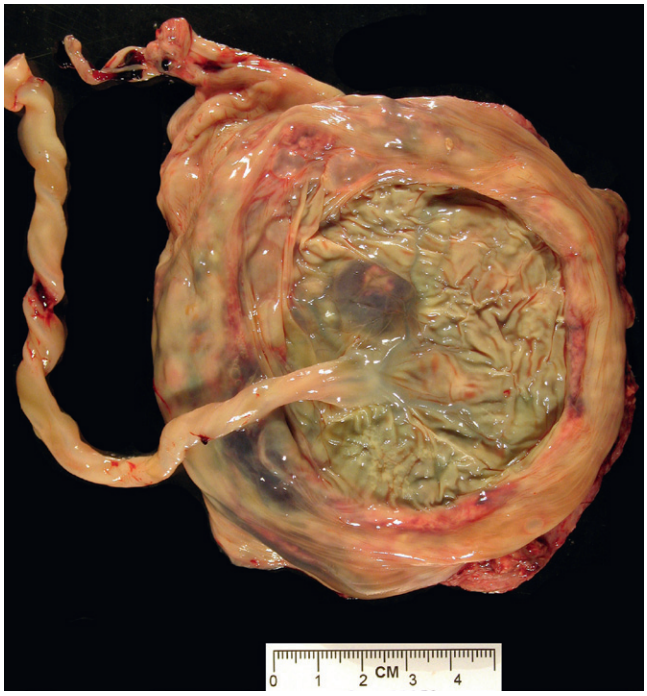

FIGURE 1

ACA. Gross image of a placenta with nearly completely opaque, white to greenish membranes.

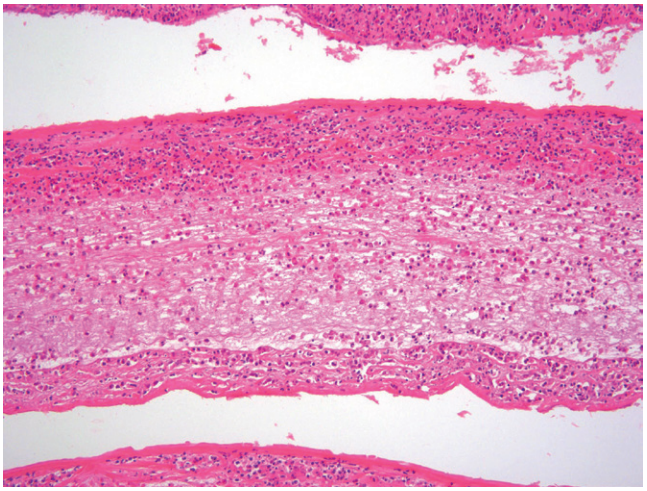

FIGURE 3

ACA. Necrotizing ACA with necrosis of the amnion and abundant neutrophils.

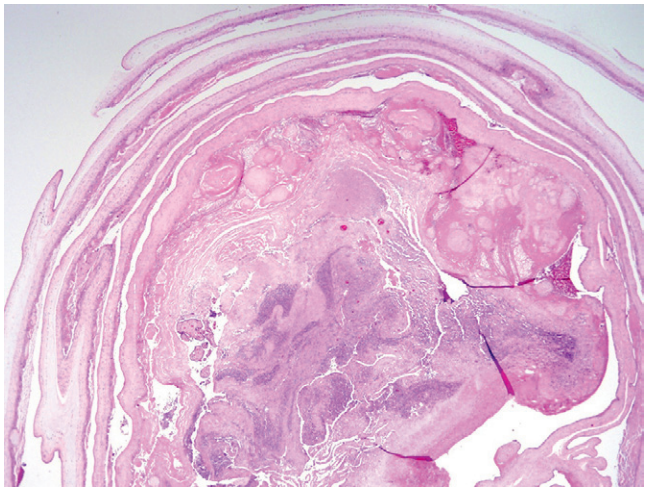

FIGURE 2

ACA. Low-power microscopic image of the membrane roll showing a dense inflammatory infiltrate of the chorion *(center)*. High-power examination *(not shown)* also revealed neutrophils in the amnion.

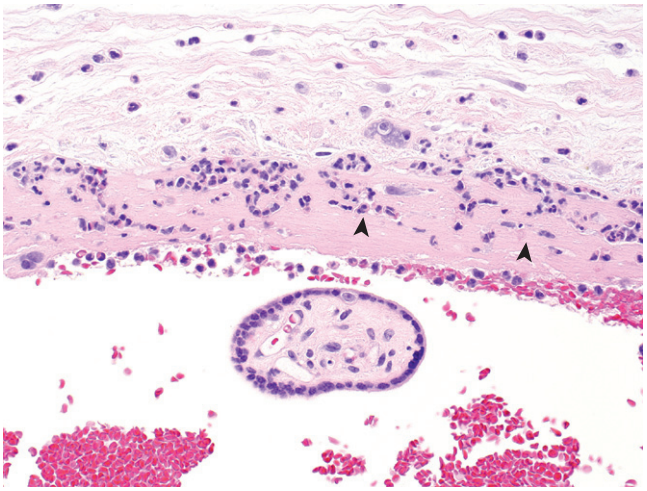

FIGURE 4

Subchorionitis, reflecting (by itself) early or mild infection. The maternal space is below with a single villous in this field. The subamnionic mesenchyme is above. The neutrophils in the chorionic plate are highlighted by the arrows.

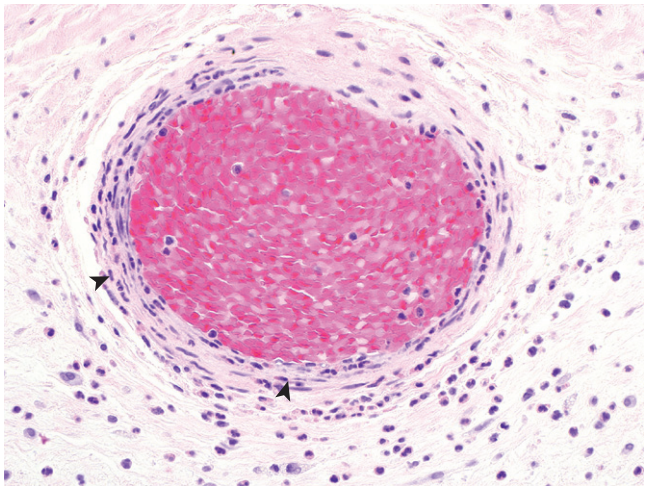

FIGURE 5

Chorionic plate vascular inflammation, a fetal neutrophilic response seen in vessels in the chorionic plate *(arrows)*.

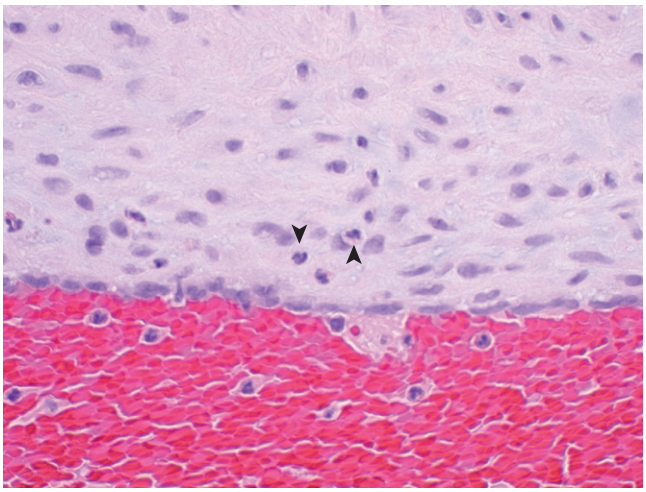

FIGURE 6

Umbilical cord vascular inflammation. This can be mimicked by early autolysis in the cord vessel subendothelial mesenchymal cells in second-trimester deliveries, which can mimic neutrophils. In this case the neutrophils in the vessel wall are easily seen *(arrows)*.

TABLE 1

Stages of Acute Amniotic Fluid Infection

Stage	Maternal	Fetal
I	Acute chorionitis, subchorionitis	Umbilical phlebitis
II	ACA	Umbilical arteritis, perivasculitis
III	Necrotizing chorioamnionitis	Concentric perivasculitis

TABLE 2

Template for Amniotic Fluid Infection

Inflammation characteristic of amniotic fluid infection

Maternal inflammatory response (choose all that apply below)
- ACA
- Acute subchorionitis, consistent with an early or mild amniotic
- Fluid infection
- Acute deciduitis

Fetal inflammatory response (choose all that apply below)
- Umbilical cord vasculitis
- Chorionic plate vasculitis
- Fungal funisitis

Inflammatory abruption (specify: marginal, retroplacental, subchorionic, intervillous) bleeding

Note: Amniotic fluid infection associated with extreme preterm delivery in midgestation raises concern for cervical incompetence. Clinical correlation may be helpful in this regard.

GESTATIONAL *CANDIDA* INFECTION

Definition—Infection by any species of *Candida* during the gestational period.

Clinical Features

Epidemiology

- Vaginal infection by *Candida* is common and is thought to occur in up to 25% of all pregnancies.
- Ascending infection of the placenta and/or fetus is rarer and occurs in less than 1% of all candidal infections during pregnancy.
- Risk factors for candidal chorioamnionitis include concurrent vaginal infection, cervical cerclage, and intrauterine device usage.

Presentation

- Chorioamnionitis.
- Preterm delivery.
- Intrauterine fetal demise.

Prognosis and Treatment

- The prognosis is variable and dependent on the extent of the infection and the corresponding inflammatory response.

Pathology

Histology

- *Candida* infection should be suspected grossly when small 1 to 2 mm white to yellow plaques or nodules are present on the umbilical cord or fetal surfaces of the placenta.
- A wedge-shaped abscess with yeast forms is characteristic microscopically.
- Accompanying chorioamnionitis should be identified.
- Severe cases may result in funisitis (inflammation of the umbilical cord) with or without necrosis.

Immunopathology (Including Immunohistochemistry)

- Special stains for fungus (periodic acid–Schiff [PAS] with diastase and Grocott's methenamine silver [GMS]) may be helpful in identifying the fungal organisms.

Main Differential Diagnosis

- Chorioamnionitis of different infectious etiologies.

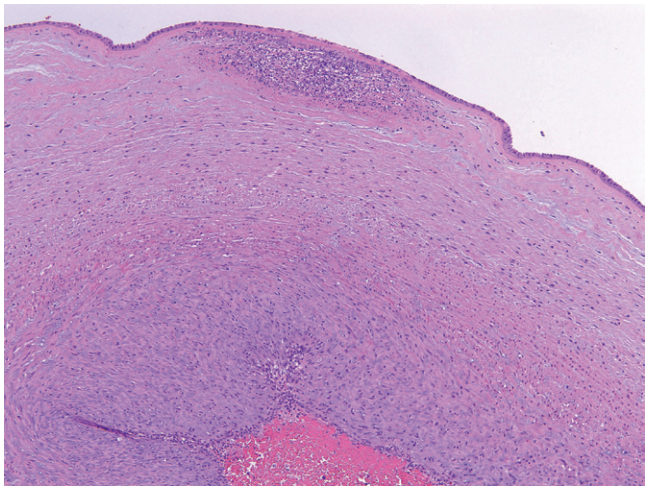

FIGURE 1

Chorioamnionitis. Umbilical cord at low power with neutrophilic infiltrate just under the surface of the cord. This is the histologic correlation of the white to yellow plaques seen grossly.

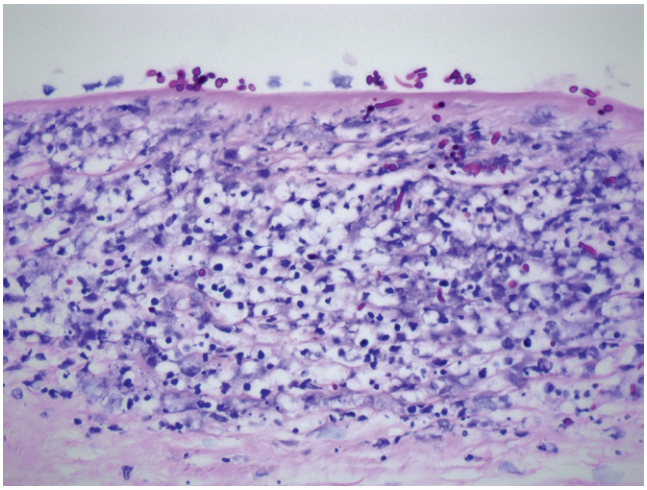

FIGURE 2

Chorioamnionitis. PAS-D stain highlighting fungal organisms in the microabscess seen in the umbilical cord.

LISTERIA PLACENTITIS

PITFALL

Definition—Placental infection by the gram-positive bacteria *Listeria monocytogenes*.

Clinical Features

Epidemiology

- Placental infection with *Listeria* is an uncommon occurrence.
- The most common method of infection is ingestion of unpasteurized dairy products, although deli meats and unwashed vegetables have also been implicated.
- *Listeria* is thought to spread hematogenously from mother to fetus.

Presentation

- At the time of initial infection the mother may experience mild flulike symptoms.
- Preterm premature rupture of membranes and accompanying chorioamnionitis are the most common presentation.
- The fetus may develop sepsis and experience preterm delivery in severe cases.
- Rarely infants present with granulomatosis infantiseptica, which includes multifocal abscesses of internal organs and skin.

Prognosis and Treatment

- *Listeria* infection carries a significant risk for fetal morbidity and mortality.
- Infection is fatal for the neonate in about 25% of cases.
- Granulomatosis infantiseptica is nearly always fatal.
- Ampicillin and/or gentamicin are the antibiotic treatments of choice.

Pathology

Histology

- In addition to characteristic findings of acute chorioamnionitis, several features are associated with *Listeria* infection in particular, including the following:
  - The placenta may be noted to have a "sweet" odor upon gross examination.
  - On sectioning the placenta may have a characteristic polka-dot appearance due to the presence of intervillous microabscesses.
  - The presence of multifocal patchy acute intervillous inflammation is the diagnostic clue.
  - The intervillous inflammation forms microabscesses.
  - In severe cases inflammation can focally extend into the villi.

Immunopathology (Including Immunohistochemistry)

- Gram stains demonstrate gram-positive bacilli within the microabscesses.
- The bacteria may form groups in characteristic shapes that are said to resemble "Chinese characters."

Main Differential Diagnosis

- Chorioamnionitis due to other causes.

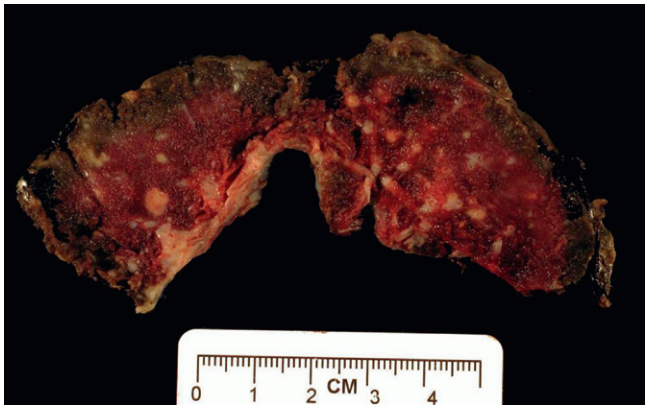

FIGURE 1

Listeria placentitis. Gross appearance. Small white patches are the gross correlate of the characteristic intervillous microabscesses.

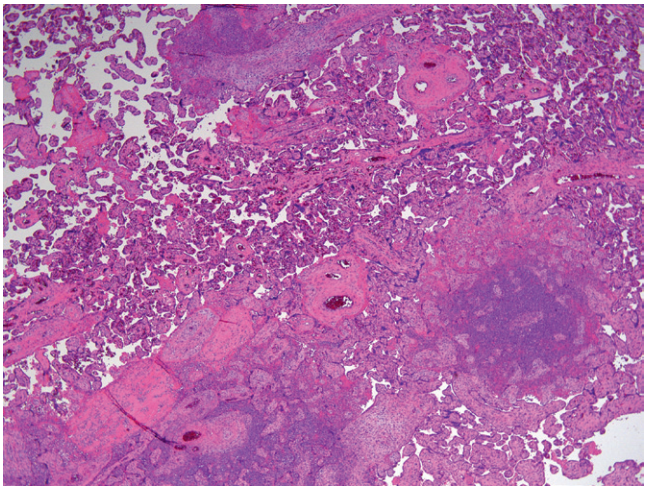

FIGURE 2

Listeria placentitis. Low power shows multifocal patchy intervillous inflammation forming microabscesses.

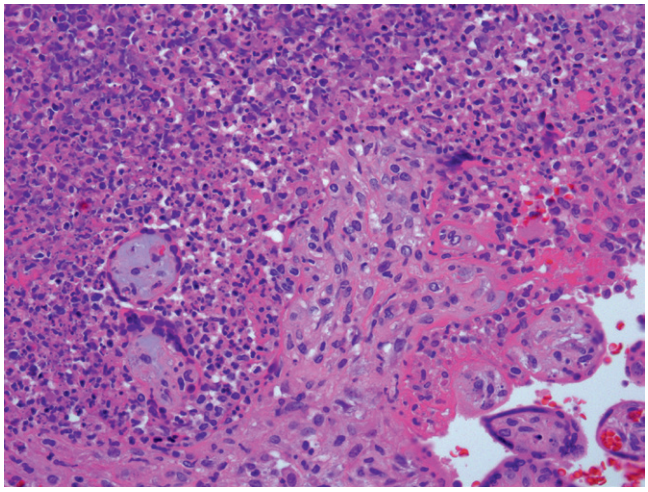

FIGURE 3

Listeria placentitis. The microabscesses are composed of neutrophils and are primarily intervillous. Note the noninflamed villi on the right. Organisms can be demonstrated with a gram stain in these areas.

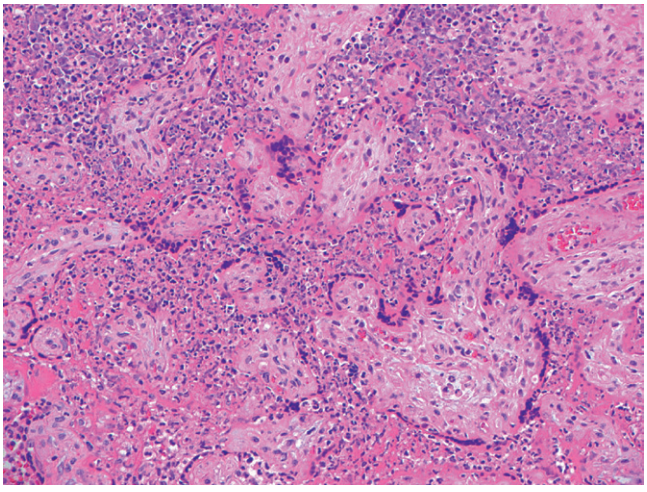

FIGURE 4

Listeria placentitis. Note that while the intervillous space is full of inflammation, the villi themselves appear uninvolved.

CHRONIC VILLITIS

Definition—Maternal chronic inflammatory cells within terminal villi, not attributable to any known infection.

Clinical Features

Epidemiology

- Present in 5% to 10% of examined placentas.
- More often seen in women with autoimmune disorders such as systemic lupus erythematosus.
- Thought by some to be an autoimmune phenomenon, and some authors consider it a maternal-placental graft rejection.
- Others suspect that chronic villitis (CV) represents a response to an as-of-yet unidentified organism.

Presentation

- Presentation varies greatly with severity.
- Often noted as an incidental finding at the time of placental examination.
- Is associated with both intrauterine growth restriction and (rarely) fetal death.

Prognosis and Treatment

- Recurs with subsequent pregnancies in about 20% of cases, and recurrence is often more severe.
- Other than supportive care, no useful treatment protocol currently exists.

Pathology

Histology

- The low-power clue to identification is that villi appear hypercellular.
- At higher power, aggregates of villi with stromal fibrosis, vascular obliteration, and chronic inflammatory cells are present.
- In some foci, lymphocytes and mononuclear histiocytes may be present (spill out) in the intervillous spaces.
- Not all villi are affected, and normal and inflamed villi are often intermixed.
- Viral inclusions are not present.
- Plasma cells should not be present in idiopathic CV; they are most commonly seen in infection, particularly cytomegalovirus (CMV).

Immunopathology (Including Immunohistochemistry)

- Special stains for infectious organisms are negative.
- Immunostains for viruses such as CMV are negative.

Main Differential Diagnosis

- Viral infection, especially CMV—viral inclusions should be present. Villous necrosis and calcifications may also be seen.
- *Toxoplasma gondii* infection.
- Fetal vascular thrombosis—this is in the differential when there is extensive villous sclerosis, which can be caused by both an obliterative villitis and fetal vascular thrombosis. The latter is more likely if there is evidence of proximal vascular occlusion with recanalization, villous karyorrhexis, and absence of CV.

Diagnostic Terminology

- If localized: Chronic nonspecific villitis.
- If involving multiple fields: Extensive CV.

A comment that extensive CV may recur and be associated with potential growth restriction or adverse fetal outcome may be included as appropriate.

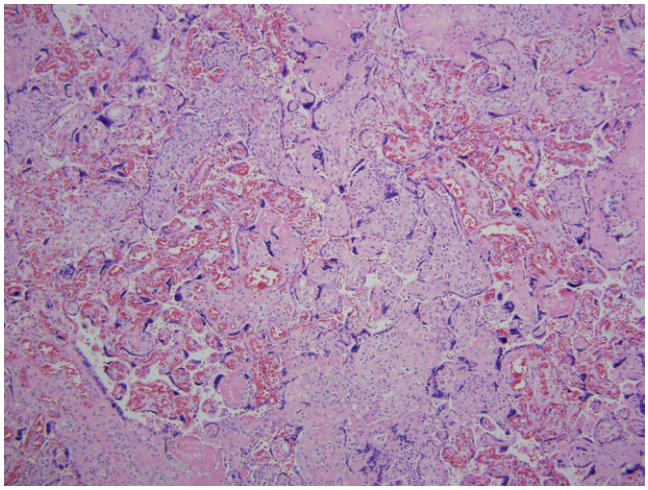

FIGURE 1

CV. Low-power image. An admixture of large, hypercellular villi and small normocellular villi.

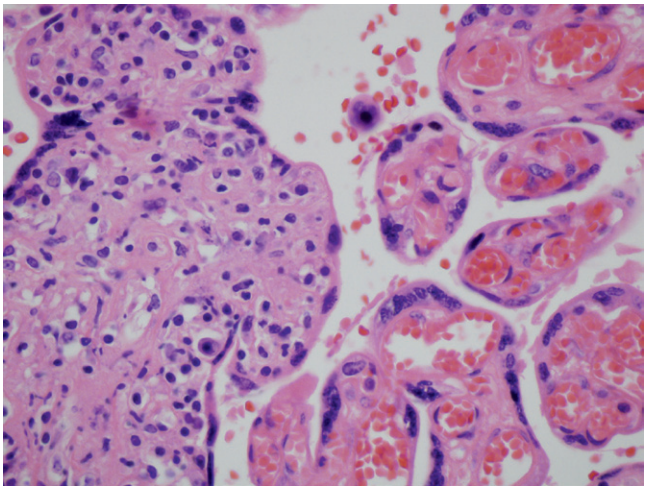

FIGURE 2

CV. High power contrasting normal villi on the right, with CV on the left. The villous on the left is infiltrated by lymphocytes, lacks normal vasculature, and had stromal fibrosis.

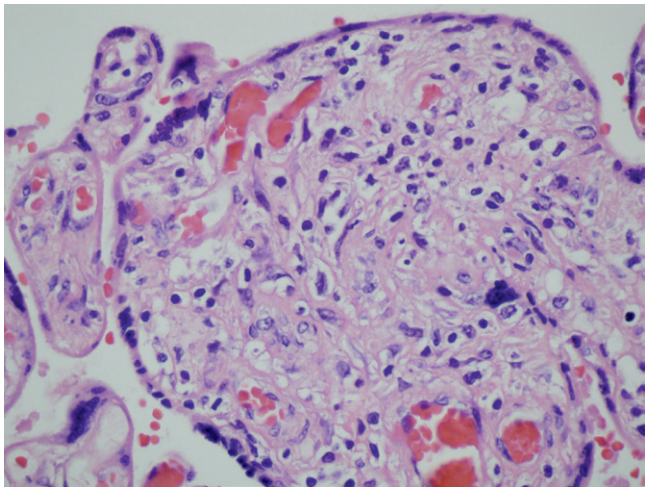

FIGURE 3

CV. A villous with numerous stromal lymphocytes and stromal fibrosis.

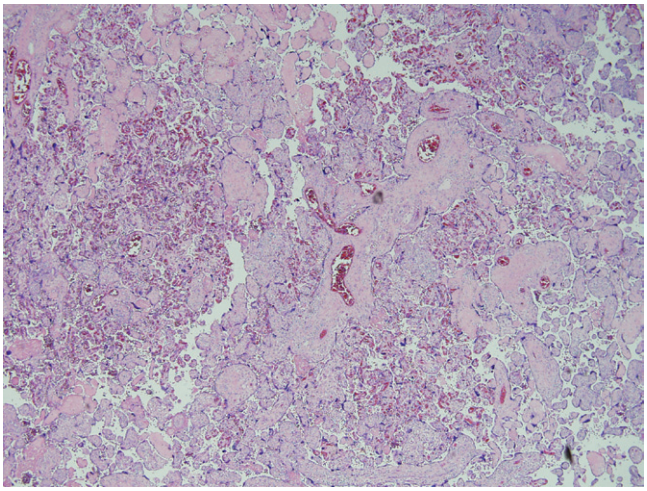

FIGURE 4

Severe CV. Note the widespread inflammation and villous obliteration, most prominent in the upper left of the image.

CHRONIC HISTIOCYTIC INTERVILLOSITIS

Definition—Infiltration of the intervillous space by a monomorphic population of histiocytes.

Clinical Features

Epidemiology

- Uncommon.
- Histiocytic intervillositis is associated with spontaneous abortion and recurrent pregnancy loss.
- Rare cases of maternal malaria or recurrent sepsis have been documented.

Presentation

- Chronic histiocytic intervillositis may present as spontaneous abortion in the first or second trimester.
- In the third trimester it is associated with intrauterine growth restriction and stillbirth.
- Some patients present with a history of multiple early pregnancy losses.

Prognosis and Treatment

- The prognosis in diagnosed cases is poor.
- Some studies indicate that three out of four cases result in fetal demise.
- The only known treatment option is aggressive immunosuppressive therapy.

Pathology

Histology

- The intervillous space is diffusely infiltrated by histiocytic cells admixed with lymphocytes.
- Intervillous fibrin deposition is also usually seen, although it is not present in all cases.
- By definition, classic chronic villitis is absent.

Immunopathology (Including Immunohistochemistry)

- The histiocytic cells are strongly and diffusely positive for CD68.
- Special stains for infectious organisms are negative.

Main Differential Diagnosis

- Chronic villitis—here the inflammatory cells are mainly confined to the villi. Some intervillositis may be present, but it is mostly lymphocytic.
- Acute and chronic intervillositis—if neutrophils are abundant, B-strep or *Listeria* must be considered.

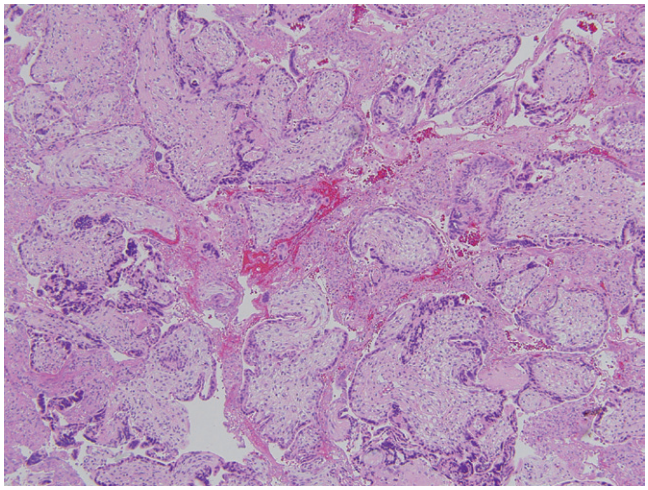

FIGURE 1

Chronic histiocytic intervillositis. Low power shows a diffuse intervillous process composed of a mixture of chronic inflammatory cells, histiocytes, and fibrin deposition.

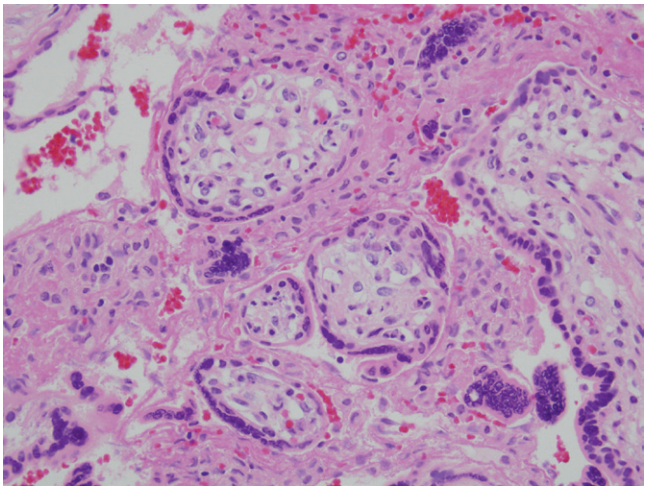

FIGURE 2

Chronic histiocytic intervillositis. High power shows that the infiltrate is composed predominantly of large histiocytic cells with abundant eosinophilic cytoplasm. Occasionally lymphocytes are present.

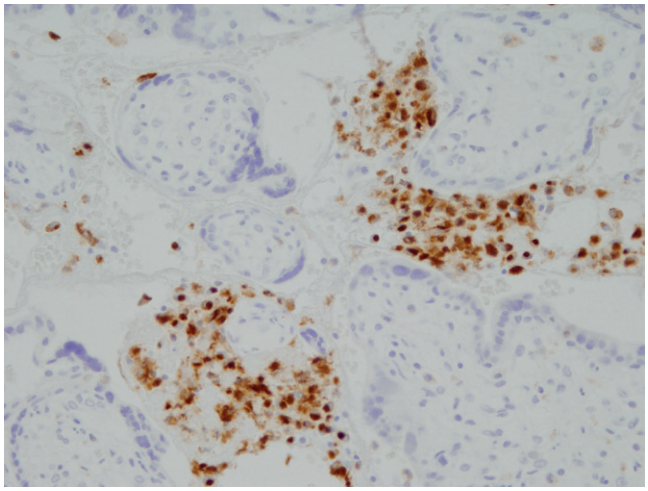

FIGURE 3

Chronic histiocytic intervillositis. An immunostain for CD68 is strongly and diffusely positive in the intervillous histiocytic infiltrate.

CONGENITAL SYPHILIS

Definition—Infection resulting from the spirochete *Treponema pallidum*.

Clinical Features

Epidemiology

- The frequency of congenital syphilis in developed countries is much lower; however, a recent rise in the incidence has been noted. It is rarely encountered in our practice.

Presentation

- Congenital syphilis causes premature delivery and stillbirth.
- Screening tests are used to detect the majority of cases; however, mothers with no prenatal care may present at the time of delivery.

Prognosis and Treatment

- Congenital syphilis carries a high rate of neonatal morbidity in the form of premature birth and neurologic deficits and mortality.
- Aggressive antibiotic therapy may lessen the chance of neonatal infection to an incidence of around 14%.

Pathology

Histology

- Examination of the placenta characteristically consists of villous changes including enlarged, hypercellular villi; acute and/or chronic villitis; and fetal vascular changes that include "onion skinning" of the vessel wall and vascular obliteration.
- Necrotizing funisitis may be present.

Immunopathology (Including Immunohistochemistry)

- Silver staining may reveal treponemal organisms.
- Detection of treponemal DNA by polymerase chain reaction (PCR) is the most sensitive method for diagnosis.

Main Differential Diagnosis

- Acute and chronic villitis, unspecified.

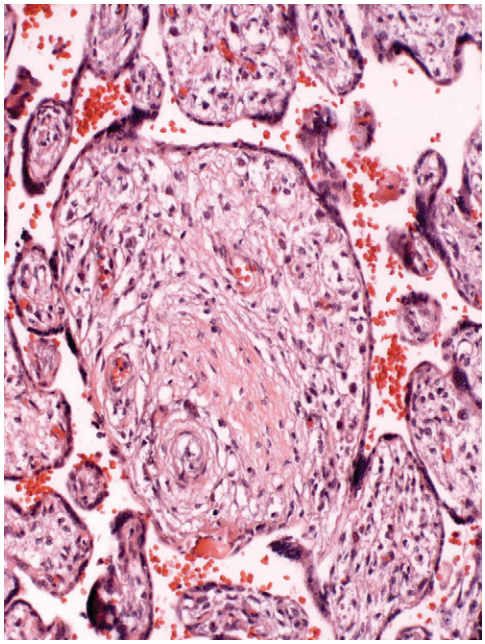

FIGURE 1
Congenital syphilis. Villi are variably sized with some increase in cellularity.

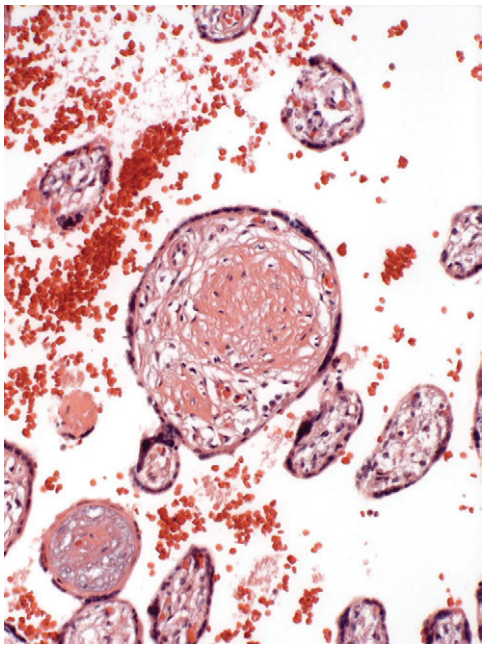

FIGURE 2
Vascular obliteration in congenital syphilis.

LYSOSOMAL STORAGE DISORDER

Definition—Metabolic deficits within the fetus that lead to the accumulation of a metabolite, typically visible in the placental villi.

Clinical Features

Epidemiology

- Lysosomal storage disorders and their placental presentations are rare events.
- The vast majority of cases are genetic disorders that manifest in placental findings.

Presentation

- Most storage disorders are unsuspected at the time of birth.
- The newborn may be asymptomatic or may display signs of compromised organ function (e.g., liver dysfunction, kidney dysfunction) with visceromegaly.

Prognosis and Treatment

- The prognosis and treatment depend on the specific storage disease that is diagnosed.
- The prognosis for storage diseases is highly variable and ranges from lethal to highly treatable with dietary modification.

Pathology

Histology

- Microscopic examination of the placenta shows extensive vacuole formation, or swelling, of the villous stromal cells due to metabolite accumulation.
- The intermediate trophoblasts, syncytiotrophoblasts, and amniocytes may also exhibit marked swelling or vacuolization.
- Variable numbers of foamy macrophages can be identified within the villous stroma.
- The vacuole formation and histiocyte infiltrate lead to a "pale placenta" at low magnification.

Immunopathology (Including Immunohistochemistry)

- Noncontributory in general.
- Alcian blue may be helpful in highlighting the Hofbauer cells.

Main Differential Diagnosis

- Clinically, the differential includes numerous metabolic storage diseases.

Lysosomal storage disorders

- ***Mucopolysaccharidoses***
  - *Hurler syndrome*
- ***Sphingolipidoses***
  - ***GM1 gangliosidosis,*** *Tay-Sachs disease, Fabry disease, Gaucher disease, Niemann-Pick disease, Krabbe disease, metachromatic leukodystrophy, multiple sulfatase deficiency*
- ***Glycoproteinoses***
  - *mannosidosis, sialidosis*
- ***Disorders of lysosomal enzyme transport***
  - *mucolipidoses*
- ***Lysosomal membrane transport disorders***
  - *sialic acid storage disease, cystinosis*

FIGURE 1

List of lysosomal storage disorders.

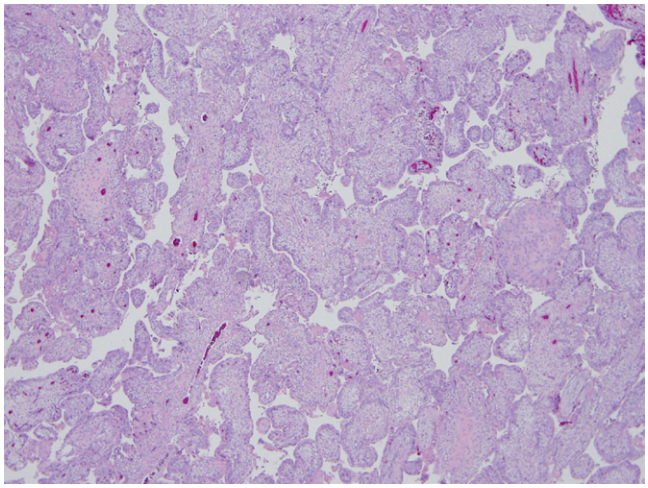

FIGURE 2

Placenta from a GM1 gangliosidosis. Note the slight villous enlargement with pallor, due to the abundant histiocytes.

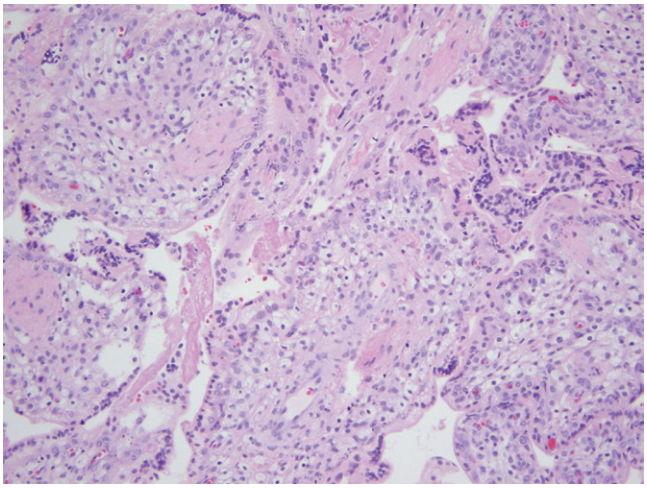

FIGURE 3

At higher magnification the villi are seen to contain numerous mononuclear cells.

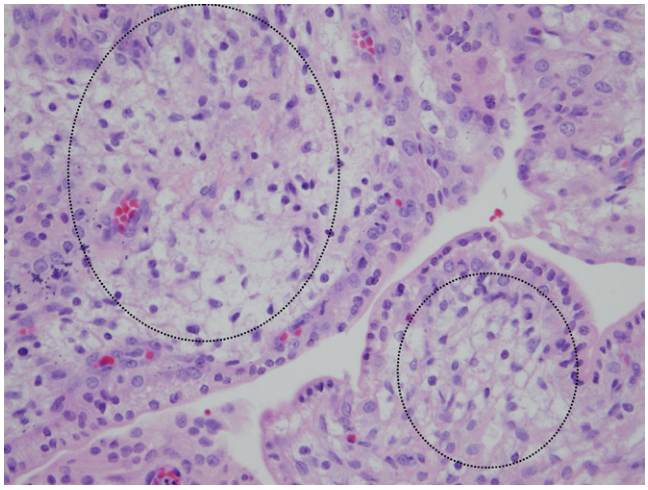

FIGURE 4

At higher magnification the numerous macrophages with small nuclei are evident *(see circles)*.

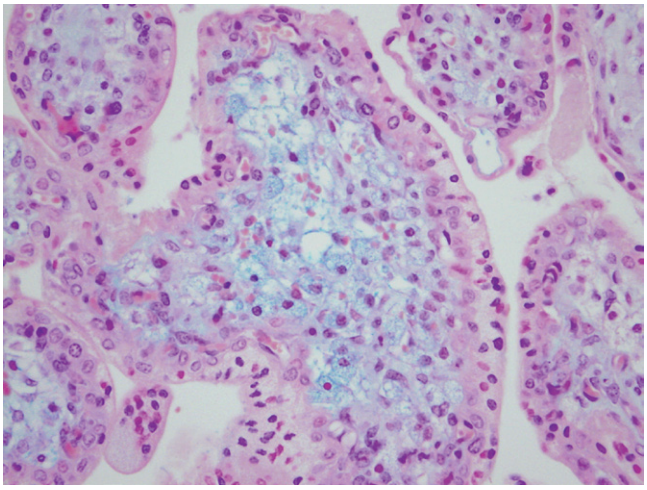

FIGURE 5

Alcian blue stain highlights the lysosomal contents as a faint blue.

INFLAMMATORY ABRUPTION

Definition—Early separation of the placental disk from the underlying maternal surface.

Clinical Features

Epidemiology

- Placental abruption is a relatively common event, with an overall incidence of 1%.
- Numerous predisposing factors are thought to lead to abruption but the focus recently has been on chronic inflammatory changes such as infarcts, decidual necrosis, and inflammation in the membranes and cord vessels. Bleeding early in pregnancy is also a risk factor.

Presentation

- Patients present with uterine bleeding and preterm labor.
- Abruption at the time of delivery may not be detected until the time of placental examination.

Prognosis and Treatment

- Small foci of retroplacental hemorrhage are often seen and are generally insignificant; this should not be confused with significant placental abruption.
- Abruption carries a significant risk of morbidity and mortality for both mother and infant.
- The extent of abruption directly impacts the chances of fetal demise.
- Any infarction in a preterm placenta is abnormal and should be carefully investigated.
- Small infarcts in term placentas are usually insignificant, but large (>3 cm) or multifocal infarcts are abnormal and associated with worse perinatal outcomes.
- Maternal morbidity can result from blood loss, disseminated intravascular coagulation, and/or renal failure.

Pathology

Histology

- Grossly, chronic abruption is suspected by the presence of a retroplacental hematoma.
- Peripartum hemorrhage is common and seen in nearly all placentas and should be distinguished from a potentially significant finding.
- If the clot is easily removed, then it is recent and likely related to the birth process.
- Clots of true chronic placental abruption will be adherent and often contain lines of Zahn on cut section.
- Another clue is the appearance of the underlying maternal surface; if the surface appears normal when the clot is removed, it is unlikely to be significant. If the clot creates a large defect or depression in the parenchyma, it may be a significant finding.
- A significant hematoma will block blood flow to the villous tree and causes a "halo" of ischemic placental infarction and villous collapse.
- Villous collapse is identified histologically by the loss of the intervillous space and confirmed by identifying the surrounding adherent hematoma.
- Acute abruptions are characterized by dissection of blood into the basal intervillous space; the time elapsed is generally not sufficient to form a true clot, and this diagnosis requires correlation with the clinical findings and impression at the time of delivery.
- Dissection of blood into the placental parenchyma may be seen as intravillous hemorrhage, although this is not always identified in cases of acute abruption.
- In some cases sudden acute abruption may produce a "ball-and-socket" appearance with a necrotic hemorrhagic core surrounded by infarcted placental parenchyma.

- Overall the histologic findings in both chronic and acute placental abruptions are nonspecific and should be correlated with the gross impression and clinical scenario.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Adherent blood clot (gross) is not uncommon at delivery. Conversely an abruption might not be appreciated if it dissects out from beneath the disk. A history of copious amounts of blood discharged at delivery or large blood clots found at cesarean section is supportive.
- Hypertensive infarct (ball-in-socket infarct) is a form of abruption where a spiral artery ruptures and produces a basal thrombus that is usually just within the parenchyma of the placenta. Unlike inflammatory abruption, which typically is diffuse and associated with chorioamnionitis, a hypertensive infarct is sharply circumscribed and associated with maternal hypertension or preeclampsia.

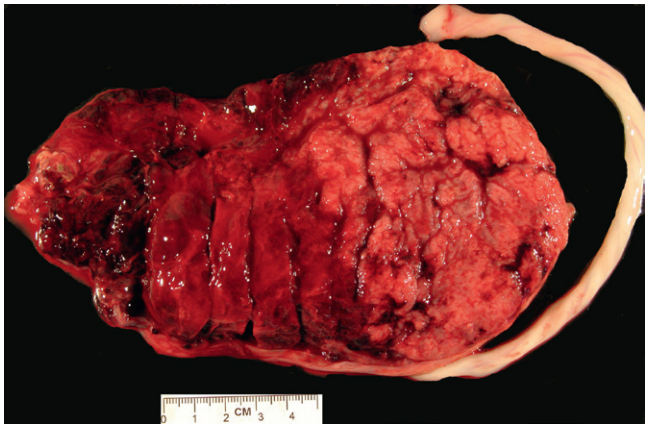

FIGURE 1

Placental abruption. Gross image of a placenta with a large (>3 cm) adherent hematoma with intraparenchymal dissection of blood.

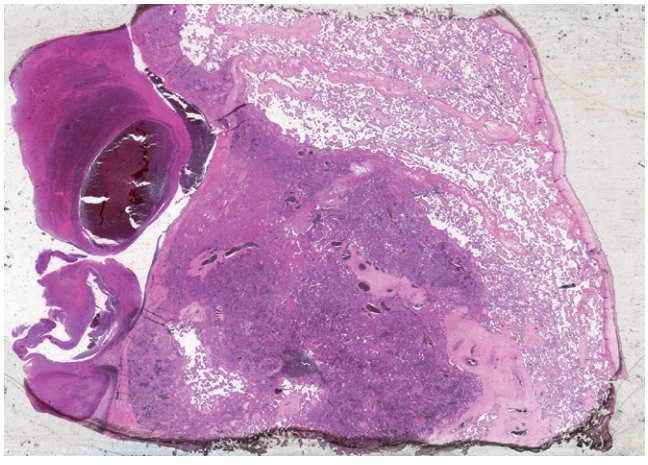

FIGURE 2

Inflammatory abruption. Note the large thrombus on the maternal surface on the left and the conspicuous zone of subjacent ischemia in the overlying placental tissue *(center),* consisting of infarct and/or intravillous hemorrhage.

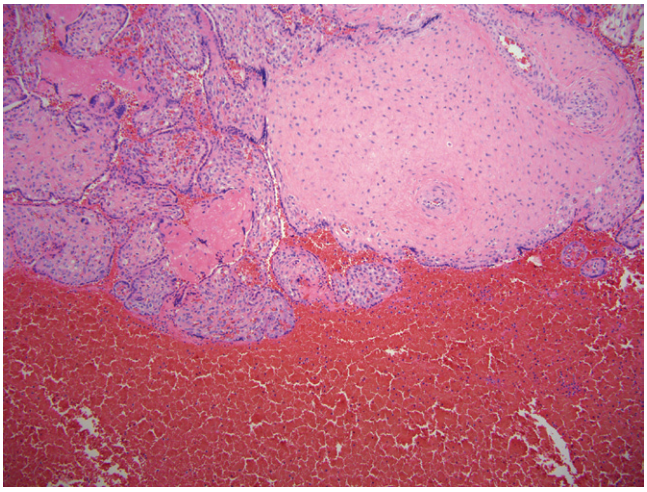

FIGURE 3

Inflammatory abruption. An acute abruption where the clot has not yet organized. There is minimal intraparenchymal dissection in this image.

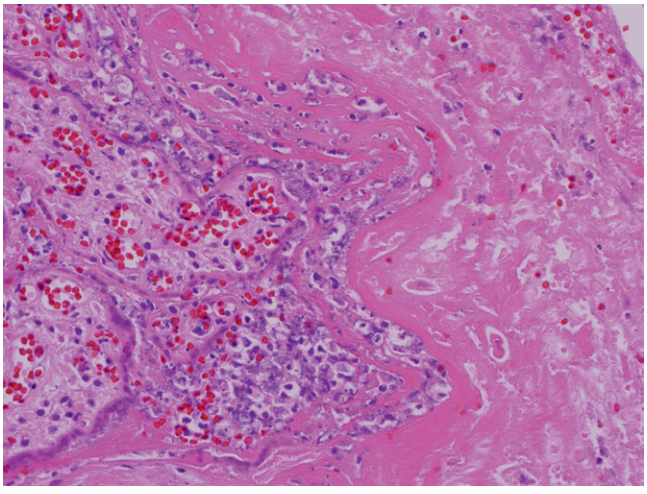

FIGURE 4

Higher magnification shows numerous neutrophils. This case was associated with a preexisting acute chorioamnionitis.

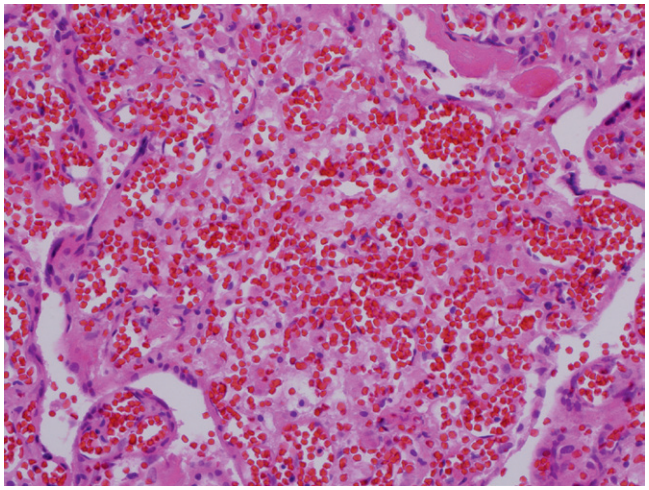

FIGURE 5

Intravillous hemorrhage in adjacent villi strongly suggests abruption; however, it can be reproduced by therapeutic terminations.

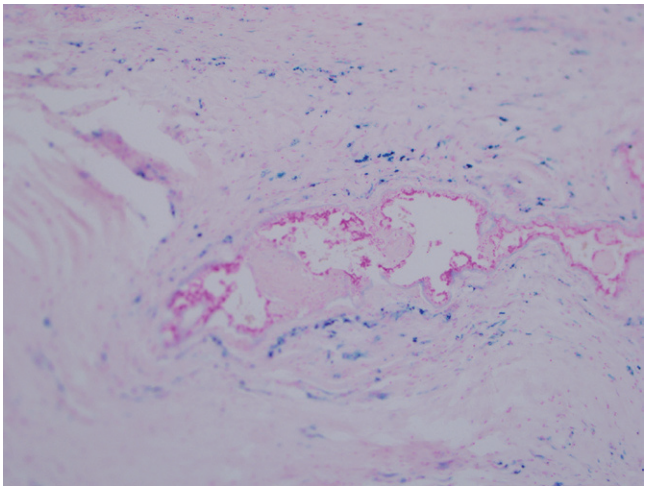

FIGURE 6

Hemosiderin on the maternal surface highlighted by an iron stain. This indicates a prior or chronic abruption and is not uncommonly found near acute retroplacental bleeding, given prior abruptions predispose the placenta to repeated bleeding.

HYPERTENSIVE BLEEDING (BALL-IN-SOCKET) INFARCT

Definition—A localized form of abruption due to acute spiral arterial bleed into the basal parenchyma associated with maternal hypertension.

Clinical Features

Epidemiology

- Most commonly associated with maternal hypertension and preeclampsia.

Presentation

- Similar to other causes of abruption with acute bleeding.

Prognosis and Treatment

- Abruption carries a significant risk of morbidity and mortality for both mother and infant.
- The extent of abruption directly impacts the chances of fetal demise.
- Recognition and treatment of the underlying disorder.
- Maternal morbidity can result from blood loss, disseminated intravascular coagulation, and/or renal failure.

Pathology

Histology

- Acute abruptions are characterized by dissection of blood into the basal intervillous space; the time elapsed is generally not sufficient to form a true clot, and this diagnosis requires correlation with the clinical findings and impression at the time of delivery.
- Sudden acute abruption produces a "ball-and-socket" appearance presumably due to rupture of a spiral artery with bleeding under pressure resulting in a necrotic hemorrhagic core surrounded by infarcted placental parenchyma.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Adherent blood clot (gross) is basal and not associated with underlying parenchymal damage. Many acute "terminal abruptions" go unnoticed at delivery; they may not be appreciated, but in any event they will not be confused with a hypertensive bleed.
- Intravillous thrombus most closely resembles a ball-in-socket infarct but is under lower pressure and is not sharply circumscribed with symmetrically arranged concentric layers of fibrin.

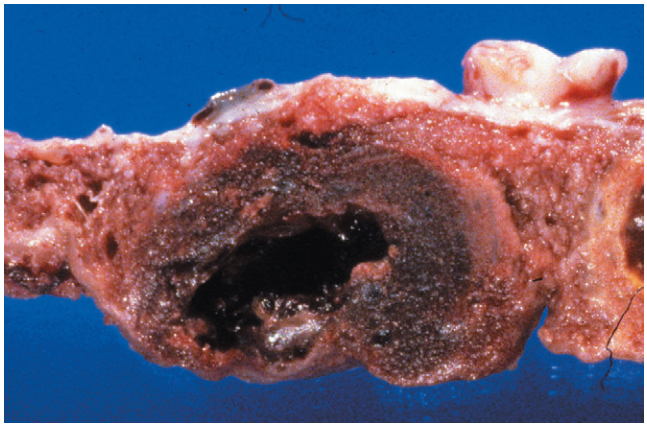

FIGURE 1

Acute abruption with a ball-in-socket infarct resulting from ruptured spiral artery in the basal parenchyma. The cause is typically maternal hypertension.

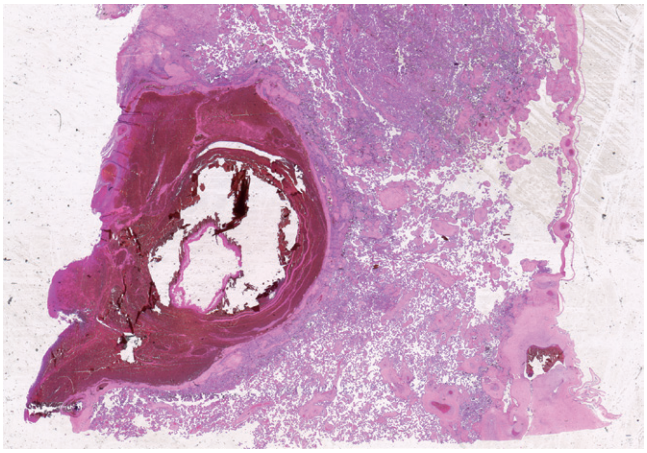

FIGURE 2

A ball-in-socket infarct at low magnification. Note the conspicuous concentric laminated blood and fibrin. A thin compressed zone of ischemic parenchyma is at the periphery.

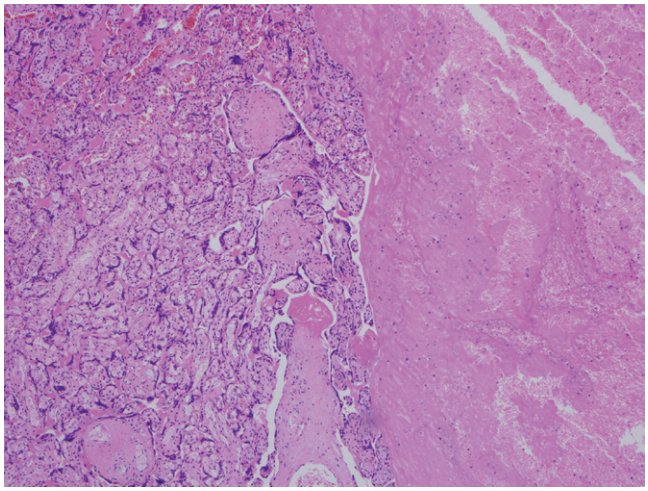

FIGURE 3

Interface of the infarct and normal parenchyma is discrete. There are mild ischemic changes in this field.

CONGENITAL PARVOVIRUS INFECTION

Definition—Fetal infection by the single-stranded DNA parvovirus B-19.

Clinical Features

Epidemiology

- Parvovirus infection is a common occurrence in adult life.
- Congenital parvovirus occurs when a woman who has not been exposed to parvovirus contracts the infection for the first time during her pregnancy.
- In this group of patients around 30% vertically transmit the infection to the fetus.
- Less than 5% of infected fetuses suffer significant morbidity or mortality.

Presentation

- Patients infected within the first trimester may present with miscarriage.
- Infection occurring in the second trimester may present with fetal (and placental) hydrops, severe anemia, and/or fetal demise.

Prognosis and Treatment

- Infection with parvovirus carries a risk of serious fetal morbidity and mortality (around 5%).
- Supportive care is the most effective treatment.

Pathology

Histology

- Placentas of fetuses display grossly evident hydrops fetalis and placental hydrops.
- The fetus exhibits varying levels of hypovolemia due to anemia.
- A fetal erythroblastic response (nucleated red blood cells) is identified within the placental vessels.
- Erythroid precursors within these vessels may show enlarged nuclei with chromatin margination to the nuclear membrane.
- "Ground-glass" precursor cells may be identified as well.
- Villitis attributable to parvovirus infection is not present.

Immunopathology (Including Immunohistochemistry)

- Immunohistochemical stains for parvovirus are positive.

Main Differential Diagnosis

- Fetal hydrops of other etiologies (i.e., immune mediated such as Rh incompatibility).

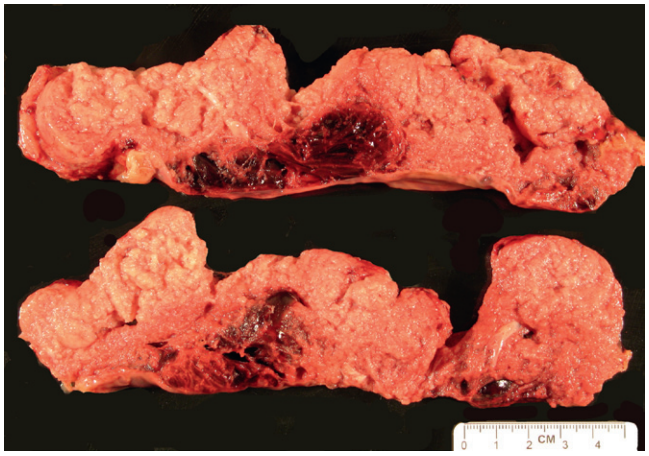

FIGURE 1

Parvovirus. Gross image of a hydropic placenta due to parvovirus infection.

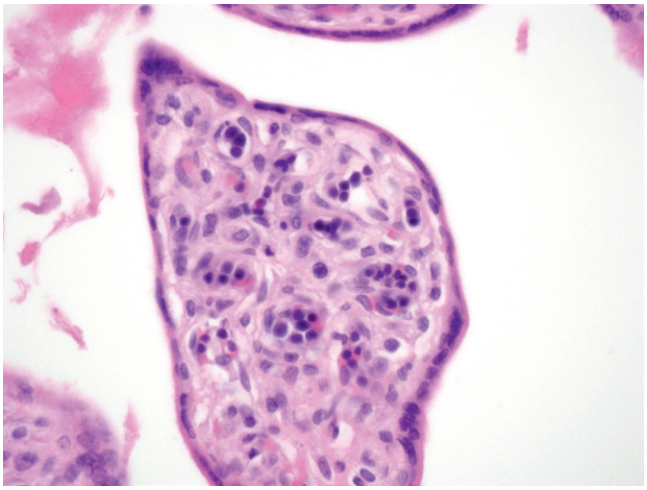

FIGURE 2

Parvovirus. Fetal erythroblastic response. Nucleated red blood cells are seen within fetal vessels.

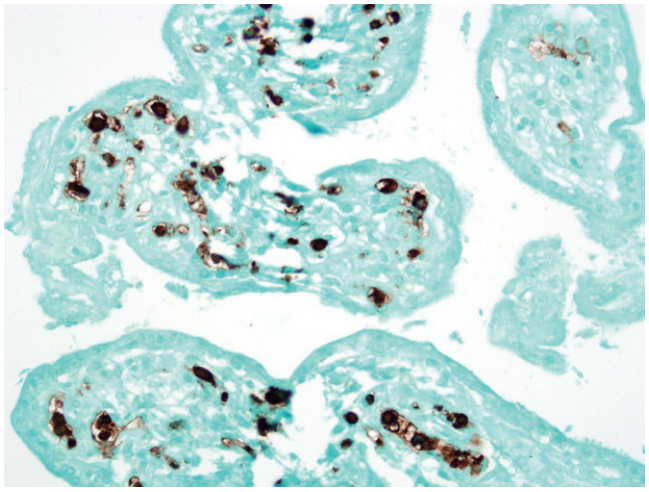

FIGURE 3

Parvovirus. Positive immunohistochemical stain for parvovirus.

FETAL LEUKEMIA

Definition—A primary white blood cell malignancy arising in the fetus.

Clinical Features

Epidemiology

- Fetal leukemia is exceedingly rare and has an incidence of approximately four to five per million live births.
- Fetal leukemia is the leading cause of neoplastic death in the neonate.
- All, or nearly all, infant leukemias are thought to originate in utero.

Presentation

- Polyhydramnios, hydrops, and hepatosplenomegaly can be seen on ultrasound.
- At birth the infant can exhibit hydrops fetalis (nonimmune) or may appear normal.
- In some forms of leukemia the infant has numerous skin nodules (blueberry muffin baby).
- Hydrops may be seen in all fetal malignancies, as well as other conditions, and is not specific.
- Prenatal umbilical cord sampling can reveal malignant cells in the fetal blood.

Prognosis and Treatment

- Fetal leukemia carries a very poor prognosis.
- Clinical remission, even with treatment, is rare.

Pathology

Histology

- If involved by the fetal leukemias, the placenta often exhibits placentomegaly.
- Microscopic evaluation reveals malignant leukocytes present in, and distending, the fetal vessels.
- Expansion or spillage of leukemic cells into the villous stroma is not prominent.

Immunopathology (Including Immunohistochemistry)

- Immunohistochemical markers and flow cytometry are used to determine the lineage of the malignancy.
- The cytogenetic aberrations seen in these malignancies are unique and distinct from those present in other childhood and adult leukemias.
- Selection and application of these tests are outside of the scope of this chapter.

Main Differential Diagnosis

- Reactive fetal leukoerythroblastosis.
- Transient abnormal myelopoiesis, seen in 10% of newborns with Down syndrome.
- Exclusion of these entities requires a detailed hematological workup.

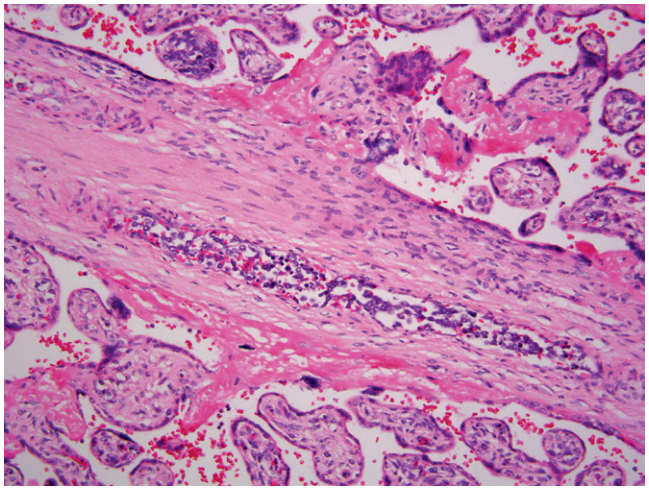

FIGURE 1

Fetal leukemia. In an infant with known leukemia, placental evaluation reveals foci of dark atypical cells in an otherwise normal-appearing placenta.

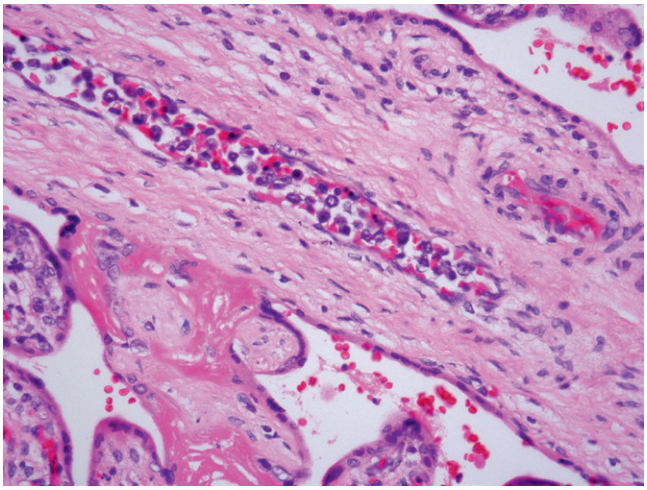

FIGURE 2

Fetal leukemia. At higher power the cells are highly atypical and morphologically consistent with blast forms.

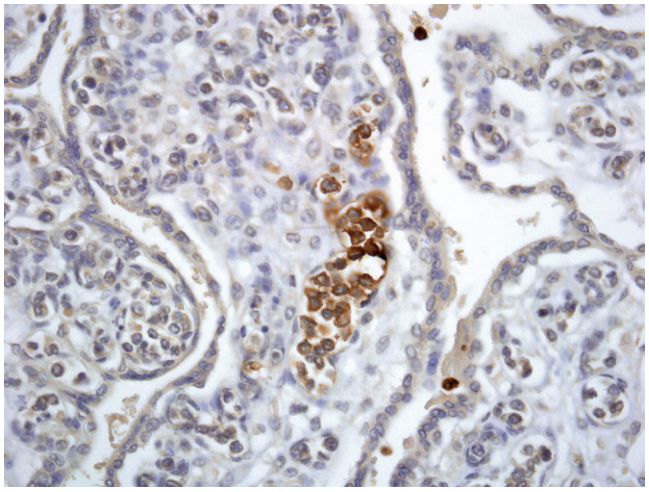

FIGURE 3

Fetal leukemia. A myeloperoxidase stain (MPO) highlights leukocytes within a fetal vessel.

PLACENTA CRETA

Definition—Abnormal adherence of the placenta to the uterine wall.

Clinical Features

Epidemiology

- Placenta creta occurs in 1 in 2500 pregnancies.
- Historically all subtypes of placenta cretas were rare.
- More than 80% of cases occur in patients with a prior cesarean section (C-section), and the rise in incidence is presumed to be due to the increased rate of C-section.
- Other risk factors include fibroids, Asherman's syndrome, previous uterine surgery (including curettage), high parity, and abnormal implantation.

Presentation

- Most patients present during labor with difficulty delivering the placenta or increased uterine bleeding following delivery.
- Mild cases of placenta accreta may be asymptomatic.
- In severe cases of placenta increta or percreta, patients may present with abdominal pain due to impending uterine rupture.
- The diagnosis can be suspected on ultrasound.

Prognosis and Treatment

- Prognosis is dependent on the extent and depth of the creta.
- Manual removal of the placenta is sufficient in half of cases.
- Sutures or artery ligation to stop bleeding may be required in about a fifth of cases.
- Uncontrollable bleeding in any form of creta may require hysterectomy.
- Placenta percreta may require hysterectomy.

Pathology

Histology

- Grossly, the placenta is often fragmented or grossly incomplete.
- In cases of hysterectomy the placenta is directly applied to the myometrium without intervening decidua (accreta), invades into the myometrial wall (increta), or rarely invades through the full thickness of the myometrial wall (percreta).
- Microscopic examination will reveal the presence of placental villi in direct contact with the myometrium, without intervening decidua.
- Implantation site fibrin with accompanying trophoblasts is present and should not be considered decidua.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Abnormal or exaggerated implantation site.

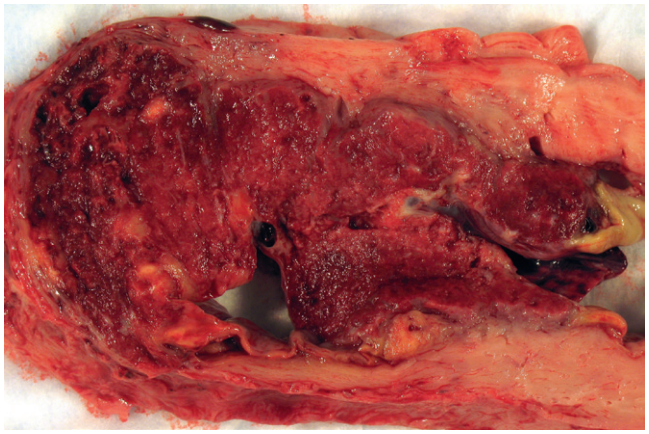

FIGURE 1

Placenta creta. Gross image of a gravid hysterectomy for placenta percreta. The placental parenchyma invades through the full thickness of the myometrial wall to involve the uterine serosa *(upper left)*.

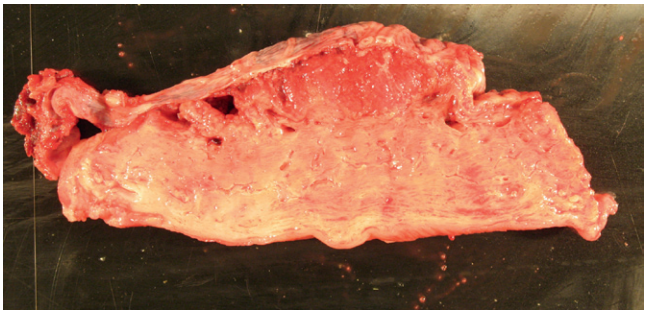

FIGURE 2

Placenta creta. Cross section from a gravid hysterectomy. The placenta is adherent directly to the myometrium, without intervening decidua.

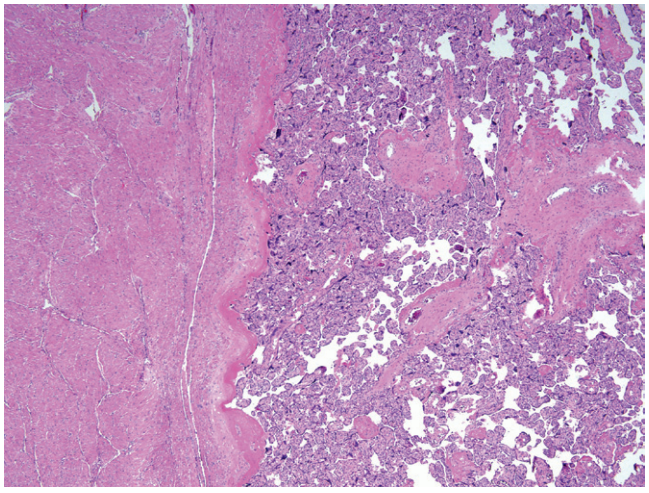

FIGURE 3

Placenta creta. Low-power image of placenta accreta. The placenta is directly adherent to the smooth muscle of the uterine wall. Decidua is absent.

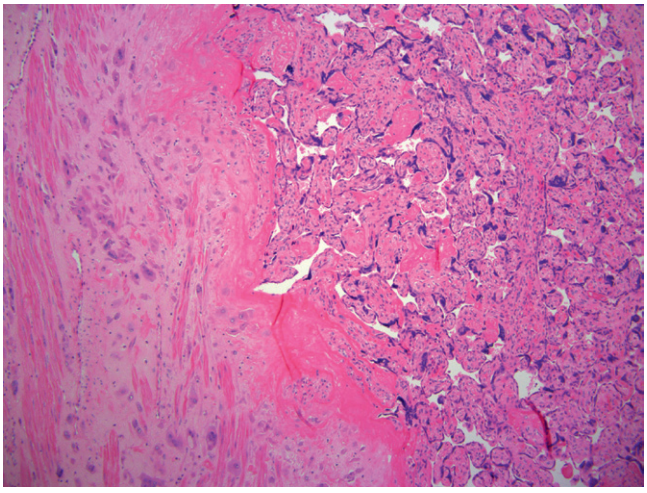

FIGURE 4

Placenta creta. Placental villi are directly adherent to the myometrium but do not invade into the myometrial wall. Trophoblasts set in brightly eosinophilic fibrin are present (implantation site), but decidua is absent.

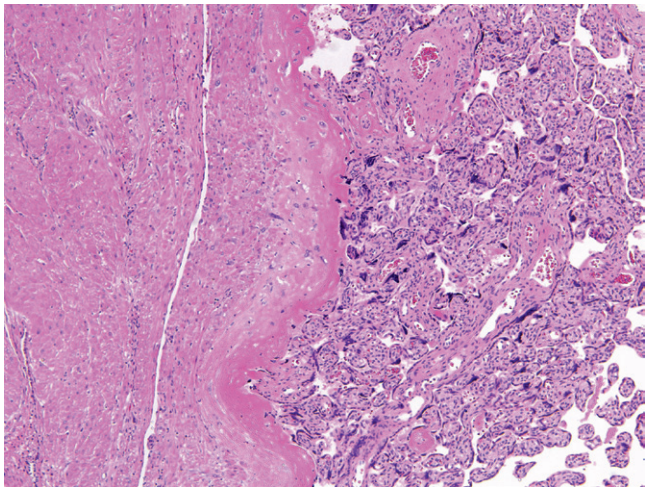

FIGURE 5

Placenta creta. Only implantation site separates placental villi from the smooth muscle of the uterine wall, consistent with a diagnosis of placenta accreta.

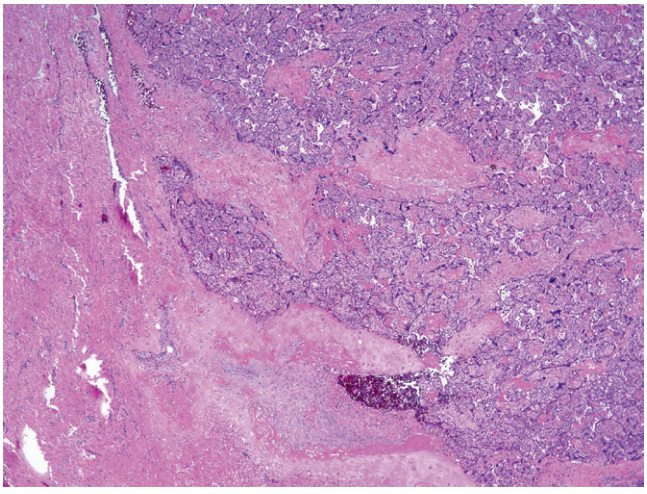

FIGURE 6

Placenta creta. Low-power image showing placental villi invading into the myometrial wall, diagnostic of placenta increta.

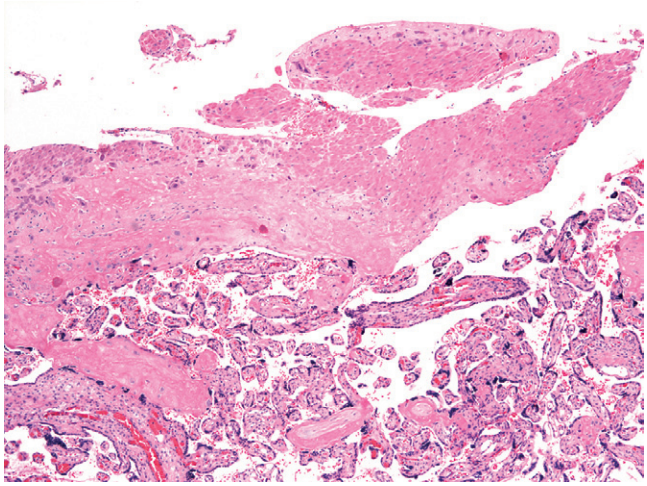

FIGURE 7

Muscle fibers adherent to the basal plate (maternal surface of the placenta, *upper right*), suggestive of placenta accreta.

PLACENTA PREVIA

Definition—Placental implantation within the lower uterine segment, overlying the cervical os.

Clinical Features

Epidemiology

- Placenta previa is a common finding in early pregnancy.
- The majority of cases spontaneously resolve during gestation.
- Less than 1% of cases persist until delivery.

Presentation

- Most cases are identified through ultrasonographic examination during routine prenatal care visits.
- Occasionally cases may present with vaginal bleeding.
- If abruption occurs, vaginal bleeding can be severe and life threatening for the mother and infant.
- Previa may be complete (complete cervical occlusion) or partial (incomplete cervical occlusion).

Prognosis and Treatment

- Prognosis for the fetus is guarded as there is a significant risk of fetal hemorrhage due to vasa previa (rupture) if the previa does not resolve.
- Early in the pregnancy, distal vaginal examination is deferred.
- In the third trimester the onset of labor may be stalled until fetal lung maturity is reached (around 36 weeks) to allow for a planned cesarean section (C-section).

Pathology

Histology

- If hysterectomy is performed, the placenta can be seen overlying the cervical os.
- Any other gross findings in placenta previa may be suggestive but are nonspecific.
- If only the placenta is received, many cases have an eccentrically placed cord, and/or the site of membrane rupture is close to the placental disk.
- Thinning of the placental disk or disruption of the maternal surface may be appreciated.
- Cases of previa also appear entirely normal, with no significant gross findings.
- There are no specific histologic findings.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Placental or membrane disruption due to C-section (gross differential).
- Placental abruption (if hemorrhage occurs).

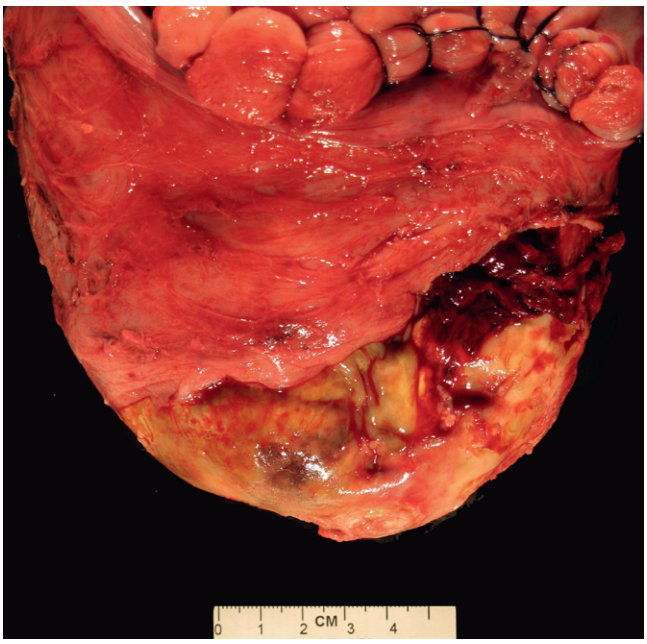

FIGURE 1

Placenta previa. Gross image showing the placenta extending over and out through the cervical os *(below)*. Sutures from the C-section are present above.

TOXOPLASMOSIS

Definition—A parasitic infection often contracted by handling cat litter, which can result in significant fetal morbidity if primary maternal infection occurs in the first trimester.

Clinical Features

Epidemiology

- Affects approximately 3500 newborns each year in the United States.
- Primary maternal infection results in fetal transmission in 25% of cases.
- Particularly common in France.

Presentation

- Primary maternal infection is usually asymptomatic.
- Ultrasound may reveal intracranial calcifications or growth restriction in the fetus.
- Large, pale placenta.

Prognosis and Treatment

- Approximately 10% of infections result in fetal death; most newborns with acute congenital toxoplasmosis will die.
- Encephalitis is the most severe manifestation of congenital infection; chorioretinitis and hydrops may also develop.
- Approximately 70% of congenital infections are subclinical at birth, with ocular problems (for example) developing later in life.

Pathology

Histology

- Histology is variable; in two thirds of cases placentas are normal appearing, even with severe fetal disease.
- Chronic villitis, sometimes with granulomatous features, can be seen.
- Organisms are rarely found; when present, the 200 μm encysted organisms are most easily identified in the umbilical cord, chorionic plate, or amniotic membranes.
- Organisms are PAS positive.

Immunopathology (Including Immunohistochemistry)

- Fluorescent antibody tests are available; however, they are not as reliable as polymerase chain reaction (PCR).

Main Differential Diagnosis

- Other toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex (TORCH) infections.

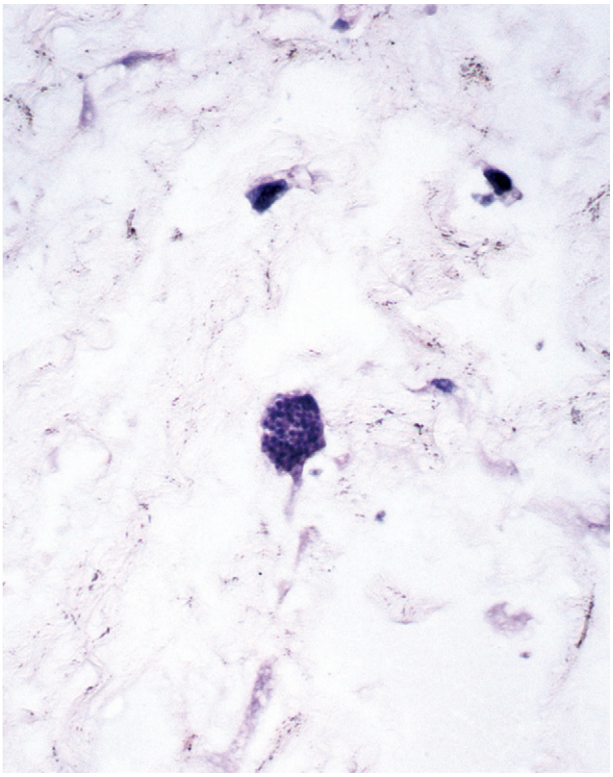

FIGURE 1
Toxoplasmosis. Encysted organisms are seen in Wharton's jelly.

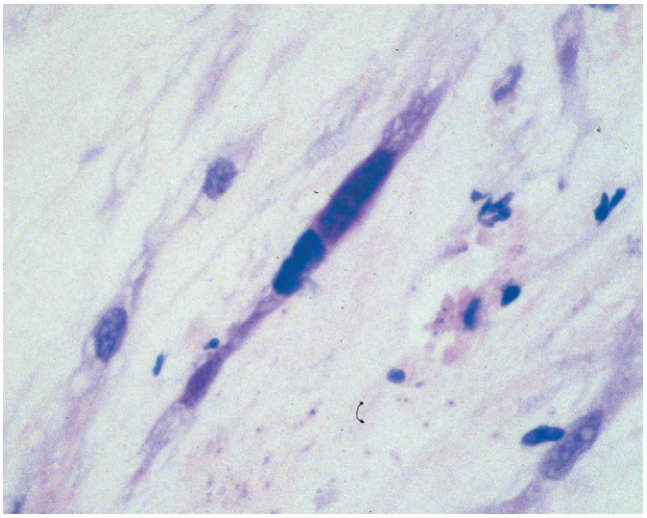

FIGURE 2
Toxoplasmosis.

TOXEMIA

Definition—A hypertensive disorder that arises during pregnancy; there are five types.

Clinical Features

Epidemiology

- Hypertensive disorders that fall under the umbrella of "toxemia of pregnancy" are common occurrences.
- Their presentations are varied and described in the following section.

Presentation

- Preeclampsia: Hypertension after 20 weeks gestation with accompanying proteinuria (>300 mg/24 hours or 1+ urine protein on dipstick). Patients usually present after 32 weeks gestation, unless associated with gestational trophoblastic disease, in which case they will present earlier. Preeclampsia may present with headache, visual problems, abdominal pain, elevated serum creatinine, oliguria, elevated liver enzymes, thrombocytopenia, fetal growth restriction, and pulmonary edema. This is the most common presentation of toxemia.
- Eclampsia: Patients display the symptoms of preeclampsia but have the additional finding of seizure.
- Gestational hypertension: Blood pressure greater than 140/90 mm Hg occurring for the first time during the pregnancy. Should resolve within 12 weeks after delivery.
- Chronic hypertension: Hypertension that is present before pregnancy, lasts longer than 12 weeks after pregnancy, or is present before 20 weeks in the absence of gestational trophoblastic disease.
- Superimposed preeclampsia on chronic hypertension: Proteinuria (>300 mg/24 hours) in the presence of chronic hypertension or the elevation of proteinuria, blood pressure, or thrombocytopenia in the presence of chronic hypertension and existing proteinuria.

Prognosis and Treatment

- The prognosis for the various types is highly variable depending on the type and severity of the toxemia.
- Mild cases of preeclampsia may resolve weeks after delivery, while severe cases of eclampsia may result in coma or maternal death.
- Delivery is the definitive treatment; however, mild cases may be treated with bed rest, dietary restriction, and medication.

Pathology

Histology

- In any type of toxemia the most common finding is a small placenta (less than 10th percentile for gestational age).
- Vascular changes and accompanying placental infarcts are also commonly seen.
- The vascular changes consist of maternal vessels that retain their smooth muscle walls, which is known as incomplete transformation of the spiral arterioles, or decidual arteriopathy.
- In more severe forms the decidual arteriopathy exhibits fibrinoid necrosis of the vessel wall with or without acute atherosis.
- These vascular changes are best seen in the membrane roll where it is clear which vessels are maternal in origin.
- Reactive changes within the placenta indicative of fetal stress are usually present.
- Increased syncytial knotting of the terminal villi, terminal villous hypoplasia, increased fetal nucleated red blood cells, and release of meconium with meconium staining of the membranes and chorionic plate are all signs of fetal distress.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Infection with fetal and maternal vasculitis.
- Other causes of fetal hypoxia.

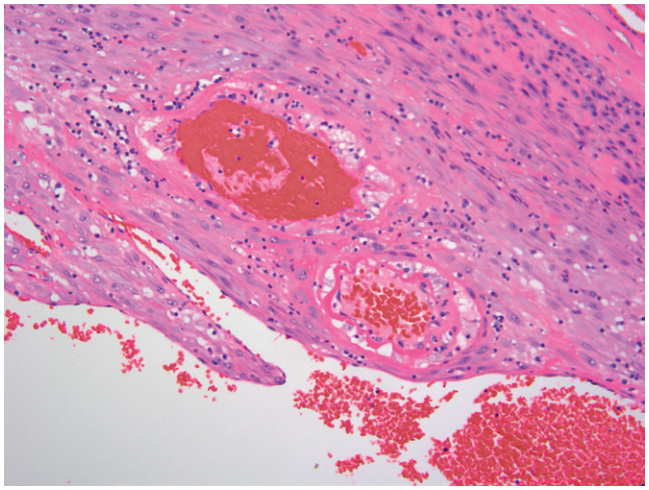

FIGURE 1

Toxemia of pregnancy. Low power of the membrane roll showing abnormal maternal vessels.

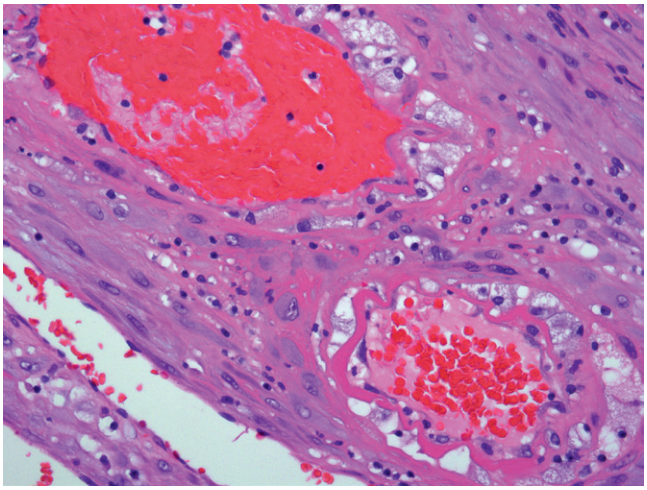

FIGURE 2

Toxemia of pregnancy. At high power the abnormal maternal vessels are characterized by a persistent smooth muscle wall and brightly eosinophilic fibrinoid change of the vessel wall. Acute atherosis is present.

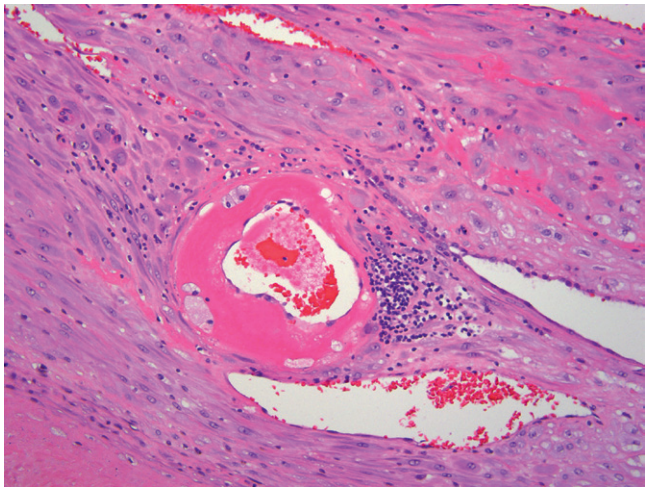

FIGURE 3

Toxemia of pregnancy. Maternal vessel showing acute fibrinoid necrosis, characterized by brightly eosinophilic change with occasional macrophages.

PLACENTAL INFARCTION

Definition—Infarction of the fetal villi due to lack of intervillous perfusion.

Clinical Features

Epidemiology

- Localized infarction within term placentas is very common.
- Abnormal infarction occurs in the setting of the intervillous hemorrhage of abruption, thrombosis, or vasoconstriction of the maternal spiral arteries.

Presentation

- Small infarcts are asymptomatic and incidental.
- Peripheral infarcts are seen in a large proportion of term placentas.
- Large infarcts (>3 cm) are associated with fetal hypoxia, morbidity, and mortality.
- Placental infarction in the first two trimesters is always abnormal.

Prognosis and Treatment

- Prognosis and treatment are dependent on the extent and severity of infarction, as well as the antecedent cause.
- The vast majority of infarctions are found in the periphery of term placentas and import no risk to the infant.

Pathology

Histology

- Grossly, a placental infarct is identified by a focus of villous pallor.
- Remote infarcts may be firm, fibrotic, and very pale.
- Early placental infarction is characterized by coalescence of the terminal villi with preservation of the trophoblasts.
- The coalescence is due to loss of the intervillous space.
- Over time, trophoblastic death leads to loss of nuclear detail and villous "ghosts" will remain.
- As the infarction becomes remote, extensive hyalinization may occur.
- In abruption-related infarction, intervillous hemorrhage will often be surrounded by a rim of placental infarction (i.e., the ball-and-socket infarct).

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Intervillous fibrin—may be impossible to distinguish from an aged infarct.
- Intervillous thrombus—may mimic an acute infarct.
- Intraplacental choriocarcinoma—reason enough to *sample all suspected intravillous thrombi.*

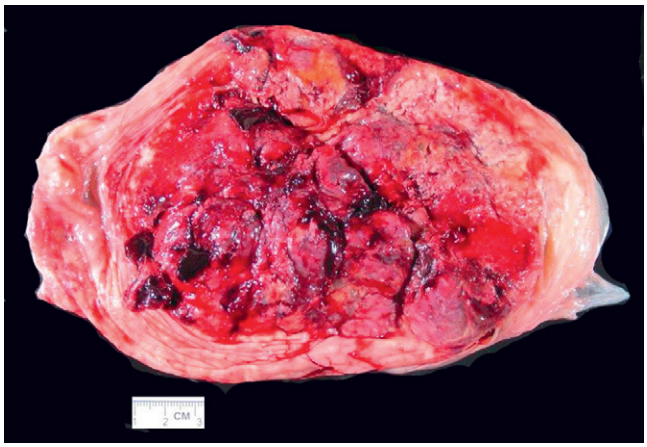

FIGURE 1

Placental infarction. The gross photo of the maternal surface reveals a markedly abnormal placental parenchyma. The discolored areas in the center correspond to recent infarcts; the pale granular areas at the upper right correspond to older infarcts.

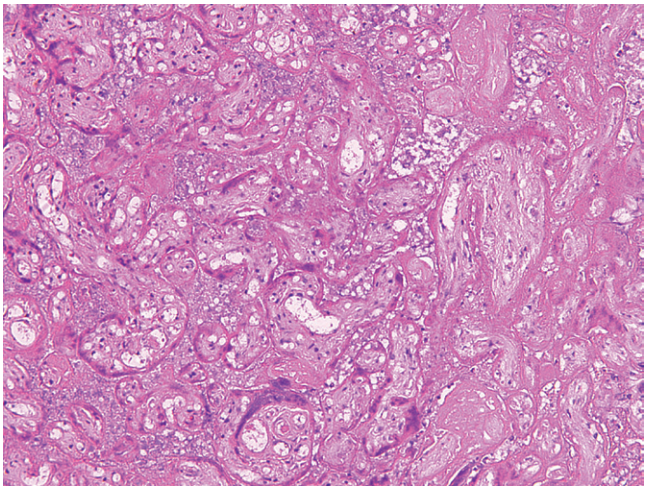

FIGURE 2

Placental infarction. A relatively recent infarct with degenerated trophoblast and collapse of the villous space.

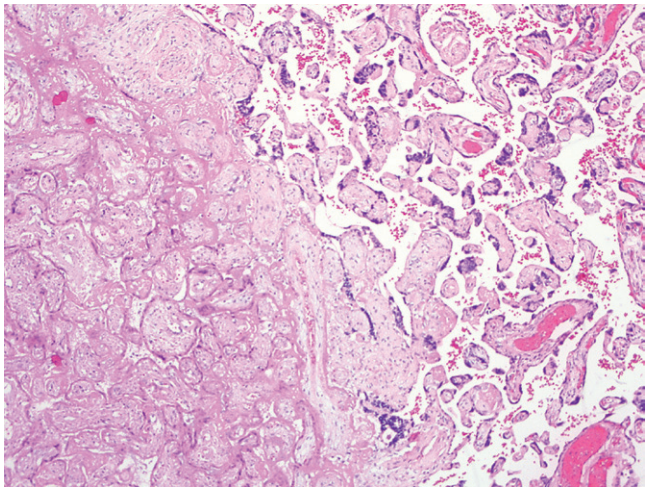

FIGURE 3

Placental infarction. A slightly older infarct on the left with juxtaposed uninfarcted but ischemic parenchyma on the right, with increased syncytial knots.

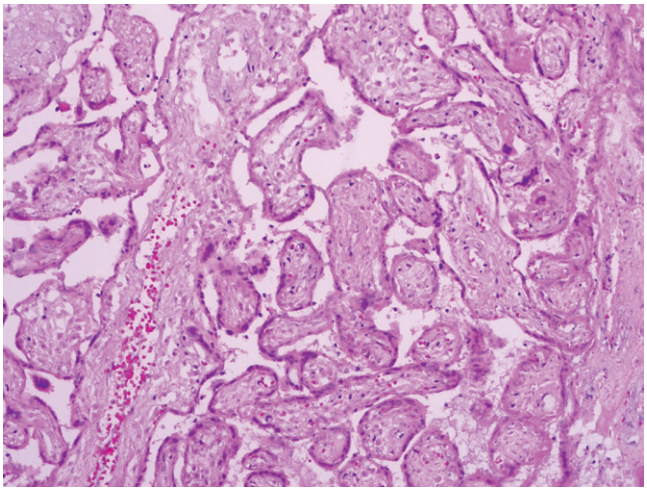

FIGURE 4

Placental infarction. This is a rather recent example, and note that the intervillous space is still preserved.

MECONIUM STAINING

Definition—Discoloration of the placenta and membranes due to staining with meconium.

Clinical Features

Epidemiology

- Meconium release is a relatively common event in term deliveries.
- Much debate exists about the pathologic nature of meconium and whether it represents a normal occurrence or is always pathologic.
- Meconium release is strongly associated with fetal stress near the time of delivery.

Presentation

- Meconium staining is obvious at birth as a green to brown discoloration of the placenta and fetal membranes.
- Severe or remote cases may result in discoloration of the umbilical cord.

Prognosis and Treatment

- Meconium passage has variable effects on the newborn ranging from none to severe meconium aspiration.
- The prognosis depends on the amount of meconium passage, length of time of exposure, and the predisposing stressor leading to meconium release.
- Supportive care in symptomatic cases is the only realistic treatment option.

Pathology

Histology

- Meconium staining is best appreciated within the membranes as a globular green to brown to orange pigment that is within macrophages.
- The amniotic surface often shows reactive changes of the amniocytes and occasionally shows necrosis.
- In severe or longstanding cases the pigment can even be identified within the umbilical cord, with associated inflammation, and rarely vascular necrosis.
- There may be a neutrophilic fetal inflammatory response that is out of proportion to the maternal inflammatory response.

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Hemosiderin.
- Deposition of another type of pigment.
- Inflammation due to infection.

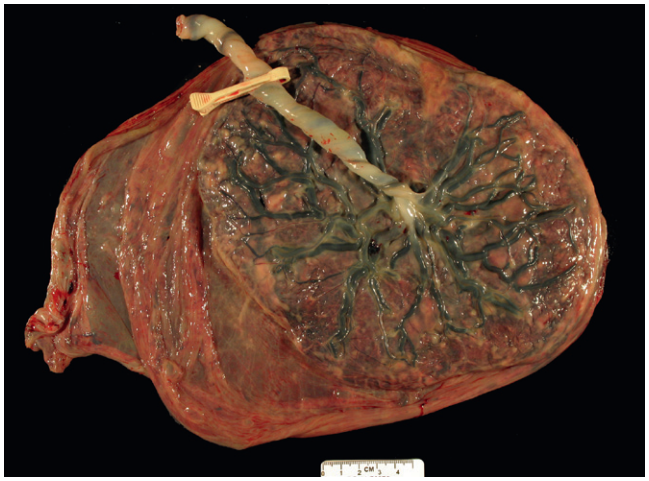

FIGURE 1

Meconium. Gross image of a meconium-stained placenta. There is greenish discoloration of the membranes and the fetal surface. The maternal surface *(not pictured)* will have normal coloration.

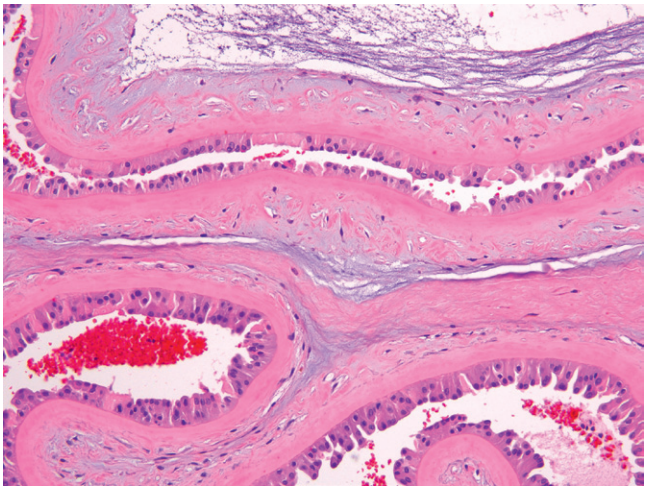

FIGURE 2

Meconium. At low power, meconium is not usually visible. Reactive amniocytes are identified by their prominence, with hobnailing and enlarged nuclei.

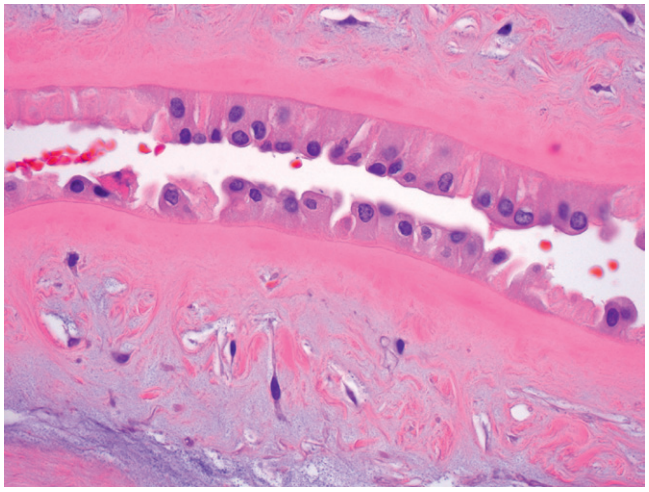

FIGURE 3

Meconium. At high power, greenish-brown pigment is seen engulfed by macrophages in the subchorionic tissue.

DISTAL VILLOUS PATHOLOGY

Definition—Abnormalities in distal villous maturation that occur late in pregnancy and are emblematic of underperfusion, including increased syncytial knots, distal villous hypoplasia (DVH), aggregated terminal villi, and chorangiosis.

Clinical Features

Epidemiology

- Seen as abnormal development of the distal villous tree as a consequence of multiple factors, including diabetes, smoking, anemia, pregnancy at high altitudes, and a number of genetic and epigenetic factors.
- Distal villous pathology (DVP) is associated with underperfusion and placental ischemia, specifically reversed end-diastolic flow.
- Linked to intrauterine growth restriction, intrauterine fetal death, and adverse neonatal neurological outcome.

Presentation

- Should be typically looked for in small-for-dates placentas or fetuses, intrauterine fetal death (IUFD), or retrospectively in the case of adverse neurologic outcome.
- In many instances these changes may be encountered in normal placentas.

Prognosis and Treatment

- Management is directed toward monitoring the neonate. In cases of IUFD these changes in a placenta may help determine cause of death.

Pathology

Histology

- DVH: The hallmark of DVH is small often widely spaced terminal villi with prominent syncytial knots.
- Terminal agglutination of villi.
- Increased syncytial knots.
- Chorangiosis: This has been associated with gestational diabetes, smoking, and pregnancy at high altitudes. It has been defined as at least 10 foci in the placenta containing at least 10 villi with 10 or more vessels seen at medium power (Altschuler criteria).

Immunopathology (Including Immunohistochemistry)

- Noncontributory.

Main Differential Diagnosis

- Normal villous maturation late in pregnancy will feature syncytial knots; however, the terminal villi are not small.

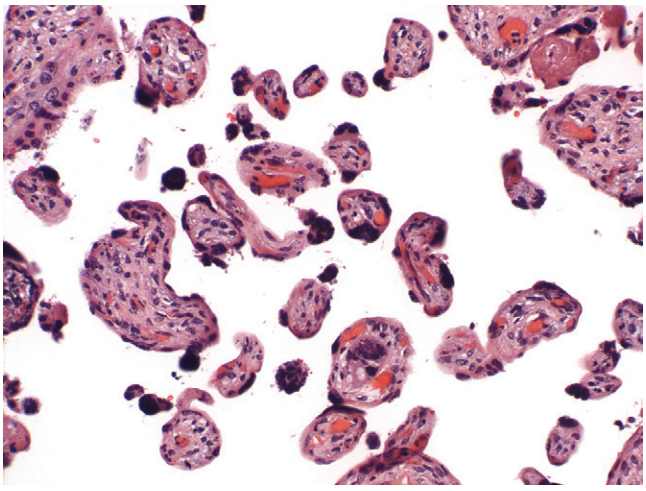

FIGURE 1

Increased syncytial knots. This is a generic correlate of placental ischemia that signifies "hypermaturity" and thus is evaluated in the context of the gestational age. It is characterized by groups of prominent syncytiotrophoblasts along stem and terminal villi.

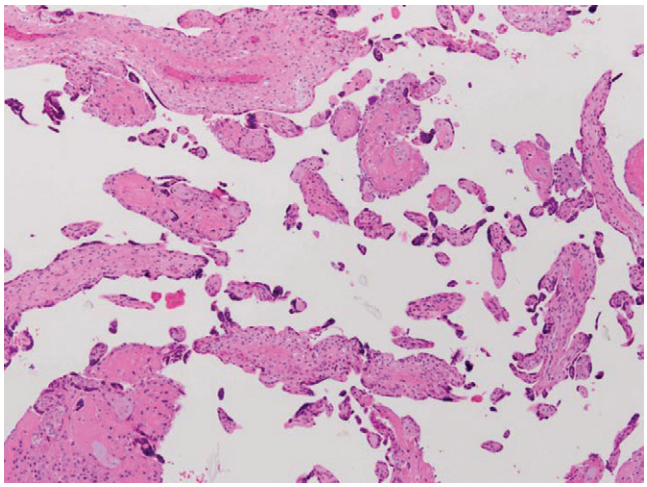

FIGURE 2

DVH. In this field there is a sudden transition from stem to small terminal villi, creating open space.

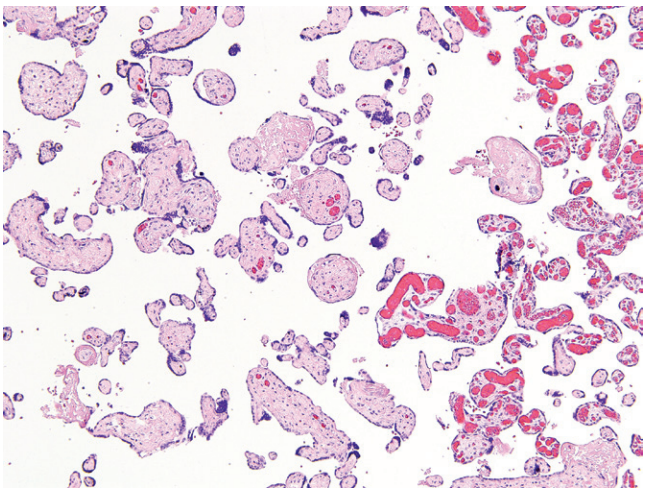

FIGURE 3

DVH at higher magnification showing the sharp contrast between very small terminal villi and stem villi.

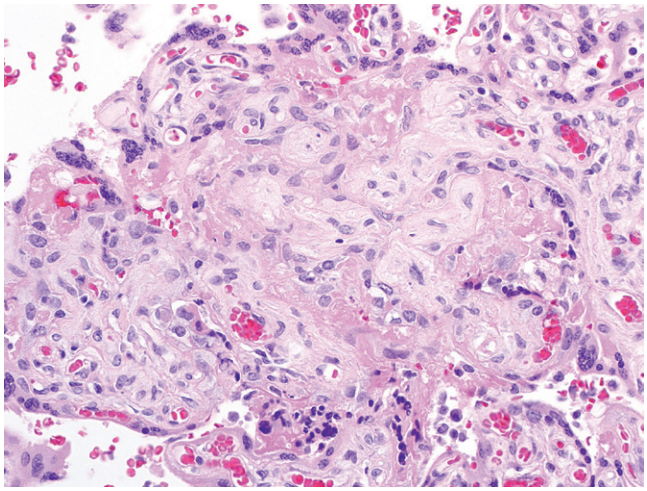

FIGURE 4

Aggregated terminal villi in which villi appear congealed in fibrin.

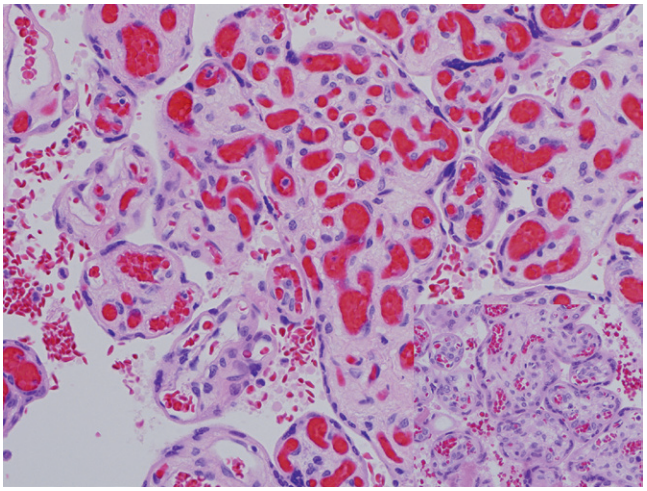

FIGURE 5

Chorangiosis. Here several villi contain at least 10 vessels each. Compare with normal villi *(inset, lower right).*

FETAL TO MATERNAL HEMORRHAGE

Definition—Bleeding under low pressure into the placental parenchyma of fetal origin.

Clinical Features

Epidemiology

- Cause is unknown.
- Rarely severe, with massive fetal to maternal hemorrhage.

Presentation

- Small fetal to maternal hemorrhages are found incidentally in the placenta as intervillous thrombi (IVTs).
- Massive hemorrhage may not be detected and may be appreciated only as a pale placenta due to exsanguination and dispersal of the fetal blood into the maternal circulation.

Prognosis and Treatment

- There is no treatment.

Pathology

Histology

- Grossly, small IVTs present as irregular laminated thrombi with minimal compression of the surrounding parenchyma.
- Focal adjacent infarcts or ischemic parenchymal changes might be appreciated.
- Massive fetal to maternal hemorrhage may be unappreciated with the exception of a pale placenta. In such cases a Kleihauer-Betke test for fetal erythrocytes in the maternal circulation will determine the extent of hemorrhage.

Immunopathology (Including Immunohistochemistry)

- Noncontributory normally, although fetal to maternal hemorrhage has been documented by appropriate immunohistochemistry.

Main Differential Diagnosis

- Intervillous fibrin: may be impossible to distinguish from an old IVT.
- Intraplacental choriocarcinoma: reason enough to *sample all suspected IVTs.*

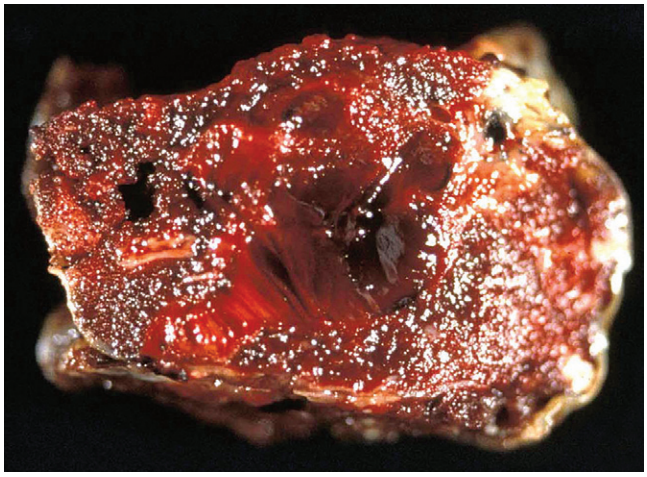

FIGURE 1

Cross section of placental disk with fresh IVT *(center)*.

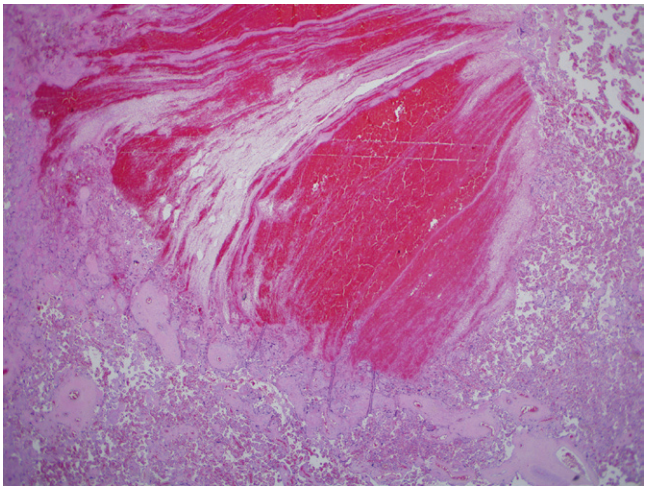

FIGURE 2

IVT. Note the layering of fibrin and blood characteristic of a thrombus. The interface of thrombus and parenchyma is not sharply circumscribed unlike a ball-in-socket infarct. However, the interface at the lower left displays some parenchymal changes in keeping with ischemia.

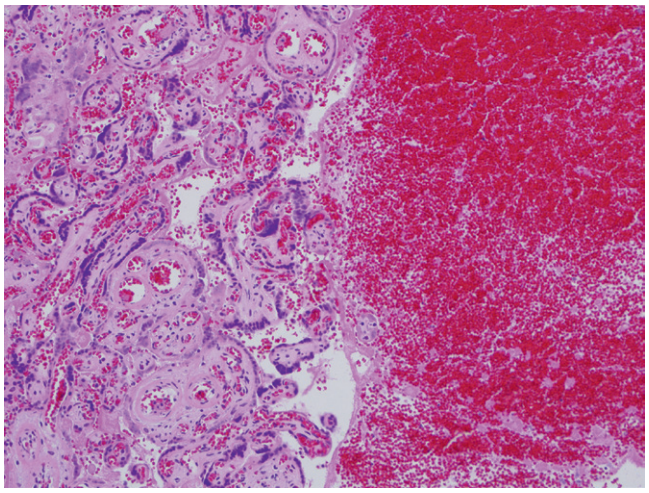

FIGURE 3

IVT. The interface with normal parenchyma displays a few ischemic villi with early trophoblastic degeneration.

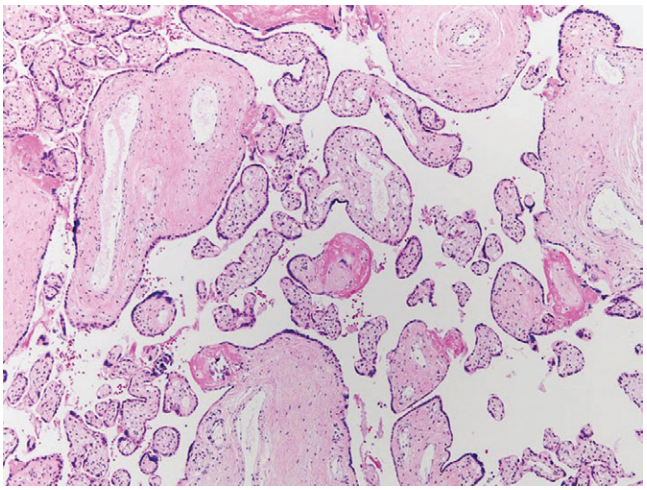

FIGURE 4

Markedly hypovolemic fetal vessels from a massive fetal to maternal hemorrhage, associated with a pale placenta. This underscores a specific cause of late intrauterine fetal death that will not provide evidence of intraplacental hemorrhage, yet like cord accident, must always be kept in the differential diagnosis until ruled out by appropriate tests.