Miscellaneous neoplasms, most of which are uncommon or rare, may be encountered in the ovary as unequivocal primary neoplasms or at least with ovarian manifestations accounting for the clinical presentation. Some, such as the small cell carcinoma of hypercalcemic type, are apparently specific to this site, but most are not, such as lymphomas and leukemias. These diverse lesions are considered in the first section of this chapter, followed by secondary tumors and then nonneoplastic lesions, with an emphasis on those that may be misinterpreted as neoplasms.

MISCELLANEOUS PRIMARY TUMORS

MESENCHYLMAL TUMORS

Benign

Fibromas, the most common mesenchymal tumors of the ovary, are discussed in Chapter 55 because they are in the sex cord-stromal family of ovarian neoplasia. Leiomyomas account for only 1% of benign ovarian neoplasms (1–3). They are usually small, with a mean size of 5.2 cm in one series (3). Their gross features are the same as their more common uterine counterparts. Microscopically, most have a routine appearance, but variants that are seen in the uterus may also occur in the ovary. Of these, cellular leiomyomas are most common, but mitotically active, epithelioid, those with bizarre nuclei, or those with myxoid change may be seen exceptionally (3). Immunostains aid in establishing the diagnosis of unusual variants and may be crucial in the distinction from metastatic gastrointestinal stromal tumor (see “Secondary Tumors” section). Most smooth muscle tumors of the ovary are either clearly benign or clearly malignant, but occasional examples present diagnostic difficulties with regard to the appropriate prognostic grouping. In one series, 4 of 54 smooth muscle tumors were considered of uncertain malignant potential (3). In that series, there was also one case in which an ovarian leiomyoma was associated with leiomyomatosis peritonealis disseminata and another case associated with intravenous leiomyomatosis.

Ovarian hemangiomas have been reported rarely (4–6). A few have been associated with isolated hemangiomas elsewhere or with generalized hemangiomatosis (4). These tumors are most often situated in the medulla and hilus, and they usually are of the cavernous type. They must be distinguished from the numerous vessels in the ovarian medulla of older women. Rare anastomosing hemangiomas composed of tightly packed, sinusoidal capillaries have been described both in the cortex and spanning the cortex and medulla (6). Some ovarian hemangiomas are associated with prominent stromal luteinization (5); in such cases, an ovarian steroid cell tumor with prominent pseudovascular degenerative change should be excluded. Uncommon vascular tumors reported in the ovary include lymphangiomata (7), infantile hemangioendothelioma (8), hemangioepithelioma (9), and glomus tumor (10). Many nonvascular tumors (fibromas, sclerosing stromal tumors, endometrial/endometrioid stromal sarcomas) contain conspicuous vessels and may enter the differential diagnosis of vascular tumors, but most have their own distinctive features.

Rare benign neural tumors, ganglioneuromas, lipomas, chondromas, and osteomas have also been found in the ovary. Ovarian epithelioid angiomylolipoma (11), myofibroblastic sarcoma (12), and fibromatosis of soft tissue type (13) have also been reported. The last should be distinguished from the more common, but still rare, fibromatosis of ovarian type (see “Fibromatosis”).

Ovarian myxomas are rare (14–17), occurring mostly in reproductive-age patients who present with asymptomatic unilateral adnexal masses; one arose in a premenarchal girl (17). The tumors have an average diameter of 11 cm, and they are soft, sometimes with areas of cystic degeneration. On microscopic inspection, the spindle-shaped and stellate cells are scattered in a myxoid background; a rich vascular network is often present, but lipoblasts are absent. Small islands within the tumor may resemble ovarian fibroma or leiomyoma. Occasionally, other tumors, such as sclerosing stromal tumor, may have prominent areas of secondary myxoid change (15,18); we would classify such tumors on the basis of the underlying parent neoplasm. One aneuploid tumor that exhibited mild nuclear atypia and slight mitotic activity recurred after many years, but it was positive for desmin, and it may have been a low-grade myxoid leiomyosarcoma (16). Sometimes, the common finding of edema in ovarian fibromas can be misconstrued as myxoid change; in doubtful cases, Alcian blue staining with and without hyaluronidase digestion aids in differential diagnosis.

Sarcomas

Fibrosarcoma is the most common ovarian sarcoma (19) and is discussed with fibromas and cellular fibromatous tumors in Chapter 55. All other sarcomas are rare, with leiomyosarcoma and endometrioid stromal sarcoma, in aggregate, accounting for the majority of the remainder. The endometrioid sarcomas are discussed along with other endometrioid neoplasms in Chapter 54. Almost every other form of soft tissue sarcoma has been reported in the ovary, and their morphologic features are the same as at other sites (20). The only ones that we will discuss briefly are leiomyosarcoma, because it is perhaps most common after fibrosarcoma, and rhabdomyosarcoma and angiosarcoma, due to some interesting issues in differential diagnosis.

In a series of 24 conventional leiomyosarcomas (3), the mean age of the patients was 58 years, the youngest being 25 years old. There is nothing specific about the presentation of these typically large tumors. On microscopic examination, the vast majority have a conventional morphology, but five examples of the myxoid variant have been reported (3,21). The microscopic diagnosis of leiomyosarcoma is usually straightforward.
LYMPHOMA AND LEUKEMIC INVOLVEMENT

The ovary contains tumor in approximately 25% of patients with non-Hodgkin lymphoma at autopsy and in up to 50% of those with leukemia. However, with the exception of Burkitt lymphoma, ovarian involvement as the initial manifestation of lymphoma or leukemia is rare (29–34). In approximately two-thirds of patients with ovarian lymphoma, extraovarian involvement is found at laparotomy. In exceptional cases, the ovary is the first site of relapse in children with acute lymphoblastic leukemia (35).

Gross Features

Lymphomas and leukemic tumors typically form intact smooth or nodular masses composed of homogeneous, usually fleshy but occasionally firm tissue that is gray, pink, white, yellow, or even green. In some cases of extramedullary myeloid tumor (granulocytic sarcoma, chloroma), a green color is a clue to the diagnosis (33). They are often more than 10 cm in diameter. Areas of hemorrhage, necrosis, and cystic degeneration may be present. Approximately half of the tumors are bilateral.

Microscopic Features

Both diffuse and follicular growth patterns are encountered, but sclerosis can distort these patterns and result in compartmentalization of the neoplastic cells as well as growth as nests and cords (Fig. 56.1). The tumor cells can infiltrate or surround ovarian follicles without destroying them, and follicle-like spaces are sometimes formed by the tumor cells themselves. In adults, a variety of histologic subtypes of non-Hodgkin lymphoma have been encountered. Most are diffuse large B-cell lymphomas, but some are follicular, and rarely, they are of T-cell lineage. In children, ovarian lymphomas are almost always diffuse, high-grade B-cell lymphomas that are often Burkitt lymphomas. Ovarian involvement has been described in Hodgkin disease (36) and plasmacytoma (37), but each...
of these is exceptionally rare. A primary ovarian diffuse large B-cell lymphoma arising in a mature cystic teratoma has also been reported (38).

**Differential Diagnosis**

Lymphoma in the ovary may be confused with several primary ovarian tumors. In such cases, it is helpful that diffuse infiltration of the adjacent fallopian tube and broad ligament is much more common in lymphomas than in most of the tumors in the differential diagnosis.

Lymphomas may be indistinguishable on gross examination from dysgerminomas. The former, however, are bilateral in 50% of cases in contrast to 10% of dysgerminomas. Although these tumors may resemble each other superficially on microscopic examination, their nuclei and immunohistochemical features are strikingly different. The single-file arrangement of lymphoma and leukemic cells may simulate metastatic carcinoma, particularly one of breast origin. Diffuse lymphoma can resemble undifferentiated carcinoma, granulosa cell tumor, or small cell carcinoma of the hypercalcemic type on low magnification. Numerous immunohistochemical markers are available to identify tumors as lymphomas. Extramedullary myeloid tumors (Fig. 56.2) can be distinguished with immunohistochemistry for myeloperoxidase (33) or chloracetate esterase staining.

The possibility of extramedullary myeloid tumor should be considered when one is entertaining a diagnosis of ovarian lymphoma because many cases of extramedullary myeloid tumor have been initially misinterpreted as such. However, extramedullary myeloid tumor on routine stains is often composed of cells with more finely dispersed nuclear chromatin and may have more abundant cytoplasm, which may be deep eosinophilic, compared to lymphoma cells with nuclei of the same size. Identification of eosinophilic myelocytes with confirmatory immunostaining may be crucial in making the diagnosis.

**SMALL CELL CARCINOMA, HYPERCALCEMIC TYPE**

This tumor (39) has occurred in females 7 months to 44 years of age, but the great majority occur between 15 and 30 years, with a peak in the early 20s, when it is the most common form of undifferentiated ovarian carcinoma. Approximately two-thirds of the tumors are associated with paraendocrine hypercalcemia, accounting for approximately 60% of all reported ovarian tumors associated with that disorder. Rare familial cases have been reported, including a remarkable occurrence in three sisters (39). Small cell carcinomas are almost always unilateral, although involvement of the opposite ovary may be seen as part of the abdominal spread encountered at laparotomy in approximately a third of the cases. Extraovarian primary examples of this neoplasm do not occur in our opinion. These are aggressive neoplasms with a poor prognosis, and the majority of patients die of their disease, usually within 2 years (39).

**Gross Features**

The tumors usually form large, predominantly solid, cream-colored gray masses, often with areas of softening, necrosis, and hemorrhage. Cystic degeneration may be seen but is only uncommonly conspicuous. They may closely resemble ovarian lymphomas and dysgerminomas when uniformly solid and cream-colored.

**Microscopic Features**

Diffuse sheets of small, closely packed, round to occasionally spindle-shaped cells with scanty cytoplasm and nuclei containing single nucleoli are typical. Mitotic figures are common. The tumor cells also often form small islands, cords (Fig. 56.3), and trabeculae. Follicle-like structures lined by tumor cells are present in 80% of cases (Fig. 56.4). These spaces typically contain eosinophilic, but occasionally basophilic, fluid. In 40% of tumors, a variable proportion of large cells is present. The large cells have
abundant eosinophilic cytoplasm, which may have a globular, hyaline quality (Fig. 56.5), and large nuclei with prominent nucleoli. Rarely, small foci of tumor cells may have clear cytoplasm.

Intracellular mucin is encountered in 10% of cases (Fig. 56.6), either focally within otherwise typical tumor cells, as groups of signet ring cells, or as columnar cells lining glands or cysts that are indistinguishable from those of mucinous cystadenomas. The stroma of the tumor is typically scanty and fibrous, but occasionally, it is edematous or even myxoid, particularly in regions where there is a conspicuous component of the larger cells. A scattering of chronic inflammatory cells may be seen in the stroma, but this is not a prominent feature. Vascular invasion is common.

The tumor cells are diffusely positive for Wilms tumor 1 with antibodies directed against the N-terminus, and most are immunoreactive for cytokeratin, epithelial membrane antigen, vimentin, calretinin, CD10, and p53 (40,41). In most cases, electron microscopy shows nonspecific epithelial features. Abundant rough endoplasmic reticulum is the most characteristic finding (42); large cells may contain whorls of microfilaments. Convincing dense-core granules have not been seen. Flow cytometry on paraffin-embedded material has shown a diploid pattern of DNA (43). A low frequency of chromosomal abnormalities has been observed in the small number of tumors that have been genotyped (44). Frequent inactivating mutations of the SWI/SNF chromatin-remodeling gene SMARCA4 have recently been identified in small cell carcinomas of hypercalcemic type, and 80% of these tumors show loss of SMARCA4 protein expression by immunohistochemistry (45,45a). In contrast, only 0.4% of other primary ovarian tumors show loss of SMARCA4 protein expression (45a).

**Differential Diagnosis**

Small cell carcinomas may be misinterpreted as many neoplasms, with the presence of follicles making adult or juvenile granulosa cell tumors the most common misinterpretations.

From a clinical viewpoint, hypercalcemia strongly favors a diagnosis of small cell carcinoma, and evidence of estrogen excess strongly favors a diagnosis of granulosa cell tumor. Extravascular spread is much more common for small cell carcinomas than juvenile granulosa cell tumors. The nuclei of small cell carcinomas, compared with those of adult granulosa cell tumors, are more hyperchromatic and mitotically active, and they lack grooves. The occasional predominance of large cells with abundant cytoplasm in small cell carcinoma, particularly if interrupted by follicles, and the young age at which it occurs may suggest the possibility of juvenile granulosa cell tumor, but the differing clinical features and the characteristic microscopic patterns of the two tumors are diagnostically helpful. The follicles of juvenile granulosa cell tumors usually contain mucicarmineophilic fluid, in contrast to the follicle-like spaces of small cell carcinomas. The occasional presence of mucinous
epithelium is more typical of small cell carcinoma than granulosa cell tumor. Immunohistochemical staining for inhibin supports a diagnosis of granulosa cell tumor.

The dysgerminoma, which occurs in an age group similar to that of the hypercalcemic small cell carcinoma and may be grossly identical to it, is also, treacherously, sometimes associated with hypercalcemia. Rare small cell carcinomas have cells with clear cytoplasm and fibrous stroma that may impart a superficial resemblance to a dysgerminoma on low-power examination. Despite these overlapping features, there are many morphologic differences, and if needed, immunohistochemistry will aid. This potential pitfall should be remembered because of the markedly differing prognosis and treatment of the two neoplasms.

Small cell carcinomas can also be confused with lymphomas and the pulmonary form of small cell carcinoma. A variety of features of these three neoplasms, particularly their cytologic features, should distinguish them, and if necessary, immunohistochemical stains facilitate their distinction. The small cell carcinoma may be considered undifferentiated carcinoma, not otherwise specified, and indeed, regions may have an appearance consistent with that diagnosis. However, in the right age group, search for features indicative of the more specific diagnosis of the small cell carcinoma of hypercalcemic type should be assiduously performed, albeit this is largely an academic distinction at this time. Metastatic tumors such as malignant melanoma and alveolar rhabdomyosarcoma can be problematic because they may have a small cell phenotype, and the follicle-like spaces of some metastatic tumors may enhance their resemblance to small cell carcinoma. Clinical features and immunohistochemical staining, if necessary, will clarify these issues.

**TUMOR OF PROBABLE WOLFFIAN ORIGIN**

Rare ovarian tumors (46,47) are microscopically identical to their more common counterparts originating within the broad ligament that have been designated female adnexal tumors of probable Wolffian origin. The ovarian tumors have no unique clinical features.

**Gross Features**

The tumors average 12 cm in diameter, are solid or focally cystic, and are almost always stage Ia. The solid tissue varies from gray-white to tan or yellow, and it may be rubbery or firm.

**Microscopic Features**

Microscopic examination reveals a cellular neoplasm with tumor cells that grow diffusely or form closely packed solid or hollow tubules. In apparently diffuse areas, a tubular pattern may be unmasked by periodic acid-Schiff (PAS) or reticulin staining. Varying amounts of fibrous stroma may result in a lobulated appearance. Cysts, which can be numerous, often punctuate these background patterns or may represent the dominant pattern and impart a characteristic sievelike appearance (Fig. 56.7). The cysts contain eosinophilic luminal secretions. The tumor cells are oval or spindle shaped, and they have scanty eosinophilic cytoplasm or pale cytoplasm in solid tubular areas. Rarely, a spindle cell pattern dominates (48). Rare tumors contain areas with poorly differentiated cells; such tumors may have malignant behavior. Areas of typical morphology should ideally be present to diagnose a malignant example.

**Differential Diagnosis**

These tumors are often misinterpreted as sex cord–stromal tumors, particularly Sertoli cell tumors, because the tubules of the two tumors may be indistinguishable. However, the other patterns of the wolffian-type tumor, which are almost always present as well, are incompatible with Sertoli cell tumor. In isolated cases, large hollow tubules resemble the glands of endometrioid adenocarcinoma, but other patterns of the neoplasm and the absence or paucity of luminal mucin help rule out this diagnosis. Wolffian tumors with a diffuse pattern can be misinterpreted as undifferentiated carcinomas on low power, but high-power evaluation generally shows cells with bland cytologic features and few mitotic figures. Rare tumors with a prominent spindle cell component may be difficult to distinguish from a cellular fibromatous tumor if not adequately sampled (48). Wolffian tumors are among the few ovarian tumors not of sex cord–stromal origin that can stain for inhibin (49); they can also show reactivity for calretinin and FOXL-2 (50–52). Accordingly, immunohistochemistry is not always definitive in differentiating wolffian tumors from sex cord tumors.

**TUMORS OF THE RETE OVARI**

These lesions are uncommon; most are cystadenomas (53), but some are adenomas (54), and rare carcinomas are of rete derivation (53). Rete cystadenomas may be functioning as a result of the presence of steroid cells at their periphery (55).
Gross Features
The cystic tumors range up to 24 cm (average, 8.7 cm) in diameter and have a hilar location; they are either unilocular or multilocular. They typically contain clear or yellow fluid and have thin walls with smooth linings. Adenomas have usually been incidental microscopic findings, and the only rete carcinoma reported had nonspecific gross features.

Microscopic Features
The walls of rete cystadenomas are composed of fibrovascular tissue that frequently contains fascicles of smooth muscle. The luminal surfaces characteristically have an undulating contour with shallow crevices lined by columnar, cuboidal, or flat cells that are only rarely ciliated (Fig. 56.8). Hyperplasia of hilus cells, which is frequently seen in the cyst wall, accounts for the virilization that is occasionally associated with these lesions (55). Intracystic papillae may be prominent. Adenomas are composed of closely packed small tubules within the ovarian hilus, some of which may be dilated and contain simple papillae. A single rete adenocarcinoma was characterized by an irregular network of branching tubules and cysts that contained papillae with fibrovascular or hyalinized cores (53). The tubules, cysts, and papillae were lined by obviously malignant, nonciliated cuboidal cells. Areas of solid growth and extensive transitional cell metaplasia were also observed.

Differential Diagnosis
Rete cystadenomas are often misdiagnosed as serous cystadenomas; this differential diagnosis has been discussed in Chapter 54. Rete adenomas may be confused with female adnexal tumors of probable wolffian origin, but the latter tumors typically have patterns other than tubular or papillary that are incompatible with the diagnosis of rete tumor. The one reported case of adenomatous hyperplasia of the rete differed from rete adenoma by the presence of a poorly defined margin that blended with the adjacent normal rete, a fibromuscular stroma, and tubules that varied in appearance (56). The rete carcinoma is distinguished from pure retiform Sertoli-Leydig cell tumor primarily by its focal solid pattern and transitional cell metaplasia. This unique tumor also occurred in an elderly woman, unlike most of the retiform tumors.

PARAGANGLIOMA
Only five examples of this neoplasm occurring in the ovary have been reported (57). The tumors have occurred in patients 15 to 68 years of age; three patients had a history of hypertension. The lesions have nonspecific gross features and have ranged in size up to 22 cm. Three have been confined to the ovary, but in one case, there were deposits on the opposite ovary and uterus, and in another, para-aortic lymph node involvement and peritoneal nodules were present. Microscopic examination showed that four cases were typical parangangliomas, but one was the gangliocytic variant. For the most part, the tumors are characterized by the typical nested pattern, but a more diffuse growth can occasionally be encountered. That feature and the occasionally moderately conspicuous amount of cosinophilic cytoplasm may bring a steroid cell tumor into the differential diagnosis, and other entities, such as granulosa cell tumor, may not be unreasonable considerations. When paranganglioma is a diagnostic consideration, immunohistochemistry can be used to confirm the diagnosis (58), but it should be noted that two ovarian parangangliomas have been positive for inhibin (57).

WILMS TUMOR
Four examples of primary ovarian Wilms tumor have been reported (59–61); the patient age range was 3.5 to 56 years. One tumor formed a multilocular cystic tumor and contained areas that resembled a metanephric adenoma. None of the tumors was clinically malignant, although follow-up of significant duration was available in only two of the cases. The tumors must be distinguished from the retiform Sertoli-Leydig cell tumor, which can form glomeruloid structures but which almost always contains other patterns of that neoplasm.

SOLID PSEUDOPAPILLARY NEOPLASM OF PANCREATIC TYPE
This recently described primary ovarian tumor is morphologically and immunophenotypically identical to its pancreatic counterpart. Only six examples have been reported (62–65). Patients ranged in age from 17 to 57 years and presented with nonspecific symptoms of an abdominal mass. The tumors, which have ranged in size from 3 to 25 cm, are solid and cystic with white-tan to red, friable cut surfaces. Hemorrhage is often present, and necrosis has been described in one malignant example. All but one of the reported tumors was confined to the ovary; the sixth was associated with widespread intra-abdominal metastases. Histologically, diffuse and pseudopapillary growth patterns predominate, with occasional nests and small cysts filled with colloid-like material. The tumor cells are cytologically bland with eosinophilic cytoplasm. Mitotic activity is absent to minimal, except in the one reported malignant example that had 62 mitotic figures per 50 hpf as well as mild cytologic atypia, extensive necrosis, and lymphovascular invasion (65). Immunohistochemical studies show nuclear positivity for β-catenin and lack of membranous E-cadherin staining. The differential diagnosis includes sex cord–stromal tumors, steroid cell tumors, and struma ovarii. Awareness of this tumor’s occurrence in the ovary, as well as
ancillary immunohistochemical studies, will aid in its recognition. It must also be distinguished from an ovarian metastasis of solid pseudopapillary neoplasm of pancreatic origin (66).

**MELANOTIC XPII TUMOR OF RENAL TYPE**
A single nonrenal case of this tumor has been described, occurring in the ovary of a 15-year-old female (67). The morphologic, immunohistochemical, and molecular features of the tumor were identical to those of the rare melanotic Xpii translocation renal cancer.

**ADENOMATOID TUMOR**
Rarely, this benign tumor of mesothelial origin is located in or immediately adjacent to the ovary. In one series of six cases, the patients ranged from 23 to 70 years of age (68). Four tumors were less than 1 cm, and one was 5 cm in diameter. Five tumors were predominantly hilar, with focal medullary extension. The tumors are identical at the microscopic level to their counterparts in the fallopian tube and uterus. Because of their rarity in the ovary, diagnostic errors are sometimes made. One example was initially considered a yolk sac tumor because it had a focal reticular pattern and contained hyaline bodies; a lack of significant nuclear atypia and a negative result with α-fetoprotein immunostaining excluded this diagnosis. One strikingly oxyphilic example that required consideration of other oxyphilic ovarian tumors has been reported (69).

**MALIGNANT MESOTHELIOMA**
Peritoneal mesotheliomas are discussed in more detail in Chapter 58. Ovarian involvement by these tumors is usually limited to the ovarian surface and occasionally the superficial cortex, but rarely, the ovary is extensively involved, with a clinical picture similar to that of ovarian cancer. In one study, ovarian involvement was present in 10 of 13 patients with peritoneal mesothelioma (70), and in another series, all nine tumors presented as ovarian masses (71); two were considered primary ovarian tumors because of confinement to the ovary. Malignant mesotheliomas, whether primary or secondary, are characterized on microscopic examination by tubular, papillary, and solid patterns and relatively uniform cells with eosinophilic cytoplasm. In routinely stained sections, these tumors are usually readily distinguishable from serous carcinoma by their pattern of growth and typically bland cytologic features as discussed in detail by Baker et al. (72). Histochemical or immunohistochemical stains are rarely necessary to confirm the diagnosis but will often aid should they be deemed necessary.

**INTRA-ABDOMINAL DESMOPLASTIC SMALL ROUND CELL TUMOR**
This tumor is discussed in detail in Chapter 58. Patients with this neoplasm may have prominent ovarian involvement, leading to confusion with primary ovarian neoplasms. The patients are typically teenagers or young adults (73); ovarian involvement is often bilateral. Laparotomy typically reveals extensive extratubal disease. Because many ovarian tumors are characterized by small cells, the differential diagnosis is wide. A prominent nesting pattern of small cells in a desmoplastic stroma, as well as the young age of the patient, should lead to consideration of this tumor. Immunohistochemical positivity for both cytokeratin and desmin almost always establishes the diagnosis.

**SECONDARY TUMORS**
This is an important area of ovarian tumor interpretation with much new information in the past two decades. For more detailed coverage than space constraints allow here, historical perspective, and more complete referencing, the reader is referred to two reviews by one of us (74,75).

Certain clinical and operative findings should alert the pathologist to the possibility of metastatic involvement of the ovary. These features include the previous or concurrent existence of a primary tumor elsewhere and a pattern of extra-ovarian spread that is atypical for ovarian cancer. For example, hepatic or pulmonary metastases at the time of presentation, especially in the absence of extensive peritoneal spread, would be unusual for ovarian cancer. Because metastases to the ovary are bilateral in two-thirds to three-fourths of the cases, metastasis should be considered in the evaluation of bilateral disease, especially if the tumor is not undifferentiated or of serous type. Approximately 10% to 20% of surgically encountered bilateral ovarian cancers are metastatic. Two other gross findings suggestive of metastasis are the presence of several nodules and the involvement of the ovarian surface without generalized peritoneal spread. Single or multiple cysts, even when they are thin-walled, do not exclude metastasis. Prominent vascular space invasion is more typical of metastasis.

A study (76) comparing primary and metastatic mucinous carcinomas in the ovary found that the following features strongly favored metastasis: nodular invasive pattern, ovarian hilar involvement, single-cell invasion, signet ring cells, vascular invasion, and microscopic surface mucin. Features strongly favoring a primary ovarian mucinous carcinoma were an expansive pattern of invasion and a complex papillary pattern. Findings that were less frequent but that also favored a primary tumor were as follows: a size greater than 10 cm, a smooth external surface, benign-appearing and borderline-appearing areas, microscopic cystic glands, and necrotic luminal debris. In a subsequent study looking at the aid provided by simple parameters such as size and laterality, particularly in the frozen section setting, it was found that 90% of neoplasms would be correctly classified regarding their primary or metastatic nature by simply following the rule that bilateral tumors less than 10 cm are metastatic and unilateral tumors greater than 10 cm are primary (77). This certainly can be helpful as a guide, but unfortunately, there are sufficient exceptions to make this of limited applicability, as has been pointed out in several subsequent publications (78–80). As an example, in one of these studies (78), it was found that 60% of metastatic mucin-producing adenocarcinomas were 10 cm or greater.

In the following sections, metastatic tumors are largely discussed according to their source, but some, such as the Krukenberg tumor, may have several origins.

**KRU肯BERG TUMOR**
Krukenberg tumors are metastatic carcinomas with a component of signet ring cells comprising at least 10% of the tumor (81–83). They usually originate in the stomach. The primary
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tumor may be very small, escaping detection at operation or even for 5 or more years after surgery. Occasional tumors originate in other portions of the gastrointestinal tract (particularly the appendix and large bowel) or its associated structures, gallbladder and pancreas. Breast, uterine cervix, urinary bladder, and renal pelvis are other rare possibilities. Women with Krukenberg tumors tend to be unusually young for patients with metastatic carcinoma. Many are between 40 and 50 years of age, and a sizable number are in their 20s, and some are even teenagers. The symptoms are usually nonspecific, but endocrine manifestations, particularly virilization during pregnancy, may be seen due to stromal luteinization.

Gross Features

Krukenberg tumors are bilateral in approximately 90% of cases. They are almost always solid with a smooth or bosselated contour (Fig. 56.9); they rarely contain thin-walled cysts. The cut surfaces vary from firm to soft and white to tan and may resemble a typical or edematous fibroma. Red, fleshy, and gelatinous appearances are quite common. Sometimes, the central region is softer and of different color from the peripheral component, leading one writer, aptly, to liken the appearance to that of a shell in some cases (84). Necrosis and hemorrhage are common.

Microscopic Features

The low-power appearance is variable but often at least somewhat nodular, like many metastatic tumors. The nodules may be confluent or separated by stroma that may be strikingly edematous. Rounded malignant epithelial cells, many of which have a signet ring cell appearance, are embedded as small nests, cords, tiny glands or cysts, or single cells in a typically spindle cell stroma (Fig. 56.10). The relative amounts of tumor and stroma vary considerably; the latter varies from very cellular to markedly edematous and hypocellular, and it may be luteinized, hyalinized, or desmoplastic (83). The stroma at the periphery may differ in appearance from that seen more centrally (Fig. 56.11). In some cases, large rounded islands of signet ring cells are suspended in pools of mucin, or they grow in pseudotubular arrangements. Occasionally, the predominant architecture is characterized by hollow or solid tubular glands that may be Sertoli-like apart from the focal component of signet ring cells lining them (tubular Krukenberg tumor) (Fig. 56.12) (85). Large intestinal-type glands may be seen, as may tiny glands (Fig. 56.13) that may have flattened lining cells. Benign to atypical to frankly malignant columnar mucinous cells may be present, as may foci that resemble mucinous carcinoid; the latter suggest a possible origin of the tumor from the appendix (86), where it may be occult at operation or even on gross examination. Vascular involvement is often conspicuous, particularly at the periphery of the neoplasm.
Examination of non–signet ring cell areas in the tumor can provide clues as to the primary site. For example, the presence of intestinal-type glands suggests a gastrointestinal or biliary origin, whereas prominent tumor cell cording suggests a mammary origin.

**Differential Diagnosis**

Numerous tumors can be misdiagnosed in cases that ultimately are shown to be Krukenberg tumor. Only the most common, or treacherous, are noted here; more detailed discussions are available elsewhere (74,83). The focal dearth of signet ring cells in some cases may make fibroma a reasonable consideration, particularly at the time of frozen section, as emphasized by Holtz and Hart (81). Other stromal neoplasms such as the sclerosing stromal tumor and signet ring stromal tumor may enter the differential, but signet ring–like cells in the former contain fat, not mucin, and, in the latter, are negative for mucin. Like the Sertoli-Leydig cell tumor, some Krukenberg tumors are virilizing, and on microscopic examination, both may be composed of densely cellular lobules. Care must be taken not to confuse luteinized stromal cells of a Krukenberg tumor, particularly one with endocrine manifestations, for the Leydig cells of a Sertoli-Leydig cell tumor. Careful evaluation of the cellular areas should disclose signet ring cells in the case of a Krukenberg tumor; these cells are only present in the rare foci of mucinous carcinoid seen in some cases of Sertoli-Leydig cell tumor with heterologous elements. Signet ring cells, or at least tiny glands that can simulate signet ring cells, can be seen in occasional surface epithelial carcinomas (87). However, well-sampled tumors will usually disclose themselves as being of primary or Krukenberg character, as the case may be. In the differential diagnosis of Krukenberg tumor, the importance of being aware of the spectrum of morphology of various ovarian tumors with somewhat overlapping features cannot be overemphasized nor can the crucial importance of fundamental aspects of ovarian tumor evaluation such as the clinical history, bilaterality, surface involvement, and miscellaneous features already noted.

**GASTRIC CARCINOMA, INTESTINAL TYPE**

Only a small number of cases of this type have been reported (88). The patients have been in a somewhat older age group than patients with Krukenberg tumors of gastric origin.

**Gross Features**

The tumors are typically large and solid and cystic. The cysts contain mucinous secretions or hemorrhagic fluid. Necrosis is often seen.

**Microscopic Features**

On microscopic examination, there is characteristically an appearance of variably sized tubular glands (Fig. 56.14), imparting a pseudoendometrioid appearance that is more commonly associated with metastatic intestinal adenocarcinoma. Dirty necrosis is common, and the epithelium lining the glands is often high grade. Less commonly, the tumors have a mucinous phenotype and may have deceptively benign foci, as is the case with other metastatic mucinous carcinomas. Unusual patterns include papillary, trabecular, and nested.
Microscopic Features

The metastases resemble, to varying degrees, primary intestinal carcinomas, typically forming glands lined by poorly differentiated stratified epithelial cells lacking mucin and containing numerous mitotic figures. A cribriform pattern of small- to medium-sized glands is common, and large cystically dilated glands are occasionally conspicuous. Necrosis is often present and can be extensive. It is often of the “dirty necrosis” type (Fig. 56.16), with central large, round aggregates composed of eosinophilic material containing abundant nuclear debris and viable glands that surround the necrotic material in a garland arrangement (90). Occasionally, cystic glands lined by well-differentiated mucin-rich cells are prominent. Rare tumors are colloid carcinomas. Occasional tumors have a prominent micropapillary pattern. The stroma varies from negligible to abundant. It may be desmoplastic, edematous, or myxoid, but it often resembles ovarian stroma. Luteinized stromal cells are present in approximately a third of cases. Indeed, metastatic bowel cancers are among those most frequently associated with stromal luteinization and endocrine manifestations (96). The rare clear cell adenocarcinoma of the intestine may also spread...
to the ovary and simulate secretory endometrioid carcinoma or clear cell adenocarcinoma (95); although the numbers are small, a disproportionate number of these cases are from the small bowel compared to metastatic intestinal cancer overall.

**Differential Diagnosis**

The most difficult tumors to exclude on microscopic evaluation are primary endometrioid and mucinous carcinomas, the differential diagnoses of which have been discussed under those headings (Chapter 54), as has the distinction of metastatic intestinal clear cell adenocarcinoma from primary clear cell adenocarcinoma.

**CARCINOID TUMORS**

Carcinoid tumors account for approximately 2% of ovarian metastases. Almost all patients are older than 40 years of age; approximately half have been reported to have the carcinoid syndrome. The ileum is usually the primary site, but the cecum, jejunum, appendix, colon, stomach, pancreas, and bronchus are rare sources (97–99).

**Gross Features**

Metastatic carcinoids are usually bilateral. They vary in size, and they are usually solid, with smooth or bosselated serosal surfaces. Sectioning demonstrates single or confluent, firm, white or yellow nodules that may resemble fibromas, thecomas, or Brenner tumors. In some cases, the presence of numerous cysts filled with watery fluid causes the tumor to resemble a cystadenofibroma. Rare tumors are predominantly cystic (Fig. 56.17). Necrosis and hemorrhage may develop in solid tumors, and some of the cysts may contain blood.

**Microscopic Features**

An insular pattern is most common (Fig. 56.18), but trabecular and sometimes solid tubular patterns are also encountered. The nests are usually uniformly solid, but occasionally, small acini punctuate them or are more typically arranged at their periphery. The acini often contain a homogeneous, eosinophilic secretion, which may calcify, sometimes forming psammoma bodies. Larger glands and cysts lined by one or a few layers of neoplastic cells are sometimes seen. The latter, when striking, may produce a follicle-like pattern. Carcinoid is the ovarian metastatic tumor that most typically elicits a fibroma-like stromal proliferation that may become extensively hyalinized. Metastatic “goblet cell carcinoids” to the ovary are reported, but classification of the primary tumors in these cases as carcinomas with neuroendocrine differentiation is probably most appropriate (86).

**Differential Diagnosis**

Metastatic carcinoids may be confused with primary carcinoid tumors (see “Carcinoids” in Chapter 55), granulosa cell tumors, Sertoli tumors or Sertoli-Leydig cell tumors, Brenner tumors, adenofibromas, cystadenofibromas (benign, borderline, and malignant), and adenocarcinomas of various types. These differential diagnoses have been discussed under the relevant headings.

**BREAST CARCINOMA**

Approximately one-third of patients with breast cancer have ovarian metastases during the course of their disease (100–103). The involvement is bilateral in approximately two-thirds of the cases, and a similar number of affected ovaries appear normal grossly (103). Rarely, metastatic breast carcinoma initially appears with signs or symptoms of an ovarian tumor (104). Only a small minority of prophylactic oophorectomy specimens from patients with breast cancer contain metastases, and particularly in the setting of patients with *BRCA* mutations, when neoplasia is seen in such specimens, it is statistically more likely to be an independent primary serous or undifferentiated carcinoma of the ovary rather than metastatic breast cancer (105).
**Gross Features**

The ovaries often have irregular, nodular surfaces and typically contain firm or gritty white nodules of various sizes; cysts may be present, but only rare specimens are entirely cystic. Nonspecific appearances consistent with the appearance of many other ovarian tumors may be seen.

**Microscopic Features**

Lobular carcinomas spread to the ovary much more frequently than ductal carcinomas (106) (Fig. 56.19). In many cases of lobular carcinoma, a diffuse pattern is conspicuous at low magnification, but small clusters, cords, or ribbons of cells are usually apparent on high-power examination. Acini, larger glands with a cribriform pattern, and rarely papillae may be conspicuous in cases of ductal carcinoma. Rare neoplasms have a prominent component of large cells with abundant eosinophilic cytoplasm. The stroma varies from sparse to abundant; stromal luteinization is uncommon in contrast to its frequency in metastatic intestinal carcinomas. Rarely, the features are those of a Krukenberg tumor in that signet ring cells are present, but these tumors generally look different from Krukenberg tumors of gastrointestinal origin due to the presence of admixed histologic patterns more typical of breast carcinoma (Fig. 56.20).

**Differential Diagnosis**

Predominantly glandular, papillary, or poorly differentiated metastases may resemble primary epithelial carcinomas, particularly serous or endometrioid carcinomas; an insular pattern may mimic that of a carcinoid tumor; and a diffuse pattern may suggest a lymphoma. The presence of background endometriosis or an underlying adenofibroma can help support a diagnosis of a primary epithelial carcinoma, whereas bilaterality, surface involvement, multinodular growth, and prominent lymphatic invasion are features more common to tumors metastatic to the ovary. Metastatic breast carcinomas have also been misinterpreted as granulosa cell tumors, but the contrasting features of the neoplastic cells, especially their nuclei; the differing patterns of growth; and the clinical findings facilitate this distinction in almost all cases.

A panel of immunohistochemical stains can aid in differentiating metastatic breast carcinoma from primary ovarian carcinoma (107,108). Immunoreactivity for gross cystic disease fluid protein-15 (GCDFP-15) strongly suggests metastatic breast carcinoma; however, rare ovarian carcinomas (<5%) may show GCDFP-15 positivity, and in one study (109), only 43% of breast cancer metastases to the ovary were positive. Recent data suggest that GATA3, which is expressed in most breast carcinomas, may be another helpful marker in this differential diagnosis because ovarian carcinomas in general are only rarely positive (110–112). Reactivity does vary by subtype of ovarian epithelial tumor, however; GATA3 positivity can also be seen in germ cell tumors (112). Although mammaglobin is considered a marker of breast origin, focal or patchy expression is frequently seen in ovarian carcinomas, and therefore, it is of limited use in this differential diagnosis. Reactivity for breast cancer–associated markers and lack of expression of other markers common in ovarian neoplasia, such as WT1 and PAX8, can help to establish a diagnosis of metastatic breast cancer. The utility of these different immunostains, however, depends on the particular subtypes of carcinoma being considered (108).

**TUMORS OF THE APPENDIX**

Metastatic appendiceal tumors (other than carcinoids—see previous section) can be considered in three groups: those that result from spread of low-grade appendiceal mucinous neoplasms, including mucinous carcinomas (115); those that fall in the Krukenberg tumor family because of an appreciable content of signet ring cells (83,86); and those of intestinal type, either in pure form or sometimes associated with another component.
(116). Appendiceal primary tumors are often overlooked at operation because the ovarian tumors are typically much larger (117).

The association between low-grade mucinous cystic tumors of the appendix and coexisting, microscopically similar tumors of the ovary in cases of pseudomyxoma peritonei (118) has been acknowledged for many years and has been controversial (115,119–121), but most investigators now believe that the appendiceal tumor is primary and the ovarian tumor is secondarily involved in most cases. The appendiceal lesion has been variously designated over the years, but we and many others use the classification of Misraji et al. (122), in which “low-grade appendiceal mucinous neoplasm” is used for the most common primary appendiceal morphologic change in this situation.

**Gross Features**

The ovarian metastases of appendiceal low-grade mucinous tumors are often bilateral, large, and multilocular, and they typically contain abundant thick, jelly-like mucin. Surface involvement is common. Those of Krukenberg type and intestinal type have gross features similar to those already described for those categories of neoplasms.

**Microscopic Features**

Ovarian involvement by low-grade mucinous tumors often exhibits prominent mucinous cystadenoma-like areas, but when these tumors are thoroughly sampled, they are usually found to contain foci of stratified epithelium. The neoplastic cells are tall columnar and engorged with mucin, the latter often seeming to exude out of the apices of the cells. The glandular structures have scalloped contours and show a distinctive pattern of subepithelial clefting, wherein the base of the epithelium is “lifted off” the underlying stroma (Fig. 56.21) (123). Mucin commonly dissected into the ovarian stroma (pseudomyxoma ovarii). In some cases, all residual ovarian stroma is obliterated by abutting multilocular cysts. In other cases, residual stroma is evident, and the mucinous cysts irregularly infiltrate through it. There is usually surface ovarian involvement. This may be in the form of mucin apparently simply “sitting” on the ovarian surface, or there may be an associated hyaline stromal reaction. The mushroomlike projections with prominent desmoplastic stroma that typify implants in many cases of metastatic mucinous carcinoma are rare.

Metastatic appendiceal tumors of Krukenberg type have the microscopic features of that category of neoplasm, the only comment of note being that those of appendiceal origin tend more often than those primary at other sites to have foci that resemble mucinous (goblet cell) carcinoma (86). The third category of metastatic appendiceal neoplasia is the group that has an intestinal-like morphology (116) and results in a differential diagnosis similar to that of metastatic intestinal adenocarcinoma itself.

**Differential Diagnosis**

Although distinguishing secondary involvement by low-grade appendiceal mucinous neoplasms from primary ovarian mucinous cystadenomas and cystadenomas of borderline malignancy may be difficult, the former tumors are bilateral much more often, and they usually have a jellylike consistency on gross examination. In addition, their mucinous lining cells are unusually tall and hypermucinous, and these cytologic features in combination with the characteristic glandular scalloping and subepithelial clefting impart a distinctive picture to metastatic low-grade appendiceal mucinous neoplasms. Pseudomyxoma ovarii is frequently present, a finding that is much less common in primary ovarian mucinous tumors. Conversely, histiocytic aggregates ("mucin granulomas") are generally not seen in appendiceal low-grade mucinous neoplasms but are common in primary mucinous tumors (123). Several investigations of the immunohistochemical profile have shown that the neoplastic epithelium in these cases is typically negative or only focally reactive for CK7 and positive for CK20, CDX2, and MUC2 (123–127).

Rare cases of pseudomyxoma peritonei are associated with primary ovarian mucinous tumors arising in a background of teratoma (123). The morphology is similar to appendiceal low-grade mucinous neoplasms involving the ovaries, including the presence of scalloped glands and subepithelial clefts, and the immunophenotype is similar as well. Teratoma-associated mucinous neoplasms are typically unilateral, however, and accurate diagnosis of such cases requires a careful search for teratomaticous components in the ovary and rigorous pathologic evaluation of the appendix.

**TUMORS OF THE PANCREAS**

Although spread of pancreatic ductal carcinoma to the ovary has historically been considered uncommon, current evidence suggests that it occurs much more frequently than once thought (128). Indeed, it is considered in retrospect to account for the poor prognosis in some older series of primary mucinous cancers of the ovary in that some of the tumors were actually metastatic to the ovary. Furthermore, pancreatic cancer spreading to the ovary is considered the prototypical situation in which a metastatic mucinous cancer in the ovary may simulate a primary neoplasm both grossly and microscopically. The usual bilateral ovarian involvement is a helpful clue to a metastasis because primary ovarian mucinous tumors are bilateral in less than 10% of cases. Additional features suggesting metastasis include extensive extraovarian tumor, ovarian surface implants (Fig. 56.22), and prominent vascular invasion within the ovary. Often, the metastases contain large areas simulating borderline
or benign mucinous ovarian neoplasia or, less often, endome-
triod adenocarcinoma. Rare metastases from the pancreas are
Krukenberg tumors (83). Loss of Dpc4 staining favors the diag-
nosis of metastatic pancreatic carcinoma over that of primary
ovarian mucinous carcinoma (129,130).

Vakiani et al. (131) reported four cases of acinar cell carci-
noma metastatic to the ovary (Fig. 56.23A). The patients were
adults, and in three patients, the ovarian tumors were detected
prior to the pancreatic primary. In some cases, determining
that there was a pancreatic primary was difficult. The ovarian
tumors were large and bilateral in three cases. Microscopic examination
showed highly cellular neoplasms with scant fibrous stroma.
In two cases, there was a predominant acinar growth, and in the
other two cases, the patterns were predominantly solid to cribri-
form with comedo-like necrosis. The cells generally had brightly
evomphilic granular cytoplasm. The major differential is with
carcinoid tumor, and positive immunostaining with antibodies
against chromogranin and synaptophysin aid in this distinction but, of course, can only be applied if the dif-
ferential diagnosis is considered based on suspicion provoked
by the routine microscopic findings. One example of an adre-
nocorticotropic hormone (ACTH)–secreting pancreatic neuro-
endocrine tumor presenting with bilateral ovarian metastases
and Cushing syndrome has been reported (132), and rare other
cases of metastatic pancreatic neuroendocrine tumor to the
ovary are documented (Fig. 56.23B, C).

TUMORS OF THE LIVER, GALLBLADDER, AND BILE DUCTS

The recent literature suggests that metastatic hepatocellular
carcinoma spreads to the ovary more often than the earlier lit-
erature would indicate, although clearly, it is still uncommon
(133,134). The tumors may be encountered throughout adult
life but have most often been seen in the young, and the ovarian
mass may be the presenting manifestation. Bilaterality and the
presence of canaliculi or bile on microscopic examination are
very helpful features pointing to metastatic hepatocellular
carcinoma (Fig. 56.23E, F). The microscopic patterns encountered
range from diffuse to various epithelial-like formations includ-
ing insular, trabecular, and pseudoglandular.

The major differential diagnosis is with primary and meta-
static hepatoid tumors of the ovary. In the young, hepatoid yolk
sac tumor is an important consideration, and thorough sampling
to rule out areas of typical yolk sac tumor is indicated.
In a postmenopausal patient, the differential diagnosis involves
hepatoid carcinoma rather than hepatoid yolk sac tumor.
Hepatoid carcinomas usually contain foci of more typical sur-
face epithelial carcinoma, typically serous carcinoma. Hepatoid
carcinomas may also arise outside the ovary, for example in the
stomach and lung, and may potentially metastasize to the ovary.
HepPar-1 is not useful in distinguishing among metastatic
hepatocellular carcinoma, hepatoid yolk sac tumor, and hepato-
oid ovarian carcinoma as it is expressed in all (135).

In certain parts of the world such as East Asia, metastatic
intrahepatic cholangiocarcinoma is a significant issue in
metastatic ovarian neoplasia (Fig. 56.23G-H). This is rarely
encountered in other parts of the world where infestation with
Opisthorchis viverrini, which is responsible for the high inci-
dence in Asia, is not endemic. Khunamornpong et al. (136)
described a series of 16 examples of this phenomenon. Most of
the patients presented with signs and symptoms referable to an
adnexal mass. The ovarian tumors were typically bilateral and
were often grossly indistinguishable from primary mucinous
cystic tumors. The general features that aid in the differential
of primary versus metastatic mucinous neoplasia, considered
earlier, are helpful in this differential.

Khunamornpong et al. (137) also reported their experience
with ovarian spread of carcinoma of the extrahepatic bile ducts
and gallbladder (Fig. 56.23D) and reviewed the prior literature
on this topic. As with ovarian spread of intrahepatic cholangio-
carcinoma, this is typically a neoplasm of adults, and the ovarian
involvement is characteristically bilateral. Generally, similar micro-
scopic features are seen. A noteworthy finding in this series was
the remarkable mimicry in some cases of cystadenoma and cyst-
adenoífbroma of nonmucinous type because of flattened epithe-
lium lining the glands and cysts and prominent fibrous stroma.
Occasional tumors were in the Krukenberg family, and a colloid-
type appearance was observed focally in a few cases. Nonmucinous
morphology that resembled high-grade endometrioid carcinoma
or papillary carcinoma with nonspecific müllerian-like features
and even undifferentiated carcinoma were also encountered.

TUMORS OF THE KIDNEYS AND ADRENAL GLANDS

A small number of striking cases of renal cell carcinoma meta-
static to the ovary have been reported (75,138). In just over half
of the cases, the ovarian tumor was discovered first, and in one
case, the renal primary was not detected until 8 years after the
ovarian tumor. Nearly all are renal clear cell carcinomas, and
the ovarian tumor in several cases was initially misdiagnosed as
primary ovarian clear cell carcinoma. The metastases ranged
from 7 to 18 cm in greatest dimension; a minority were bilat-
eral. Microscopic examination shows solid nests composed of
clear epithelial cells or tubules lined by clear cells and contain-
ing intratumoral eosinophilic material or blood. A prominent
sinusoidal vascular pattern is characteristic. The ho-
memogeneous clear cell pattern without hobnail cells or other pat-
terns of ovarian clear cell carcinoma aids in recognizing these
tumors as metastatic, but radiologic studies of the kidneys are
necessary in some cases to make the diagnosis. We have seen one

FIGURE 56.22
Metastatic pancreatic adenocarcinoma. The corti-
cal surface is involved by a surface implant showing infiltrating tumor
cells associated with a stromal reaction that causes an elevation above
the level of the adjacent cortex. Note the underlying cystic component
of the metastatic cancer.
FIGURE 56.23 Metastatic tumors from the pancreas, gallbladder, bile ducts, and liver. (A) Metastatic acinar cell carcinoma of the pancreas. The small acinar pattern poses a broad differential with many other ovarian tumors, primary and metastatic, that may have similar formations. (B) Metastatic neuroendocrine carcinoma of pancreas. Numerous follicle-like spaces are present. (C) High-power view of metastatic neuroendocrine carcinoma illustrated in (B). (D) Metastatic gallbladder carcinoma. The glands are cystic and do not appear overtly malignant. That and the cellular stroma result in a resemblance to an atypical adenofibroma. (E) Metastatic hepatocellular carcinoma. A discrete nodule of tumor protrudes from the ovarian surface. A small amount of parenchymal involvement is barely visible at the bottom. (F) Metastatic hepatocellular carcinoma. Note bile pigment. (G) Metastatic intrahepatic cholangiocarcinoma. The appearance of a primary mucinous cystic tumor is mimicked. (Courtesy of Dr. S. Khunamornpong, Chiang Mai, Thailand.) (H) Metastatic intrahepatic cholangiocarcinoma. Large cysts are lined by deceptively benign flattened epithelium.
unpublished case of renal papillary carcinoma with metastasis to the ovary. One renal pelvic urothelial cell carcinoma with gland differentiation spread to the ovary in the form of a Krukenberg tumor (139). Cameron et al. (140) reported that primary ovarian clear cell carcinomas are immunoreactive for CK7 but not for CD10 and only rarely for renal cell carcinoma (RCC) marker. In contrast, renal cell clear cell carcinomas are characteristically positive for CD10 and RCC marker but negative for CK7. Leroy et al. (141) found similar results and also found mesothelin (favoring ovarian origin) to be of some aid.

One rhabdoid tumor of the kidney appeared as an ovarian mass before the renal neoplasm was discovered (142). Among childhood tumors, adrenal neuroblastomas spread to the ovary most frequently; more than 25% are found to involve the ovary at autopsy (142,143). Rare patients present with ovarian metastases (142). These tumors must be distinguished from immature teratomas with a predominant neuroblastoma component or the extremely rare primary pure ovarian neuroblastoma. We have seen one unpublished case of adrenal cortical carcinoma that spread to the ovary, but this is a rare event (144).

TUMORS OF THE URINARY BLADDER, URACHUS, URETER, AND URETHRA

Distinguishing a metastatic urothelial carcinoma of the urinary tract from a borderline or malignant Brenner tumor may be difficult (145). The presence of benign Brenner elements supports an ovarian origin, as does the presence of other forms of surface epithelial carcinoma (often serous). A WT1+/CD20−/uroplakin III− immunophenotype also favors a diagnosis of ovarian Brenner cell tumor rather than metastasis. Three signet ring cell carcinomas metastatic from the bladder have been Krukenberg tumors (145). Rare urachal adenocarcinomas have metastasized to the ovaries and have mimicked mucinous cystic tumors (146).

MALIGNANT MELANOMA

Ovarian involvement is often found at autopsy in patients with malignant melanoma, and clinically evident tumors are also encountered (147–149). Most melanomas metastatic to the ovary have been primary in the skin, but some have arisen in the choroid or elsewhere. The average age of the patients has been only 38 years, and rare patients are teenagers. Approximately 80% of the patients also have metastatic tumor outside the ovary, usually within the pelvis and upper abdomen. The remote history of the primary tumor, over 5 years in 20% of the reported cases, may result in the information not being conveyed to the pathologist.

Gross Features

Both ovaries are involved in approximately one-third of the cases. Tumors average 10 cm in size. Only a minority are black or brown in color. There is commonly a minor cystic component in a specimen that is generally nondistinctive grossly; rare tumors may be predominately cystic.

Microscopic Features

The most common microscopic appearance is that of large cells with abundant eosinophilic cytoplasm growing diffusely or in nodular aggregates. Occasionally, however, small cells with scanty cytoplasm predominate; in some cases, spindle cells are present, but they rarely predominate. Growth in discrete rounded aggregates with a nevoid appearance is helpful diagnostically. A confusing feature is the presence of follicle-like spaces in approximately 40% of tumors (Fig. 56.24). A helpful feature is intracytoplasmic melanin pigment, but melanin is frequently inconspicuous or absent.

Differential Diagnosis

Metastatic melanoma must be distinguished from the rare primary ovarian melanomas that arise in the walls of dermoid cysts, sometimes accompanied by junctional activity beneath the squamous lining of the cyst. Recognition of teratomatous elements is important in establishing the primary nature of a melanoma. Metastatic melanomas may closely resemble lipid-poor steroid cell tumors or even pregnancy luteomas; the latter, like melanomas, are often bilateral. Melanin can be misinterpreted as lipochrome pigment, which may be a feature of steroid cell tumors. Sometimes, small cells with scanty cytoplasm and nuclear grooves result in a resemblance to adult granulosa cell tumor. In one report (147), 3 of 10 metastatic melanomas were initially misinterpreted as sex cord–stromal tumors. The follicle-like spaces (Fig. 56.24) of metastatic melanoma (75) can lead to confusion with juvenile granulosa cell tumor or small cell carcinoma of the hypercalcemic type. Melanomas with pale cytoplasm have sometimes been misinterpreted as dysgerminoma. Undifferentiated carcinoma may also be in the differential. Immunohistochemical staining is almost always helpful in confirming or excluding the diagnosis of malignant melanoma, but obviously, the diagnosis must be entertained in the first place. S-100, HMB-45, and MART-1 will be positive in most melanomas, whereas only the first and third will be positive in occasional sex cord tumors. Overt immunohistochemical differences exist with most others tumors that would reasonably be in the differential diagnosis.

METASTATIC LUNG CANCER

The average age of patients with metastatic lung cancer in one series was 47 years (150). In 53% of the cases, the ovarian tumor was found in a patient with a known history of lung cancer, and in 31%, the pulmonary and ovarian tumors were discovered at the same time. In the remaining 16% of cases, the ovarian
tumors were discovered first, with the interval to detection of the lung cancer ranging from 2 to 26 months. Tumor was limited to the lung and ovaries in 40% of the cases.

**Gross Features**

One-third of the ovarian tumors are bilateral, and the average size is approximately 10 cm. The gross features are, for the most part, nonspecific, although occasionally the nodularity common to many metastatic tumors is observed.

**Microscopic Features**

In one study (150), the metastatic tumors were small cell carcinoma (44%), adenocarcinoma (34%), large cell carcinoma (16%), and squamous cell carcinoma (3%). Various confusing morphologic features such as follicle-like spaces, trabecular patterns, nests, and cords are quite common.

**Differential Diagnosis**

There may be a broad differential diagnosis in these cases, and alertness to aspects of morphology that do not fit well for primary ovarian neoplasia is crucial to the interpretation, particularly, of course, in cases in which a primary lung tumor is not suspected. Primary ovarian small cell carcinoma of pulmonary type is usually not associated with any lung involvement, facilitating its distinction; the focal presence of concomitant surface epithelial tumor is also sometimes helpful in excluding a metastasis. Immunohistochemical positivity for TTF-1 and napsin A suggests a metastasis from the lung in cases of adenocarcinoma, but occasional primary ovarian carcinomas can be positive for napsin A and TTF-1, at least focally (150a, 150b). Although most pulmonary small cell carcinomas are positive for TTF-1, so are many extrapulmonary small cell carcinomas, including one example of ovarian small cell carcinoma of pulmonary type (151).

**METASTATIC GASTROINTESTINAL STROMAL TUMORS**

Ovarian spread of this neoplasm may be diagnostically challenging (152). The majority of tumors in a series of five cases with ovarian spread were primary in the small bowel or mesentery, but one was primary in the stomach. In two cases, the ovarian tumor was discovered 18 months before the primary, and in another case, the tumor was discovered 27 years after the primary had been resected. Most of the ovarian tumors were initially misinterpreted, most often as leiomyosarcoma. In accord with that error, most of the tumors microscopically have had a spindle cell picture, but other findings such as signet ring-like cells and a schwannoma-like appearance have been seen, and potentially, an array of diagnostic issues can arise. Alertness to this issue must be high in the mind of the pathologist when an appearance not typical of any primary ovarian spindle cell neoplasm is seen, and immunohistochemistry for CD117 should be called upon whenever this diagnosis is a possibility.

**MISCELLANEOUS OTHER OVARIAN METASTASES OF NONGENITAL ORIGIN**

Unusual metastases to the ovary have included small cell carcinomas from sites other than the lung (153), adenoid cystic carcinoma of salivary gland origin, follicular and papillary carcinomas of the thyroid, malignant thymoma, alveolar rhabdomyosarcomas (154), and, rarely, other sarcomas (75).

**TUMORS OF THE UTERINE CORPUS, CERVIX, AND FALLOPIAN TUBE**

**Endometrial Carcinoma**

The differentiation of metastatic endometrial and primary endometrioid carcinoma of the ovary is discussed in Chapter 54 (see “Differential Diagnosis” under “Endometrioid Tumors”).

**Endometrial Sarcomas**

The differentiation of metastatic endometrial stromal sarcoma (155) from primary endometrioid stromal sarcoma of the ovary is discussed in Chapter 54 (see “Endometrioid Stromal Sarcomas”).

**Cervical Carcinoma**

Cervical adenocarcinomas metastasize to the ovaries approximately five times as frequently as cervical squamous cell carcinomas (6.3% vs. 1.3% in one study) (156). The risk of ovarian spread increases with the involvement of the outer third of the cervical wall, the parametrium, and/or lymph nodes (157). Most of the reported cases in this category have been adenocarcinomas of the so-called usual type, but some have been mucinous adenocarcinomas, including those of adenoma malignum type (158,159). Inasmuch as the typical endocervical adenocarcinoma of the usual type does not have an overtly mucinous phenotype, it is not surprising that many metastatic endocervical adenocarcinomas in the ovary do not simulate mucinous tumors primarily, although they certainly can have focal mucinous cells, but rather have a picture that can mimic endometrioid carcinoma (159). In such cases, determining whether the tumors are metastatic from one organ to the other or are independent primary tumors may be difficult. Consideration of the criteria used in diagnosing coexistent ovarian and corpus carcinomas and in evaluating metastatic tumors in general usually allows distinctions to be made. Strong, diffuse positivity for p16 suggests metastatic endocervical adenocarcinoma when this issue arises (160).

The occasional association of ovarian squamous cell carcinoma with squamous cell carcinoma in situ of the cervix suggests that, in exceptional cases, squamous cell carcinomas of both organs may be separate primary tumors. Rarely, however, the cervical tumor reaches the ovary via the fallopian tube by spreading upward in the genital tract (161). Cervical adenosquamous carcinoma, undifferentiated carcinoma, and transitional cell carcinoma metastatic to the ovary have also been documented (162). Cervical neuroendocrine carcinomas, including cervical small cell carcinomas, have also metastasized to the ovary, sometimes resulting in their misdiagnosis as primary ovarian tumors (162).

**Trophoblastic Tumors**

Discriminating between primary ovarian choriocarcinoma of either gestational or germ cell origin and metastasis from a uterine choriocarcinoma that has regressed may be impossible. The tumor should be thoroughly sampled in an attempt to discover
teratomatous elements, to establish a germ cell origin, or to find evidence of a primary ovarian gestation. Invasive hydatidiform mole and placental site trophoblastic tumor have also been reported to spread to the ovary (163). The latter should be distinguished from the rare primary placental site trophoblastic tumor that occurs in the ovary. This can generally be done by evaluating the distribution of the tumor, with there being a lack of uterine disease in the rare cases of primary ovarian tumor.

**Carcinoma of the Fallopian Tube**

The ovary is involved in approximately 13% of carcinomas of unquestionable tubal origin, usually by direct extension (164). Determination of whether a carcinoma affecting both organs is primary in one or the other is generally made on the basis of the gross pathologic findings. If they yield an equivocal answer, the tumor has usually been considered a primary ovarian carcinoma because of its much higher incidence. However, recent findings of an unexpectedly high frequency of early tubal carcinoma, both in a screening study for the detection of ovarian cancer and in prophylactic salpingooophorectomy specimens in **BRCA**-positive women, suggest that an ovarian origin has been overdiagnosed in cases in which tumor involves both organs (165–167). Tumors of apparent ovarian origin may arise from implantation of malignant cells from intraepithelial or early tubal carcinomas, with subsequent growth in the ovary becoming the dominant picture (see Chapter 57). The term *tubo-ovarian carcinoma* might be more accurate in cases of more advanced disease that are not clearly primary in either organ (168). Because most tubal carcinomas resemble serous or undifferentiated carcinomas of the ovary, microscopic examination is rarely helpful in establishing a primary site. Primary mucinous and clear cell carcinomas of the tube are very rare, however, so tumors of these types involving both organs are probably of ovarian origin. Occasionally, metastatic spread to the tube may mimic a pattern of intraepithelial carcinoma (169), so the presence of apparent in situ neoplasia suggesting a tubal primary should be interpreted cautiously in the context of the overall pathologic findings.

**NONNEOPLASTIC LESIONS**

Nonneoplastic lesions of the ovary may form pelvic masses, and they may be associated with hormonal manifestations, clinically simulating ovarian neoplasms. These lesions can also resemble ovarian tumors at operation and even on gross pathologic examination. Recognizing them is important from the viewpoints of therapy and prognosis. Endometriosis is considered in Chapter 58.

**ARTIFACTS AND NORMAL FINDINGS**

Normal ovarian structures are occasionally misinterpreted as neoplasms on histologic examination. The granulosa cells of the normal follicle and normal theca externa cells typically exhibit brisk mitotic activity, which, in the former case, can lead to misinterpretation as malignant epithelial cells (Fig. 56.25) and, in the latter case, to misinterpretation as an early fibrosarcoma, especially if the follicle is cut along its edge and its more central components are absent in the plane of section (Fig. 56.26). Moreover, the granulosa cells of normal follicles can also be introduced as artifacts into tissue spaces or vascular channels (170) during sectioning, and they may be confused with small cell carcinoma, especially when they are shrunk or crushed. Occasionally, luteinized granulosa cells are present on the surface of the ovary as the result of follicle rupture, and they may be misinterpreted as mesothelial cells or, if they are numerous, even as malignant mesothelioma. Immunostaining for inhibin can facilitate the diagnosis of granulosa cells in these unusual cases.

**INFLAMMATORY DISORDERS**

**Common Bacterial Infections**

Pelvic inflammatory disease of bacterial origin accounts for most ovarian infections in the Western world. Ovarian involvement almost always stems from salpingitis and typically takes the form of a tubo-ovarian abscess that is usually bilateral. With resolution of the infection, the only sequelae may be tubo-ovarian fibrous adhesions; occasionally, a healed abscess is converted into a tubo-ovarian cyst, which may mimic an ovarian cystic neoplasm at operation. These inflammatory cysts may even be
misdiagnosed as ovarian serous or endometrioid cystadenomas on microscopic examination. In some cases, the presence of focal inflamed tubal plicae in the lining of the cysts is an important clue to the diagnosis. Ovarian changes similar to those of polycystic ovarian disease have been reported in cases of tubo-ovarian inflammatory disease (171).

A unilateral or bilateral ovarian abscess without tubal involvement is much rarer than a tubo-ovarian abscess. The former is the result of direct or lymphatic spread from a nongynecologic pelvic inflammatory process (diverticulitis, appendicitis, inflammatory bowel disease, postoperative pelvic infection) or, uncommonly, of a blood-borne infection (172). Rarely, an ovarian abscess develops within an endometriotic cyst (173). The external surface of an ovary harboring an abscess is often unremarkable, and the nature of the process may not be apparent until the organ is sectioned. An uncommon complication of an ovarian or tubo-ovarian abscess is rupture, typically into the peritoneal cavity with secondary peritonitis (174) and, infrequently, into an adjacent organ, such as the colon, bladder, or vagina, with fistula formation. Rarely, a chronic ovarian abscess may evolve into a solid, yellow, tumorlike xanthogranuloma composed of foamy histiocytes admixed with multinucleated giant cells and other chronic inflammatory cells (175).

**Uncommon Bacterial Infections**

Pelvic actinomycosis, an uncommon disorder, is usually a complication of the use of an intrauterine device (IUD) (176), although most cases of IUD-associated pelvic inflammatory disease are nonactinomycotic. The adnexal involvement is typically unilateral (Fig. 56.27), with large abscesses in which actinomycosis may be visible. Microscopic examination reveals the characteristic colonies of *Actinomyces* and a nonspecific inflammatory response composed predominantly of neutrophils, foamy histiocytes, lymphocytes, and plasma cells. The *Actinomyces* colonies may be rare, necessitating extensive sampling to identify them; a fluorescent antibody stain may facilitate their recognition (177).

Ovarian involvement is present in only 10% of cases of pelvic tuberculosis, and it is usually secondary to tuberculous salpingitis, which is much more frequent (178). On inspection, the ovaries typically have tubal-ampullary adhesions; visible caseous lesions are rare. On histologic examination, the involvement is typically confined to the ovarian cortex. Spread to the peritoneum may result in intraoperative misdiagnosis of an ovarian neoplasm with peritoneal implants (178,179). Extremely rare bacterial infectious affecting the ovary include syphilis, leprosy, and malacoplakia; the last lesion may be related to infection by several species of bacteria (180).

**Other Rare Infections**

Ovarian schistosomiasis is relatively common in endemic areas (181). An enlarged tube and ovary, numerous fibrous adhesions, and scattered peritoneal nodules may be encountered at operation. A granulomatous inflammatory infiltrate that often contains eosinophils is seen in response to *Schistosoma ova*; dense fibrosis is frequently found at later stages of the disease. Ovarian involvement by *Enterobius vermicularis* is usually an incidental operative finding on the ovarian surface (182). The granulomas, which typically contain eosinophils and which may exhibit caseous necrosis, surround the adult female worms and ova. Rare cases of ovarian echinococcosis have been described (183).

Fungal infections of the ovary are unusual, even in patients with disseminated mycoses. Rare examples of ovarian involvement by blastomycosis, coccidioidomycosis, aspergillosis, and histoplasmosis have been described (20).

Oophoritis stemming from cytomegalovirus has been an uncommon finding in immunosuppressed patients, usually detected at autopsy as part of a generalized infection (184,185). Foci of superficial cortical hemorrhagic necrosis may be seen on gross inspection; microscopic examination reveals coagulative necrosis, an inflammatory response, and cytomegalic inclusion bodies within the stromal and endothelial cells.

**NONINFECTIOUS GRANULOMAS**

Foreign material may evoke a granulomatous reaction on the ovarian and peritoneal surfaces, mimicking metastatic carcinoma. Starch granules from surgical gloves or, less often, from starch-containing douche fluid or lubricants can evoke a foreign body or tuberculoid granulomatous response (186). Foreign body granulomas may also be a result of suture material (187), talc (188), hysterosalpingographic contrast material (189), keratin from ruptured dermoid cysts or endometrial or ovarian endometrioid adenocarcinomas with squamous differentiation (190), and bowel contents (191). Rare examples of a florid granulomatous reaction to oxidized cellulose (Surgicel) have mimicked a primary ovarian tumor (192).

Isolated noninfectious ovarian granulomas typically develop in patients who have previously undergone ovarian operation (193,194). These granulomas are usually multiple and bilateral, and they have hyalinized or necrotic cores surrounded by palisading histiocytes and a fibrous pseudocapsule. Diathermy or...
laser therapy typically results in granulomas containing carbon pigment (195).

Granulomatous oophoritis can be caused on occasion by sarcoidosis (196) and Crohn disease (197). In Crohn disease, involvement generally results from the direct extension of the inflammatory process from the bowel; the ipsilateral fallopian tube is often affected as well (197). So-called cortical granulomas are common incidental microscopic lesions of unknown origin and no significance within the ovarian cortex of women in the late reproductive and postmenopausal age groups. These lesions consist of a variable admixture of epithelioid cells, lymphocytes, and multinucleated giant cells. So-called ceroid granulomas have rarely been encountered as incidental microscopic findings in the ovary (198). They consist of nodular aggregates of histiocytes containing ceroid pigment, and they may represent a reaction to local hemorrhage or necrosis. Mucicarminophilic histiocytosis, which can occasionally involve the ovaries, is discussed in Chapter 58.

**SURFACE PROLIFERATIVE LESIONS**

**Epithelial Inclusion Glands**

Epithelial inclusion glands arise from cortical invaginations of the surface epithelium that have lost their connection with the surface. Although epithelial inclusion glands are most numerous in postmenopausal women, they have also been found in fetuses, infants, and adolescents (199,200). These inclusions can measure up to 1 cm in diameter, and they may be visible grossly, but most are incidental microscopic findings in the form of multiple glands or cysts scattered singly or in clusters throughout the superficial cortex; less commonly, they are found in the deeper cortical or medullary stroma.

Inclusion cysts may be particularly numerous in cases of peritoneal serous borderline neoplasia and other low-grade peritoneal serous tumors. In these and other cases, they may be associated with striking numbers of psammoma bodies either within them or in the adjacent stroma; they may be accompanied by surface fibrous adhesions. The inclusion cysts are typically lined by a single layer of columnar epithelium which may be ciliated. Less often, the lining is a single layer of endometrioid or, rarely, endocervical-type epithelium (201). An Arias-Stella–like reaction may be evident in the lining cells in pregnant patients. Occasionally in adults and typically in fetal and premenarchal ovaries, the cysts have a flat or cuboidal lining. The infrequent finding of dysplastic epithelium lining the cysts supports the hypothesis that they may give rise to surface epithelial carcinomas. In a few instances, a striking hydropic change of the cells lining epithelial inclusion glands is observed, creating an appearance that can mimic that of a signet ring cell carcinoma (20).

The presence of ciliated tubal-type epithelium lining inclusion glands and cysts has traditionally been attributed to metaplasia of the invaginated surface epithelium. Recent investigations have also raised the possibility that some inclusions may arise from implanted benign tubal epithelium rather than ovarian surface epithelium (202).

**Surface Stromal Proliferations**

Papillary or sometimes nodular stromal projections from the ovarian surface are common incidental histologic findings in the late reproductive and postmenopausal age groups. They are composed of ovarian stroma exhibiting variable degrees of fibrosis, sometimes even hyalinization, covered by a single layer of surface epithelium (20). This process should not be confused with a surface neoplasm, a distinction that is usually straightforward. More challenging, albeit rare, is the differential that arises when there is limited ovarian surface involvement by malignant mesothelioma. Papillary foci of that neoplasm may be quite similar to the surface stromal proliferation. If small surface proliferations are covered by cells with an unequivocal mesothelial, as opposed to surface epithelial, nature, this issue should be considered. We have seen one case of that type in which penetration of mesothelial cells into underlying ovarian stroma supported a malignant diagnosis, although awareness of a malignant peritoneal lesion in extravascular tissues was helpful.

**Mesothelial Proliferations**

Proliferation of bland to mildly atypical mesothelial cells may be encountered on the surface of the ovaries or periovular adhesions. When they are present in association with an ovarian tumor, they may be misinterpreted as representing spread of the tumor (203). These proliferations are similar to those seen elsewhere on the peritoneal surfaces and are discussed in detail in Chapter 58.

**SOLITARY FOLLICLE CYSTS**

**Clinical Features**

Solitary (i.e., one or, occasionally, a few) follicle cysts are common, particularly soon after menarche and around the time of menopause. They may be encountered, however, at any age, from the fetal period to 7 years after the clinical onset of menopause (204–207). Corpus luteum cysts (see Fig. 56.29) usually occur during the reproductive years, but in exceptional cases, they can develop after an isolated ovulation several years after the clinical onset of menopause. Corpora lutea have been encountered very rarely in the ovaries of newborns (208). Follicle cysts may be incidental findings, or they may result in either palpable adnexal masses or manifestations related to increased estrogen production, such as isosexual precocity (209), menstrual disturbances, or endometrial hyperplasia. An uncommon result of both follicle and corpus luteum cysts is rupture with hemoperitoneum, especially in patients who have been receiving anticoagulant therapy or who have a bleeding diathesis (210). The bleeding may be massive and even fatal. A corpus luteum cyst arising in residual ovarian tissue is the most common finding in the ovarian remnant syndrome (see “Ovarian Remnant Syndrome” later in this chapter).

The great majority of follicle cysts result from abnormal gonadotropin stimulation. In most children, however, including those with the McCune-Albright syndrome, the cysts appear to be autonomous, and the triggering mechanism is unknown. Isosexual pseudoprecocity caused by these cysts may regress spontaneously or following puncture of the cyst (211). Autonomous cysts may be single or multiple. In the McCune-Albright syndrome, they may be accompanied by corpora lutea and a potential for pregnancy, and they may recur after excision (212). One study found that women with breast carcinoma undergoing tamoxifen treatment have an increased risk of follicle cysts (213).
Microscopic Features

Follicle cysts are lined by an inner layer of granulosa cells, typically having abundant eosinophilic cytoplasm, and an outer layer of theca interna cells (Fig. 56.30). Distinction between the two layers is usually easy but can be difficult and, if so, can be facilitated by a reticulin stain, which reveals a dense network of reticulin in the theca cell layer but few or no fibrils in the granulosa cell layer. Either layer, but more often the granulosa cell layer, may be present only focally or may be completely absent.

The large solitary luteinized follicle cyst of pregnancy and the puerperium has a distinctive appearance, with a lining of one to several layers of luteinized cells that may vary markedly in size and shape (Fig. 56.31). The luteinized cells typically exhibit focal marked nuclear pleomorphism and hyperchromatism.

Gross Features

Follicle and corpus luteum cysts are unilocular, smooth surfaced, and thin walled, and they rarely exceed 8 cm in diameter (Figs. 56.28 and 56.29). The reported examples of large solitary luteinized follicle cyst of pregnancy and the puerperium, however, have had a median diameter of 25 cm. Corpus luteum cysts are usually recognizable on gross examination because all or part of the wall may be yellow or convoluted (Fig. 56.29). The contents of follicle and corpus luteum cysts vary from serous or serosanguineous fluid to clotted blood.

A rare type of solitary follicle cyst, the “large solitary luteinized follicle cyst of pregnancy and the puerperium,” is presumably related to chorionic gonadotropin stimulation (214). The ovarian cyst is usually discovered at cesarean section or on pelvic examination at the time of the first postpartum visit. None of the cysts of this type reported to date has been bilateral or associated with clinical evidence of an endocrine disturbance.

FIGURE 56.30 Follicle cyst. Typical lining of nonneoplastic granulosa cells with abundant eosinophilic cytoplasm.

FIGURE 56.31 Large solitary luteinized follicle cyst of pregnancy and puerperium. The lining cells are luteinized, and some have enlarged bizarre nuclei.
CHAPTER 56
■ Miscellaneous Primary Tumors, Secondary Tumors, and Nonneoplastic Lesions of the Ovary

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GRANULOSA CELL PROLIFERATIONS

Focal proliferations of granulosa cells that resemble small tumors of microscopic size may be encountered as incidental findings in the ovary. Most of the reported examples have been discovered in pregnant women (219). The lesions typically develop in atretic follicles, but only a minority of the follicles is affected in a given pregnancy. Simple cysts have no lining or one composed of a layer of nonspecific flattened cells; some are probably of follicular origin but cannot be proven to be, whereas others are likely of surface epithelial origin. When the granulosa cells of a follicle cyst are denuded, a retained layer of theca cells may be helpful in pointing to the diagnosis of follicle cyst rather than another form of benign cyst, such as a simple cyst, which may be in the differential.

Differential Diagnosis

Cysts that otherwise are similar to follicle and corpus luteum cysts but that measure less than 2 cm in diameter are generally regarded as physiologic and are designated cystic follicles and cystic corpora lutea, respectively. Differentiation of large solitary luteinized follicle cyst of pregnancy and the puerperium from unilocular cystic granulosa cell tumor is discussed under the latter heading. Simple cysts have no lining or one composed of a layer of nonspecific flattened cells; some are probably of follicular origin but cannot be proven to be, whereas others are likely of surface epithelial origin. When the granulosa cells of a follicle cyst are denuded, a retained layer of theca cells may be helpful in pointing to the diagnosis of follicle cyst rather than another form of benign cyst, such as a simple cyst, which may be in the differential.

HYPERREACTIO LUTEINALIS

Clinical Features

Hyperreactio luteinalis, the presence of bilateral multiple luteinized follicle cysts, is most commonly associated with disorders of pregnancy in which the levels of circulating human chorionic gonadotropin (hCG) are high, such as hydatidiform mole, choriocarcinoma, fetal hydrops, and multiple gestations (215,216), but it has also been reported during single pregnancies (217). The disorder may become clinically apparent at any time during pregnancy, or it may be an incidental finding at cesarean section. Much less often, clinical manifestations arise within the first 10 days postpartum or, exceptionally, late in the puerperium. The patients usually have pain or palpable adnexal masses or both. In patients with hyperreactio luteinalis stemming from trophoblastic disease, cystic ovarian enlargement may be detected at the time of dilatation and curettage or during the postoperative follow-up period. In approximately 25% of the cases that have been unassociated with trophoblastic disease, the patient has been virilized. Complications include ascites, torsion, and rupture with intra-abdominal bleeding.

Hyperreactio luteinalis typically regresses in the postpartum period, but it sometimes persists for up to 6 months. An iatrogenic form of hyperreactio luteinalis, which is referred to as the ovarian hyperstimulation syndrome, develops in women undergoing ovulation induction, typically with follicle-stimulating hormone followed by hCG and less often with clomiphene citrate (Clomid) alone (218). Patients with this disorder may also have ascites and occasionally hydrothorax of acute onset (acute Meigs syndrome).

Pathologic Features

On gross examination, multiple, almost invariably bilateral cysts result in moderate to massive ovarian enlargement (up to 26 cm in diameter) (Fig. 56.32); the cysts may be filled with clear or hemorrhagic fluid. One or more corpora lutea are present in patients with the ovarian hyperstimulation syndrome. Microscopic examination reveals large follicle cysts with marked luteinization of the theca interna layer and, to a lesser extent, the granulosa cell layer (Fig. 56.33). Usually, marked congestion and edema of the stroma exist, and stromal luteinization may be present as well.

FIGURE 56.32 Hyperreactio luteinalis. Both ovaries are replaced by multiple thin-walled cysts.

FIGURE 56.33 Hyperreactio luteinalis. Two cysts are lined by luteinized granulosa cells; outside is a thick layer of luteinized theca cells.
POLYCYSTIC OVARIAN DISEASE, STROMAL HYPERPLASIA, AND STROMAL HYPERTHECOSIS

Morphologic and physiologic investigations have shown that these disorders, which may be associated with androgenic or estrogenic manifestations or both, are part of a continuum and that sharp distinctions cannot always be made among them. Despite this overlap, describing the typical clinical and pathologic features of each separately is appropriate inasmuch as they generally differ in each category.

Polycystic Ovarian Disease

**Clinical Features.** Polycystic ovarian disease (PCOD) has been estimated to affect 3.5% to 7% of the female population. The pathogenetic and endocrinologic features of the disorder are complex, and they have been reviewed elsewhere (220). Patients typically present in their third decade with a history of oligomenorrhea (rarely, primary amenorrhea) or, occasionally, menometrorrhagia accompanied by infertility and, in approximately half the cases, hirsutism; virilization is rare. The ovaries may be palpably enlarged. An examination of the endometrium may reveal a hypoactive proliferative appearance; cystic hyperplasia; atypical hyperplasia; or, in a small number of cases, adenocarcinoma that is almost always well differentiated.

**Gross Features.** Both ovaries are usually enlarged, but they may be of normal size. They have a white surface, with cysts that are less than 1 cm in diameter visible just below them. The central portion of the ovary is composed of stroma with few or no signs of ovulation (i.e., corpora lutea or albicantia).

**Microscopic Features.** A hypocellular, fibrotic superficial cortex that resembles a fibrous capsule is evident (Fig. 56.35). Most of the cystic follicles contain relatively few granulosa cells, but typically, they have a prominent layer of luteinized theca interna cells (follicular hyperthecosis). Maturing follicles and atretic follicles exhibiting prominent luteinization of the theca interna are twice as numerous as in normal ovaries. Although corpora lutea and albicantia are typically absent, the former have been described in up to 30% of otherwise typical cases (221). The deeper cortical and medullary stroma is often hyperplastic, and it may exhibit hyperthecosis; if hyperthecosis is more than minor in extent, stromal hyperthecosis should also be diagnosed.

Findings similar to those of PCOD may also be seen during or shortly after puberty, in childhood hypothyroidism, and in disorders in which normal cyclic gonadotropin release is disrupted. These include late-onset congenital adrenal hyperplasia and primary hypothalamic-pituitary disorders, particularly those associated with hyperprolactinemia. Polycystic ovaries have also been described in patients after the cessation of long-term use of oral contraceptives as well as in those with periovarian adhesions. In the former group of patients, the disorder may have been present in at least some cases before the initiation of oral contraceptives.

Stromal Hyperplasia and Hyperthecosis

The proliferation of ovarian stromal cells is common in perimenopausal and early postmenopausal women, and a sharp distinction cannot be drawn between normal stromal proliferation and so-called stromal hyperplasia (222). Nonetheless, the latter designation is appropriate for cases in which the proliferation is of moderate to marked degree. Stromal hyperthecosis refers to the presence of luteinized stromal cells within an almost invariably hyperplastic ovarian stroma.

**Clinical Features.** Stromal hyperplasia is most common in patients in their sixth and seventh decades (222). It is difficult to assess the endocrine significance of stromal hyperplasia per se because no investigators have separately analyzed cases of pure hyperplasia and those in which the hyperplasia is accompanied by hyperthecosis. Evidence suggests, however, that stromal hyperplasia may be associated with androgen hypersecretion as well as obesity, hypertension, and disorders of glucose metabolism, although not as often or as obtrusively as in cases of stromal hyperthecosis. Snowden et al. (223) have shown an association between stromal hyperplasia and endometrial adenocarcinoma for which evidence of an estrogenic background is present in some cases. Androgen production by nonluteinized, as well as luteinized, ovarian stromal cells is consistent with their content of oxidative enzymes, the so-called enzymatically active stromal cells (224).

Stromal hyperthecosis is usually encountered in patients in their sixth to ninth decades. It has been documented at autopsy in a third of patients older than 55 years of age (222). In this...
cytoplasm containing variable amounts of lipid and a round nu-
ucleus with a central small nucleolus. Associated ovarian findings
have included small foci of metaplastic smooth muscle in the
ovarian stroma, Leydig cell hyperplasia, Leydig cell tumors, and
stromal luteomas. In patients with the HAIR-AN syndrome, an
additional microscopic finding is the presence of a hypocellular
stroma exhibiting edema or fibrosis; the prominent stromal hy-
perplasia of typical stromal hyperthecosis is often absent (225).

**MASSIVE EDEMA AND FIBROMATOSIS**

Tumorlike enlargement of one or both ovaries as the result of
an accumulation of edema fluid within the ovarian stroma has
been designated massive ovarian edema (226,227). Another
tumorlike lesion that is termed ovarian fibromatosis (to distin-
guish it from ovarian involvement by fibromatosis of soft tis-
sue type) has clinical and pathologic features that overlap with
those of massive edema, which suggests a probable relationship
between the two entities (227).

**Massive Edema**

**Clinical Features.** Patient age ranges from 6 to 33 years, with
an average of 21 years. Three-fourths of patients have experi-
enced abdominal or pelvic pain, which may be acute and ac-
companied by abdominal swelling. In the remaining patients,
the clinical manifestations have been menstrual irregularities,
evidence of androgen excess, or both; the plasma testosterone
level has been increased in some cases. Examination typically
reveals a palpable mass. The ovarian enlargement is unilateral
in approximately 90% of cases. Partial or complete torsion of
the involved ovary is present in at least half the cases. Rare pa-
tients have had Meigs syndrome. Although usually an entirely
nonneoplastic lesion, rarely massive edema is secondary to ob-
struction of lymphatic drainage by metastatic carcinoma (228).

**Gross Features.** Both stromal hyperplasia and hyperthecosis
may cause bilateral ovarian enlargement, with each ovary mea-
suring up to 8 cm in diameter, potentially mimicking ovarian
neoplasia. A neoplasm is more strongly suggested in the ex-
tremely rare cases of unilateral stromal hyperthecosis in viril-
ized patients. The cut surface is homogeneous, firm, and white
to yellow (Fig. 56.36). In premenopausal patients with hyper-
thecosis, sclerocystic changes similar to those seen in PCOD
usually are also present.

**Microscopic Features.** Both the cortical and the medullary
stroma may be hyperplastic. In stromal hyperthecosis, lutein-
zized stromal cells appear singly, in small clusters (Fig. 56.37),
or in nodules. They have abundant eosinophilic to vacuolated

**FIGURE 56.37**

Stromal hyperthecosis. Clusters of luteinized cells with vacuolated cytoplasm lie in the ovarian stroma.

**FIGURE 56.38**

Massive edema. The ovary is replaced by edematous tissue.
Fibromatosis

Clinical Features. Patient age ranges from 13 to 39 years, with the average being 25 years (227). Clinical manifestations include menstrual abnormalities, abdominal pain, and, rarely, hirsutism or virilization. An adnexal mass is usually palpable. The process is usually unilateral; in 15% of cases, the involved ovaries have undergone torsion.

Gross Features. Gross examination shows ovaries that are 6 to 14 cm in diameter with smooth, white external surfaces. The cut surfaces are firm, white, and solid, although cystic follicles are recognizable within the lesion in a third of the cases (Fig. 56.40).

Microscopic Features. On microscopic examination, a proliferation of spindle cells producing variable amounts of collagen is visible. The appearance varies from moderately cellular fascicles of spindle cells with a focal storiform pattern to relatively acellular bands of dense collagen (Fig. 56.41). The process typically surrounds normal follicle structures and produces collagenous homogeneous, and soft, exuding a watery fluid. The superficial cortex appears white and fibrotic. The presence of follicles, which are often cystic, within the edematous tissue distinguishes massive edema from an edematous fibroma, which displaces rather than envelops follicles.

Massive edema. Pale, edematous stroma surrounds several graafian follicles.

Differential Diagnosis. Massive edema can be distinguished from ovarian neoplasms with an edematous or myxoid appearance, such as edematous fibroma, sclerosing stromal tumor, Krukenberg tumor, and the rare ovarian myxoma, by the absence of characteristic features of those tumors as well as by the inclusion of follicular derivatives within the lesion. The Krukenberg tumor, however, often has extensive central edema enveloped by a pseudocapsule of solid tumor, and it occasionally encloses preserved follicular derivatives.

FIGURE 56.39 Massive edema. Pale, edematous stroma surrounds several graafian follicles.

FIGURE 56.40 Fibromatosis. The sectioned surfaces of the ovary reveal dense white tissue surrounding cystic follicles.

FIGURE 56.41 Fibromatosis. Dense, hyalinized fibrous tissue has replaced the normal ovarian stroma and surrounds a primary follicle.
thickening of the superficial cortex. Foci of stromal edema similar to that of massive edema are present in approximately half the cases. Luteinized stromal cells and microscopic foci of sex cord cells have been seen in a few cases.

**Differential Diagnosis.** Ovarian fibromatosis should be distinguished from fibroma; the latter usually appears in older age groups, is typically nonfunctioning, and almost never contains follicles or their derivatives. The few small aggregates of sex cord cells in fibromatosis should not cause confusion with a sex cord–stromal tumor.

**PREGNANCY LUTEOMA**

Pregnancy luteoma is characterized by tumor-like ovarian enlargement during pregnancy as the consequence of solid proliferations of luteinized cells derived from theca lutein or luteinized stromal cells (229,230). The disorder is probably related to hCG stimulation, but the rarity of pregnancy luteomas in association with trophoblastic disease and the almost exclusive occurrence of the lesions during the third trimester when hCG levels are lower than earlier in pregnancy indicate that this hormone is not the only factor in their development.

**Clinical Features**

Most patients are in their third or fourth decades, black, and multiparous. The lesion is usually discovered incidentally at term during cesarean section or postpartum tubal ligation. Infrequently, a pelvic mass is palpable, or it causes obstruction of the birth canal. In approximately 25% of cases, hirsutism or virilization is observed; two-thirds of female infants born to such mothers also show signs of virilism. Regression of the enlarged ovaries usually begins within days after delivery, and they become normal in size within several weeks.

**Gross Features**

The lesions range from small nodules to masses up to 20 cm in diameter, with soft, fleshy, circumscribed, brown (Fig. 56.42) or gray cut surfaces; foci of hemorrhage are common. They are multiple in at least half the cases and bilateral in a third. On examination of the ovaries days to weeks postpartum, focally infarcted lesions or brown puckered scars are visible (231).

**Microscopic Features**

The sharply circumscribed nodules are composed of polygonal cells intermediate in size between the luteinized granulosa and theca cells of adjacent follicles. Occasionally, the cells are arranged in cords or small clusters, and in 70% of cases, they surround follicle-like spaces containing colloid-like material (Fig. 56.43) (232). The cytoplasm is abundant, eosinophilic, and finely granular, and it contains little or no lipid. Less common features include focal ballooning degeneration of the cytoplasm and small numbers of intracellular hyaline droplets similar to those seen in the corpus luteum of pregnancy. The nuclei may be slightly pleomorphic and hyperchromatic; mitotic figures range up to 7 per 10 hpf, with an average of 2 or 3; occasionally, atypical forms are seen. The intercellular stroma is typically scanty, and reticulin fibrils surround groups of cells. Postpartum examination of the lesions shows lipid accumulation in the cells, round cell infiltration, and fibrosis.

**Differential Diagnosis**

If several bilateral nodules are present, the intraoperative differential diagnosis is with metastatic carcinoma, especially Krukenberg tumor and metastatic malignant melanoma. Like the pregnancy luteoma, Krukenberg tumor can also cause virilization if luteinization of its stroma occurs. Frozen section of a biopsy specimen or an excised nodule should establish the correct diagnosis and should obviate the possibility of an unwarranted bilateral oophorectomy. Although several lesions containing luteinized cells that arise during pregnancy may enter the differential diagnosis on microscopic examination, the gross appearance of multiple, bilateral, solid nodules is distinctive of pregnancy luteoma. Neoplasms composed in part or totally of luteinized cells (i.e., those in the sex cord–stromal and steroid cell categories) are almost always unilateral and solitary. Sex
cord-stromal tumors typically contain nonluteinized foci and have a denser reticulin pattern and more abundant intracellular lipid than do pregnancy luteomas. Tumors in the steroid cell group that are composed entirely of lipid-poor or lipid-free steroid cells may closely resemble or be indistinguishable from solitary pregnancy luteomas (see “Differential Diagnosis” under “Steroid Cell Tumor, Not Otherwise Specified” in Chapter 55), and clinical context is important. Pregnancy luteomas contain follicle-like spaces much more often than steroid cell tumors.

**HILUS CELL HYPERPLASIA**

**Clinical Features**

Hilus cell hyperplasia may be seen during pregnancy, as a result of hCG administration, and in postmenopausal women, in whom the process may be related to their high luteinizing hormone level (233). Prominent degrees of hilus cell hyperplasia were found in more than 40% of women older than 70 years of age in one autopsy study (222). The assessment of the role of hilus cell hyperplasia in endocrine disturbances is often complicated by the coexistence of stromal hyperthecosis, a hilus cell tumor, or both, but rare cases in which isolated hilus cell hyperplasia has apparently been responsible for androgenic or estrogenic manifestations have been reported. In some cases, elevated plasma testosterone levels have been documented.

**Pathologic Features**

Hilus cell hyperplasia may be grossly visible as several yellow hilar nodules that are usually less than 2 mm in diameter. On microscopic examination, the hilus cells are arranged in nodular or diffuse patterns; multinucleated cells and a few mitotic figures may be seen. In elderly women, the hyperplastic hilus cells may be enlarged, and they may have bizarre shapes and hyperchromatic nuclei. Hilus cell hyperplasia may also develop adjacent to an ovarian tumor and may result in endocrine, particularly androgenic, manifestations.

**STROMAL-LEYDIG CELL HYPERPLASIA**

Leydig cells containing Reinke crystals have been rarely encountered within the ovarian stroma away from the hilus, usually as a focal microscopic finding in an ovary exhibiting otherwise typical stromal hyperthecosis, hilus cell hyperplasia, or a hilus cell tumor. Rarely, Leydig cells have also been described within the nonneoplastic stroma of a variety of ovarian neoplasms or in the ovarian stroma adjacent to an ovarian neoplasm.

**STROMAL METAPLASIAS**

**Decidual Reaction**

**Clinical Features.** An ectopic decidual reaction may be confined to the ovarian stroma, or it may be part of a more widespread decidual transformation of the submesothelial pelvic stroma (see Chapter 58). An ovarian decidual reaction is usually a response of the stromal cells to high circulating or local levels of estrogen and progesterone. The process is seen most often during pregnancy as early as the ninth week of gestation; it is present in almost all ovaries at term (234). Less often, ectopic decidua is associated with trophoblastic disease, progestin treatment, an adjacent corpus luteum, an adjoining metastatic tumor, or a steroid-secreting lesion of the ovary or adrenal gland. Ovarian irradiation may be followed by a decidual reaction, possibly by increasing the sensitivity of the stromal cells to hormonal stimulation. Occasionally, ectopic decidua occurs within the ovaries of premenopausal and postmenopausal women without an obvious cause.

**Pathologic Features.** The decidual foci may be grossly visible as soft, red surface nodules; ridges; or patches, but more frequently, they are incidental findings on microscopic examination. The decidual cells are typically found in the superficial cortical stroma or surface adhesions, where they may be disposed singly, as small nodules, in sheets, or as small polygonoid projections from the ovarian surface. Most of the cells are indistinguishable from eutopic decidual cells; occasionally, they mimic signet ring cells because of mucin-containing cytoplasmic vacuoles that may displace the nuclei to the periphery. The mucin in these cells, however, is acidic rather than neutral. Cells that are transitional in appearance between spindle-shaped ovarian stromal cells and fully decidualized cells are also usually present. In some cases, ultrastructural examination has revealed smooth muscle cells. A rich network of capillaries and a sprinkling of lymphocytes are typically found within the decidual foci. Florid examples can simulate metastatic carcinoma, particularly if the decidual cells show focal cytologic atypia or have signet ring-like features. Degenerative changes within the decidua are typically seen postpartum.

**Other Stromal Metaplasias**

Small nodules of metaplastic smooth muscle are occasionally encountered within otherwise unremarkable ovarian stroma, the hyperplastic stroma of stromal hyperthecosis, and the stroma surrounding nonneoplastic or neoplastic cysts (235). Foci of mature fat also have been described as occasional incidental findings within the superficial stroma (236). Heterotopic bone formation in the ovary in the absence of an ovarian neoplasm is rare. It typically occurs within periovarian adhesions or in the walls of endometriotic cysts; in exceptional cases, it develops within otherwise normal ovaries (237).

**DISORDERS CAUSING OVARIAN FAILURE**

Premature ovarian failure is generally defined as secondary amenorrhea and infertility before the age of 35 years. If one excludes cases of gonadal maldevelopment and obvious chromosomal abnormalities, as well as surgical, radiation-induced, or drug-induced ablation of ovarian function, the following three disorders are associated with distinctive ovarian changes in patients with premature ovarian failure: premature follicle depletion (true premature menopause), the resistant ovary syndrome, and autoimmune oophoritis. All of these disorders probably include several subtypes of diverse pathogenesis (238,239).

**True Premature Menopause**

True premature menopause is characterized by ovaries that are typically small and that resemble microscopically normal perimenopausal or postmenopausal ovaries (240,241). Some cases...
may be caused by relatively minor chromosomal abnormalities, or they may represent an end stage of autoimmune oophoritis that is no longer diagnosable as such (see “Autoimmune Oophoritis”).

**Resistant Ovary Syndrome**

The resistant ovary syndrome is found in approximately 20% of patients with premature ovarian failure and is characterized by primary or secondary amenorrhea, high gonadotropin levels, and resistance to both endogenous and exogenous gonadotropins, even when these are administered in massive doses (242). The pathogenesis of the disorder is unknown, but a deficiency of follicle-stimulating hormone and luteinizing hormone receptors in the follicles, the presence of antibodies to these receptors, and a postreceptor defect have all been implicated.

The ovaries typically have a normal prepubertal or adult appearance on gross inspection. On histologic examination, an appropriate number of normal-appearing primordial follicles is present, but the absence of developing follicles beyond the antral stage is complete or nearly complete. Atretic follicles and signs of previous ovulation may be seen. Unusual histologic findings have included focal or diffuse hyalinization of atretic follicles in the preantral stage and central calcification within atretic follicles (243). In rare instances, stromal luteinization and hilus cell hyperplasia result from a high level of luteinizing hormone, and they are associated with virilization. A histologic pattern similar to that seen in the resistant ovary syndrome may occur in the context of morbid obesity, Cushing syndrome, and hypogonadotropic ovarian failure stemming from hypothalamic-pituitary dysfunction.

**Autoimmune Oophoritis**

Most of these patients have had oligomenorrhea or amenorrhea; occasionally, symptoms related to enlarged polycystic ovaries or abnormal vaginal bleeding have been the initial manifestations. In most of these cases and others in which ovarian biopsy has not been performed, antibodies to steroid hormone–producing cells, including granulosa and theca cells, have been present in the serum. The ovarian failure is usually preceded or accompanied by one or more of the following disorders, most of which are thought to have an autoimmune basis: idiopathic Addison disease, idiopathic hypoparathyroidism, hyperthyroidism, Hashimoto disease, hypothyroidism, myasthenia gravis, juvenile-onset diabetes mellitus, juvenile rheumatoid arthritis, systemic lupus erythematosus, sicca syndrome, vitiligo, pernicious anemia, alopecia, autoimmune hemolytic anemia, idiopathic thrombocytopenia purpura, and mucocutaneous candidiasis.

On gross examination, the ovaries are usually of normal size, but they may be enlarged and polycystic (244). On histologic inspection, the primordial follicles appear normal, but inflammatory cells begin to infiltrate the theca cell layer as it differentiates at the edge of early maturing follicles (Fig. 56.44) (245). The intensity of the infiltrate increases with the degree of follicular maturation, and as the follicles enlarge, the inflammatory cells and degenerating granulosa cells desquamate into the lumen. If corpora lutea are present, they are similarly inflamed. Lymphocytes and plasma cells predominate, but eosinophils, histiocytes, and sarcoid-like granulomas have also been described. Occasionally, lymphoid infiltrates have been found in the ovarian hilus, sometimes in a perineural distribution, accompanied by an absence of Leydig cells, which suggests destruction of the latter by the inflammatory process. In 25% of the cases in one series (245), abnormal follicles with hyalinization were encountered.

**CYTOTOXIC DRUG AND RADIATION EFFECTS**

Cytotoxic drugs may be associated with a variety of ovarian changes, including a reduction or depletion of follicles, impaired follicular maturation, and focal or diffuse cortical fibrosis. These findings are consistent with clinical evidence of diminished ovarian endocrine function or ovarian failure in some patients. The ovarian failure is sometimes reversible after the cessation of therapy.

The ovary is among the most radiosensitive of organs, and ovarian failure occurs in most patients who receive pelvic radiation. Relatively low doses (500 to 600 R) are associated with complete or nearly complete disappearance of primordial and developing follicles, fibrosis of the ovarian stroma, and vascular sclerosis in more than 90% of patients. The ovarian stroma is more radioresistant than the follicles, and it may continue to secrete androgens after exposure.

**OVARIAN PREGNANCY**

The diagnosis of ovarian pregnancy, which accounts for as many as 3% of ectopic pregnancies, should be restricted to those cases without involvement of the fallopian tube (246). The typical clinical presentation is severe pain, often with hemoperitoneum, and laparotomy reveals an ovarian hemorrhagic mass that can simulate a neoplasm. Gross examination may reveal fetal tissue; in other cases, microscopic examination is diagnostic. Distinction of ovarian pregnancy from rare examples of primary ovarian gestational trophoblastic disease is made using criteria similar to those used in the uterus. We have seen one case of placental site nodules, with focal cystic degeneration, involving the ovary (Fig. 56.45).

**OVARIAN “TUMOR” OF THE ADRENOCORTICAL SYNDROME**

One example of this phenomenon, which is well known in the testis, has been reported in the ovary (247). A 36-year-old woman with congenital adrenal hyperplasia from 21-hydroxylase deficiency...
experienced an abrupt aggravation of her virilizing symptoms and underwent an adrenalectomy and partial left oophorectomy; persistent virilization led to completion left oophorectomy and right oophorectomy. Each adnexa contained ovarian or paraovarian soft brown masses that were microscopically identical to the testicular “tumor” of the adenogenital syndrome.

ECTOPIC TISSUES

One ovarian example of splenic hamartoma (“splenoma”) has been described (248); it formed a 1.5-cm nodule of splenic red pulp within the ovarian cortex. The differential diagnosis includes splenic-gonadal fusion (see “Congenital Lesions”).

Smith et al. (249) reported a unique case of ovarian prostatic tissue that was associated with a hilar proliferation of mesonephric remnants. The authors proposed that the prostatic tissue was a result of metaplastic induction by the mesonephric remnants.

Several cases of implantation of gallstones on the surface of the ovary have been reported as a complication of laparoscopic cholecystectomy (250).

AMYLOIDOSIS

When ovarian involvement by amyloidosis occurs, this is almost always an incidental microscopic finding on histologic examination. In one reported case, however, bilateral ovarian masses caused by amyloidosis were the presenting manifestation of the disease in a patient receiving renal dialysis (251).

CALCIFICATION

One case of extensive idiopathic bilateral ovarian calcification has been described (252). The normal-sized ovaries had a stony-hard consistency as a result of innumerable spherical laminated calcific foci without associated epithelial cells within the ovarian stroma.

CONGENITAL LESIONS

These very rare lesions include lobulated, accessory, and supernumerary ovaries; splenic-gonadal fusion; and adrenal cortical rests.

FIGURE 56.45 Placental site nodules. The process caused a small cystic ovarian mass.

OVARIAN REMNANT SYNDROME

The differential diagnosis of accessory and supernumerary ovaries includes the ovarian remnant syndrome (253). Patients with this syndrome have a history of a presumably total bilateral oophorectomy but then present with findings related to the presence of residual ovarian tissue. The oophorectomy in such cases was often complicated by the presence of adhesions. Weeks to years after the oophorectomy, the patient may present with chronic or cyclic pelvic pain and, in some cases, a pelvic mass. In some cases, the mass has resulted in ureteric or bowel obstruction. Pathologic examination usually reveals one or several follicular or corpus luteum cysts within a remnant of ovarian tissue embedded within adhesions. Less common findings have included endometriosis or ovarian tumors.

OVARIAN ARTERIAL EMBOLIZATION

Payne et al. (254) have reported embolic microspheres within ovarian arterial vasculature in a woman undergoing uterine artery embolization for the treatment of uterine leiomyomas. They postulated that this finding in some patients could possibly lead to ovarian hypoxia and premature ovarian failure.

REFERENCES


SECTION X ■ Female Reproductive System and Peritoneum


