
The ovary is a fairly straightforward organ as far as the pathologist is concerned. Find tumor, remove tumor, identify tumor. No messing around with nonneoplastic pathology, reactive lesions, and so forth. If it looks malignant, it probably is.

Normal Histology and Definitions

Surface epithelium: Surface epithelium is essentially a mesothelial lining. It is easily rubbed off the surface, so you do not always see it. Most epithelial tumors (the most common neoplasms) are thought to arise from this epithelium or from invaginations of it. Think of it as a pluripotent stem cell layer.

Stroma: The ovarian stroma is blue and spindly, with a streamy, fascicular look. Most of the cells in the stroma are fibroblasts (Figure 15.1).

Sex cord cells: Sex cord cells are the hormone-secreting supporting cells of the ovary, the thecal cells and granulosa cells. The thecal cells, under luteinizing hormone stimulation, secrete androgens, and the granulosa cells, under follicle-stimulating hormone control, convert androgens to estrogen. Together they nurture an oocyte to ovulation.

Follicles: The follicles are characterized by a halo of thecal cells outside a ring of granulosa cells (see Figure 15.1), all surrounding the giant oocyte (germ cell). In developing follicles, the granulosa cells form Call-Exner bodies, rosettes of granulosa cells surrounding pink globules.

Luteinized: Similar to decidualized, luteinized indicates cells that have become plump with abundant pink cytoplasm.

Corpus luteum: The corpus luteum is a newly ovulated follicle (Figure 15.2). The capsule of luteinized granulosa cells collapses in on itself, becoming undulating, and there is associated hemorrhage. The corpus luteum produces progesterone until (and if) the placenta takes over. If there is no pregnancy, it involutes.

Corpus albicans: The former corpus luteum ultimately hyalinizes to form cloud-shaped pink islands in the ovary, scars of old follicles (see Figure 15.2).

Walthard's rests: Walthard's rests are nests of transitional (urothelial) type epithelium in the ovary and fallopian tube.

Rete ovarii: Analogous to the rete testis in men, rete ovarii are rudimentary gland spaces located in the hilum of the ovary. They are angulated, slit-like spaces with a low cuboidal epithelium (Figure 15.3). Do not mistake them for cancer.

Follicle cyst: A follicle cyst is lined with the normal components of the follicle, the granulosa cells, and the thecal layer (Figure 15.4). A similar lesion is the hemorrhagic corpus luteum cyst, which is a blood-filled corpus luteum.

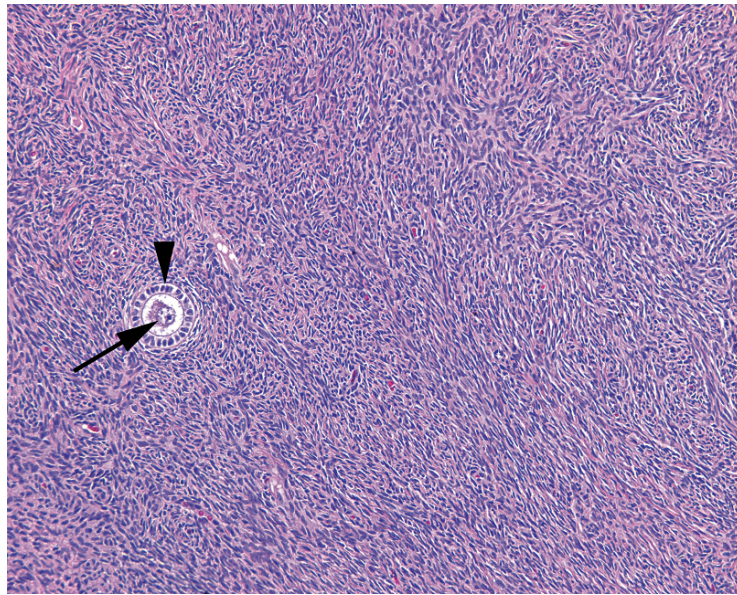


FIGURE 15.1. Ovarian stroma with follicle. Typical ovarian stroma is blue and cellular, with a vaguely fascicular or storiform pattern. A small primary follicle is seen with the central oocyte (arrow) and a ring of granulosa cells (arrowhead).

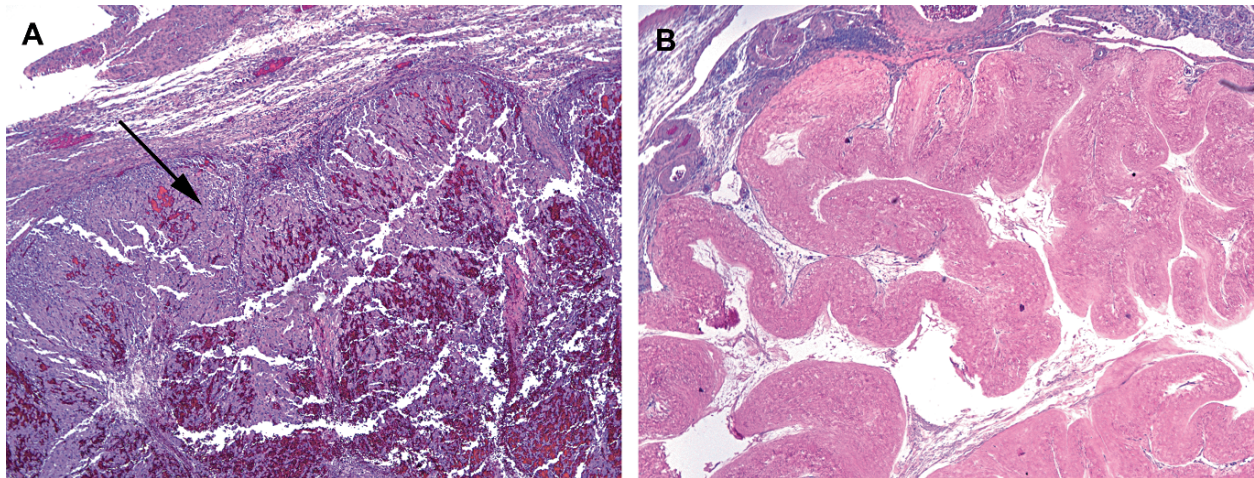


FIGURE 15.2. (A) Hemorrhagic corpus luteum, with undulating layers of luteinized granulosa cells (arrow) and associated blood. (B) A corpus albicans, the remnant of a prior corpus luteum.

Inclusion cyst: An inclusion cyst is a simple cyst lined with a cuboidal, columnar, or ciliated epithelium, often budding inward from the ovarian surface (see Figure 15.4). When small, these can be called surface inclusion cysts. However, if they are large, they are best referred to as serous cystadenomas (see later).

Neoplasms

For each cell type defined above (and then some), there are families of neoplasms that can arise. Table 15.1 lists the types of neoplasms that can occur. Those in parentheses are rare enough that we will not talk about them here.

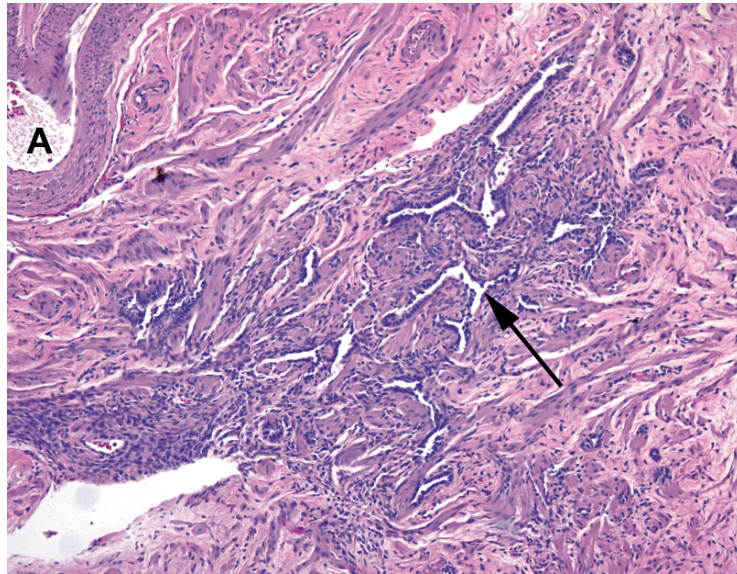


FIGURE 15.3. Rete ovarii. This vestigial structure is found at the hilum of the ovary, adjacent to large arteries (A) and veins. The rete consist of slit-like channels with a cuboidal cell lining (arrow).

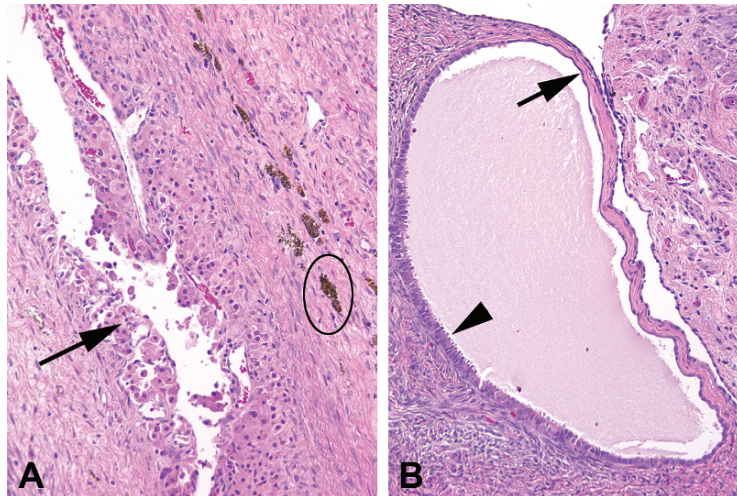


FIGURE 15.4. Follicular cyst versus inclusion cyst. (A) A follicle cyst is lined by luteinized cells, similar to those seen in the corpus luteum (arrow). There is adjacent hemosiderin (oval). (B) An inclusion cyst may be lined by an attenuated epithelium, similar to the surface epithelium (arrow), or may show tubal metaplasia (arrowhead).

TABLE 15.1. Neoplasms of the ovary.

Surface epithelial tumors	Germ cell tumors	Sex cord stromal	Metastases
Serous	Teratoma	Fibroma	Gastrointestinal
Mucinous	(Dysgerminoma)	Thecoma	Urothelial
Endometrioid	(Yolk sac)	Granulosa cell tumor	Others
Clear cell	(Choriocarcinoma)	(Sertoli cell tumor)	
Brenner or transitional	(Embryonal)	(Leydig cell tumor)	
		(Sertoli-Leydig cell tumor)	

Note: Entries in parentheses are rare tumors that are not discussed in this chapter.

Epithelial Neoplasms

Epithelial neoplasms are one of three types: benign, borderline, and malignant. Benign tumors do not metastasize, malignant ones do, and borderline tumors may recur or rarely metastasize. The nomenclature is as follows:

Adenoma: An adenoma is a benign epithelial proliferation. When cystic, as they often are, it is a *cystadenoma*. If biphasic with a secondary fibrous stromal component, it is an *adenofibroma*. If all three, it is a *cystadenofibroma*. Histologically, the cystadenomas are simple or multilocular cysts with a flat epithelial lining.

Borderline tumor (atypical proliferative tumor, low malignant potential): Borderline lesions have an increasing epithelial complexity over the adenomas. Their epithelium begins to ruffle up in papillary fronds and may “ruffle down” into the stroma in a way that looks similar to invasion. However, they do not cross the basement membrane, do not invade as single cells, and do not induce a desmoplastic reaction. Borderline tumors can shed cells into the peritoneum, which may stick onto other organs and begin to grow like weeds. However, they often do not technically invade and are called noninvasive implants, not metastases. Invasive implants can also occur and act like true metastases.

Carcinoma: Carcinomas commonly present as combination cystic/solid tumors and are called *cystadenocarcinomas*. However, there is not a significant clinical difference between calling something a *carcinoma* and a *cystadenocarcinoma*. These can be divided into low- and high-grade carcinomas, but all types can metastasize.

Carcinosarcoma: A carcinosarcoma (malignant mixed mullerian tumors in the gynecologic tract) is a carcinoma in a sarcomatous stroma. An adenosarcoma would be a benign epithelial neoplasm in a sarcomatous stroma, which is rare.

Within the surface epithelial group, there are five types of epithelial neoplasms. Each type can be subdivided into benign, borderline, or malignant, as shown in Table 15.2.

Serous (Most Common, Formerly Papillary Serous)

Cystadenoma: Cystadenomas are simple cysts lined by a tubal-like epithelium with columnar and/or ciliated cells. They can become huge, but the lining remains simple. The contents are watery.

Borderline tumor (atypical proliferative tumor; tumor of low malignant potential): Borderline tumors have increasingly complex papillary fronds, looking grossly granular. The papillary pattern is characterized by tree-like branching of smaller and smaller papillae (Figure 15.5). However, the epithelium lining the papillae is usually a single layer without significant atypia. When the papillae acquire secondary epithelial proliferations called *micropapillae* (the medusa-head look; Figure 15.6), they are on their way to *micropapillary serous carcinoma* (MPSC). A few millimeters of confluent micropapillary pattern upgrades this to an actual MPSC, in some textbooks.

Micropapillary serous carcinoma (micropapillary borderline tumor): Micropapillary serous carcinoma is a low-grade carcinoma characterized by the medusa-head pattern (see Figure 15.6). The nuclei should not be too pleomorphic. This carcinoma can occur within a confined cyst (noninvasive MPSC) or break out of the cyst and into the stroma (invasive). This perplexing concept of a noninvasive carcinoma is somewhat like the papillary urothelial carcinomas of the bladder or the papillary carcinomas of breast. Psammoma bodies are common. When

TABLE 15.2. Five types of epithelial neoplasms.

	Serous	Mucinous	Endometrioid	Clear cell	Transitional
Cystadenoma	60%	80%	Rare	Rare	>90%
Borderline tumor	15%	15%	Rare	Rare	Rare
Carcinoma	25%	>5%	>95%	>95%	6%

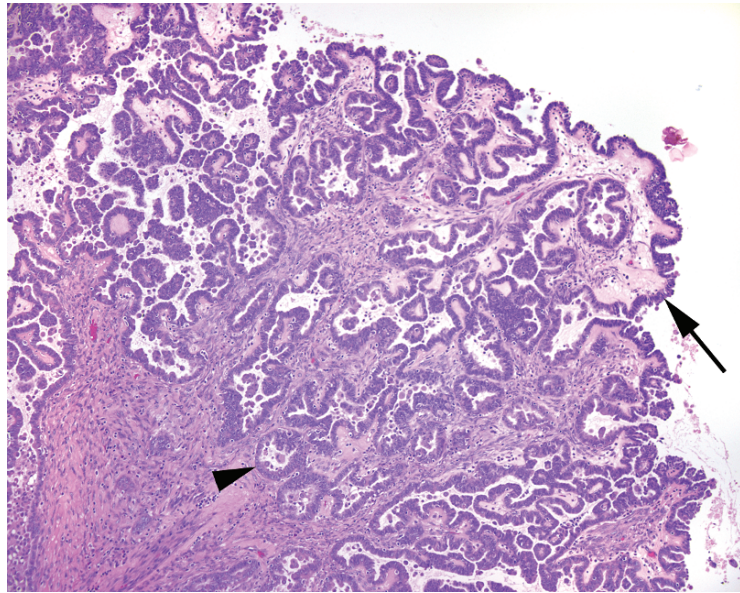


FIGURE 15.5. Borderline serous tumor. The epithelial lining is composed of serous, or nonmucinous, cells (arrow). The overall architecture is quite complex, with papillary branching and invaginated folds that should not be mistaken for invasion (arrowhead). However, the epithelial component is mostly a monolayer.

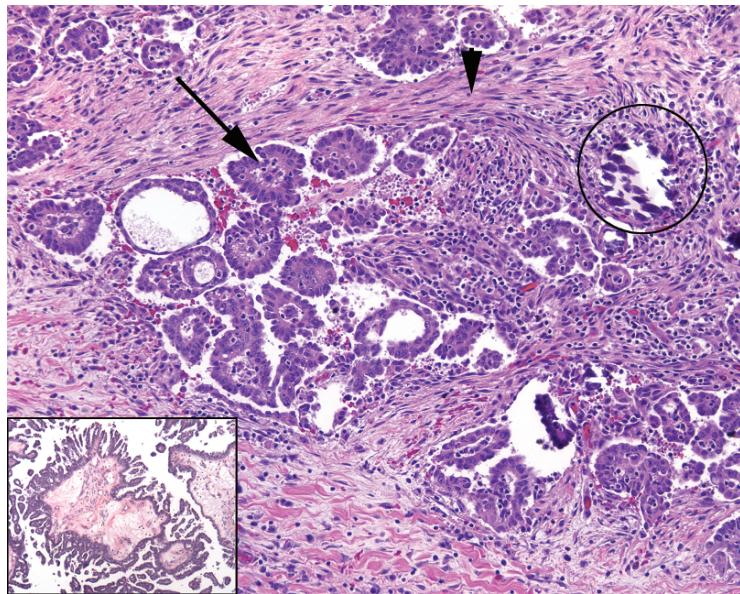


FIGURE 15.6. Micropapillary serous carcinoma. When invasive, micropapillary serous carcinoma looks like tiny florets of cells (arrow) in a desmoplastic stroma (arrowhead). Psammoma bodies are common (circle). **Inset:** The medusa-head, or micropapillary, pattern is indicative of micropapillary serous carcinoma. Compare the epithelial micropapillae to the simple epithelium of the borderline tumor (see Figure 15.5).

invasive, the tumor nests have a flower-like shape, with nuclei pointing outwards, and often sit in small cleft-like spaces (Figure 15.6)

High-grade serous carcinoma: High-grade serous carcinoma has very high-grade, mitotically active, apoptotic, pleomorphic blue nuclei (Figure 15.7). The architecture can be papillary, micropapillary, solid, or in nests with slit-like spaces.

Mucinous

Cystadenoma: Cysts (often multilocular) are lined with fairly flat mucinous epithelium.

Borderline tumor (atypical proliferative tumor; tumor of low malignant potential): The vast majority of these are of the intestinal type, which means they imitate intestinal epithelium, with goblet cells and glandular architecture. However, 15% are of the endocervical type, which presents as papillary architecture (like serous) with low-grade, squared-off, endocervical-like mucinous cells (Figure 15.8).

Cystadenocarcinoma: Mucinous cystadenocarcinoma is very uncommon. Mucinous carcinoma in the ovary is usually a metastasis from the gastrointestinal tract.

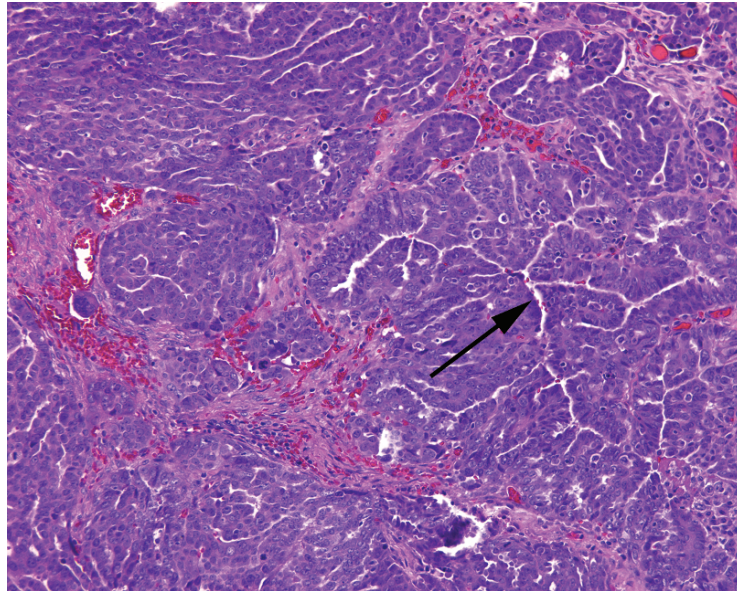


FIGURE 15.7. High-grade serous carcinoma. This tumor is shown invading the stroma. The cells are pleomorphic and dark, with prominent nucleoli, and grow in solid nests with slit-like spaces (arrow).

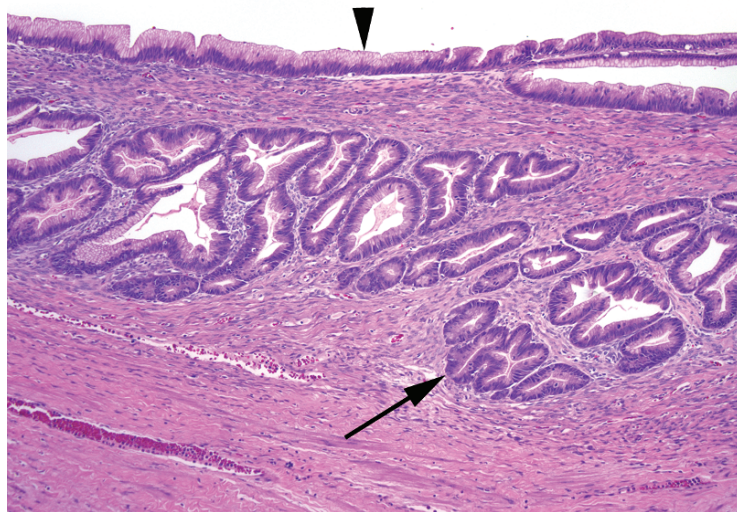


FIGURE 15.8. Borderline mucinous tumor. The cyst lining (arrowhead) is mucinous and resembles endocervical cells in this example. As with the borderline serous tumor, invaginations into the stroma should not be mistaken for invasion (arrow).

Endometrioid

Adenoma: How is endometrioid adenoma different from endometriosis? It has no endometrial stroma. Also, these adenomas are rare. Endometriosis is common.

Carcinoma: Endometrioid carcinomas imitate endometrial carcinoma and so have similar architecture to the patterns found in the uterus, including tubular to cribriform glands and villous structures (Figure 15.9). They may arise within endometriosis, they are often found along with endometriosis, and a concurrent endometrial carcinoma is not uncommon. They may be low or high grade.

Clear Cell

Carcinoma: Clear cell carcinomas are clear cells occurring in papillary, glandular, nested, or trabecular patterns. Cells tend to fall out of the center of the nests, leaving a hobnailed layer of cells outlining the nest (Figure 15.10). These are high grade and, like endometrioid carcinoma, are also associated with endometriosis.

Transitional

Adenoma/adenofibroma: Transitional adenomas/adenofibromas are the Brenner tumor, characterized by nests of transitional epithelium in a fibrous stroma (Figure 15.11). There may be a mucinous layer surrounding a central lumen in each nest.

Malignant Brenner tumors: Malignant Brenner tumors are characterized by very atypical cells. *Transitional cell carcinoma* (resembling that seen in the bladder) is a term used when there is no coexisting Brenner element.

How can you tell which pattern you have?

If you see...	Think...
Clear cells	Clear cell
Hobnail cells lining spaces	Clear cell
Mucinous cells with papillary fronds	Mucinous
Mucin-secreting cells	Mucinous
Papillary fronds	Serous, or any other type
Sheets of high-grade nuclei	Serous or undifferentiated
Solid growth with slit-like spaces	Serous
Squamous-like nests of round cells	Transitional
Tall villi	Endometrioid or mucinous
Tubular glands	Endometrioid

Cancer Pathways

There are thought to be two cancer pathways for serous neoplasms:

Cystadenoma → Atypical proliferative serous tumors → Micropapillary serous carcinoma → Invasive micropapillary serous carcinoma

Terribly bad luck → High-grade serous carcinoma (de novo), often p53 positive

Nonepithelial Neoplasms

For the purposes of this chapter, we will gloss over the germ cell and sex cord stromal neoplasms, except for the most common entities.

Germ Cell Neoplasms

Anything that can occur in the testis can occur in the ovary. The most common germ cell neoplasm in the ovary is the teratoma, but you can also see dysgerminoma (seminoma), yolk sac tumor, choriocarcinoma (arising unrelated to gestational trophoblastic disease), and embryonal carcinoma. Each looks similar in testis and ovary.

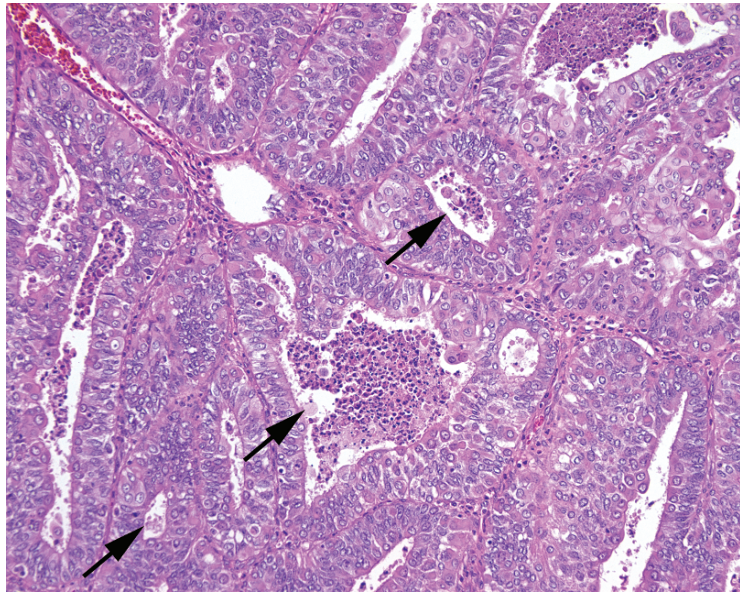


FIGURE 15.9. Endometrioid carcinoma. The nuclei are cleared out and pleomorphic, like endometrioid carcinoma of the endometrium. Distinct glandular spaces are visible (arrows), some with central necrosis.

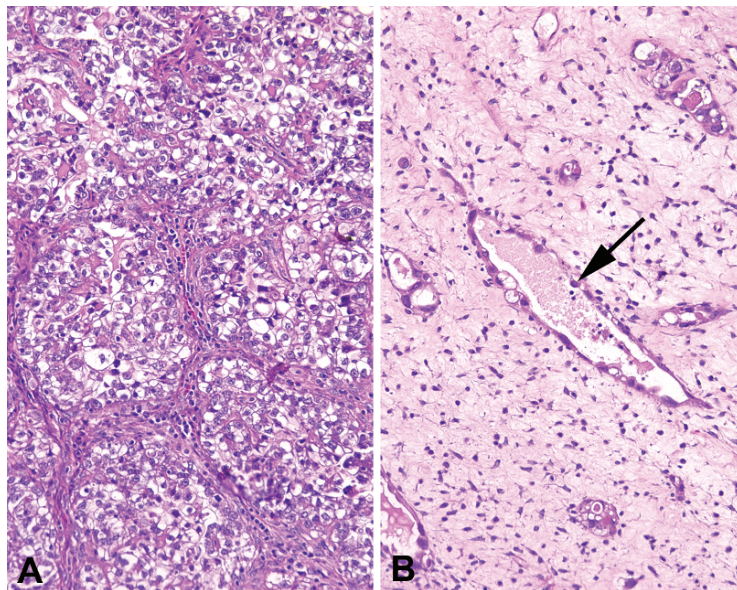


FIGURE 15.10. Clear cell carcinoma. (A) In this field, nests of clear cells are seen separated by fibrovascular septa. (B) A less cellular area of the same tumor shows vessel-like spaces lined by atypical cells that protrude into the lumen in hobnail fashion (arrow).

Teratomas are usually composed of at least two of three embryonic derivatives: ectoderm, endoderm, and mesodermal cells. They are often cystic (dermoid cyst) and may grow to a large size. Common elements include squamous epithelium, skin adnexal structures, hair, fat, cartilage, thyroid, brain and nerve tissue, gut epithelium, and respiratory epithelium. Primary nonovarian neoplasms can arise in teratomas, creating an endless list of case reports. Teratomas restricted to mature elements are benign in the ovary.

All teratomas must be carefully evaluated for immature (embryonal-looking) elements. The most common immature tissue type is brain. After a few products-of-conception (POC) specimens

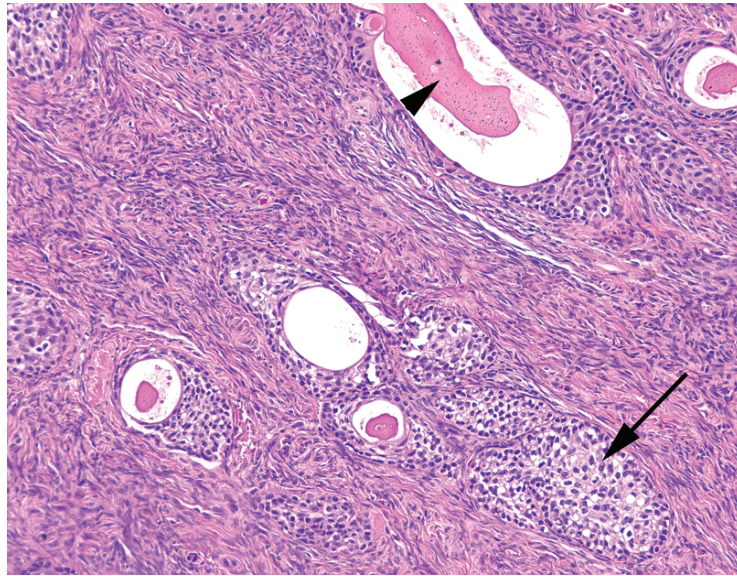


FIGURE 15.11. Brenner tumor. Nests of transitional-type epithelium (resembling urothelium; arrow) in a fibrotic stroma are typical. Some form gland-like spaces with pink secretions (arrowhead).

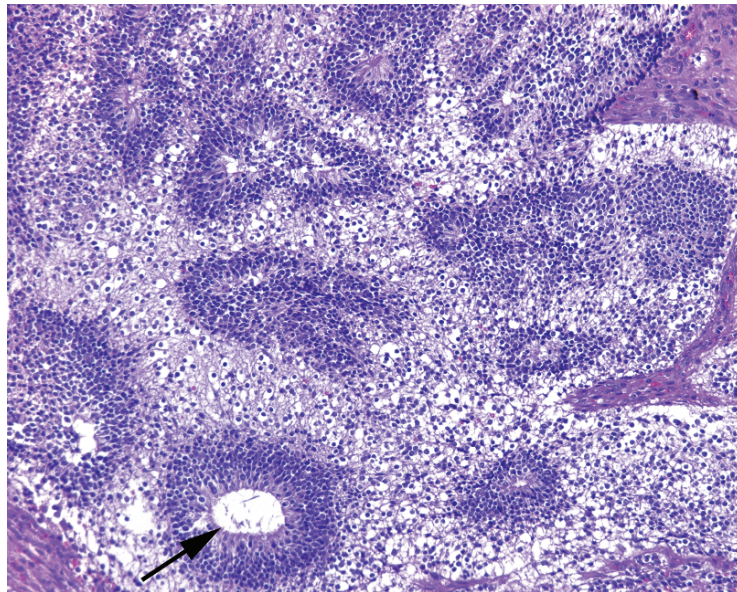


FIGURE 15.12. Immature neural tissue, teratoma. The combination of hypocellular areas and dense small round blue cell areas are suggestive of fetal brain. Rosettes (arrow) may also be seen. Finding this histology in a teratoma indicates an immature component.

or fetal autopsies, you should recognize fetal brain—dark blue cells in a myxoid, clear background (Figure 15.12).

Sex Cord Stromal Neoplasms

Sex cord stromal neoplasms include all of the fibrous and sex hormone cell types. The most common tumors are the fibroma/thecoma group. Granulosa cell tumors are also not uncommon. However, many of the weird and paradoxical ovarian lesions (Sertoli-Leydig?) fall into this group. Cell types in these tumors may be luteinized, just like their normal counterparts.

The fibroma/thecoma group is a spectrum of lesions from the pure fibroma, to the common mixed fibrothecoma, to the pure thecoma. Grossly they look like leiomyomas, which are very rare in the ovary. On cross section, the thecoma areas are butter-colored, and stand out from the grey-white fibroma. Histologically the tumors are also similar to leiomyomas but have more of a sheet-like pattern with bland, spindled cells (Figure 15.13). However, the tiny lipid

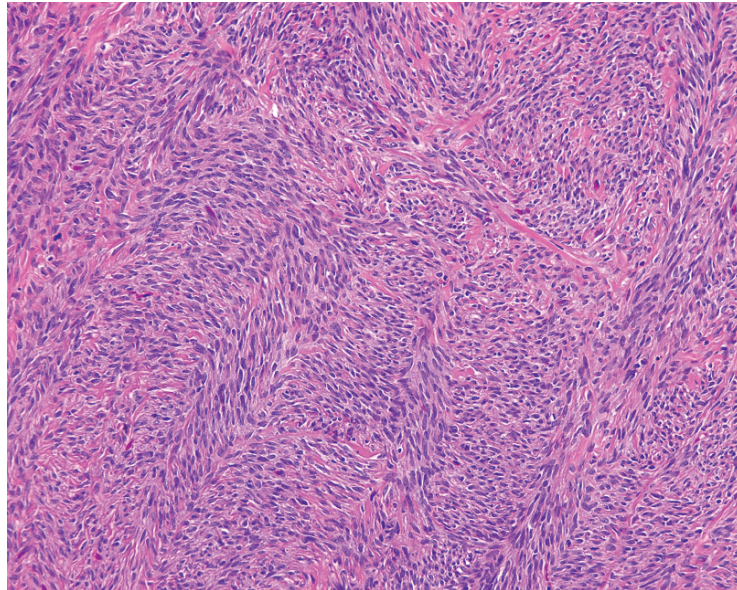


FIGURE 15.13. Fibrothecoma. This specimen shows mainly the fibroma component, with fascicles of bland spindled cells.

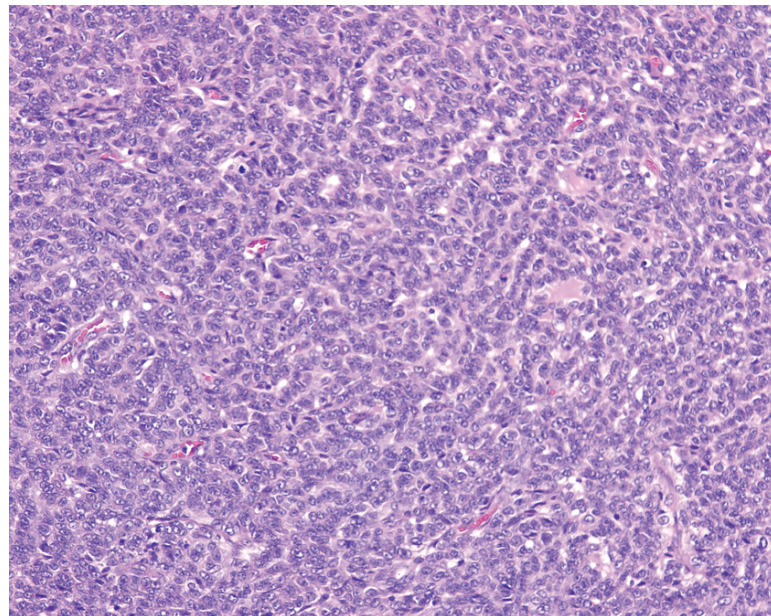


FIGURE 15.14. Granulosa cell tumor, low power. This section shows the characteristic cords and rows of granulosa cells, creating a pattern like watered silk, or (for those not frequenting fabric stores), a topographic map.

vacuoles that identify the thecoma component (steroid cells, remember?) are very hard to see on H&E stain, so the gold standard is an oil red O done on frozen section. Bright red lipid globules indicate a thecoma component. These are benign tumors.

Granulosa cell tumor cells appear similar to the normal granulosa cells in the ovary but have more distinctive oval folded or angulated nuclei with a longitudinal groove (the “coffee bean” nuclei). In a tumor, these cells may become more closely packed, almost giving the impression of nuclear molding, but they are not as blue, hyperchromatic, or crowded as small cell carcinoma. At low power the cells are arranged in sheets, with a zigzag “watered silk” pattern (think of a topographic map; Figure 15.14). The cells appear very uniform throughout. Rarely, you may see the pathognomonic Call-Exner bodies as seen in the developing follicle. These are technically of low malignant potential but may recur after many years.