Ovarian Sex Cord Stromal Tumors:
Uncommon Tumors That May Mimic A Variety of More Common Tumors
An Overview of Helpful Morphology and Immunomarkers

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Introduction: Sex cord-stromal tumors are uncommon ovarian neoplasms, accounting for 5% to 12% of ovarian tumors, yet many of these tumors may mimic a range of more common epithelial and germ cell tumors, both benign and malignant. Two growth patterns in ovarian tumors that are problematic in terms of overlap between sex cord-stromal, epithelial and germ cell tumors are 1.) tubuloglandular growth and 2.) sex cord-like growth. A third but much less common pattern is that of single infiltrative clusters or cells with signet ring features or vacuoles. This lecture will focus on differential diagnosis of these three growth patterns, with emphasis on granulosa cell tumors.

Outline of Lecture:

- Immunohistochemistry of Sex Cord-Stromal Ovarian Tumors
- Pattern 1: Tubuloglandular:
  - Granulosa Cell Tumor
  - Sertoli Cell Tumor / Sertoli Leydig Cell Tumor
  - Sex Cord Tumor with Annular Tubules
    - Endometrioid Adenocarcinoma
    - Carcinoid Tumor
    - Struma Ovari
    - Strumal Carcinoid Tumor
    - Yolk Sac Tumor, glandular variant
- Pattern 2: Sex cord-like:
  - Granulosa cell Tumor
  - Fibroma with sex cord elements
    - Endometrioid Adenocarcinoma (sex cord variant)
    - Adenofibroma/Adenosarcoma with sex cord-like elements
- Pattern 3: Single infiltrating cells/clusters +/- signet ring/mucin/vacuoles
  - Sclerosing Stromal Tumor
    - Metastatic Gastric / Breast Cancer
    - Mucinous Carcinoid (primary or metastatic)

Clinical Context, Gross Findings and Differential Diagnosis:
Patient age, clinical setting and gross findings are useful since many patients with ovarian sex cord stromal tumors are young, have hormonal alterations (estrogenic or androgenic manifestations, elevated serum markers (e.g. AFP) or syndromic associations (e.g. Peutz Jeghers syndrome); the tumors are often unilateral, yellow/orange, and multicystic. In contrast, many of the mimics, particularly adenocarcinoma, would be unusual in a young patient and would not likely present with such clinical or gross features. Thus, discordance between the clinical context and the pathologic impression should prompt for further confirmation of the pathologic diagnosis. Generally, we prefer to confirm the morphologic diagnosis of granulosa cell tumor, Sertoli cell tumor or Sertoli Leydig cell tumor with immunohistochemistry given the potential for overlap with so many other tumor types.
**Immunohistochemistry**

Inhibin and calretinin are the traditional markers of ovarian sex cord-stromal differentiation. Expression tends to be stronger and more diffuse in granulosa cell tumors, Sertoli and Sertoli-Leydig cell tumors than in fibroma or thecoma. Ovarian steroid cell tumors will also mark with inhibin and calretinin, as will ovarian hilus cells and cells of stromal hyperthecosis. Nuclear expression of WT1 and membrane expression of CD99 also characterize many sex cord-stromal tumors, but in our practice, we don’t use these markers since they are not as reliable as others in our laboratory. ER and PR may be expressed in many granulosa cell tumors. When trying to distinguish sex cord-stromal tumors from epithelial tumors, care must be exercised in selection of epithelial markers: pan-keratin may mark granulosa cell tumors and Sertoli cell tumors to variable degrees and this may cause confusion with adenocarcinoma. EMA (epithelial membrane antigen) is a better choice since it is negative in sex cord-stromal tumors. Conversely, some endometrioid adenocarcinomas may express inhibin, calretinin or WT-1, albeit in a weak, patchy pattern.

Steroidenic factor 1 (SF 1) is a recently studied nuclear protein that appears to be a useful marker of ovarian sex cord differentiation. It marks lesions of sex cord-stromal differentiation in a nuclear pattern and is negative in epithelial tumors. SF 1, also known as Adrenal Binding Protein 1, is found in many of the same tissues that mark with inhibin. SF 1 is a transcription factor regulating steroidogenesis of the adrenal and pituitary glands. Immunoexpression is observed in adrenal cortical tumors and pituitary adenoma. It is also thought that SF 1 is involved in gonadal development. In the testis, SF 1 marks Sertoli cells and Leydig cells. Recently it was demonstrated that SF 1 marks ovarian sex cord tumors (granulosa cell tumor, Sertoli cell tumor, Sertoli Leydig cell tumor, and fibroma/thecoma) but not endometrioid adenocarcinoma or carcinoid tumor. The nuclear expression pattern makes it a preferred marker.

**Recommended panel:**

To confirm a diagnosis of granulosa cell tumor, we prefer the quartet of SF-1, inhibin, calretinin and EMA and we avoid cytokeratin stains. The following table lists the results expected in most tumors, keeping in mind that exceptions do occur.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Granulosa Cell Tumor</th>
<th>Sertoli Cell Tumor</th>
<th>Endometrioid Adenocarcinoma</th>
<th>Carcinoid Tumor</th>
<th>Struma Ovarii</th>
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<td>SF-1</td>
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<td>Negative</td>
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<td>Calretinin</td>
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<tr>
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</table>
Differential Diagnosis by Patterns

PATTERN 1: TUBULOGLANDULAR GROWTH:

Granulosa Cell Tumor versus Endometrioid Adenocarcinoma
The microfollicular and solid pattern of granulosa cell tumor may resemble endometrioid adenocarcinoma. Morphologic features favoring granulosa cell tumor include nuclear grooves, Call-Exner bodies, a mixture of growth patterns including trabecular growth, and an absence of squamous differentiation.

Potential Pitfall: Nuclear grooves are not pathognomonic of granulosa cell tumor. Nuclear grooves may be seen endometrioid adenocarcinoma.

Endometrioid adenocarcinoma is favored by the presence of endometrioid appearing cells and squamous differentiation. In questionable cases, immunostains may be helpful (positive EMA, negative SF-1, calretinin, inhibin).

Granulosa Cell Tumor versus Sertoli Cell Tumor
Microfollicular growth in granulosa cell tumor may resemble the hollow packed tubules of Sertoli cell tumor, however the latter usually does not exhibit the mixed array of other growth patterns seen in granulosa cell tumor. In difficult cases, cytokeratin expression can be used to confirm a diagnosis of Sertoli cell tumor.

Granulosa Cell Tumor versus Carcinoid Tumor
Microfollicular and trabecular growth can be seen in both these tumors but the typical cytologic features of granulosa cell tumor (nuclear grooves, Call-Exner bodies) will not be seen in carcinoid tumor. Teratomatous elements favor a diagnosis of carcinoid tumor, as does the presence of nuclei with neuroendocrine type chromatin texture (stippled or so-called salt and pepper texture). Neuroendocrine markers such as chromogranin and synaptophysin can be useful to identify carcinoid tumor.

Granulosa Cell Tumor versus Struma Ovarii
Microfollicular growth of granulosa cell tumor may sometimes resemble the follicles of struma ovarii but otherwise, each entity should show other morphology that clearly leads to the correct diagnosis. Struma ovarii may be accompanied by other teratomatous elements, something not expected in granulosa cell tumor. Generally the mixture of other growth patterns in the latter is not seen in struma ovarii. The nuclear shape may also helpful. Struma ovarii usually exhibits a uniform, monotonous round/oval nuclear shape without nuclear contour irregularities whereas most granulosa cell tumors show more nuclear atypia, folds, and grooves.

Granulosa Cell Tumor versus glandular variant Yolk Sac Tumor
Microfollicular and trabecular growth of granulosa cell tumor can resemble the glandular variant of yolk sac tumor but, again, there are usually other morphologic findings that allow for a straightforward diagnosis. Yolk sac tumor often shows a mixture of growth patterns (i.e. reticular, papillary, solid, microcystic) and may be mixed with other germ cell tumor components that are not expected in granulosa cell tumor. Immunostaining for SALL-4, Glypican 3, AFP

PATTERN 2: SEX CORD LIKE GROWTH

Fibroma with sex cord elements versus Granulosa Cell Tumor
Some fibromas may contain foci of sex cord elements. Typically these are microscopic foci and only a few foci are present; this does not alter the behavior.
Conversely, some granulosa cell tumors may show a fascicular, spindled growth pattern that resembles thecoma or cellular fibroma. Though it is unusual for such a tumor to lack other distinctive patterns of granulosa cell tumor growth (such as microfollicular or trabecular), rare cases may be difficult to resolve based on morphology alone. Immunohistochemistry is not of great value since calretinin, inhibin, WT-1, and SF 1 can be seen in both tumor groups. Reticulin staining, however, is useful. In granulosa cell tumor, the reticulin fibers will highlight bundles, fascicles and nests of tumor cells but the fibers will not surround individual cells. In contrast, the reticulin fibers will surround individual spindle cells.

**Adenofibroma/Adenosarcoma with sex cord elements versus Granulosa Cell Tumor**
Similar to fibroma with sex cord elements, both adenofibroma and adenosarcoma may contain these elements, typically in a microscopic amount. There usually is sufficient morphology present to easily make the diagnosis of adenofibroma or adenosarcoma and these tumors are not typically confused with granulosa cell tumor. Behavior is not affected by sex cord elements.

**Endometrioid Adenocarcinoma, Corded and Hyalinized Variant, versus Granulosa Cell Tumor**
A rare variant of endometrioid adenocarcinoma of the ovary or uterus may contain a sex cord-like or sertoliform growth pattern that resembles granulosa cell tumor. The unusual growth zones may be embedded in hyalinized stroma, thus giving the name “corded and hyalinized endometrioid adenocarcinoma”. Such tumors generally exhibit clear cut areas of typical endometrioid adenocarcinoma that allow for the correct diagnosis. However, we have encountered some cases that lack such areas and truly resemble granulosa cell tumor. Identification of squamous differentiation is a key clue to correctly diagnosis adenocarcinoma. Immunostaining can be helpful in difficult cases.

**PATTERN 3: INFILTRATING CLUSTERS/CARDS with SIGNET RING/MUCIN/VACUOLES**

**Sclerosing stromal tumor versus metastatic carcinoma**
Lobular breast cancer and metastatic gastric carcinoma involving the ovary may grow as single infiltrating polygonal tumor cells embedded within fibrotic stroma, resembling a sclerosing stromal tumor. Such metastases generally lack the distinctive blood vessels and the pseudolobular growth pattern of sclerosing stromal tumor. In addition, clinical history of a primary gastrointestinal or breast cancer should be informative in the differential diagnosis. Because sclerosing stromal tumor affects young women, the likelihood of a metastatic cancer to the ovaries is comparatively low. EMA immunostaining should highlight metastatic carcinoma cells and confirm that diagnosis.

**Sclerosing stromal tumor versus mucinous carcinoid tumor**
A rare variant of carcinoid tumor is the mucinous carcinoid tumor, which may be primary to the ovary or metastatic. A range of growth patterns can be seen. Infiltrative dispersed clusters or single tumor cells with a mucin droplet or signet ring appearance may raise consideration of either sclerosing stromal tumor or metastatic mucinous/signet ring adenocarcinoma. Generally, however, there will be clear cut areas of carcinoid morphology in the tumor. Distinguishing primary versus metastatic origin of mucinous carcinoid is important; appendiceal origin or other intestinal origin should be considered. CK7 and CK20 may be helpful for that purpose. Keratin or EMA positivity will separate carcinoid from sclerosing stromal tumor, as will calretinin and inhibin.
SUMMARY OF TUMOR TYPES

Granulosa Cell Tumor

Granulosa cell tumors range from small incidentally discovered nodules only a few millimeter in diameter to large tumors more than 30 cm in diameter. Some are totally solid, but most are partly cystic. The solid portions are pink, tan, brown, or light yellow and vary from soft to firm in consistency. Rare granulosa cell tumors grow as large cysts with a wall only a few mm thick. These are supposedly more likely than other granulosa cell tumors to be androgenic.  

Microscopically, the tumor cells resemble normal granulosa cells. They are small and round, cuboidal, or fusiform with pale cytoplasm and ill-defined cell borders. The nuclei are round or oval with fine chromatin and a single small nucleolus. Longitudinal folds or grooves are present in many nuclei and are a characteristic feature of the adult type of granulosa cell tumor. Mitotic figures are usually infrequent and pleomorphic or atypical nuclei are uncommon. Rare granulosa cell tumors contain foci of cells with bizarre nuclei, but this does not appear to imply an adverse prognosis. Extensive tumor cell luteinization is seen in about 1% of adult granulosa cell tumors. Luteinized granulosa cells have abundant eosinophilic cytoplasm, well-defined cell borders, and central nuclei, and resemble the luteinized granulosa cells of the corpus luteum. Some luteinized granulosa cell tumors occur in pregnant women, but they are also seen in patients with androgenic granulosa cell tumors, and as idiopathic findings.  

A diverse range of growth patterns are exhibited by adult granulosa cell tumors, often mixed together. The patterns do not have any prognostic significance, but because they may mimic other tumor types, awareness of them is critical. The microfollicular pattern is the most typical one and consists of nests and sheets of granulosa cells that contain small spaces filled with eosinophilic secretions and cellular debris. The spaces resemble the Call-Exner bodies of developing follicles. In the macrofollicular pattern, large, often irregularly shaped follicles are lined by stratified granulosa cells. Granulosa cells grow in anastomosing bands, ribbons, and cords in the trabecular pattern; and in irregular undulating ribbons in the gyriform or watered-silk pattern. Nests and islands of tumor cells are surrounded by fibrous stroma in the insular pattern. The cells grow in large irregular sheets with no organized substructure in the solid or diffuse pattern. Many granulosa cell tumors contain large cysts lined by granulosa cells. The cysts may contain blood and hemosiderin-laden macrophages are often present in the walls. Rare cystic granulosa cell tumors grow as large unilocular cysts lined by stratified granulosa cells among which are microfollicles or areas of trabecular growth. 

Granulosa cell tumors have a variable amount of fibrous or thecomatous stroma. Tumors with a prominent fibrothecomatous stroma have been called granulosa-theca cell tumors but when granulosa cells comprise > 5-10% of the a tumor it can be classified as a granulosa cell tumor. Tumors with only a minor granulosa cell component are best classified as a thecoma or fibroma with minor sex cord elements (<5%). Rarely, a granulosa cell tumor contains heterologous mucinous epithelium. Equally rare is the finding of foci of hepatic cell differentiation in a granulosa cell tumor.  

It is difficult to predict the prognosis of a granulosa cell tumor, but some pathologic findings correlate to a degree with the clinical outcome. Unfavorable findings include a tumor diameter > 15 cm, bilateral tumors, rupture, and spread beyond the ovary (FIGO stage > IA). Diffuse moderate or marked nuclear atypia or a high mitotic rate (variably defined as greater than 2 or 4 mitotic figures per 10 high power fields) appears to predict a higher risk of recurrence. The stage is the single most powerful predictor of prognosis. There is no correlation between the microscopic pattern and the clinical outcome. More than 80% of granulosa cell tumors are DNA diploid. Some authors have found ploidy or s-phase fraction to provide significant prognostic information, but others have not.
Fibroma / Thecoma

Ovarian fibroma is a benign stromal tumor in which spindle shaped stromal cells grow in abundant collagenous stroma. Immunohistochemistry is rarely performed on fibromas because their appearance on H&E stained slides is usually distinctive. Fibromas and related tumors such as cellular fibromas and fibrosarcomas stain only infrequently for inhibin but most are calretinin positive. They show patchy and weak to moderate staining for WT-1. SF-1 is positive, though may have variable intensity/distribution.

Thecoma is a benign spindle cell stromal tumor that differs from fibroma in that it is often hormonally active, usually secreting estrogen. There are morphologic differences as well, as the tumor cells in a thecoma tend to be plump, with clear or vacuolated cytoplasm, and there is less collagen in the background stroma than is present in a fibroma. Thecoma is usually positive for both inhibin and calretinin. Strong positive staining for inhibin favors classifying a stromal tumor as a thecoma rather than as a fibroma. Stains for myoid markers, such as smooth muscle actin, are often positive as well.

The diagnosis of fibroma and thecoma is generally straightforward, however, in addition to distinction from granulosa cell tumor, there is one problem that may occasionally present difficulty: presence of mitoses and/or presence of cellularity. The differential diagnosis that is raised is fibrosarcoma, an exceedingly rare tumor in the ovary.

Mitotically active cellular fibroma

A recent outcome study suggests that mitotic activity in cellular fibroma (that lacks nuclear atypia) is not associated with recurrence or spread. The study had an average follow up period of 4.7 years. Isolated case reports of similar tumors that did spread do exist, therefore the authors recommend that mitotically active cellular fibromas be considered low malignant potential tumors and that careful surveillance should be offered. Ovarian fibrosarcoma should be reserved for the rare case in which hypercellularity and unequivocal nuclear atypia are present.

Sertoli-Leydig Cell Tumor

Sertoli-Leydig cell tumors (SLCT) are tumors of young women and girls and are notable for virilizing effects. They may be of well, intermediate, or poor differentiation and any of these may be accompanied by heterologous elements or by retiform growth. In well differentiated variants Sertoli cells line well formed tubules that grow in a fibrous stroma that contains clusters of polygonal Leydig cells. Immature stromal and Sertoli cells are not present. The more common intermediate and poorly differentiated Sertoli-Leydig cell tumors contain variably mature Sertoli cells growing in trabeculae or nests or lining round or retiform tubules. The stroma is cellular and immature, and Leydig cells, present either singly or in clusters, are present in most tumors. Most patients present with tumors confined to the ovary and have a favorable prognosis.

SLCT versus sertoliform variant of endometrioid adenocarcinoma

Rare ovarian endometrioid adenocarcinomas may exhibit areas of growth that mimic Sertoli cell proliferation. Because pan-keratin can be expressed in the Sertoli cells of SLCT, it is important to use EMA in this particular differential diagnosis since Sertoli cells will be negative while adenocarcinoma will be positive. Because some SLCT will express estrogen and/or progesterone receptors, these markers are less helpful in this setting.

Heterologous elements in SLCT

Two types of heterologous elements can create diagnostic problems. These are present in about 20% of cases, mostly consisting of gastrointestinal type epithelium. If prominent, this component can be confused for a mucinous tumor. Less commonly, hepatoid differentiation can be found. These cells can secrete alpha fetoprotein and this may lead to elevated serum AFP. Awareness of this can prevent confusion with yolk sac tumor, which also results in elevated serum AFP.
Sclerosing Stromal Tumor

Sclerosing stromal tumor is a rare though benign, hormonally inactive ovarian tumor with a distinct low magnification growth pattern that arises almost exclusively in young women. The tumor shows a pseudolobular pattern of cellular, spindle cell zones alternating with paucicellular fibrous zones. Scattered throughout are branched dilated blood vessels having a “hemangiopericytoma-like” appearance. The tumor cells adjacent to the vessels are often polygonal, vacuolated (lipid, not mucin) or vaguely myoid in appearance. In rare cases these cells may exhibit signet ring features. The tumor cells are vimentin positive and they often stain for smooth muscle actin. Immunostains for inhibin and calretinin are positive in more than 50% of sclerosing stromal tumors.

References


