Sex Cord Stromal Tumors of the Testis

- Uncommon testicular neoplasms
- Account for about 5% of testicular tumors
- Wide age range, children to elderly
- Usually present because of a testicular mass
- Some are functional, but most are not
- Classification similar to that for analogous ovarian tumors

Classification of Testicular Sex Cord-Stromal Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Classification</th>
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</thead>
<tbody>
<tr>
<td>Leydig cell tumor</td>
<td>Most common testicular sex cord-stromal tumor</td>
</tr>
<tr>
<td>Malignant Leydig cell tumor</td>
<td>Bimodal age distribution</td>
</tr>
<tr>
<td>Sertoli cell tumor</td>
<td>Adults over a wide age range, 20-60 years</td>
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<tr>
<td>Lipid rich Sertoli cell tumor</td>
<td>Children</td>
</tr>
<tr>
<td>Sclerosing Sertoli cell tumor</td>
<td>Reported in patients with germline fumarate hydratase mutations (hereditary leiomyomatosis and renal cell carcinoma syndrome)</td>
</tr>
<tr>
<td>Large cell calcifying Sertoli cell tumor</td>
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<tr>
<td>Malignant Sertoli cell tumor</td>
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<tr>
<td>Granulosa cell tumor</td>
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<tr>
<td>Juvenile granulosa cell tumor</td>
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<tr>
<td>Adult type granulosa cell tumor</td>
<td></td>
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<tr>
<td>Tumors of fibroma/thecoma group</td>
<td></td>
</tr>
<tr>
<td>Unclassified sex cord-gonadal stromal tumor</td>
<td></td>
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</tbody>
</table>
Leydig Cell Tumors in Adults

- Mean age in large series mid 30's
- Usual presentation is with a testicular mass
- About 30% have gynecomastia, which may bring the patient to attention
- Other presentations include testicular pain and infertility
- About 1/3 have increased androgens and 1/3, mainly those with gynecomastia, have increased estrogens

Leydig Cell Tumors in Children

- 4% of testicular tumors in boys < 12
- 3/40 in Kim, Young and Scully series of Leydig cell tumors
- Small tumors
- Most present with precocious pseudopuberty due to androgen secretion
- About 10% have gynecomastia, and elevated estrogens
- Leydig cell tumors in children are benign

Leydig Cell Tumor

- Most tumors 3-5 cm diameter
- Average 3 cm
- Tumors in children are small
- Yellow brown or tan
- Solid
- Take sections to show interface with normal parenchyma, tunica
Spindle cells, fat, ossification (Am J Surg Pathol 2002;26:1424-1433)

Leydig Cell Tumor

**Immunohistochemistry**

- **Distinctive positive stains**
  - Inhibin, calretinin, melan-A, sf-1
- **Typically positive**
  - Vimentin, CD99, chromogranin, synaptophysin
- **Mostly negative but can be positive**
  - Cytokeratin, S100 (8%)
- **Negative**
  - EMA
UCSF Immunostain Panel for Leydig Cell Tumor

<table>
<thead>
<tr>
<th>Stain</th>
<th>Anticipated Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibin</td>
<td>Positive, cytoplasm</td>
</tr>
<tr>
<td>SF-1</td>
<td>Positive, nuclei</td>
</tr>
<tr>
<td>Melan-A</td>
<td>Positive, cytoplasm</td>
</tr>
<tr>
<td>CK</td>
<td>Negative (30-40%+)</td>
</tr>
<tr>
<td>EMA</td>
<td>Negative</td>
</tr>
<tr>
<td>SALL4</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Treatment of Leydig Cell Tumors

- Standard treatment has been orchiectomy
- Testis sparing surgery appears safe provided
  - Diagnosis can be made at FS
  - Tumor small
  - No gross or microscopic features suggestive of malignancy
- Neither chemotherapy nor radiotherapy shown to be effective in malignant Leydig cell tumors
- Role of retroperitoneal lymph node dissection unclear
- Malignant Leydig cell tumors uncommon in clinical series, but more frequent in consultation series.

Features Suggestive of Malignancy

- Old age (never malignant in young children)
- Large size (tumor > 5 cm)
- Frequent mitotic figures (> 3 mf/10 hpf)
- Atypical mitotic figures
- Lymphovascular space invasion
- Nuclear atypia
- Necrosis
- Invasive growth
Leydig Cell Tumor
Differential Diagnosis

- Nodular Leydig cell hyperplasia
  - Small nodules, multiple
- Testicular tumor of adrenogenital syndrome (TTAGS)
  - Multifocal bilateral hyperplastic nodules that can mimic Leydig cell tumor, often involve hilum
- Large cell calcifying Sertoli cell tumor
  - Abundant eosinophilic cytoplasm
- Seminoma

Testicular Tumor of Adrenogenital Syndrome

Arch Pathol Lab Med 2000;124:785-786
Sertoli Cell Tumor

Many Patterns

- Sertoli Cell Tumor, NOS
- Sclerosing Sertoli Cell Tumor
- Large Cell Calcifying Sertoli Cell Tumor
- Sertoli Cell Tumor Associated with the Peutz-Jeghers Syndrome

Sertoli Cell Tumor

- Most occur in adults, some in children
- Average age 45 years
- Present with slowly enlarging mass
- Unilateral
- Most are nonfunctional
- Occasional tumors secrete estrogens and cause gynecomastia or impotence
Sertoli Cell Tumor Testis

Histology

- Nodular pattern at low magnification
- Bands of fibrous tissue
- Sheets, nests, trabeculae or cords
- Need to see solid or hollow tubules for a definite diagnosis
- Rete like tubules seen in some
- Variants include spindle cell and lipid rich
Cords of cells  Trabeculae of cells

Spindly cells
Sertoli Cell Tumor
Immunohistochemistry

- Often positive, and diagnostically useful
  - Inhibin
  - Cytokeratin
- Typically positive
  - Vimentin
- Sometimes positive
  - Calretinin, WT-1, CD99, MelanA
- Usually negative
  - EMA (can be positive in malignant cases)
Malignant Sertoli Cell Tumor

- About 10% of Sertoli cell tumors are malignant
- Malignant tumors occur in children as well as in adults
- Gynecomastia is more common in malignant cases
- Do not respond to chemotherapy or radiotherapy
- Metastases typically go to retroperitoneal lymph nodes and lungs
- Retroperitoneal lymph node dissection often performed, but value remains unproven

Sertoli Cell Tumor
Pathologic Findings Suggestive of Malignancy

- Marked nuclear atypia
- Frequent mitotic figures (> 5mf/10hpf)
- Vascular invasion
- Necrosis
- Predominance of diffuse growth pattern
- Large size (> 5 cm)
Dysgerminoma Mimic

Differential Diagnosis

- Sertoli cell nodules in androgen insensitivity syndrome
- Small Sertoli cell nodules
  - Common finding in orchiectomy specimens from cryptorchid patients
  - Incidental microscopic finding
- Seminoma
Androgen Insensitivity Syndrome

- Phenotypic females
- Y chromosome generally present
- 4 patterns described
  - Diffuse tubulostromal
  - Lobular tubulostromal
  - Mixed tubulostromal
  - Stromal predominant
- Sertoli cell hamartomas with mixed in Leydig cells in 63%
- Sertoli cell adenomas in 35% of the cases

UCSF Immunostain Panel for Sertoli Cell Tumor

<table>
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</table>
**Sclerosing Sertoli Cell Tumor**

- Young patients, average age 35
- Painless slowing growing mass
- Incidental finding
- No evidence of hormonal activity
- Most are small (<1.5 cm)
- All reported examples have been benign
Large Cell Calcifying Sertoli Cell Tumor

- Patients are young, with an average age of 16 years
- Can occur over a wide range, from children to older adults
- Usual presentation is with a painless slowly enlarging testicular mass
- Hormones secreted by some tumors, or the surrounding Leydig cells, can cause symptoms such as gynecomastia or precocious pseudopuberty
- About 40% of patients have the Carney syndrome or Peutz-Jeghers syndrome

Carney Complex

- Many possible findings, listed in handout
- Complex has a genetic basis
- LCCSCT in Carney patients occur at a young age
- LCCSCT are small and tend to be bilateral and multifocal

Large Cell Calcifying Sertoli Cell Tumor

- Tan or yellow
- Most < 4 cm
- Gritty areas of calcification
- Can be multifocal and bilateral

Microscopic Features

- Nests, cords, trabeculae and solid tubules
- Polygonal cells with abundant eosinophilic cytoplasm
- Round nuclei, prominent nucleoli
- Intratubular growth and calcifications commonly present
- Myxoid to collagenous stroma
- Neutrophilic infiltrate
- Inhibin and melanA positive, CK negative, and can stain for S100
Malignant LCCSCT

- Rare
- Patients are older than those with benign tumors
- Patients with malignant tumors do not have Carney complex
- Possible indicators of malignancy: large size (>4 cm), necrosis, nuclear atypia, frequent mitotic figures (>3 mf/10 hpf), vascular invasion
- If one present, suggest malignancy; if two or more diagnose as malignant
Sertoli Cell Proliferations in Patients with the Peutz-Jeghers Syndrome

- Mainly detected in children
- All have gynecomastia and some have precocious pseudopuberty
- Testes enlarged, but no palpable nodules; echogenic foci
- Diagnosis made by testicular biopsy
- Tubules expanded and filled with cells like those in LCCSCT
- Abundant hyalinized basement membrane material
- Usually no calcifications
- A few patients have invasive Sertoli cell tumor in additional to the intratubular proliferation

Granulosa Cell Tumors of the Testis

- Two types, as in the ovary
- Juvenile granulosa cell tumor
- Adult type granulosa cell tumor
- Juvenile type is more extensively reported in the literature

Juvenile Granulosa Cell Tumor

- 31% of sex cord stromal tumors in Kiel pediatric tumor registry
- Almost all occur in young children
- Most are detected in the first weeks of life and 95% occur before age 1
- The presentation is with a painless scrotal mass or, rarely, torsion
- All reported patients well after orchiectomy or enucleation
Juvenile Granulosa Cell Tumor, Testis

- Gray or yellow
- Nodular
- Varying sized cysts typically present
- Average diameter about 2 cm

Adult Granulosa Cell Tumor

- Rare
- Largest series 7 cases from MDAH, 6 consults 1 hospital patient
- Wide age range, average mid 40s
- Presentation is with painless testicular mass
- Hormone production and symptoms varies
- Some are asymptomatic and detected at routine exam
- Most clinically benign, but cases with metastases are reported (2/5 with follow-up in MDAH series)
**Adult Granulosa Cell Tumor**

- Solid, cystic or solid/cystic
- Yellow to gray
- Average size 5 cm
- Same patterns as seen in ovarian granulosa cell tumors: diffuse, microfollicular, trabecular, gyriform, and insular
Sex Cord Stromal Tumors Summary

- Similar types of tumors as seen in ovary
- Leydig cell tumors, granulosa cell tumors most like ovarian counterparts, with similar immunostaining patterns
- Sertoli cell tumors come in many varieties, some with a genetic basis, and are different from the ovarian tumors
- Most sex cord stromal tumors are clinically benign
- Malignant tumors are often large and show histologic features of malignancy