Gynaecological Pathology / Uropathology: Tumours of the Ovary and Testis: an Update

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• 13 year-old with left adnexal mass
Sertoli-Leydig Cell Tumor

- Mean age, 25 years (75% < 30)
- Only 10% > 50
- Endocrinologic symptoms: androgenic (33%), estrogenic less common
- Unilateral, <5% extra-ovarian spread at diagnosis
Sertoli-Leydig Cell Tumor

• Typically solid yellow, often cystic
• Hollow or solid Sertoli cell tubules or cords & Leydig cells
• Heterologous elements (20%)
• Retiform pattern (15%)
Immunohistochemistry

• Positive:
  • Inhibin, calretinin, SF-1, CD56, FOX-L2, WT1, CD99
  • Cytokeratin, vimentin

• Negative:
  • CK7, EMA
Sertoli-Leydig Cell Tumor

• Well differentiated
• Moderate (intermediate) differentiated
• Poorly differentiated (so-called sarcomatoid)
Well Differentiated

- Open or compressed Sertoli cell tubules, admixed with clusters of stromal Leydig cells
- Sertoli cells are low columnar to cuboidal with oval to round nuclei, small nucleoli, and may show nuclear grooves. Leydig cells have round nuclei and abundant eosinophilic cytoplasm with (+/-) Reinke crystals and lipofuscin pigment.
- No significant atypia or mitotic activity
Moderately Differentiated

• Diffuse or lobulated architectural pattern
• May have alternating hypo and hypercellularity on low magnification
• Sertoli cells form compressed tubules, cords or diffuse sheets & have hyperchromatic nuclei
• Occasional mitotic figures (mean, 5 per 10 high power fields)
• Rare small clusters of Leydig cells admixed with the Sertoli cell component
Poorly Differentiated

• Diffuse sheets of immature, sarcomatoid Sertoli cells with moderate to marked nuclear atypia & only rare foci of vague cord formation

• Increased mitotic activity, up to 20 mitoses per 10 high power fields

• Leydig cells are difficult to find; a few small clusters are typically located at the periphery of tumor nodules
Sertoli-Leydig Cell Tumor
Heterologous Elements

- Mucinous (gastric or intestinal type)
- Hepatoid
- Neuroendocrine (assoc with mucinous elements)
- Embryonal rhabdomyosarcoma
- Cartilage
Differential Diagnosis

• Endometrioid carcinoma – esp sertoliform variant
• Adult granulosa cell tumor
• Metastatic tubular Krukenberg tumor
• Fibroma
• Yolk sac tumor – retiform variant
• Low-grade serous carcinoma – retiform variant
Additional Clinical History

• Follicular variant, papillary carcinoma of thyroid at age 10
Final Diagnosis

• *Sertoli-Leydig cell tumor, intermediate grade, associated with germline DICER1 mutation*
DICER1

- Chromosome 14q32.13
- Highly conserved RNase III enzyme involved in the biogenesis of most small RNAs including microRNA (miRNA)
- DICER1 processes pre-miRNA into mature miRNA & loads small RNAs onto AGO proteins to form an effective complex that silences messenger RNAs
- Central to miRNA-mediated silencing of RNAs involved in cancer gene networks

Cancers 2018; 10: (143)1-17
DICER1 Syndrome

- Truncating germline mutation
- Second hit missense point mutation

Mod Pathol 2015;28:1603-12.
DICER Syndrome

- Pleuropulmonary blastoma
- Cystic nephroma
- Multinodular goiter, well differentiated thyroid carcinoma
- Intra-ocular medulloepithelioma
- Pinealblastoma
- Wilms tumor

Virchows Arch 2016;468:631–636
DICER Syndrome: Gynecologic Manifestations

- Sertoli-Leydig cell tumor*
- Cervical embryonal rhabdomyosarcoma
- Cervical PNET

*50% or more may be associated with germline DICER. May be initial presentation

Gynecol Oncol 2011;122:246-50
<table>
<thead>
<tr>
<th>Condition</th>
<th>Germline DICER mutation</th>
<th>Somatic DICER mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleuropulmonary blastoma</td>
<td>66.9%</td>
<td>92.4%</td>
</tr>
<tr>
<td>Cystic nephroma</td>
<td>73.2%</td>
<td>87.9%</td>
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<tr>
<td>Sertoli-Leydig cell tumor</td>
<td>57.1%</td>
<td>43.3%</td>
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</tbody>
</table>

Pediatr Hematol Oncol 2017;39:355-361
Sertoli-Leydig Cell Tumor in DICER Syndrome

• Intermediate or poorly differentiated
• Some evidence more aggressive than wild-type Sertoli-Leydig cell tumor

Am J Surg Pathol 2017;41:1178
Sertoli-Stromal Cell Tumors in DICER

- Sertoli-Leydig cell tumor
- Sertoli cell tumor
- Gynandroblastoma
- Juvenile granulosa cell tumor
- May show mixed sertoliform, juvenile granulosa cell tumor-like & unclassifiable elements
- May have heterologous mucinous epithelial, rhabdomyoblastic & neuroendocrine differentiation

Int J Gynecol Pathol 2015;34:266–274; Gynecol Oncol 2017;147:521-527; Hum Pathol 2017;59:41-47
Thank you

Stanford University