TESTICULAR GERM CELL TUMORS: UNCOMMON BUT OFTEN CHALLENGING

Alaskan Rocky Mountains

TESTICULAR TUMORS CLASSIFICATION

• GERM CELL TUMORS
• GONADAL STROMAL TUMORS
• MIXED GERM CELL – GONADAL STROMAL TUMORS
• MESENCHYMAL TUMORS
• LYMPHORETICULAR NEOPLASMS
• METASTATIC TUMORS

TESTICULAR GERM CELL TUMORS INTRODUCTION

• Estimated 9,310 new cases and 400 related deaths in USA in 2017 (Siegel et al. CA Cancer J Clin 68:7, 2018)
• Incidence (5 per 100,000) has been steadily increasing over last few decades
• Major risk factors are cryptorchidism and low birth weight
• Higher incidence in infertile men
• More common in Caucasians vs African Americans
• A disease of young adults (late teens to early 40’s)
TESTICULAR GERM CELL TUMORS CLASSIFICATION (WHO 2016)

Germ Cell Tumors Related to GCNIS
• Germ cell neoplasia in situ
  – Specific forms of intratubular germ cell neoplasia
• Seminoma
  – With syncytiotrophoblastic giant cells
• Embryonal carcinoma
• Yolk sac tumor
• Trophoblastic tumors
  – Choriocarcinoma
  – Non-choriocarcinomatous trophoblastic tumors
    • Placental site trophoblastic tumor
    • Epithelioid trophoblastic tumor
    • Cystic trophoblastic tumor
• Teratoma, postpubertal-type
• Teratoma, with somatic-type malignancy
• Germ cell tumors of unknown type (regressed GCT)

Germ Cell Tumors Unrelated to GCNIS
• Spermatocytic tumor
• Teratoma, prepubertal type
  – Dermoid cyst
  – Epidermoid cyst
  – Well differentiated neuroendocrine tumor (monodermal teratoma)
• Mixed teratoma and yolk sac tumor, prepubertal type
• Yolk sac tumor, prepubertal type

GERM CELL NEOPLASIA IN SITU
• Most frequent adjacent to GCTs (up to 100%)
• Also seen in association with:
  • cryptorchid testis (2% - 8%)
  • biopsies of infertile men (1% - 2%)
  • contralateral testis in GCT patients (5% - 8%)
  • adjacent to regressed GCTs
• Infrequent in pediatric age group
• Progresses to invasive GCT in ~50% at 5 years
GERM CELL NEOPLASIA IN SITU

- Large cells (approx. 3x size of normal germ cells) with abundant clear cytoplasm (glycogen)
- Large nuclei with single macro nucleolus
- Hug the tubule basement membrane
- Tubules are usually but not always atrophic
- IHC: PLAP +, OCT4 +, CD117 +, CD30 -
- If fill the tubules: seminoma or embryonal ca in situ
- Watch for microinvasive disease
SEMINOMA

- Young to middle aged adults
- Circumscribed, lobulated, homogeneous, pale tan
- Can see necrosis and hemorrhage
- Pale to clear cytoplasm, arranged in nests separated by fibrous septae with lymphocytic infiltrate
- Granulomatous inflammation
- Syncytiotrophoblastic giant cells
- Problems with fibrosis or necrosis, amphophilic cytoplasm, pseudotubular or pseudoglandular architecture
- IHC: PLAP +, OCT4 +, CD117 +, CK +/−, CD30 −
SEMINOMA

SEMINOMA - LYMPHOCYTE POOR

SEMINOMA WITH AMPHOPHILIA
SEMINOMA WITH TUBULES

SEMINOMA WITH PSEUDOGLANDS

SEMINOMA WITH PSEUDOPAPILLAE
Large B-Cell Lymphoma with MYC rearrangement

**EMBRYONAL CARCINOMA**
- Young adults (~10 years younger than seminoma)
- No typical gross – often with hemorrhage and necrosis
- Solid, papillary and glandular growth
- Pleomorphic cells with amphophilic to basophilic cytoplasm, poorly defined cell borders
- Problems with clear cytoplasm
- IHC: PLAP +, OCT4 +, CD117 -, CK +, CD30 +
EMBRYONAL CARCINOMA

POLYEMBRYOMA

EMBRYONAL CA & SEMINOMA
EMBRYONAL CA & SEMINOMA

• Most common GCT in pediatric age group
• Rarely pure in adults
• Associated with alphafetoprotein production
• In children typically circumscribed and yellow; no typical features in adults
• Wide range of histologic patterns – one of the more frequent causes of disagreement
• IHC: AFP (+/-), PLAP +, Glypican-3 +, OCT4 -, CD117 -, CK +, CD30 -

YOLK SAC TUMOR

• Most common GCT in pediatric age group
• Rarely pure in adults
• Associated with alphafetoprotein production
• In children typically circumscribed and yellow; no typical features in adults
• Wide range of histologic patterns – one of the more frequent causes of disagreement
• IHC: AFP (+/-), PLAP +, Glypican-3 +, OCT4 -, CD117 -, CK +, CD30 -
Yolk Sac Tumor - Histologic Patterns

- Endodermal sinus (most distinctive)
- Reticular or microcystic (most common)
- Macrocystic
- Solid
- Glandular / alveolar
- Papillary
- Myxomatous (magma reticulare)
- Spindle cell
- Polyvesicular vitelline
- Hepatoid
- Enteric (primitive intestinal)
- Parietal
YOLK SAC TUMOR

YOLK SAC TUMOR – LATE RECURRENCE

YOLK SAC TUMOR – LATE RECURRENCE

CK (AE1/AE3)

AFP

GLYPICAN-3
CHORIOCARCINOMA

- Pure form very rare
- Associated with production of βHCG
- Metastases can be associated with hemorrhage
- Grossly are hemorrhagic
- Made up of syncytiotrophoblasts and cytotrophoblasts
- IHC: HCG +, PLAP +, OCT4 -, CD117 -, CK +, GATA3 +, CD30 -
CHORIOCARCINOMA EPITHELIOLID TYPE

CYSTIC TROPHOBlastic Tumor

- Most commonly seen in post-chemotherapy RPLND specimens with teratoma
- Can be found in primary germ cell tumors
- Serum ßHCG not or minimally elevated
- Considered to be “benign” in RPLND (not an indication for additional chemotherapy)
TERATOMA, POSTPUBERTAL-TYPE

• Can be pure or mixed
• Postpubertal are malignant; prepubertal are benign
• Cystic areas almost always are teratoma
• Combination of ectodermal, endodermal and mesodermally derived tissues
• No longer separated into mature and immature elements (overgrowth of PNET)
• Development of somatic malignancies
• Not responsive to chemotherapy/radiation therapy
• IHC: SALL4 +, OCT4 -, AFP +/- (depending on elements)
TERATOMA, POSTPUBERTAL-TYPE

- Defined as “a teratoma that develops a distinct secondary component that resembles a somatic-type malignant neoplasm, as seen in other organs and tissues”
- Most often present in RP lymph nodes but also in primary site
- Reported in 3% - 6% of germ cell tumors
- Sarcomas most common
- Requires at least one 4x field
- Distinguish from sarcomatoid YST
- Worse prognosis when present in post chemotherapy RP lymph nodes (or elsewhere)

TERATOMA, WITH SOMATIC MALIGNANCY

-SOMATIC MALIGNANCY - RHABDOMYOSARCOMA

SOMATIC MALIGNANCY - RHABDOMYOSARCOMA
SOMATIC MALIGNANCY - RHABDOMYOSARCOMA

Myo D1

Myogenin

SOMATIC MALIGNANCY - PNET

Synaptophysin

GERM CELL TUMOR OF UNKNOWN TYPE
(REGRESSED "BURNED OUT" GCT)

• Patients presenting with metastatic GCT without testicular mass
• US shows scar or microcalcifications
• Morphologic features include:
  – Fibrosis with ghost tubules at periphery
  – Lymphoplasmacytic infiltrate
  – Angiomatous foci +/- hemosiderin
  – Coarse calcifications (+/- intratubular)
• GCNIS +/- microinvasive GCT
SPERMATOCYTIC TUMOR

- Older age group
- Benign unless an associated sarcoma
- Circumscribed with mucoid surface
- Sheets of cells with fibrous septae and lymphocytic infiltrate of seminoma
- Discohesive with mucinous background
- Admixture of 3 sizes of cells: small, lymphocyte like; intermediate seminoma-like; and large cells
- IHC: PLAP -, OCT4 -, SALL4+, CD117 +/−, CK +/−, CD30 -,
SPERMATOCYTIC TUMOR

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TERATOMA, PREPUBERTAL-TYPE

- Tumor unrelated to GCNIS
- Can occur in post-pubertal males
- Stringent criteria required for diagnosis
  - No immature elements
  - No GCNIS
  - No scar
  - No evidence of dysgenetic gonad
    * Impaired spermatogenesis, tubular atrophy, microthiasis, Sertoli cell nodule
- Clinically these are benign
TERATOMA, PREPUBERTAL TYPE

GCNIS
Sertoli cell nodule
Impaired spermatogenesis
Microlithiasis

EPIDERMOID CYST
WELL DIFFERENTIATED NEUROENDOCRINE TUMOR (MONODERMAL TERATOMA)

GERM CELL TUMORS: IMMUNOHISTOCHEMISTRY

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Germ cell tumors</th>
<th>Non-seminomatomous Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>Oct34 positive</td>
<td>Oct34 positive</td>
</tr>
<tr>
<td>Embryonal Carcinoma</td>
<td>Oct34 positive</td>
<td>Oct34 negative</td>
</tr>
<tr>
<td>Yolk Sac Tumor</td>
<td>Oct34 negative</td>
<td>Oct34 negative</td>
</tr>
<tr>
<td>Intestinal Carcinoma</td>
<td>Oct34 negative</td>
<td>Oct34 negative</td>
</tr>
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TESTICULAR TUMORS PATHOLOGY FEATURES IMPACTING TREATMENT

- Type of tumor
  - Germ cell tumors
    - Seminoma
    - Non-seminomatous
  - Other tumor types

- Tumor stage (TNMS)
  - Primary tumor
  - Nodal status
  - Metastases
  - Serum markers

**TESTIS – DEFINITION OF TNM (2018)**

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>pTX</th>
<th>Primary tumor cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT0</td>
<td>No evidence of primary tumor (eg. histologic scar)</td>
</tr>
<tr>
<td>pTis</td>
<td>Germ cell neoplasia in situ</td>
</tr>
<tr>
<td>pT1</td>
<td>Tumor limited to testis without lymphovascular invasion</td>
</tr>
<tr>
<td>pT1a</td>
<td>Seminoma smaller than 3 cm in size</td>
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<tr>
<td>pT1b</td>
<td>Seminoma 3 cm or larger in size</td>
</tr>
<tr>
<td>pT2</td>
<td>Tumor limited to the testis but with vascular/lymphatic invasion or tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial surface of tunica albuginea with or without lymphovascular invasion</td>
</tr>
<tr>
<td>pT3</td>
<td>Tumor invades the spermatic cord with or without lymphovascular invasion</td>
</tr>
<tr>
<td>pT4</td>
<td>Tumor invades the scrotum with or without lymphovascular invasion</td>
</tr>
</tbody>
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**TESTIS – pT1 (2018)**

**TESTIS – pT1-Seminoma (2018)**
LYMPH VASCULAR INVASION
HILAR EPIDIDYMAL INVASION

"penetrating visceral mesothelial surface of tunica albuginea"

pT2 – intravascular tumor
pM1 – discontinuous spread
pT3 – direct invasion to level of vas

TESTIS – pT2 (2018)

TESTIS – T AND THE SPERMATIC CORD
Spermatic cord margin

"Southern Alps" South Island, NZ