TESTICULAR GERM CELL TUMORS: UNCOMMON BUT OFTEN CHALLENGING

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
INFERTILITY BIOPSY: 29 yo with a history of varicocele
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 -
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 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 - 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
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 EPITHELIOID 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)

CYSTIC TROPHOBLASTIC TUMOR
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

TERATOMA, WITH SOMATIC MALIGNANCY

- 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)

SOMATIC MALIGNANCY - RHABDOMYOSARCOMA
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SOMATIC MALIGNANCY - PNET

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
REGRESSED “BURNED OUT” GCT

REGRESSED “BURNED OUT” GCT

REGRESSED “BURNED OUT” 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

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, microlithiasis, Sertoli cell nodule
• Clinically these are benign
WELL DIFFERENTIATED NEUROENDOCRINE TUMOR (MONODERMAL TERATOMA)

GERM CELL TUMORS: IMMUNOHISTOCHEMISTRY

<table>
<thead>
<tr>
<th>Table 1: Useful algorithm for the distinction between various types of germ cell tumors. Alternative names in parentheses.</th>
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</thead>
<tbody>
<tr>
<td>OCT4 positive Ovarian Neoplasms (anti-SOX2 on saliva squamous)</td>
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<tr>
<td>OCT4 negative Small Cell Tumor</td>
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<tr>
<td>Other tumor types</td>
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<tr>
<td>Seminoma</td>
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<tr>
<td>Teratoma</td>
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<td>Choriocarcinoma</td>
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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>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>pTX</td>
<td>Primary tumor cannot be assessed</td>
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<tr>
<td>pT0</td>
<td>No evidence of primary tumor (e.g., 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>
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<tr>
<td>pT1a</td>
<td>Seminoma smaller than 3 cm in size</td>
</tr>
<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>
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<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>
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</tbody>
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#### TESTIS – pT1 (2018)

- [Image: pT1a seminoma smaller than 3 cm in size](image1.png)
- [Image: pT1b seminoma 3 cm or larger in size](image2.png)

#### TESTIS – pT1-Seminoma (2018)

- [Image: pT1a seminoma smaller than 3 cm in size](image3.png)
- [Image: pT1b seminoma 3 cm or larger in size](image4.png)
TESTIS – pT2 (2018)

LYMPH/VASCULAR INVASION

HILAR/EPIDIDYMAL INVASION

TESTIS – pT2 (2018)

“penetrating visceral mesothelial surface of tunica albuginea”

TESTIS – T AND THE SPERMATIC CORD

_pT2 – intravascular tumor

_pM1 – discontinuous spread

_pT3 – direct invasion to level of vas
Spermatic cord margin

“Southern Alps” South Island, NZ