Germ Cell Tumours of Testis

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Classification of GCT

- British Testicular Tumour Panel (BTTP)
  - Seminoma; spermatocytic seminoma
  - Yolk sac tumour (only infantile)
  - Malignant teratoma differentiated (MTD)
  - Malignant teratoma undifferentiated (MTU)
  - Malignant teratoma intermediate (MTI)
  - Malignant teratoma trophoblastic (MTT)

- WHO
  - Seminoma, spermatocytic seminoma
  - Teratoma:
    - Mature/immature/overtly malignant
  - Embryonal carcinoma
  - Yolk sac tumour
  - Choriocarcinoma
  - Malignant mixed germ cell tumour

BTTP vs. WHO

- Proportion of components in mixed tumours
  - WHO: recommends determination of proportions
    - Eg. 75% EC, 10% YST, 10% seminoma, 5% teratoma
  - BTTP: purely descriptive
    - MTI may be 95% MTD or 95% MTU
    - MTT may be <5% choriocarcinoma
    - Focal choriocarcinoma in EC has good prognosis

- Meaning of the term Teratoma
  - Different in BTTP and WHO

Testicular Teratoma

- WHO:
  - Only tumours analogous to ovarian teratoma

- BTTP
  - All non-seminomatous germ cell tumours
  - Embryonal carcinoma = malignant teratoma undifferentiated

Teratoma (WHO)

- In contrast to ovarian teratomas
  - Most are solid (cf benign cystic teratoma of ovary)
  - All testicular teratomas in post-pubertal males potentially malignant
    - Pure mature teratoma in post-pubertal males has metastatic potential
    - Pure mature teratoma in pre-pubertal males is benign
**Testicular Teratoma**

- Presence and extent of immaturity generally not important
  - Do not report “immature teratoma”
- PNET: area greater than 1 low-power field of pure immature neuroepithelium
  - Presence in testis does not alter prognosis
  - Presence in metastasis very poor outcome
  - Chemoresistant

**Epidermoid cyst**

- Unilocular, squamous epithelium lined cyst
  - Keratinous contents
- No other components
- Testis away from cyst normal
  - No atrophy
  - No ITGCN
- Adjacent testis may show pressure effects
  - Atrophy, fibrosis

**Dermoid cyst**

- Similar criteria for diagnosis as epidermoid cyst but more organised and includes other components
  - Skin adnexae: hair follicles, sebaceous glands, sweat glands
  - Cartilage
  - Intestinal or ciliated epithelium
- Benign

**Dermoid cyst vs. “Mature” Teratoma**

<table>
<thead>
<tr>
<th></th>
<th>Dermoid Cyst</th>
<th>Teratoma</th>
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</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Almost always prepubertal</td>
<td>Generally adults</td>
</tr>
<tr>
<td><strong>Architecture</strong></td>
<td>Unilocular cyst</td>
<td>Multilocular solid/cystic</td>
</tr>
<tr>
<td><strong>Cytological atypia</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Associated ITGCN</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Other germ cell tumour elements</strong></td>
<td>Absent</td>
<td>May be present</td>
</tr>
<tr>
<td><strong>Neuroepithelium</strong></td>
<td>Absent</td>
<td>May be present</td>
</tr>
<tr>
<td><strong>Background testis (away from lesion)</strong></td>
<td>Normal</td>
<td>May be atrophic with impaired spermatogenesis</td>
</tr>
<tr>
<td><strong>Metastatic potential</strong></td>
<td>None</td>
<td>Yes (as Teratoma or non-teratomatous GCT)</td>
</tr>
</tbody>
</table>

**Intratubular Germ Cell Neoplasia (ITGCN)**

- Also referred to as IGCNU (intratubular germ cell neoplasia unclassified)
- Precursor of all invasive germ cell tumours except spermatocytic seminoma and prepubertal germ cell tumours (yolk sac tumour and mature teratoma in young children)
- NOT associated with epidermoid cyst/dermoid cyst
- Untreated progresses to invasive GCT in 50% over 5 years (probably 100% lifetime risk)

**ITGCN**

- Morphology and immunoprofile similar to seminoma
- Located along basement membrane
- Differential diagnosis: vacuolated seminiferous cells mimicking ITGCN
  - Lack cytology of ITGCN
- Don’t use c-kit to confirm ITGCN
  - Spermatogonia may be positive
**Vacuolated seminiferous cells mimicking ITGCN**
- Lacks cytology of ITGCN
  - No cytological atypia
  - No prominent nucleoli
- Negative for PLAP, c-KIT and OCT 3/4

**Intratubular seminoma**
- Must not be confused with ITGCN
- Tumour cells fill lumens of seminiferous tubules
  - The tubules may show spermatogenesis
- Intratubular spread may be seen in many germ cell tumours
  - Classical seminoma
  - Spermatocytic seminoma
  - Embryonal carcinoma

**Classical Seminoma**
- 50% of all germ cell tumours
- Age incidence:
  - Peak 30 - 40 yrs (10 years later than non-seminoma GCT)
- Typical histology:
  - Clear cytoplasm, central nucleus, prominent nucleoli
- Atypical histologies:
  - Intertubular, tubular, microcystic, signet ring
- Overall survival >95%

**Spermatocytic Seminoma**
- Rare (1-2% of testicular GCTs)
- Bilateral in up to 9%
- Peak incidence 55 years, rare below 30 years
- Only in testis (no ovarian counterpart, not in mediastinum or retroperitoneum)
- Serum markers normal
- No association with cryptorchidism, ITGCN or i(12p)
- Excellent prognosis
  - Except following sarcomatous change (about 6% cases)

**Seminoma: immunoprofile**
- Positive
  - PLAP, c-KIT, OCT 3/4
- Negative
  - AE1/AE3, CD30
  - AE1/AE3 positivity may suggest transformation to EC

**Classical vs. Spermatocytic Seminoma**

<table>
<thead>
<tr>
<th></th>
<th>CLASSICAL SEMINOMA</th>
<th>SPERMATOCYTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Peak incidence: 30-40</td>
<td>Generally older (&gt;55) but can occur in younger men</td>
</tr>
<tr>
<td>Bilateral</td>
<td>More common (up to 9%)</td>
<td></td>
</tr>
<tr>
<td>Ovarian counterpart</td>
<td>Dysgerminoma</td>
<td>None</td>
</tr>
<tr>
<td>Extra-testicular sites</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Associated ITGCN</td>
<td>Almost always</td>
<td>No</td>
</tr>
<tr>
<td>PLAP</td>
<td>Present</td>
<td>Generally absent</td>
</tr>
<tr>
<td>Isochromosome 12p</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Tumour cells</td>
<td>Monomorphous</td>
<td>Polymorphous (3 sizes)</td>
</tr>
<tr>
<td>Fibrous septae with lymphoid infiltration</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Risk of metastasis</td>
<td>Present</td>
<td>Almost never (exception: sarcomatous change)</td>
</tr>
</tbody>
</table>
**Embryonal Carcinoma**
- Undifferentiated malignant GCT
- Most common component of mixed GCT
- Pure EC rare
- Peak incidence at about 30 years
- <40% present as stage I disease

**EC: immunoprofile**
- OCT 3/4 (+)
  - Post-chemo embryonal carcinoma may be OCT 3/4 (-)
- AE1/AE3 (+), Cam5.2 (+)
- CD30 (+)
- EMA (-)
  - Unlike somatic carcinomas

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**Seminoma vs. Embryonal Carcinoma**

<table>
<thead>
<tr>
<th></th>
<th>Seminoma</th>
<th>EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>Sensitive</td>
<td>Resistant</td>
</tr>
<tr>
<td>Peak age group</td>
<td>30-40</td>
<td>20-30</td>
</tr>
<tr>
<td>Cytology</td>
<td>Uniform cells</td>
<td>Anaplastic</td>
</tr>
<tr>
<td>Cell membranes</td>
<td>distinct</td>
<td>Less distinct</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Pale to clear</td>
<td>More dense amphophilic</td>
</tr>
<tr>
<td>Fibrous bands</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Lymphocytic reaction</td>
<td>Prominent</td>
<td>Generally absent</td>
</tr>
<tr>
<td>Granulomatous reaction</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>C-KIT</td>
<td>Positive</td>
<td>Negative (may be focally +)</td>
</tr>
<tr>
<td>AE1/AE3, Cam 5.2</td>
<td>Negative (may be focally +)</td>
<td>Strongly +</td>
</tr>
<tr>
<td>CD30</td>
<td>Negative (may be focally +)</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Unusual features in Seminoma Mimicking Embryonal Carcinoma**
- Cytological atypia (anaplastic seminoma)
  - Nuclear atypia, cellular crowding, darker cytoplasm
- Tubular differentiation
  - Pseudoglandular rather than true gland lumina
- Cytokeratin immunoreactivity
  - Generally very focal
  - More AE1/AE3 positivity in otherwise typical seminoma would suggest transformation to EC

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**Yolk Sac Tumour**
- Part of mixed GCT in 40%
  - More common in younger patients
- YST as part of mixed GCT
  - Pure YST very rare in adults
  - Presence in primary: good prognosis (better staging?)
  - Presence in metastasis: poor prognosis (chemoresistant)
- Paediatric pure YST
  - Most common childhood testis tumour, usually <4yrs old
  - No association with cryptorchidism and ITGCN
  - Good prognosis

**May resemble seminoma**
- Solid sheets with clear cytoplasm and well defined cytoplasmic membranes
  - Usually associated with more typical areas of YST
### Unusual Patterns of YST

- Solid, hepatoid, parietal, endometroid
- Generally in post chemoRx late recurrences
- Chemoresistant sy
- May be treated effectively with surgery

### Seminoma vs. YST

<table>
<thead>
<tr>
<th></th>
<th>Seminoma</th>
<th>Solid pattern of YST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic hyaline globules</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Lymphocytic reaction</td>
<td>Common</td>
<td>Unusual</td>
</tr>
<tr>
<td>Granuloma</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>OCT 3/4</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>AE1/AE3</td>
<td>Negative</td>
<td>Diffusely +</td>
</tr>
<tr>
<td>Glypican-3</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

### Differential Diagnosis of GCT

**CRITICAL**

- Germ cell vs. non-germ cell tumour
- Seminoma vs. non-seminoma GCT (if markers normal)
- Classical seminoma vs. spermatocytic seminoma
- Dermoid/epidermoid cyst vs. monodermal teratoma

**LESS IMPORTANT**

- Seminoma vs. non-seminoma (if serum AFP high)
  - Treated as non-seminoma if no other explanation for serum AFP level
- Presence of seminoma in non-seminoma GCT
- Focal choriocarcinoma in non-seminoma GCT
- Embryonal carcinoma vs. Yolk Sac Tumour
- ITGCN in background testis
  - Absence suggests non-germ cell tumour

**LEAST IMPORTANT**

- Mature vs. immature teratoma
  - No clinical significance
- Vascular invasion in seminoma
- Isolated syncitiotrophoblasts in seminoma and EC
  - Could explain raised serum HCG

### Critical Differential Diagnosis

**GCT vs. Non-GCT**

- Non-germ cell tumours
  - Non-Hodgkin’s lymphoma
  - Sex cord stromal tumours
  - Seminoma-like Sertoli cell tumour
  - Metastasis into testis
    - Most common is prostate cancer
**Critical Differential Diagnosis**

**GCT vs. Non-GCT**

- **Importance**
  - **Therapy:** GCT very responsive to BEP chemoRx
  - **Prognosis:** GCT much better than non-GCT even following metastasis

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**Seminoma vs. Clear Cell Sex Cord Tumours**

<table>
<thead>
<tr>
<th></th>
<th>Seminoma</th>
<th>Clear cell SCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response to RadioRx</strong></td>
<td>Excellent</td>
<td>Resistant</td>
</tr>
<tr>
<td>and ChemoRx</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nuclei</strong></td>
<td>Polygonal</td>
<td>Round/irregular</td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td>Uniform</td>
<td>Polymorphic</td>
</tr>
<tr>
<td><strong>Intranuclear cytoplasmic inclusions</strong></td>
<td>Absent</td>
<td>May be present</td>
</tr>
<tr>
<td><strong>Associated ITGCN</strong></td>
<td>Present in &gt;90%</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Immunohistochemistry</strong></td>
<td>Oct3/4+, c-KIT+</td>
<td>Melan A+, calretinin+, inhibin+ (Sertoli cell tumours often inhibin-)</td>
</tr>
</tbody>
</table>

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**GCT Immunohistochemistry**

<table>
<thead>
<tr>
<th></th>
<th>Seminoma (and ITGCN)</th>
<th>EC</th>
<th>Spermatocytic Seminoma</th>
<th>VST</th>
<th>ChorioCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLAP</td>
<td>+</td>
<td>+/-</td>
<td>- (or focal)</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>OCT4</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SALL4</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>C-KIT</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>AE1/AE3, Cam 5.2</td>
<td>- (or focal)</td>
<td>+</td>
<td>- (or focal)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD30</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AFP</td>
<td></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>SALL4</td>
<td></td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Alpha-Inhibin</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Calretinin</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</table>