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**)

Classification of GCT

- **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

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

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%**

Seminoma: immunoprofile

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

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)

Classical vs. Spermatocytic Seminoma

	CLASSICAL SEMINOMA	SPERMATOCYTIC
Age	Peak incidence: 30-40	Generally older (>55) but can occur in younger men
Bilateral		More common (up to 9%)
Ovarian counterpart	Dysgerminoma	None
Extra-testicular sites	Yes	No
Associated ITGCN	Almost always	No
PLAP	Present	Generally absent
Isochromosome 12p	Present	Absent
Tumour cells	Monomorphous	Polymorphous (3 sizes)
Fibrous septae with lymphoid infiltration	Present	Absent
Risk of metastasis	Present	Almost never (exception: sarcomatous change)

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

Seminoma vs. Embryonal Carcinoma

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

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

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

Yolk Sac Tumour

- **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
- Chemoresistantsy
- May be treated effectively with surgery

Seminoma vs. YST

	Seminoma	Solid pattern of YST
Eosinophilic hyaline globules	Rare	Common
Lymphocytic reaction	Common	Unusual
Granuloma	Common	Rare
OCT 3/4	Positive	Negative
AE1/AE3	Negative (may be focally +)	Diffusely +
Glypican-3	Negative	Positive

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

Differential Diagnosis of GCT

- **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

Differential Diagnosis of GCT

- **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

Seminoma vs. Clear Cell Sex Cord Tumours

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

GCT Immunohistochemistry

	Seminoma (and ITGCN)	EC	Spermatocytic Seminoma	YST	ChorioCa
PLAP	+	+/-	- (or focal)	+/-	+/-
OCT4	+	+	-	-	-
SALL4	+	+	-/+	+	+
C-KIT	+	-	+/-	-/+	-
AE1/AE3, Cam 5.2	- (or focal)	+	- (or focal)	+	+
CD30	-	+	-	-	-
AFP	-	-	-	+	-
SALL4	+	+	-	+	+/-
Alpha-Inhibin	-	-	-	-	+
Calretinin	-	-	-	-	-