Testicular germ cell tumours – Pathology & therapeutic decision making.

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University Hospital Southampton. BDIAP / Pathological Society – Edinburgh June 2013.
Wessex Medical Oncology Unit

Central South Coast Cancer Network

3rd largest cancer network in UK. 2.4 million population. 120 new GCTs / year.
TESTICULAR TUMOURS

2100 cases annually in UK.

Germ cell tumour (95%) - Seminoma (50%+).
  - NSGCT.
  - Combined.

Non germ cell tumour - sex cord stromal
  - lymphoma
  - other
TESTICULAR TUMOURS

Accurate diagnosis essential as pathology determines management.

Germ cell tumour:

- Classical Seminoma – radio or chemotherapy, observation.

- Non seminomatous (& combined GCTs).
  - metastatic disease - chemotherapy +/- surgery.
  - stage 1 - no vascular invasion – observation.
    - +ve VI – chemotherapy or observation.

- Spermatocytic seminoma – observation.
WHY RECOGNISE GERM CELL TUMOUR SUBTYPES?

- Primary tumours:
  - avoid misclassification eg Seminoma v embryonal carcinoma Spermatocytic seminoma.
  - accurate and reproducible classification to guide treatment.

- Germ cell tumours presenting as metastases:
  - confident identification of germ cell tumour.
  - relatively confident exclusion of germ cell tumour.

- Better achieved through WHO classification rather than BTTP.
TESTICULAR TUMOURS.

• Most can be reliably diagnosed by careful histological assessment and recognition of typical patterns.

• Use of appropriate immunohistochemistry.
Placental alkaline phosphatase (PLAP).

Classical seminoma, ITGCN.

Some embryonal carcinoma and yolk sac tumour.

But – technical issues, failure to express, background staining.
Transcription factor in maintaining pluripotentiality in embryonic stem cells and primordial germ cells.


Classical seminoma, embryonal carcinoma & ITGCN.

Occasional other carcinomas; paraganglia.

Classical seminoma - 268/268

Embryonal carcinoma - 174/174

ITGCN - 267/267

Yolk sac tumour - 0/125

Choriocarcinoma - 0/33

Teratoma - 0/137

Spermatocytic seminoma – 0/21

Metastatic seminoma or embryonal carcinoma – 47/47.
SALL4

• SALL4 regulates transcription of OCT4.
• Strongly expressed in ITGCN, seminoma, embryonal carcinoma, yolk sac tumour (adult/paediatric).
• Expressed in spermatocytic seminoma / choriocarcinoma.
• Weak in many teratomas.
• Can be seen in some spermatocytes & spermatogonia.
• Occasional weak staining in rare non-GCTs (11/275). NB – oesophago-gastric carcinoma “YST”.
• Am J Surg Path 2009, 33, 1065
Mixed yolk sac tumour and embryonal carcinoma.

YST – SALL4+, OCT3/4 -ve.
CD30.
Embryonal carcinoma.

Cytokeratin.
Embryonal carcinoma.
Yolk sac tumour.
Trophoblastic.
Seminoma (focal).
Non germ cell tumours.
Immunohistochemistry – others.

Inhibin – Sex cord stromal.  

CD45 – lymphoma.

CD117 – seminoma & ITGCN.

HCG – AFP - ???. Value in most problem situations.
## Immunohistochemistry of germ cell tumours.

<table>
<thead>
<tr>
<th></th>
<th>Seminoma (ITGCN)</th>
<th>Embryonal carcinoma</th>
<th>Spermatocytic seminoma</th>
<th>Yolk sac tumor</th>
<th>Chorio-carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PLAP</strong></td>
<td>+</td>
<td>+ or -</td>
<td>- or focal +</td>
<td>+ or -</td>
<td>+ or -</td>
</tr>
<tr>
<td><strong>OCT3/4</strong></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>SALL4</strong></td>
<td>+</td>
<td>+</td>
<td>+ or -</td>
<td>+</td>
<td>variable</td>
</tr>
<tr>
<td><strong>CD117</strong></td>
<td>+</td>
<td>_</td>
<td>+ or -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>CK</strong></td>
<td>- or focal</td>
<td>+</td>
<td>- or focal</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>CD30</strong></td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
CLASSICAL PATTERN SEMINOMA
CLASSICAL PATTERN SEMINOMA
CLASSICAL PATTERN SEMINOMA

HISTOLOGICAL PATTERNS:

- solid / sheet like
- small nests / individual cells in fibrous stoma
- diffuse interstitial growth between tubules
- with syncytiotrophoblast cells
- “granulomatous”
- regressed
- tubular
- signet ring
Intertubular Seminoma – single cell interstitial pattern.
Syncytiotrophoblasts seen in 4-7% on light microscopy & 20-25% on immunohistochemistry. Correlates with serum HCG.
Tubular seminoma.
Solid tumour.
Intratubular growth.,
Lymphocytic infiltrate.

Male aged 85.
Normal serum markers
Some tubular / cribriform areas. CK +ve, inhibin & OCT3/4 –ve. **Metastatic prostate carcinoma.**
ANAPLASTIC SEMINOMA.

Mitotic rate.
More pleomorphic.
Behaves as seminoma.
? Ischaemic change.

CD30
SPERMATOCYTIC SEMINOMA

Nodular solid tumour.
No significant inflammation.
Oedematous stroma – yolk sac tumour like.
No ITGCN.
• Mixture of cell types – small, medium & large.
SPERMATOCYTIC SEMINOMA

- Rare tumour.
- Wessex – 20 cases in past 20 years.
- 1% of testicular tumours.
- Individual pathologist experience limited.
- Age range - 35 – 82 years (50% < 50 years).
- Bilateral.
- Classical seminoma commoner in this age group.
ANAPLASTIC SPERMATOMATOCYTIC SEMINOMA

- Sheets of more monomorphic intermediate cells simulating classical seminoma or embryonal carcinoma
Embryonal carcinoma.

OCT3/4, CK, CD30 +ve.

Seminoma

Embryonal carcinoma (solid)
• Seminoma & solid embryonal carcinoma.
• About 10% GCTs.
Yolk sac tumour.
• Yolk sac tumour
• Microcystic pattern.
• Myxoid stroma.
- Yolk sac tumour
- Schiller Duval body
- Endodermal sinus.
- Hyaline globules
- Yolk sac tumour
  Not as pleomorphic as embryonal carcinoma.
• Yolk sac tumour
  Solid pattern (hyaline globules).

Parietal pattern
Sub-nuclear vacuolation.
Endometrioid like.

Hepatoid pattern
Cytoplasmic globules.
TERATOMA.

4% of GCTs.

ITGCN +ve.

Up to 25% progress.
- Carcinoid.
- PNET.
- Single cell type – (eg cartilage & ITGCN).
# TESTICULAR GERM CELL TUMOURS

<table>
<thead>
<tr>
<th>EPIDERMOID CYST</th>
<th>TERATOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single thin walled cyst</td>
<td>Complex cyst shape</td>
</tr>
<tr>
<td>No other elements</td>
<td>Other elements</td>
</tr>
<tr>
<td>ITGCN -ve</td>
<td>ITGCN +ve</td>
</tr>
</tbody>
</table>

- Inflammation + regression
- Typical ultrasound appearances.
- Usually sub-tunical.
- Not considered a teratoma.
Teratoma with somatic malignancy

Teratoma with PNET.
Overgrowth – x 4 objective.
Significance in metastatic disease.
TESTICULAR GERM CELL TUMOURS & PNET

- 29 cases.
- Did not include small foci of immature neuroepithelium.
- Testicular tumours mixed. 12/17 included teratoma.
- 9 in testis; 8 in testis and nodes; 12 in metastases only.
- Patterns variable from neuroblastoma to PNET.
- Histological pattern in testis did not predict progress.
- Confined to testis - did not influence prognosis.
- 13/20 in nodes dead. 4/20 - recurrent disease.

Choriocarcinoma.
Haemorrhagic.
Importance of serum HCG.
Treated before orchidectomy.
TESTICULAR GERM CELL TUMOURS TREATED BY SOUTHAMPTON ONCOLOGISTS 1979 - 2006. OVERALL SURVIVAL BY DECADE

DECADE
- 1970’s
- 1980’s
- 1990’s
- 2000’s

CUM SURVIVAL

SURVIVAL (YEARS)
DEATHS IN TESTICULAR TUMOURS.

• Advanced disease at presentation.
  - choriocarcinoma - haemorrhage.
  - patient neglect.

• Progressive / recurrent disease:
  - chemoresistant – platinum resistance.
  - somatic transformation.
  - growing teratoma.

• Complications of treatment:
  - immunosuppression.
  - bleomycin lung.
  - idiosyncratic.

• Second malignancies.
TESTICULAR TUMOURS – Pathology determines management.

Germ cell tumour:

- Classical Seminoma – radio or chemotherapy, observation.

- Non seminomatous (& combined GCTs).
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  - stage 1- no vascular invasion – observation.
    - +VI – chemotherapy or observation.

- Spermatocytic seminoma – observation / discharge.
Pure Seminoma

Clinical Stage I
Pre-orchidectomy - Normal AFP
Post-orchidectomy - Normal HCG & CT

Evolution of treatment options
Radiotherapy
Surveillance
Single agent carboplatin chemotherapy

Fig 1. Development in the treatment of clinical stage 1 seminoma, 2000 to 2006.

J Clin Oncol 29:719-725. © 2011
Excellent Clinical Outcome

Clinical stage 1 seminoma.

<table>
<thead>
<tr>
<th></th>
<th>No of patients</th>
<th>Relapse free</th>
<th>Relapses</th>
<th>5 year CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1384</td>
<td>92.6</td>
<td>90</td>
<td>99.9</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>481</td>
<td>99.2</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Surveillance</td>
<td>512</td>
<td>85.7</td>
<td>65</td>
<td>99.8</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>188</td>
<td>96.1</td>
<td>7</td>
<td>100</td>
</tr>
</tbody>
</table>
Prognostic markers – Stage I seminoma

Vascular invasion of equivocal prognostic significance. T stage not particularly helpful in guiding clinical management!

Retrospective pooled analysis 4 surveillance studies (638). Median 7yr FU. Overall relapse free survival 82%. J Clin Oncol 2002, 20, 4448

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>No rete invasion</th>
<th>+ve rete invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>4cm or less</td>
<td>176</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>87.8%</td>
<td>85.6%</td>
</tr>
<tr>
<td>&gt; 4cm</td>
<td>107</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>83%</td>
<td>68.5%</td>
</tr>
</tbody>
</table>
Seminoma:

Rete invasion.

Pagetoid involvement by ITGCN
Vascular invasion assessment in seminoma.

Smear artefact
Vascular invasion assessment in seminoma.

Undisturbed lymph.  Granuloma in vessel
NSGCT or mixed GCT – Stage I

Lymphovascular invasion most important risk factor for relapse.

No LV invasion ~ 15% risk of relapse. Close surveillance alone. BEP chemotherapy if relapse.

LV invasion +ve ~ 40-50% risk of relapse. Adjuvant BEP or close surveillance plus BEP if relapse.

Direct invasion of rete.
Vascular invasion assessment in embryonal carcinoma.
PERCENTAGE OF EMBRYONAL CARCINOMA AS PROGNOSTIC FACTOR

-MRC studies (1980s) – vascular invasion;

Also - presence of embryonal carcinoma, absence of yolk sac elements.

- AFIP – 1994 – Can Research 54, 362

<table>
<thead>
<tr>
<th>% EC</th>
<th>VI +ve</th>
<th>VI -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>92%</td>
<td>58%</td>
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<tr>
<td>75</td>
<td>83%</td>
<td>37%</td>
</tr>
<tr>
<td>50</td>
<td>67%</td>
<td>20%</td>
</tr>
<tr>
<td>25</td>
<td>46%</td>
<td>10%</td>
</tr>
<tr>
<td>0</td>
<td>27%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Probability of occult disease in stage 1 NSGCT (RPLND).
Myth, legend or fact?
Testicular germ cell tumours