Germ Cell Tumors of the Testis
Pathology, Immunohistochemistry, and the Often Confusing Appearance of Their Metastases

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UCSF

Male Genital Cancers in the US in 2015

<table>
<thead>
<tr>
<th>Site</th>
<th>Estimated Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>220,800</td>
</tr>
<tr>
<td>Bladder</td>
<td>56,320</td>
</tr>
<tr>
<td>Kidney</td>
<td>38,270</td>
</tr>
<tr>
<td>Testis</td>
<td>8430</td>
</tr>
</tbody>
</table>

Germ Cell Tumors of the Testis

<table>
<thead>
<tr>
<th>Intratubular Germ Cell Neoplasia, Unclassified (IGCNU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intratubular Germ Cell Neoplasia, Specific Types</td>
</tr>
<tr>
<td>Seminoma</td>
</tr>
<tr>
<td>Spermatocytic Seminoma</td>
</tr>
<tr>
<td>Embryonal Carcinoma</td>
</tr>
<tr>
<td>Yolk Sac Tumor</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Other Trophoblastic Tumors</td>
</tr>
<tr>
<td>Teratoma</td>
</tr>
<tr>
<td>Mixed Germ Cell Tumor</td>
</tr>
</tbody>
</table>

Frequency of Types

- Seminoma is the most common pure type
- Mixed germ cell tumor is the most common nonseminomatous germ cell tumor

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed GCT</td>
<td>78</td>
</tr>
<tr>
<td>Embryonal CA</td>
<td>16</td>
</tr>
<tr>
<td>Teratoma</td>
<td>5</td>
</tr>
<tr>
<td>Yolk Sac Tumor</td>
<td>2</td>
</tr>
</tbody>
</table>

Calgary, Canada Mod Pathol 2013; 26: 579-586
Intratubular Germ Cell Neoplasia (Carcinoma in Situ)

- Precursor of most invasive germ cell tumors
- Most likely in high risk patients; found in <1% of the normal population
- Thought to be established in the fetus at the time the gonads develop
- Switched on at puberty
- Lacks 12p abnormalities found in invasive tumors
- 50% develop invasive germ cell tumor by 5 years, 70% by 7 years

I had a couple of previous papers returned from American journals, which for a long time did not appreciate the existence of a CIS pattern. However, even there, CIS is now officially recognized.

Advances in Anatomic Pathology 2015; 22(3): 202-212
The Background

IGCNU

IGCNU – OCT4
IGCNU – SALL4

IGCNU – CD117

IGCNU – Pagetoid Spread to the Rete Testis

Treatment of IGCNU

- Unilateral: Orchiectomy
- Bilateral: Low dose radiation
  - Prevents development of invasive germ cell tumor
  - Causes sterility
Staging Testicular Tumors

<table>
<thead>
<tr>
<th>pT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT1</td>
<td>Limited to testis and epididymis. No lymphovascular invasion. No tunica vaginalis invasion.</td>
</tr>
<tr>
<td>pT2</td>
<td>Limited to testis and epididymis. Lymphovascular invasion present. Tunica vaginalis invasion present.</td>
</tr>
<tr>
<td>pT3</td>
<td>Invasion of the spermatic cord.</td>
</tr>
<tr>
<td>pT4</td>
<td>Invasion of the scrotum.</td>
</tr>
</tbody>
</table>

Clinical Stage I

- **Stage IA**
  - pT1 N0 M0
- **Stage IB**
  - pT2 N0 M0
  - pT3 N0 M0
  - pT4 N0 M0
- **Stage IS**
  - Any pT N0 M0 Elevated markers

What Information is Needed to Decide on Treatment?

- pT category
- Types of tumor present
  - Embryonal CA, choriocarcinoma high risk
  - YST may reduce risk
- Lymphovascular invasion
- Rete testis invasion (tumor grows around the rete tubules)
- Hilar soft tissue invasion
- Involvement of epididymis

From CAP Testis Checklist
Seminoma

- The most common germ cell tumor; can be pure or part of a MGCT
- Average patient age = 40.5; does not occur in children
- Bilateral in 2% of patients
- The clinical presentation is with a testicular mass
- Serum hCG can be elevated (~10%), but AFP should not be elevated

Seminoma

Current Treatment

- **Stage I**
  - Most treated by surveillance; some may receive radiation
  - About 20% relapse rate, but nearly 100% survival
  - Risk factors include large tumor (> 4 cm) and rete testis involvement

- **Stage II**
  - Radiation (small masses < 3 cm) or chemotherapy
  - 98% survival; may need to resect large residual masses
Seminoma Immunohistochemistry

<table>
<thead>
<tr>
<th>Marker</th>
<th>Staining Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT4 ✓</td>
<td>Nuclear</td>
</tr>
<tr>
<td>SALL4</td>
<td>Nuclear</td>
</tr>
<tr>
<td>CD117</td>
<td>Membrane/cytoplasm</td>
</tr>
<tr>
<td>D2-40 (podoplanin) ✓</td>
<td>Membrane/cytoplasm</td>
</tr>
<tr>
<td>PLAP</td>
<td>Membrane/cytoplasm</td>
</tr>
<tr>
<td>hCG</td>
<td>STGC only</td>
</tr>
<tr>
<td>SOX2</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Seminoma

Diagnostic Problems

- Necrosis – Complete Regression
- Unusual growth patterns: alveolar, tubular, trabecular
- Unusual stromal changes or tumor cell drop out: fibrosis, excessive granulomas or lymphocytes
- Small foci of intertubular seminoma
- STGC
Seminoma

**Differential Diagnosis**

- Embryonal carcinoma
- Yolk sac tumor, especially the solid pattern
- Lymphoma
- Malignant Sertoli cell tumor
- Malignant Leydig cell tumor
Spermatocytic Seminoma

- Not related to IGCNU or other conventional germ cell tumors
- 3 types of cells: intermediate, large, small
- Intratubular spermatocytic seminoma; no IGCNU
- Arises from spermatogonia
- Amplification of DMRT1 gene on p9p24.2 may be involved; no i12p

Spermatocytic Seminoma

- Less than 1% of testicular tumors
- Unrelated to classic seminoma
- Older patients, average mid 50’s
- Present with painless testicular mass
- Most do not spread beyond the testis
- Some develop sarcomatous transformation, and these metastasize
Spermatocytic Seminoma
Immunohistochemistry

<table>
<thead>
<tr>
<th>Marker</th>
<th>Seminoma</th>
<th>Spermatocytic Seminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT4</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>SALL4</td>
<td>+</td>
<td>+, mod</td>
</tr>
<tr>
<td>CD117</td>
<td>+</td>
<td>+, mod/weak</td>
</tr>
<tr>
<td>PLAP</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>D2-40</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Intratubular Spermatocytic Seminoma
**Embryonal Carcinoma**

- Anaplastic primitive cells growing in a variety of patterns: solid, glands, papillae
- Uncommon as a pure tumor, very common as a component of a MGCT
- Average age 32, most 25-35
- Most present with a testicular mass
- Only 40% confined to the testis at diagnosis; 40% LN, 20% distant mets
Immunohistochemistry of Embryonal Carcinoma

<table>
<thead>
<tr>
<th>Stain</th>
<th>Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT4</td>
<td>Positive, nuclei</td>
</tr>
<tr>
<td>SALL4</td>
<td>Positive, nuclei</td>
</tr>
<tr>
<td>SOX2</td>
<td>Positive, nuclei</td>
</tr>
<tr>
<td>Keratin AE1/AE3</td>
<td>Positive, membranes</td>
</tr>
<tr>
<td>EMA</td>
<td>Negative</td>
</tr>
<tr>
<td>CD30</td>
<td>Positive, membranes</td>
</tr>
<tr>
<td>PLAP, D2-40</td>
<td>-/+ , weak, focal</td>
</tr>
<tr>
<td>hCG</td>
<td>Positive in STGC</td>
</tr>
</tbody>
</table>

Embryonal Carcinoma Differential Diagnosis

- Seminoma
- Yolk sac tumor
- Choriocarcinoma
- Lymphoma
- Metastatic carcinoma from some other site
Surveillance for Stage I Nonseminoma Testicular Cancer

- All patients with stage I put on this program
- 1,226 patients
- Relapse rate was 30.6% at 5 years; most within the first year
- Survival rate 99.1%
- High risk group: vascular invasion, embryonal carcinoma, rete testis invasion
- High risk had 50% recurrence rate; no risk factors only 12% recurrence rate

What Information is Needed to Decide on Treatment?

- pT category
- Types of tumor present
  - Embryonal CA, choriocarcinoma high risk
    - YST may reduce risk
- Lymphovascular invasion
- Rete testis invasion (tumor grows around the rete tubules)
- Hilar soft tissue invasion
- Involvement of epididymis

Embryonal Carcinoma
Diagnostic Problems in Metastases/Post Chemotherapy

1. Loss of antigenicity.

<table>
<thead>
<tr>
<th>Stain</th>
<th>&gt; 50% Positive</th>
<th>2+ or 3+ Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD30</td>
<td>8/25</td>
<td>13/25</td>
</tr>
<tr>
<td>OCT4</td>
<td>19/25</td>
<td>19/25</td>
</tr>
<tr>
<td>CK AE1/AE3</td>
<td>13/25</td>
<td>19/25</td>
</tr>
</tbody>
</table>

2. Tumor necrosis.

Hum Pathol 2006;37:662-667
Yolk Sac Tumor

- Differentiates to form structures typical of the embryonic yolk sac, allantois and extraembryonic mesenchyme
- In adults accounts for 6% of pure tumors but is seen in 53% of MGCT
- Patients 15-40 years old
- Serum AFP typically elevated

Yolk Sac Tumor in Children

- Most common testicular tumor in children (teratoma is second)
- Median age 16-20 months, most < 2 years old. Rare after age 4
- Unlike JGCT, virtually never congenital
- Serum AFP elevated
- Very favorable prognosis, most put on surveillance; spreads to the lungs
### Yolk Sac Tumor Histologic Patterns

<table>
<thead>
<tr>
<th>Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticular (microcystic) ✔</td>
</tr>
<tr>
<td>Macrocystic</td>
</tr>
<tr>
<td>Endodermal sinus (festoon) ✔</td>
</tr>
<tr>
<td>Papillary</td>
</tr>
<tr>
<td>Solid</td>
</tr>
<tr>
<td>Glandular-alveolar</td>
</tr>
<tr>
<td>Myxomatous</td>
</tr>
<tr>
<td>Sarcomatoid</td>
</tr>
<tr>
<td>Polyvesicular vitelline (PVV)</td>
</tr>
<tr>
<td>Hepatoid</td>
</tr>
<tr>
<td>Parietal</td>
</tr>
</tbody>
</table>

- **Microcystic YST**
- **Macrocystic YST**

- **Festoon**
- **Schiller-Duval Body**

- **Glandular pattern**
- **Mixed with EC**
**Yolk Sac Tumor Immunohistochemistry**

<table>
<thead>
<tr>
<th>Stain</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT4</td>
<td>Negative</td>
</tr>
<tr>
<td>SALL4</td>
<td>Positive, nuclei</td>
</tr>
<tr>
<td>HNF-1</td>
<td>Positive, nuclei</td>
</tr>
<tr>
<td>Alpha-fetoprotein (AFP)</td>
<td>Positive, patchy, cytoplasm</td>
</tr>
<tr>
<td>Glypican-3</td>
<td>Positive, cytoplasm</td>
</tr>
<tr>
<td>Keratin AE1-AE3</td>
<td>Positive, cytoplasm</td>
</tr>
<tr>
<td>EMA, CK7</td>
<td>Negative</td>
</tr>
<tr>
<td>CD117</td>
<td>Patchy staining in solid pattern</td>
</tr>
</tbody>
</table>

**Somatic Malignancies in Germ Cell Tumors**

- Can be found in association with primary and metastatic germ cell tumors
- In one study
  - 7 of 45 glandular tumors reclassified as glandular yolk sac tumors
  - 26/76 sarcomatoid tumors reclassified as sarcomatoid yolk sac tumors
Many Postchemotherapy Sarcomatous Tumors in Patients With Testicular Germ Cell Tumors Are Sarcomatoid Yolk Sac Tumors: A Study of 33 Cases

- Evaluated 33 sarcomatoid tumors that lacked features of a defined sarcoma type
- Graded tumors using French sarcoma system
- All occurred after chemotherapy
- Tumors with at least 2+ staining for glypican and keratin in at least 10% of tumor cells were considered to be sarcomatoid YST
- 22/33 were classified as sarcomatoid YST
- 15/22 positive for SALL4
- 8/14 DOT, 5/14 ANED, 1 DOC
- Behavior correlated with tumor grade

“Somatic-type” Malignancies Arising From Testicular Germ Cell Tumors: A Clinicopathologic Study of 124 Cases With Emphasis on Glandular Tumors Supporting Frequent Yolk Sac Tumor Origin

- 7/45 adenocarcinomas were reclassified as glandular yolk sac tumors
- Criteria were: positive staining for glypican and/or AFP and scant/absent EMA and CK7
- YST and adenocarcinoma expressed CDX-2
- SALL4, BerEp4 and MOC1 commonly present in both
Choriocarcinoma

- Less than 1% of testicular tumors.
- In the largest series
  - 1010 testicular tumors reviewed
  - 6 (0.6%) pure choriocarcinomas
  - 9 (0.9%) choriocarcinoma predominant
- Patients mainly 20-40
- Almost all have metastases at diagnosis and presentation often due to symptoms caused by metastases
- Serum hCG typically markedly elevated
### Choriocarcinoma

**Immunohistochemistry**

<table>
<thead>
<tr>
<th>Stain</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>hCG</td>
<td>Positive, STGC cytoplasm</td>
</tr>
<tr>
<td>Keratin, including CK7</td>
<td>Positive, cytoplasm</td>
</tr>
<tr>
<td>P63</td>
<td>Positive in cytotrophoblasts</td>
</tr>
<tr>
<td>HPL</td>
<td>Positive in some STGC and intermediate trophoblasts</td>
</tr>
<tr>
<td>Inhibin</td>
<td>Positive in STGC and some mononuclear trophoblasts</td>
</tr>
<tr>
<td>Glypican-3</td>
<td>Positive in STGC</td>
</tr>
<tr>
<td>OCT4</td>
<td>Negative</td>
</tr>
<tr>
<td>SALL4</td>
<td>Variable</td>
</tr>
</tbody>
</table>

### Choriocarcinoma

**Treatment and Prognosis**

- Widespread hematogenous metastases; worse prognosis than other germ cell tumors
- In largest recent series, 14 patients with follow up
  - 11 DOT despite BEP therapy
  - 1 AWT
  - 2 with lung metastases NED
- Not clear how much choriocarcinoma must be present for poor prognosis
Teratoma

- Germ cell tumor that differentiates to form mature or embryonic somatic tissues
- Uncommon as a pure tumor, 3-4%, but common component of MGCT
- Occur in two age groups

Prepubertal Teratoma

- Median age 13 m, almost all < 4 years
- Almost all are pure teratomas
- Clinically benign
- Can be treated by orchiectomy alone
- Organoid morphology, immature tissue less common than in adults
- No atypia or MF, no IGCNU

Prepubertal Benign Teratoma, Age 4
Prepubertal Benign Teratoma, No IGCNU

Teratomas in Adults

- Same age range as other germ cell tumors
- Pure teratomas reported to exhibit malignant behavior with retroperitoneal metastasis
- Usually mixed with other germ cell elements
- 12p abnormalities and associated IGCNU in 90% of cases
- No demonstrated differences in behavior between immature and mature teratomas and they are all classified as teratoma

Testicular Teratoma in an Adult
Testicular Teratoma in an Adult: Glands

Testicular Teratoma in an Adult – Immature Neural Tissue

Next to a Teratoma

OCT4
Teratoma

Special Situations

- Dermoid cysts
- Benign mature teratomas
- Epidermoid cysts
- No IGCNU or 12p abnormalities in any of the above
- Local excision with sufficient surrounding tissue to evaluate

Teratoma with a Secondary Malignant Component

- Can be in the testis, in a metastatic site or both
- Proliferation of atypical embryonic elements such as primitive neuroectodermal tissues
- Rhabdomyosarcoma most common sarcomatous element
- Larger than one 40x LPF
- Same 12p abnormalities as in teratoma
- Poor prognostic finding in a metastasis but not necessarily if only in the primary site
Testicular Germ Cell Tumors With Sarcomatous Components
An Analysis of 33 Cases

Charles C. Gao, MD*; Wolk Pomerance, MD*; Alejandro Loza-Castanon, MD*;
Shi-Ming Tu, MD; Louis Pinero, MD; Francis Wandell, MD*; and Regina Lencioni, MD, MD*.


- 33 cases at MD Anderson 1985-2007
- 30 had a testicular GCT with teratoma
- Most were MGCT
- 3 had received neoadjuvant chemo
- Sarcoma in the primary in 19; 2 died of GCT, 11 NED
- Sarcoma in the metastasis in 14; 7 died of GCT, 7 NED
- Patients with a sarcoma confined to the testicular GCT may not have a higher risk than same stage GCT without sarcoma
- Patients with a sarcoma in the metastases have a higher risk of dying

Differentiated rhabdomyomatous tumors after chemotherapy for metastatic testicular germ-cell tumors: a clinicopathological study of seven cases mandating separation from rhabdomyosarcoma

Jessica A Clevenger¹, Richard S Foster² and Thomas M Ulbright*²

- 7 cases with differentiated skeletal muscle but no primitive cells or mitotic figures
- All had a history of a NSGCT, 5 with a teratoma component
- One testis had foci of embryonal rhabdomyosarcoma
- Mild to moderate atypia often with prominent nucleoli, but no mf, necrosis, primitive elements
- No patient with follow up developed progressive sarcoma
- Clinical behavior similar to teratoma, not RMS