Testicular Germ Cell Tumors; A Simplistic Approach

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Objectives

- Histogenesis and possible precursors of Testicular GCTs
- WHO 2016 (ISUP) classification of Testicular GCT
- Immunohistochemistry panels in the differential diagnosis of Testicular GCTs
Histogenesis of Testicular Germ Cell Tumors (GCTs)

- Genetic and epigenetic factors

- Sex determining region of chromosome Y (SRY) (short arm of chromosome Y)

- Chromosome 12p abnormalities:
  - isochrome and overexpression
  - Genetic hallmark for postpuberal malignant GCT

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WHO 2016 (ISUP) classification of Testicular GCT

REVIEW

The World Health Organization 2016 classification of testicular germ cell tumours: a review and update from the International Society of Urological Pathology Testis Consultation Panel

The World Health Organization 2016 classification of testicular germ cell tumours: a review and update from the International Society of Urological Pathology Testis Consultation Panel
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<td>Teratoma</td>
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<td>Prepubertal-type GCTs</td>
<td>Prepubertal-type yolk sac tumor</td>
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<td>Combined prepubertal-type teratoma and yolk sac tumor</td>
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<td>Spermatocytic tumor</td>
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**NOTE.** Modified from the 2016 *WHO Classification of Tumours* of the testis [3].
Testicular GCT: WHO 2016 Classification

What is new….

- Pathogenetically derived classification (IGCNU and CIS)

- Two main groups:
  - Prepuberal: non-GCNIS derived tumors
  - Postpuberal: GCNIS derived tumors

- Spermatocytic tumor

- Non-choriocarcinoma trophoblastic tumors

- Benign prepuberal type teratoma of postpuberal testis

- Prepuberal types can occur in postpuberal age

- Postpuberal types can occur in prepuberal age (in disorders of sex development)
Germ cell neoplasia in situ and specific forms of intratubular neoplasia

Chromosome 12p alterations (isochromosome 12p)

Seminoma
- Embryonic structures
  - Embryonal carcinoma
  - Mixed germ cell tumor
  - Yolk sac tumor
- Extra-embryonic structures
- Embryonic ectoderm, mesoderm, endoderm
  - Choriocarcinoma
  - Postpubertal teratoma
  - Teratoma with somatic type malignancy

Germ cell
- Prepubertal type teratoma
- Epidermoid cyst
- Dermoid cyst

Prepubertal type yolk sac tumor

Spermatocytic tumor

Not Prepuberal
Non-Invasive GCN
Intratubular seminoma
Intratubular embryonal ca
intratubular yolk sac tumor
Intratubular teratoma
NO Intratubular ChorioCa

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Non-Invasive GCN

Germ Cell Neoplasia In Situ (GCNIS)

- IGCNU- Intratubular germ cell neoplasm unclassified in 2004 WHO
- Seminoma-like cells
- + for OCT4
- Common precursor lesion for most malignant GCT
- In approximately 90% of postpuberal GCT
- In approximately 5% of contralateral testis
Best Practices Recommendations in the Application of Immunohistochemistry in Testicular Tumors

*Report From the International Society of Urological Pathology Consensus Conference*

Thomas M. Ulbright, MD,* Satish K. Tickoo, MD,†
Daniel M. Berney, FRCP,‡ John R. Srigley, MD,§|| and Members of the ISUP
Immunohistochemistry in Diagnostic Urologic Pathology Group

(Am J Surg Pathol 2014;38:e50–e59)
TABLE 1. Useful Algorithm for the Distinction Between Various Types of Germ Cell Tumors - Alternative Stains in Parentheses

Germ Cell Tumor

+ OCT4

- CD117 (Podoplanin, SOX17)
  - CD30 (AE1/AE3, SOX2)
  
  +CD117 (Podoplanin, SOX17)
  - CD30 (AE1/AE3, SOX2)

Seminoma

Embryonal Carcinoma

+Glypican 3
  ± AFP
  - hCG
  +PLAP

Yolk Sac Tumor

- Glypican 3
  - AFP
  - hCG
  - PLAP

Spermatocytic Seminoma

Choriocarcinoma

- OCT4

- CD117 (Podoplanin, SOX17)
  + CD30 (AE1/AE3, SOX2)

+ Glypican 3
  - AFP
  + hCG
  ± PLAP
Non-Invasive GCN: Specific forms

- **Intratubular Seminoma**
  - Complete filling of the tubule
  - Tubular architecture is lost
  - Tubules may be expanded

- **Intratubular Embryonal Ca**
  - Complete filling of the tubule
  - Necrosis and Calcifications
Intratubular Seminoma
Intratubular Seminoma
Intratubular Embryonal Ca
Intratubular Embryonal Ca
Intratubular Embryonal Ca
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+CD117 (Podoplanin, SOX17)  
- CD30 (AE1/AE3, SOX2)
  
  Seminoma

- CD117 (Podoplanin, SOX17)  
+ CD30 (AE1/AE3, SOX2)
  
  Embryonal Carcinoma

+Glypican 3  
+ AFP  
+ PLAP
  
  Yolk Sac Tumor

- Glypican 3  
- AFP  
- hCG  
- PLAP
  
  Spermatocytic Seminoma

- OCT 4

+Glypican 3  
- AFP  
+ hCG  
+ PLAP
  
  Choriocarcinoma
IGCNU vs Nonneoplastic Atypical Germ Cells

+ OCT4
   (PLAP, Podoplanin)
   (not SALL4, SOX17 or CD117)
   IGCNU (rule out maturation arrest in young children)

− OCT4
   (PLAP, Podoplanin)
   (not SALL4, SOX17 or CD117)
   Nonneoplastic Atypical Germ Cells
OCT4
Invasive Postpuberal Type GCTs
Not Prepuberal

**INVASIVE GCT**

- Spermatocytic tumor
- Prepubertal type teratoma
- Epidermoid cyst
- Dermoid cyst
- Prepubertal type yolk sac tumor

**Germ cell neoplasia in situ and specific forms of intratubular neoplasia**

**Chromosome 12p alterations (isochromosome 12p)**

- Seminoma
- Tumor of totipotent cells

- Embryonic structures
- Extra-embryonic structures
- Embryonic ectoderm mesoderm, endoderm

- Embryonal carcinoma
- Mixed germ cell tumor
- Yolk sac tumor
- Choriocarcinoma
- Postpubertal teratoma

Teratoma with somatic type malignancy
Seminoma

- Most frequent GCT (in its pure form)
- Normal AFP, May have elevated LDH and hCG
- Monomorphic primitive germ cell and lymphocytes
- Granulomatous reaction
- Morphologic variants: microcystic, cribiform, solid tubular, interstitial --- *same prognosis*
- Syncytiotrophoblasts in 10-20% (OCT4 +) --- *same prognosis*
- Atypia --- *same prognosis*
Seminoma

Positive
OCT4, SALL4, CD117, D2-40 (podoplanin), SOX17, PLAP

Negative
HMW Keratin, CD30, SOX2, GATA3, Glypican-3,
TABLE 1. Useful Algorithm for the Distinction Between Various Types of Germ Cell Tumors - Alternative Stains in Parentheses

- **Germ Cell Tumor**
  - **+ OCT4**
    - **+CD117** (Podoplanin, SOX17)
      - **− CD30** (AE1/AE3, SOX2)
        - **Seminoma**
    - **− CD117** (Podoplanin, SOX17)
      - **+ CD30** (AE1/AE3, SOX2)
        - **Embryonal Carcinoma**
  - **− OCT 4**
    - **+ Glypican 3**
      - **± AFP**
      - **− hCG**
      - **+ PLAP**
        - **Yolk Sac Tumor**
    - **− Glypican 3**
      - **− AFP**
      - **− hCG**
      - **− PLAP**
        - **Spermatocytic Seminoma**
    - **± Glypican 3**
      - **− AFP**
      - **+ hCG**
      - **± PLAP**
        - **Choriocarcinoma**
Germ Cell Tumor vs Sex Cord–Stromal Tumor

+ OCT4

Embryonal Carcinoma or Seminoma (see Algorithm 1)

- OCT4

+ Glypican 3
  ± AFP
  ± PLAP
  - Inhibin & Calretinin

Yolk Sac Tumor

- Glypican 3
  - AFP
  - PLAP
  ± Inhibin & Calretinin

Sex Cord–Stromal Tumor
Embryonal Carcinoma

- Elevated AFP, May have elevated HCG
- Arises from GCNIS/Intratubular embryonal ca
- Solid, glandular and papillary
- Necrosis is frequent
- Cells are of epithelial appearance, pleomorphic, frequent mitosis
Embryonal Carcinoma

Positive
OCT4, SALL4, CD30, AE1/3, SOX2

Negative
CD117, D2-40, Glypican-3
TABLE 1. Useful Algorithm for the Distinction Between Various Types of Germ Cell Tumors - Alternative Stains in Parentheses

Germ Cell Tumor

+ OCT4

- CD117 (Podoplanin, SOX17) - CD30 (AE1/AE3, SOX2)

+CD30 (AE1/AE3, SOX2)

Seminoma

Embryonal Carcinoma

Yolk Sac Tumor

Spermatocytic Seminoma

Choriocarcinoma

- OCT 4

- CD117 (Podoplanin, SOX17) + CD30

+Glypican 3 + AFP - hCG + PLAP

-Glypican 3 - AFP - hCG - PLAP

+Glypican 3 - AFP + hCG + PLAP
Germ Cell Tumor vs Metastatic High Grade Carcinoma

+ SALL4  + OCT4*  - EMA
Germ Cell Tumor (see Algorithm 1)

± SALL4 (usually −)
- OCT4  + EMA
Metastatic High Grade Carcinoma

*Embryonal carcinoma and Seminoma only
Yolk Sac Tumor, Postpuberal type

• Rare in pure form in adults; seen as part of MGCT
• Elevated AFP, May have elevated HCG
• Complex architectural patterns: microcystic or reticular, macrocystic, endodermal sinus pattern (20%)- Schiller-Duval bodies, papillary and glandular, myxomatous.
• Other uncommon forms: polyvesicular vitelline, hepatoid and glandular/primitive endodermal(Intestinal)
## Yolk Sac Tumor, Postpuberal type

<table>
<thead>
<tr>
<th>Positive</th>
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<tbody>
<tr>
<td>Glypican-3, SALL4, AE1/3, GATA-3, AFP(V), PLAP (V)</td>
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Germ Cell Tumor

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- CD117 (Podoplanin, SOX17)
  - CD30 (AE1/AE3, SOX2)
  + OCT4
  - CD117 (Podoplanin, SOX17)
  + CD30 (AE1/AE3, SOX2)

Seminoma

Embryonal Carcinoma

Yolk Sac Tumor

Glypican 3 ± AFP
  - hCG
  + PLAP

Glypican 3
  - AFP
  - hCG
  - PLAP

Glypican 3 ± AFP
  + hCG
  + PLAP

Spermatocytic Seminoma

Choriocarcinoma
Germ Cell Tumor vs Sex Cord-Stromal Tumor

- + SALL4
  - Inhibin & Calretinin
    - Germ Cell Tumor (see Algorithm 1)
  - Germ Cell Tumor
    - Sex Cord-Stromal Tumor
- - SALL4
  + or - Inhibin & Calretinin
    - Sex Cord-Stromal Tumor
Glypican 3
Choriocarcinoma and other throphoblastic Tumors

- Rare even as part of MGCT
- Frequently presents as metastatic
- Elevated hCG
- Hemorrhagic tumor, Pleomorphic
- GATA 3 useful IHC
Choriocarcinoma and other throphoblastic Tumors

- Non-choriocarcinoma trophoblastic tumors:
  - Cystic trophoblastic tumor
  - Epithelioid trophoblastic tumour
  - Placental site trophoblastic tumour,
  - Regressing choriocarcinoma,
  - Hybrid trophoblastic tumours.
Choriocarcinoma

Positive
HCG, SALL4, Glypican-3, AE1/3, GATA-3, PLAP

Negative
OCT4, CD30, hCG
TABLE 1. Useful Algorithm for the Distinction Between Various Types of Germ Cell Tumors - Alternative Stains in Parentheses

Germ Cell Tumor

+ OCT4

-CD117 (Podoplanin, SOX17)
-CD30 (AE1/AE3, SOX2)

Seminoma

-CD117 (Podoplanin, SOX17)
+CD30 (AE1/AE3, SOX2)

Embryonal Carcinoma

+Glypican 3
±AFP
-hCG
+PLAP

Yolk Sac Tumor

-Glypican 3
- AFP
- hCG
- PLAP

Spermatocytic Seminoma

+Glypican 3
- AFP
+ hCG
+ PLAP

Choriocarcinoma
Seminoma and Embryonal Ca with Syncytiotrophoblasts vs Choriocarcinoma

- + OCT4 (SOX17)
  - Seminoma and Embryonal Ca with Syncytiotrophoblasts
- − OCT4 (SOX17)
  - Choriocarcinoma
Teratoma, postpuberal type

- Histologically different from prepuberal
  - Solid appearance
  - Disordered arrangement of tissues
  - Less thyroid gland, no pituitary gland
  - Atypia and mitosis
- Associated to GCNIS (Primary criteria for distinction between pre and postpuberal)
- May be associated to somatic malignancies
  - Primitive type similar to neuroectodermal tumor - neg for t(11;22), nephroblastoma, or sarcoma
  - Adult type: Neuroendocrine tumors (carcinoids), carcinomas.
Mixed GCT

- Contains 2 or more malignant GCT components
- Most frequent: Embryonal Ca
- Most frequent combination: Embryonal Ca with teratoma, seminoma and/or yolk sac
- Metastatic teratoma is the most frequent form of recurrent or metastatic component after chemotherapy for mixed GCT
- Combination of prepuberal teratoma and yolk sac tumor is not considered mixed GCT
Prepuberal Type GCN

- Spermatocytic tumor
- Prepubertal type teratoma
- Prepubertal type yolk sac tumor
- Epidermoid cyst
- Dermoid cyst

Germ cell neoplasia in situ and specific forms of intratubular neoplasia

Not Prepuberal

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Teratoma, prepuberal-type

- Composed of elements resembling somatic tissues derived from one or more of the germinal layers (ectoderm, mesoderm and endoderm)
- Similar to mature cystic teratoma of ovary
- Testicular prepuberal teratoma 46 XY (Ovary 46XX).
- Specialized forms: Dermoid cyst – from ectoderm

Epidermoid cyst:
- Extremely rare
- Squamous epithelium without skin appendages
- Relationship with teratoma is unknown
Yolk-sac, prepuberal-type

- Pure prepuberal Yolk-sac tumor is the most frequent testicular GCT in infants and children (peaking at 1.5 y)
- Elevated AFP
- Histologically identical to the postpuberal-type: Better prognosis
- Not associated to GCNIS or 12p abnormalities
Spermatocytic Tumor
Spermatocytic tumor

- The term spermatocytic tumor has replaced the older term spermatocytic Seminoma
- Similarly to prepubertal-type GCTs, lacks association with GCNIS and chromosomal abnormalities on the short arm of chromosome 12
- Considered distinct from prepubertal types of GCT
- Only GCT exclusively described in the testis
- Older patients (10% < 30 y)
- NO GCNIS
- YES: intratubular growth of spermatocytic tumor
Spermatocytic tumor

- Tripartite population of cells that vary greatly in nuclear size
  - small cells resemble spermatogonia
  - Intermediate and large cells resemble primary spermatocytes that have entered meiosis
- Indolent behavior (metastases are very rare)
  - orchiectomy without additional treatment
- Consistent gain in chromosome 9 === additional copies of the DMRT1 (double sex and mab related gene)
- complete loss of biparental genomic imprinting and reestablishment of paternal-only imprinting
Spermatocytic Tumor

Positive
SALL4, CD117 (50%)
NUT (nuclear protein in testis), GAGE7, NY-ESO-1; CTAG1B, GAGE1, MAGEA3, MAGEA4, and MAGEC1

Negative
OCT4, CD30, AFP, PLAP, hCG
Germ Cell Tumor
VS
Large Cell Lymphoma

- SALL4*

Germ cell tumor
(see Algorithm 1 for subtyping)

- SALL4*

+ Specific lymphoid markers
   (CD45, CD20, PAX5, CD79a, CD3, others)

Large Cell Lymphoma

*Some lymphoblastic &
anaplastic large cell lymphomas
& myeloid leukemias are SALL4 +
QUESTIONS......

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