GERM CELL TUMORS

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GERM CELL TUMORS

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• Germinoma
• Nongerminomatous GCTs
  • Embryonal carcinoma
  • Yolk sac tumor
  • Choriocarcinoma
  • Teratoma
    • Benign/mature teratoma
    • immature teratoma
  • Teratoma with “malignant transformation”
  • Mixed GCTs

WHO 2016

**Introduction**

- Largely homologues of GCTs elsewhere
- Different from non-CNS GCTs?
  - Morphology
    - No precursor lesions (GCNIS)
    - No spermatocytic “seminoma”
  - Clinical behavior
    - Prepubertal vs postpubertal
  - Origin

**Historical perspective**

- 1923 (Krabbe): “Pinealoma” Adenoma of the pineal body
  J Endocrinol 1923;7:379-414
- 1944 (Russel): “Atypical pineal teratoma” Pinealoma-Its relationship to teratoma
  J Pathol Bacteriol 1944;56:145-50
- 1946 (Friedman and Moore): “Germinoma” Tumors of the Tests: A report on 922 cases.
  Mil Surgeon 1946;99:573-93
- 1976: “Ultrastructural study of histogenesis of pinealoma”
  No To Shinkei 1976;28:41-56

**Pathogenesis**

- Germ cell theory
  - Primordial germ cells (PGC)
  - Common cell of origin: totipotent
  - Embryonic cell theory
    - Embryonic cell; pluripotent-blastocyst stage
    - Multiple embryonic cells at various stages of embryogenesis

**Incidence**

  - Adults: ~0.4% of all CNS neoplasms
    - 0.10/100,000
  - Children: ~4%
    - 0.21/100,000
  - Geographical variation: up to 15% in Far-East Asia and Japan (pediatric brain and tumors)
Incidence: Age-Adjusted

Localization

- Midline locations
  - Pineal/third ventricle
  - Suprasellar
  - BG, thalamus, ventricles, cerebral hemispheres, SC, etc.
  - Multifocal: synchronous/metachronous
  - Holocranial variants rare
- Germinomas: suprasellar, BG, thalamus
- NGGCTs: other sites

Incidence Rate Ratios by Sex (Males:Females)

Gender Distribution According to Location (Germinoma)

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Clinical Manifestations

- Pineal
  - Aqueductal compression (increased ICPs, hydrocephalus)
  - Distortion of quadrigeminal plate (mental status changes, upward gaze palsies, etc., Parinaud syndrome)
  - Precocious puberty (NCGS)
- Suprasellar
  - Visual (loss of visual acuity, hypopituitarism)
  - Higher incidence / association
  - Klinefelter syndrome
  - Down syndrome

Radiographic Features

- Nonspecific
- Well-circumscribed, lobulated lesions
- T1: hypointense
- T2/FLAIR: mainly hyperintense
- Enhanced intensity and heterogeneously on both CT and MR
- Calcification (usually pineal)
- Hydrocephalus common
- Often partially cystic
- Local invasion common

Histology of CNS GCTs

Germinoma


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Germinoma


Embryonal Carcinoma


OCT4

CD30

Yolk Sac Tumor


Yolk Sac Tumor
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**Yolk Sac Tumor**

**Choriocarcinoma**

**Mature Teratoma**

**Immature Teratoma**

**β-hCG**

**Immunohistochemistry: recent advances**

α-fetoprotein

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**PLAP**
- Previously the marker of choice
- Lacks specificity (epithelial malignancies)
- Nonspecific staining
- 23/25 (92%) positive membranous staining (only 2 at 3+)

**“New” IHC Markers**
- Glypican 3
- NANOG
- LIN28A
- OCT4
- Podoplanin/aggruss
- SALL4
- SOX2
- SOX17

**OCT4**
- Transcription factor
- Regulates initiation, maintenance, and differentiation of pluripotent and germine cells during normal development
- Normally expressed in embryonic stem cells
- Germinoma and embryonal ca
- High sensitivity/specificity

**C-Kit**
- Tyrosine-kinase glycoprotein
- Germinomas
- 23/25 (92%), 20 at 3+
- Negative or weak in EC
- No correlation with KIT mutations

**SALL4**
- Transcription factor
- Maintains embryonic stem cell pluripotency and self renewal (OCT4, NANOG, & SOX2)
- PanGCT marker
- Ideal screening marker
- Superior to AFP and glypican 3 in YST

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<table>
<thead>
<tr>
<th>Transcription Factors</th>
<th>Podoplanin</th>
<th>Glypican 3</th>
<th>LIN28A</th>
<th>SALL4</th>
<th>OCT4</th>
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<td>C/C</td>
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</tbody>
</table>

**Membrane-based proteoglycan**

- Highly expressed in fetal tissues
- Regulation of cell growth and differentiation
- Highly expressed in YST and CC
- HCC, hepatoblastoma, ovarian clear cell ca

Useful immunohistochemical stains in intracranial GCTs

<table>
<thead>
<tr>
<th>Stain</th>
<th>Germinoma</th>
<th>Embryonal Carcinoma</th>
<th>Yolk Sac Tumor</th>
<th>Choriocarcinoma</th>
<th>Mature Teratoma</th>
<th>Immature Teratoma</th>
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<td>C</td>
<td>M</td>
<td>C</td>
<td>M</td>
<td>C</td>
<td>C</td>
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Germinoma
- +++
- ++++
- ++++
- –
- 

Embryonal Carcinoma
- +++
- +++
- +++
- –
- –

Yolk Sac Tumor
- +++
- –
- –
- –
- –

Choriocarcinoma
- +
- ±
- –
- –
- +
- –

Mature Teratoma
- –
- –
- –
- –
- C

Immature Teratoma
- ±
- –
- ±
- –
- ±
- –

Other differential diagnosis
- Infiltrative glioma
- Lymphoma
- Sarcoïdosis or infection
- Metastatic carcinoma
- Other differential diagnosis
- Infiltrative glioma
- Lymphoma
- Sarcoïdosis or infection
- Metastatic carcinoma

Genetics of CNS Germ cell tumors
- Mostly sporadic
- Syndromic associations:
  - Trisomy 21
  - Klinefelter (47 XXY): intracranial, mediastinal
  - NF1
  - 12p abnormalities common

Treatment and prognosis
- Prognostic variables: histology, location, and proximity to vital structures
- Germinomas:
  - CSI/whole brain, plus local boost
  - Recent trend: less radiation, in favor of cisplatin-based chemotherapy
  - >90%, 10-year survival
- Non-GCTs:
  - Mature teratomas: gross total resection
  - Immature teratomas: GTS + radiation
  - Congenital teratomas: invariably fatal
  - EC, YST, Chori: multimodal therapy; <45% 5-year survival
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Age Distribution According to Location (Germinoma)


Mature Teratoma


OCT4

- Transcription factor
- Regulates initiation, maintenance, and differentiation of pluripotent and germine cells during normal development
- Normally expressed in embryonic stem cells
- Germinoma and embryonal ca are undifferentiated neoplasms with pluripotential
- 25/25 (100%); 22 at 3+
- Add CD30 or Aggrus if embryonal ca is in differential

Aggrus/Podoplanin

- Transmembrane sialoglycoprotein
- Physiological role
- Expressed in lung type I alveolar cells, lymphatic endothelial cells (lymphatic endothelial marker)
- Identified on surface of some tumor cells: platelet aggregation-inducing effect that did not require plasma components
- Not expressed in EC
- 19/20 (95%); 17 at 3+
Useful immunohistochemical stains in intracranial germ cell tumors

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<th>Transcription Factors</th>
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<td>M/C</td>
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<td>YM-1</td>
<td>M/C</td>
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Demographics

• Age distribution:
  • >90% younger than 25 years; peripuberty
  • Younger: teratoma and choriocarcinoma
  • Older: pure germinoma
  • Congenital forms
• Sex predilection:
  • M:F of 3.8:1
  • Pineal and BG: males
  • Suprasellar and congenital: slight female predominance

Genetics of CNS GCTs

• 12p abnormalities common
• Frequent gain in CCND2 (12p13) and PRDM14 (8q13), and losses of RB1 (13q14) = ? cyclin/CDK-RB-E2F pathway
• Mutually exclusive somatic mutations in KIT and RAS (germinomas) = ? KIT/RAS signaling pathway
• 8q, 1q, and X gains
• 18q, 9q and 11q losses

CNS vs Non-CNS GCTs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-CNS</th>
<th>CNS</th>
<th>Similar?</th>
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<tr>
<td>Morphology</td>
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<tr>
<td>Genetics</td>
<td>✓</td>
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12p Abnormalities in CNS Germinomas
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CNS vs Non-CNS GCTs

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Testicular</th>
<th>Ovarian</th>
<th>CNS</th>
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<tbody>
<tr>
<td>12p OR</td>
<td>&gt;90%</td>
<td>81%</td>
<td>96%</td>
</tr>
<tr>
<td>i(12p)</td>
<td>80%</td>
<td>76%</td>
<td>57%</td>
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</table>

- 12p overrepresentation (aneuploidization) precedes the formation of i(12p)
- FISH analysis for 12p abnormalities: Pathway diagnostic tool

• First described by Atkin and Baker, 1982
• Gain of extra copies of the short arm of chromosome 12 (overrepresentation), occasionally in tandem (isochromosome 12p)
• Hallmark genetic marker of testicular GCTs
• All types of GCTs, except Sertoli cell tumors
• Early event in GCT tumorigenesis vs progression
• Target genes overexpressed, 75 genes (GLUT3, REA, CCND2, FLJ23038, NARG1, STELLA, GDF3, BBG, TSEX1, ROX2, etc)
• "12p gain is a functionally relevant change leading to activation of proliferation and reestablishment/maintenance of stem cell function through activation of key stem cell genes" Korkola et al, Cancer Research 2006
• 12p overrepresentation may also be seen in esophageal, pancreatic and ovarian carcinomas

Outcome of CNS GCTs

Question?
Do CNS germinomas share the same genetic alterations known to non-CNS GCTs (12p abnormalities)?

Genetics of Testicular GCTs

- 12p gain
  - FISH analysis for 12p abnormalities: Pathway diagnostic tool
  - Target genes overexpressed, 75 genes (GLUT3, REA, CCND2, FLJ23038, NARG1, STELLA, GDF3, BBG, TSEX1, ROX2, etc)
  - "12p gain is a functionally relevant change leading to activation of proliferation and reestablishment/maintenance of stem cell function through activation of key stem cell genes" Korkola et al, Cancer Research 2006
  - 12p overrepresentation may also be seen in esophageal, pancreatic and ovarian carcinomas

Genetics of Ovarian Dysgerminoma

- 81% of cases showed 12p abnormalities
- 57%: i(12p) only
- 5%: 12p overrepresentation only
- 19%: i(12p) + 12p OR

How i(12p) is formed

- "12p gain is a functionally relevant change leading to activation of proliferation and reestablishment/maintenance of stem cell function through activation of key stem cell genes" Korkola et al, Cancer Research 2006
- 12p overrepresentation may also be seen in esophageal, pancreatic and ovarian carcinomas
- 12p overrepresentation may correlate with invasive growth of seminomas and nonseminomas

- "12p gain is a functionally relevant change leading to activation of proliferation and reestablishment/maintenance of stem cell function through activation of key stem cell genes" Korkola et al, Cancer Research 2006
- 12p overrepresentation may also be seen in esophageal, pancreatic and ovarian carcinomas
- 12p overrepresentation may correlate with invasive growth of seminomas and nonseminomas
Dual-color FISH
- Metaphase: whole isochromosome
- Interphase: numerical abnormality
- DNA Probes:
  - CEP12: Centromeric α-satellite – Ch12p; Vysis
  - Tel12: Subtelomeric – Ch12p; Vysis
- Controls:
  - Positive: classic testicular seminoma
  - Negative: internal lymphocytes

FISH Scoring
- 100 nuclei scored for CEP12 (red) and 12p (green) signals.
- Green : Red ratio calculated.
- 12p Overrepresentation:
  - Cutoff: average signal number plus 3X standard deviation (3SD), which represented about 99% accuracy.
  - Isochromosome 12p:
    - Spatial distribution of green / red signals analyzed: specific pattern of signal aggregation.

Correlation with clinical behavior?
- Followup available on 15/23 cases:
  - 12p abnormalities detected (22 cases):
    - Recurrence: 4/14, all with 12p OR and i(12)p
    - Death: 1/14
  - 12p abnormalities not detected (1 case):
    - 15-year-old male
    - Suprasellar
    - Alive, free of disease
    - Morphologically and immunohistochemically typical

Pure Germinomas: The IU Experience
- 32 primary intracranial germinomas over 22 year period:
  - Incidence: ~2% of all primary pediatric tumors at IUMC
  - One patient had mediastinal germinoma 16 years earlier (2nd primary)
- 14/28 received CT + Focal XRT:
  - 5 (36%) relapsed:
    - 4 salvaged by CSI, 1 died of disease progression
  - 5/28 received CT:
    - 2 (40%) relapsed, 3 others are recent cases:
      - 1 salvaged by CSI, 1 died of disease progression
  - 9/28 received CSI:
    - None relapsed
    - 1 died of radiation complications

Important Information Regarding CME/SAMs
The Online CME/Evaluations/SAMs claim process will only be available on the USCAP website until September 30, 2017.

GCTs and Indiana University
- Cis-platinum:
  - First member of platinum antitumor agents
  - Cross links DNA; triggers apoptosis
  - 1845: M. Peyrone (Peyrone salt)
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GCTs and Indiana University

- Cis-platinum and GCTs:
  - 1974: Lawrence Einhorn
  - Phase II study
  - Patients with disseminated testicular GCTs
  - Cisplatin + etoposide + bleomycin
  - 74% complete remission
  - 26% partial remission
  - With postchemo surgery: 85% remission
  - Standard therapy
  - No phase III study conducted!