Germ cell tumors of CNS

• Heterogeneous group of neoplasms:
  • Germinoma
  • Nongerminomatous GCTs:
    • Embryonal carcinoma
    • Yolk sac
    • Choriocarcinoma
    • Teratoma
      • Benign/mature teratoma
      • Immature teratoma
      • Teratoma with "malignant transformation"
  • Mixed GCTs


Germ cell tumors of CNS

• Different from non-CNS GCTs?
  • Morphology:
    • No precursor lesions
    • No spermatocytic "seminoma"
  • Clinical behavior
    • Prepubertal and postpubertal
  • ? Origin


Germ cell tumors of CNS

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

Germ cell tumors of CNS

- Incidence:
  - Adults: ~0.4% of all CNS neoplasms
  - ~0.10/100,000
  - Children: ~4%
  - ~0.21/100,000
  - Geographical variation: up to 14% in Far-East Asia and Japan

Germ Cell Tumors

Incidence Rate Ratios by Sex (Males:Females) for Selected CBTRUS Histology Groupings and Histology, CBTRUS Statistical Report: NPCR and SEER, 2009-2013

Localization

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

Locations of CNS GCTs

Clinical Manifestations

- Pineal:
  - Aqueductal compression (increased ICPs; hydrocephalus)
  - Distortion of quadrigeminal plate (mental status changes, upward gaze palsy, etc; Parinaud syndrome)
  - Precocious puberty
- Suprasellar:
  - Triad: DI; loss of visual acuity, hypopituitarism

Age Distribution According to Location (Germinoma)
GERM CELL TUMORS

Gender Distribution According to Location (Germinoma)

Incidence Rate Ratios by Race (Whites:Blacks) for Selected CBTRUS Histology Groupings and Histologies, CBTRUS Statistical Report: NPCR and SEER, 2009-2013

Radiographic Characteristics

• Well-circumscribed, lobulated lesions demonstrating mostly isointense signals on T1, T2, Flair, PD, and DWI sequences
• 23/28 (82%) of germinomas enhanced heterogeneously on both CT and MR
• Tumor volume: 0.4 cm³ to 12.5 cm³ (average 18.7 cm³)
• 8/31 (26%) showed calcification (all pineal)
• 13/31 (42%) showed hydrocephalus (6 pineal, 3 SS, 4 synch)
• 19/31 (61%) were partially cystic

GERM CELL TUMORS

Pineal region GCT

Suprasellar region GCT

BG Synchronous
Histology of CNS GCTs

Germinoma

Yolk Sac Tumor

Choriocarcinoma

Mature Teratoma
GERM CELL TUMORS

Mature Teratoma

Immature Teratoma

Immunohistochemistry: recent advances
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 Immunohistochemistry is Superior to Placental Alkaline Phosphatase (PLAP) in the Diagnosis of Central Nervous System Germinoma

Lynne M. Hochberg, MD; J. Sean Haney, MD; Jon D. Wilcox, MD; and Issac Cheng, MD*

Am J Surg Pathol • Volume 29, Number 3, March 2005
**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
  - 25/25 (100%); 22 at 3+
  - Add CD30 or Aggrus if embryonal ca is in differential


**C-Kit**
- Tyrosine-kinase glycoprotein
- 23/25 (92%), 20 at 3+
- ? Therapeutic application
- HER2: 0/25 (0%)

**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

**Glypican 3**
- Membrane-based proteoglycan Xq26.2
- 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>Tumor Type</th>
<th>CAM</th>
<th>N</th>
<th>N</th>
<th>N</th>
<th>MIC</th>
<th>M</th>
<th>C</th>
<th>M</th>
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<tbody>
<tr>
<td>Embryonal carcinoma</td>
<td>+++</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±±</td>
<td>±±</td>
<td>±</td>
<td>±</td>
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<tr>
<td>Yolk sac tumor</td>
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<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Choriocarcinoma</td>
<td>−</td>
<td>±</td>
<td>±</td>
<td>±±</td>
<td>−</td>
<td>±±</td>
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<tr>
<td>Mature teratoma</td>
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<td>±±</td>
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<td>−</td>
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<tr>
<td>Immature teratoma</td>
<td>±</td>
<td>±±</td>
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<td>−</td>
<td>−</td>
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GERM CELL TUMORS

Genetics of CNS GCTs

• Mostly sporadic
• Syndromic associations:
  • Trisomy 21
  • Klinefelter (47 XXY): intracranial, mediastinal
  • NF1
• Cong CNS teratomas: diploid
• Other CNS GCTs: aneuploid; complex chromosomal imbalances
• X chromosome gains common

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
GERM CELL TUMORS

Isochromosome 12p


12p overrepresentation


12p Abnormalities in CNS Germinomas

GERM CELL TUMORS

CNS vs Non-CNS GCTs

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Testicular</th>
<th>Ovarian</th>
<th>CNS</th>
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<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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- 12p overrepresentation (aneuploidization) precedes the formation of i(12p)
- FISH analysis for 12p abnormalities: adjunct diagnostic tool


GERM CELL TUMORS

Outcome of CNS GCTs

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

THANK YOU