Primary Intracranial Germ Cell Tumor (GCT)

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Case

• 10 year-old boy presents with headache x 2 weeks.
• Associated symptoms include nausea, vomiting, and fatigue
• PMH/PSH: none
• Soc: Lives with mom and dad. 4th grader. Does well in school.
Presentation of Intracranial GCTs

- Symptoms depend on location of tumor.
  - Pineal location
    - Acute onset of symptoms
    - Symptoms of increased ICP due to obstructive hydrocephalus (nausea, vomiting, headache, lethargy)
    - Parinaud’s syndrome: Upward gaze and convergence palsy
  - Suprasellar location:
    - Indolent onset of symptoms
    - Endocrinopathies
    - Visual field deficits (i.e. bitemporal hemianopsia)
  - Diabetes insipidus can present due to tumor involvement of either location.
  - 2:1 pineal:suprasellar involvement. 5-10% will present with both ("bifocal germinoma").
Anatomy

Suprasellar cistern
Optic chiasm
Prepontine Cistern
Interpeduncular Cistern
3rd ventricle
Pineal gland
Quadrigeminal Cistern
Cerebral (Sylvian) aquaduct
4th ventricle
Anatomy

Frontal horn of lateral ventricle

3rd ventricle
Interpeduncular cistern
Suprasellar cistern

Occipital horn of lateral ventricle

Quadrigeminal cistern
Ambient cistern
Case

**CT head:** Hydrocephalus with enlargement of lateral and 3rd ventricles. 4.4 x 3.3 x 3.3 cm midline mass isodense to grey matter with calcifications.
Case

**MRI brain:** Intermediate- to hyper-intense 3\textsuperscript{rd} ventricle/aqueduct mass with heterogenous enhancement.
Imaging Characteristics

• Imaging cannot reliably distinguish different types of GCTs, however non-germinomatous germ cell tumors (NGGCTs) tend to have more heterogenous imaging characteristics compared to germinomas.

• **CT**: hyperdense compared to normal brain, vivid contrast enhancement, calcifications due to normal pineal gland component or due to tumor

• **MRI**: T1 & T2 isointense to grey matter, vivid contrast enhancement
## Differential Diagnosis

### Pineal region tumor
- Germ cell tumor  
  - (most common)
- Pineoblastoma
- Pineocytoma
- Pineal parenchymal tumor of intermediate differentiation
- Meningioma
- Ependymoma
- Central neurocytoma
- Metastasis
- Benign cyst

### Suprasellar region tumor
- Pituitary adenoma  
  - (most common)
- Germ cell tumor
- Craniopharyngioma
- Glioma
- Meningioma
- Metastasis
- Vascular lesion
- Infectious
- Granulomatous
What additional work-up is necessary when GCT is suspected?

- Basic labs
- MRI total spine
- Serum/CSF tumor markers (bHCG, AFP)
- CSF cytology
- Biopsy*

* Biopsy may not be required when tumor markers are characteristically elevated, however patients will often require surgical intervention due to hydrocephalus (pineal tumors) or visual field deficits (suprasellar tumors).
Case

• CBC, metabolic panel normal.
• No evidence of drop metastases on MRI total spine.
• Serum AFP: < 2.0 ng/mL (nl <= 8.8 ng/mL)
• Serum bHCG: 5.9 ng/mL (nl <= 2.5 ng/mL)
If CNS GCT is suspected, when is biopsy indicated?

- Tissue biopsy is required in the absence of tumor marker elevation.
- When tumor markers suggest NGGCT (AFP abnormal, bHCG > 50 ng/dL), biopsy is not required.
- When imaging suggests bifocal germinoma (pineal and pituitary involvement) with moderately elevated bHCG and normal AFP, biopsy is not required.
Case

- Pt underwent endoscopic third ventriculostomy with biopsy.
- CSF AFP: < 0.5 (nl < 0.5 ng/mL)
- CSF bHCG: 45.1 (nl < 5.0 mIU/mL)
- CSF cytology: No malignant cells
- Final pathologic diagnosis: Germinoma (CD117+, OCT3/4+, CD30-)
**Epidemiology**

- In US & Europe, GCTs represent 0.5 to 3% of pediatric CNS tumors.
- In Asian countries, GCTs represent up to 11% of pediatric CNS tumors.
- Peak incidence: 10-12 years old
  - Germinomas: Older patients
  - NGGCTs: Younger patients
- Male predominance
  - Germinomas: 1.8:1 (male: female)
  - NGGCTs: 3:1
Pathogenesis

• There are multiple theories regarding pathogenesis. Most hold that multiple histologic subtypes share a common cell of origin. For example:
  – “Germ cell theory”: Primordial germ cells mismigrate during embryonic development and subsequently undergo malignant transformation.
  – “Embryonic cell theory”: Pluripotent embryonic cells mismigrate and give rise to GCTs.
Extragonadal GCTs

• GCT with no evidence of primary in the testes or ovaries.
• Typically occur in midline structures
• Location varies with age:
  – Adults: mediastinum > retroperitoneum
  – Pediatric: sacrococcygeal > intracranial
WHO Classification of Intracranial GCTs

• Broadly categorized as germinoma (~2/3) and NGGCT (~1/3)

• NGGCT types include:
  – Endodermal sinus tumor (aka yolk sac tumor)
  – Choriocarcinoma
  – Embryonal carcinoma
  – Mixed malignant germ cell
  – Teratoma (immature, mature, malignant transformation)
### Tumor Markers

<table>
<thead>
<tr>
<th>Type of GCT</th>
<th>Beta-HCG</th>
<th>Alpha-fetoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratoma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Germinoma (pure)</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Germinoma (syncytriotoxidroplastic)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Mixed germ cell</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Endodermal sinus (Yolk Sac Tumor)</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Table adapted from Packer et al. *The Oncologist*. 2000.

AFP > 10 ng/mL excludes pure germinoma  
Beta-HCG typically < 50 ng/mL in pure germinoma
Staging

• No formal staging system
• Modified Chang system (from medulloblastoma) has been used to characterize M-stage
  – M0: No neuro-axial or extra-CNS metastases
  – M1: + CSF cytology
  – M2: Nodular intracranial seeding
  – M3: Nodular spinal seeding
  – M4: Extra-neural spread
Staging

- Pragmatically, disease extent is categorized as M0 (localized) or M+ (disseminated)
- 10-15% will have leptomeningeal dissemination at time of diagnosis
Staging – Disseminated Disease

Example of subependymal spread in a patient with a pineal germinoma and no evidence of spine metastases. Treated as disseminated disease.

Example of disseminated disease with drop metastases in a patient with a pineal mixed germ cell tumor.
Staging – Bifocal disease (Localized)

Example of pituitary stalk thickening in a patient with a pineal germinoma and no other signs of spread of disease. Treated as localized disease.
Treatment Overview

• Histology (germinoma versus NGGCT) is most important prognostic factor

<table>
<thead>
<tr>
<th>Histology</th>
<th>5-year PFS</th>
<th>5-year OS</th>
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<tbody>
<tr>
<td>Germinoma</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>NGGCT</td>
<td>40-70%</td>
<td>60-70%</td>
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</table>

• Histology and M-stage are major determinants of treatment approach.
Treatment Overview

• Target volumes reflect tendency for subependymal/CSF spread.
• Historical standard treatment for GCTs was single modality radiotherapy with 36 Gy craniospinal irradiation (CSI) + primary boost to 50-54 Gy.
• Given the overall excellent prognosis (particularly for germinomas) and recognition of late effects of radiation (endocrine, neurocognitive, secondary malignancy, musculoskeletal, auditory/visual), practice has evolved towards combined-modality treatment (CMT) with chemotherapy, lower RT doses, and smaller RT volumes.
Treatment Overview

• Pure germinoma:
  – Localized
    • Single modality: Whole ventricle radiotherapy (WVRT)(21-24 Gy) + tumor boost (40-45 Gy total)
    • Combined-modality: chemotherapy → reduced dose WVRT + tumor boost. For example, ACNS 1123 is an ongoing trial looking at response-based RT doses after chemotherapy
      – CR: 18 Gy WVRT + primary boost (30 Gy total)
      – PR/SD: 24 Gy WVRT + primary boost (36 Gy total)
  – Disseminated
    • Single modality: 30 Gy CSI + tumor boost (45 Gy total)
    • Combined modality: chemotherapy → 24 Gy CSI + tumor boost (40 Gy total)
• NGGCTs:
  – Typical approach: 4-6 cycles platinum-based chemotherapy → CSI (30-36 Gy) + tumor boost (50.4-54 Gy total)
  – CSI is the current standard regardless of M-stage
  – Chemotherapy is mandatory and improves survival (OS 20-40% RT alone → 60-70% CMT)
  – Consider “second-look” surgery if residual disease after chemoradiation.
Reducing Dose: MAKEI 83/86/89

- Series of German prospective, nonrandomized trials enrolling from 1983 to 1993
- Assessing dose reduction in CNS germinomas
- MAKEI 83/86 (pilot studies)
  - 11 patients
  - 36 Gy CSI + 14 Gy boost (1.8-2.0 Gy fx)
  - No relapses
- MAKEI 89
  - 49 patients
  - 30 Gy CSI + 15 Gy boost (1.5 Gy fx)
  - 5 relapses (4 outside of CNS)
- Conclusion: CSI dose can be reduced to 30 Gy in germinomas

Reducing Volume: SIOP GCT 96

- Prospective, nonrandomized, international trial enrolling from 1996 to 2005.
- Included germinomas and NGGCTs.
- Comparing CMT with involved-field radiation (IFRT) versus radiotherapy alone with CSI.
- Treatment was assigned according to national practice

Calaminus et al. Neuro oncol. 2013.
In **CSI group**, all failures were at primary site.
In **IFRT group**, majority of failures were outside of the primary site within ventricles.

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**Reducing Volume: SIOP GCT 96**

<table>
<thead>
<tr>
<th>Patient Sex</th>
<th>Variable</th>
<th>1 Male</th>
<th>2 Female</th>
<th>3 Male</th>
<th>4 Female</th>
<th>5 Male</th>
<th>6 Female</th>
<th>7 Male</th>
<th>8 Male</th>
<th>9 Male</th>
<th>10 Male</th>
<th>11 Male</th>
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<tr>
<td>Primary Diagnosis</td>
<td>age (years/months) tumour site</td>
<td>11:2</td>
<td>10:6</td>
<td>15:9</td>
<td>4:10</td>
<td>7:3</td>
<td>15:7</td>
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<td>16:4</td>
<td>12:10</td>
<td>14:11</td>
<td>10:4</td>
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<td>2.9 ng/mL</td>
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<td>n.d.</td>
<td>n.d.</td>
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<td>1 ng/mL</td>
<td>2.9 ng/mL</td>
<td>3.3 ng/mL</td>
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<td>6 U/L</td>
<td>29.3 mlU/L</td>
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<td>Chemotherapy + focal irradiation</td>
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<td>PR</td>
<td>PR</td>
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<td>CR</td>
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<td>Time to relapse from original diagnosis</td>
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<td>19 months</td>
<td>9 months</td>
<td>34 months</td>
<td>13 months</td>
<td>21 months</td>
<td>9 months</td>
<td>8 months</td>
<td>4 months</td>
<td>10 months</td>
<td>8 months</td>
<td></td>
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<td>AFP serum</td>
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<td>2 kU/L</td>
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<td>734 mlU/L</td>
<td>&lt;2 U/L</td>
<td>22 U/L</td>
<td>&lt;2 U/L</td>
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<td>27 U/L</td>
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<td>&lt;2 U/L</td>
<td>&lt;2 U/L</td>
<td>&lt;2 U/L</td>
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<tr>
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<td>not done</td>
<td>not done</td>
<td>not done</td>
<td>not done</td>
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<td>not done</td>
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<td>not done</td>
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<td>Site of relapse</td>
<td>Right frontal horn at bottom of 4th ventricle</td>
<td>Leptomeningeal</td>
<td>Local ventricles</td>
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<td>Lateral ventricles, CSF, cytology positive</td>
<td>Frontal horn, corpus callosum</td>
<td>Spinal C1-5, 3rd Ventricle</td>
<td>Pineal area</td>
<td>Right parietal lobe incl. Pineal area</td>
<td>Pineal area</td>
<td>Pineal area</td>
<td>Local</td>
</tr>
</tbody>
</table>

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Reducing Volume: SIOP GCT 96

- **Conclusion:** Combined modality treatment with reduced dose is a treatment option. When combined modality treatment is used, volume should cover at least ventricles.

- See also Rogers *et al.* Lancet Oncol 2005.
  - Individual patient data meta-analysis
  - Compared recurrence rates using WB/WVRT versus CSI in localized germinoma.
  - Found there was no notable increased risk of isolated spinal relapse (2.9% v 1.2%).

Calaminus *et al.* *Neuro oncol.* 2013.
Case

- **Clinical diagnosis:** Localized germinoma
- **Treatment recommendation:** Neoadjuvant chemotherapy followed by whole ventricle radiotherapy (WVRT) + tumor boost.
Case

- Pt underwent 4 cycles carboplatin + etoposide
- MRI brain following chemotherapy showed good response.
- Repeat serum and CSF tumor markers within normal limits.
- Repeat spinal imaging & CSF cytology showed no evidence of dissemination.
- Recommended to proceed with radiotherapy.

April 19, 2019
Radiotherapy Planning

• Simulate supine with mask
• Technique: IMRT
• Dose and volume
  – WVRT: 21 Gy in 1.5 Gy fractions
  – Sequential IFRT boost: 9 Gy in 1.5 Gy fractions
• Fuse imaging
  – Pre-chemo post-contrast T1 & T2 MRI brain
  – Post-chemo post-contrast T1 & T2 MRI brain
Target Volume Delineation

• See ACNS 1123 protocol atlas for details (https://www.qarc.org/cog/ACNS1123_Atlas.pdf)

• Generate Involved Field PTV
  – Contour pre-chemotherapy GTV
  – Expand 5mm to CTV
  – Expand 3-5mm to PTV
Target Volume Delineation

• Generate whole ventricle PTV
  – Generate whole ventricular volume (WVV). Includes
    • Pre-chemotherapy GTV
    • Lateral, 3rd, 4th ventricles
    • Suprasellar cistern, pineal cistern
    • If large sellar tumor or s/p endoscopic third ventriculostomy, then include prepontine cistern
  – Expand 5mm to CTV
  – Expand 3-5mm to PTV
ACNS 1123 Dose Constraints

• Optic chiasm/nerve/tract: Max 54 Gy
• Single cochlea:
  – Goal: D50% < 3000 cGy
  – Preferred: D50% < 2000 cGy
• Brainstem/spinal cord: Max 54 Gy
• Optic globes: Max 45 Gy
Whole Ventricle RT (21 Gy)
Whole Ventricle RT (21 Gy)

ROI Statistics

<table>
<thead>
<tr>
<th>Line Type</th>
<th>ROI</th>
<th>Total or Record</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>Std. Dev</th>
<th>% Outside Grid</th>
<th>% &gt; Max</th>
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<tr>
<td>PTV/2100</td>
<td>Brain</td>
<td>1404.4</td>
<td>2236.9</td>
<td>2183.9</td>
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<td>Left Lens</td>
<td>Brain</td>
<td>98.1</td>
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<td>99.3</td>
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<tr>
<td>Right Lens</td>
<td>Brain</td>
<td>83.3</td>
<td>111.4</td>
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<tr>
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<td>Brain</td>
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<td>63.8</td>
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<td>1892.6</td>
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<td>Left Optical Nerve</td>
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Sequential IFRT boost (9 Gy)
Sequential IFRT boost (9 Gy)
References


Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com

April 19, 2019

ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY

ARRO