ARRO Case:
Pediatric Ependymoma

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Presentation

- 10 year old boy presents with dizziness and morning nausea x 2.5 months followed by double vision x several weeks
- MRI brain with contrast (T1+ Gad)
Initial Work-Up

• **H & P**
  - History: ask about symptoms of increased ICP: HA, N/V
  - Physical exam:
    - Cranial nerve deficits, ataxia, fundoscopic exam to look for papilledema
    - “Setting sun” sign: downward deviation of gaze from increased ICP (CN III, IV, VI)

• **Family history:**
  - Ask about FH history of cancer
    - Gorlin’s (PTCH) or Turcot’s (APC)

• **MRI brain**
Differential: BEAM HIM Juvenile

- Brainstem Glioma
- Ependymoma
- Astrocytoma/Atypical teratoid rhabdoid tumor (ATRT)
- Medulloblastoma
- Hemangioblastoma
- Infection
- Mets
- Juvenile pilocytic astrocytoma
Next steps

No biopsy will be done on a posterior fossa mass prior to resection→ these patients go straight to resection (with the exception of diffuse intrinsic pontine glioma)
Case continued

• Patient goes on to gross total resection
• Pathology shows:
  – Anaplastic ependymoma (focal Ki-67 labeling up to 38%)

http://www.pathologyoutlines.com/topic/cnstumoranaplasticependymoma.html
Case continued

- Next steps in work-up
  - MRI spine $\rightarrow$ negative for metastases
  - CSF $\rightarrow$ negative
Overview

• Ependymoma arises from lining of the ventricular system and central spinal canal
• Adults:
  • Tumors primarily arise in the spine
• Pediatrics:
  • 90% are intracranial, 60% arise in the posterior fossa
  • 8-10% of childhood CNS tumors
  • 30% occur in children who are <3 years old
    • Mean age is 5 years old
• NF2: increased incidence of spinal cord tumors
Pathology

• Grade 1: myxopapillary (not seen in brain) and subependymoma
• Grade 2: classic ependymoma
  • Includes cellular, papillary, clear cell, tancytic types
• Grade 3: anaplastic ependymoma
  • High mitotic rate, microvascular proliferation, and pseudopalisading necrosis
• Grade 4: ependymoblastoma: extremely rare, highly malignant primitive embryonal tumors
  • NOT considered in classification of ependymoma
  • Renamed embryonal tumor with abundant neuropil and true rosettes (ETANTR)
Risk stratification

• Extent of resection (dominant prognostic factor)
  • Event free survival 50-75% after GTR vs 30-45% with incomplete removal
• Age
  • Inferior likelihood of disease control at age <3 years
• Lower doses of radiation (worse local control)
• Higher expression of Ki67 or MIB-1 → greater risk of treatment failure
• Anaplastic histology
• Chromosome 1q25 gain: inferior outcome for both posterior fossa and supratentorial ependymoma
• Expression of hTERT and Nestin (worse prognosis)
• Supratentorial and infratentorial ependymomas have different genomic, gene expression, and IHC signatures
Further risk stratification

- Molecular subtypes

<table>
<thead>
<tr>
<th>Molecular Subgroups of Ependymoma</th>
<th>Location in CNS</th>
<th>Molecular and Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A/CIMP+</td>
<td>Posterior Fossa</td>
<td>Epigenetic changes, chromosome 1q gain, young children, and intermediate to poor prognosis; CPG island methylator phenotype, WHO grade III (common); 70% + of PF tumors</td>
</tr>
<tr>
<td>Group B/CIMP−</td>
<td>Posterior Fossa</td>
<td>Chromosomal defects; adolescent children, adults, good prognosis; &lt;30% of PF tumors</td>
</tr>
<tr>
<td>RELA Fusion positive</td>
<td>Supratentorial</td>
<td>C11orf95-RELA fusion (70% of supratentorial tumors); typically young children, WHO grade II/III</td>
</tr>
<tr>
<td>Yap1 fusion positive</td>
<td>Supratentorial</td>
<td>MAML1-YAP1 or FAM1188-YAP1 fusions, Children, WHO grade II/III; 30% of supratentorial tumors</td>
</tr>
<tr>
<td>Myxopapillary</td>
<td>Spinal</td>
<td>WHO grade I, adolescent children/adults; good prognosis (80% + of spinal tumors)</td>
</tr>
<tr>
<td>Classic/Spinal</td>
<td>Spinal</td>
<td>Adolescent children, adults, who grade II, good prognosis</td>
</tr>
<tr>
<td>Subependymoma</td>
<td>All CNS compartments</td>
<td>WHO grade I, balanced genome, adults, good prognosis</td>
</tr>
</tbody>
</table>


**EPN-PFA:** High rates of disease recurrence→33% PFS at 5 years, 68% OS at 5 years

**EPN-PFB:** 5 year PFS of 73% and OS of 100%

**ST-EPN-RELA:** gain of ch 1q (poor prognostic factor) in 25% of cases, unfavorable outcome compared to other ependymoma subtypes (5 yr PFS 29% and OS 75%)

**YAP1:** relatively favorable, 5 year PFS 66% and OS 100%

(Yock, et al. Ch 4: Tumors of the posterior fossa and spinal canal. from Constine, Tarbell et al. 2016)
# Treatment

Current treatment paradigm—all patients get surgery

<table>
<thead>
<tr>
<th>Tumor subtype</th>
<th>Treatment following surgery</th>
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<tbody>
<tr>
<td>Subependymoma</td>
<td>Observation</td>
</tr>
<tr>
<td>Spinal cord ependymoma, GTR</td>
<td>Observation</td>
</tr>
<tr>
<td>Spinal cord ependymoma, STR</td>
<td>Adjuvant RT to 50.4 Gy (in general, field should include 2 VB above and below)</td>
</tr>
<tr>
<td>Myxopapillary ependymoma, GTR</td>
<td>Observation (some evidence that focal RT may improve PFS and reduce dissemination to other parts of neuroaxis—so possible RT)</td>
</tr>
<tr>
<td>Myxopapillary ependymoma, STR</td>
<td>Adjuvant RT can improve local control</td>
</tr>
<tr>
<td>Grade II/III, GTR, M0</td>
<td>Conformal RT to tumor bed (59.4 Gy for photon, 54 Gy for proton)</td>
</tr>
<tr>
<td>Grade II/III, GTR, M1</td>
<td>CSI 30-36 Gy + focal boost (54-60 Gy for local disease, 45 Gy for spine)</td>
</tr>
<tr>
<td>Grade II/III, STR, M0</td>
<td><strong>Second look surgery</strong> then conformal RT to tumor bed (59.4 Gy for photon, 54 Gy for proton)</td>
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<tr>
<td>Grade II/III, STR, M1</td>
<td><strong>Second look surgery</strong> then CSI 30-36 Gy + focal boost (54-60 Gy for local disease, 45-50 Gy for spine metastases)</td>
</tr>
<tr>
<td>&lt;12 months</td>
<td>Chemotherapy with delayed radiation</td>
</tr>
</tbody>
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(Modified from Hansen, Roach 2018)
Improved OS with RT

• Pollack, et al. showed 5 year OS of 45% with surgery + RT vs 13% with surgery alone (Pollack, Gerszten et al. 1995)

• Rousseau, et al. showed 63% survival at 5 years with surgery + RT vs 23% with surgery alone (Rousseau, Habrand et al. 1994)
Role of radiation

- Historically, patients <3 years old would be treated with chemotherapy and patients >3 years old would be treated with radiotherapy.
- A retrospective SEER analysis by (Snider, Yang et al. 2018) which evaluated 482 patients between 1973 and 2013 showed that:
  - RT significantly benefitted OS for both grade II and grade III ependymoma.
## ACNS0121: Phase II trial

Enrolled patients >12 months, intracranial ependymoma

<table>
<thead>
<tr>
<th>Stratum</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Gross total resection(^1)(no visible tumor under microscope)</td>
<td>Subtotal resection (residual tumor &gt;0.5 cm on post-op imaging)</td>
<td>Near total resection (residual tumor on imaging) or Gross total resection(^2) (microscopically visible residual tumor, negative imaging)</td>
<td>Gross total resection(^1)(no visible tumor under microscope)</td>
</tr>
<tr>
<td>WHO Grade</td>
<td>II</td>
<td>II-III</td>
<td>II-III</td>
<td>II-III</td>
</tr>
<tr>
<td>Site</td>
<td>Supratentorial</td>
<td>Any</td>
<td>Any</td>
<td>Supratentorial III Infratentorial II-III</td>
</tr>
<tr>
<td>Treatment</td>
<td>Observation</td>
<td>Chemotherapy +/- second surgery + RT</td>
<td>Radiation therapy</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Treatment Group</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

(merchant, Bendel et al. 2019)
Event-Free and Overall Survival

(Merchant, Bendel et al. 2019)
• GTR/nGTR with radiation did best (stratums 3 and 4)

• STR with chemotherapy and adjuvant RT did the worst (statum 2)

• Supratentorial/GTR/W HO grade II only→observation: A priori felt to be best prognosis group (statum 1) – did worse than expected with 5 year EFS (61% +/- 14%)

(Merchant, Bendel et al. 2019)
Neurocognitive outcomes:

- Merchant, et al. evaluated 316 patients who received focal RT for localized ependymoma (Merchant, Mulhern et al. 2004)
- Mean scores on all neurocognitive outcomes were within normal limits (no more than 10 pts from the normative mean for age group)
- 3 year progression free survival was 74.7% +/- 5.7%
- Studies are in process evaluating whether long-term toxicities are less with proton compared to photon RT (Indelicato, Bradley et al. 2018)
Chemotherapy

• Only prospective randomized trial looked at CCNU, vincristine, and prednisone after surgery and RT in the 1980s (Evans, Anderson et al. 1996)
  • No improved disease control with chemotherapy

• Randomized trial of adjuvant CCNU/vincristine/prednisone vs “8 in 1” regimen (Robertson, Zeltzer et al. 1998)
  • No improvement in either arm of trial
Radiation treatment planning

- **MO patients:**
  - Target volumes have evolved from whole brain to posterior fossa to now tumor bed only
    - Posterior fossa ependymomas tend to adhere to the floor of fourth ventricle and cranial nerves, does not invade brainstem or adjacent normal brain → trend toward smaller margins (CTV margin for ACNS0831 is 5 mm although 1 cm is commonly used)
      - (Constine, Tarbell et al. 2016)
  - Recommendations for GTV include tumor bed and residual tumor based on pre and post-operative imaging
  - Common patterns of disease extension such as encasement of basilar artery and extension into foramina of Luschka should be assessed; pay attention to spread along cervical spine (10-30% of 4th ventricle tumors)
  - Recommendation to limit dose to optic chiasm and spinal cord to 54 Gy
  - Standard to limit brainstem to 54 Gy; Merchant suggests limiting brainstem to <60 Gy (no more than 53 Gy to center of brainstem or 64 Gy to surface) is safe (Merchant, Chitti et al. 2010)
  - Dose is 54-59.4 Gy in 1.8 Gy fractions

- **M1 patients:**
  - CSI 30-36 Gy + focal boost (45 Gy for spine metastases, 54-60 Gy for primary site)
Case continued

- Went to resection → GTR
- Treated with adjuvant radiation:
  - VMAT plan
  - 59.4 Gy to primary tumor
  - 5 mm margin for CTV
  - 3 mm margin for PTV
  - Reduced dose to portion of CTV involving brainstem
Ongoing trials

- ACNS0831: evaluating patients with GTR + RT, post-radiation VCEC vs no post-radiation chemotherapy

- SIOP Ependymoma II: Primarily a chemotherapy trial, but patients with tumors that persist despite pre-RT chemo and RT (59.4 Gy/1.8 Gy fractions) will get a boost of 4 Gy x 2 to residual tumor bed
References


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

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ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY

ARRO