ARROCase: Pediatric Ependymoma

Ariel Pollock, MS-4
Anna Lee, PGY-4
Faculty: Suzanne Wolden, MD
Memorial Sloan Kettering Cancer Center
Department of Radiation Oncology
November 2017
Outline

• Case Presentation
• Introduction
• Epidemiology
• Pathology
• Clinical Presentation
• Workup/Diagnosis
• General Management
• Radiation Treatment Planning
Case Presentation

- CC: Unsteady gait worsening over a 2-month period
- HPI: 2yo boy born NSVD, FT with age appropriate milestones met, UTD immunizations and no significant medical history
Physical Exam

• Normocephalic with CN II-XII intact, muscle strength and tone normal in both arms and legs proximally and distally, no evidence of atrophy or fasciculations. Able to stand and can take a few steps with minimal ataxia.
Work Up

• MRI Brain & Spine
  – s/p VP shunt placement; expansile lobulated tumor filling the fourth ventricle, involving the prepontine and premedullary cisterns extending down to the posterior aspect of the foramen magnum
  – No evidence of metastatic disease in the spine
  – Likely representing ependymoma or medulloblastoma, less likely choroid plexus papilloma or carcinoma
Pathology

- s/p gross total resection
  - WHO grade III anaplastic ependymoma
  - No evidence of gain of 1q25
    - Gain of 1q corresponds with more aggressive phenotype
  - Tumor cells exhibit complete loss of H3K27me3 expression
    - This has been correlated with aggressive behavior of posterior fossa ependymomas, group A

Bayliss et al. Sci Transl Med 2016
Panwalkar et al. Acta Neuropathol 2017
Zhang et al. Neurosurgery 2017
Further Work Up

• MRI on POD #1 revealed no residual disease
• Lumbar puncture 14 days post-op showed CSF cytology was negative for any malignant cells
  – If positive, indication for chemotherapy as bridge treatment or CSI (the latter only if patient is ≥3 years old)
Adjuvant RT

• Preop GTV (light green)
• CTV = Preop GTV + 1cm (pink)
• PTV = CTV + 0.3cm

• Proton therapy (uniform scanning) with 5940cGy in 33 fractions
Dose Volume Histogram (DVH)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV5940</td>
<td>142.54</td>
<td>5206</td>
<td>5296</td>
<td>5540</td>
<td>6046</td>
<td>6105</td>
<td>6353</td>
<td>6358</td>
<td>0</td>
</tr>
<tr>
<td>PTV5940 3mm</td>
<td>200.21</td>
<td>5167</td>
<td>5228</td>
<td>5490</td>
<td>6013</td>
<td>6077</td>
<td>6350</td>
<td>6357</td>
<td>0</td>
</tr>
<tr>
<td>BRAINSTEM</td>
<td>13.24</td>
<td>4019</td>
<td>4329</td>
<td>4770</td>
<td>5276</td>
<td>5232</td>
<td>5644</td>
<td>5648</td>
<td>0</td>
</tr>
<tr>
<td>COCHLEA_L</td>
<td>0.08</td>
<td>4216</td>
<td>4221</td>
<td>4247</td>
<td>4492</td>
<td>4340</td>
<td>5129</td>
<td>5142</td>
<td>0</td>
</tr>
<tr>
<td>COCHLEA_R</td>
<td>0.12</td>
<td>1108</td>
<td>1108</td>
<td>1145</td>
<td>2096</td>
<td>2058</td>
<td>3629</td>
<td>3838</td>
<td>0</td>
</tr>
</tbody>
</table>
Pediatric Ependymoma
Introduction

• Glial tumors that arise within or adjacent to the ependymal lining of the ventricular system

• Occur within the brain parenchyma or outside the CNS

• Account for <10% of tumors arising in the CNS
Epidemiology

• Incidence equal in males and females
• About 300 cases per year
• Median age at diagnosis is 5 years
  – 25-40% are less than 2 years old
• Fourth ventricle is the most common infratentorial site and extension into the subarachnoid space is frequent
• 90% of ependymoma in children are intracranial
  – 60% at the posterior fossa
  – Infratentorial most common in children <3 years of age
Pathology

- Molecular markers of posterior fossa tumors
  - Group A: poor prognostic subgroup
    - CpG island methylator phenotype and transcription silencing of polycomb repressive complex 2, leading to repressed expression of differentiation genes
  - Group B: more favorable subgroup
Ependymoma Sub-Groupings

Pajtler et al. Cancer Cell 2015
Clinical Presentation

• Increased intracranial pressure
  – Headaches, nausea, vomiting, ataxia, vertigo, papilledema

• Seizures or focal neurologic deficits

• Dissemination of tumor in CSF is higher with infratentorial compared to supratentorial tumors
Work Up/Diagnosis

• MRI Brain- Preop
  – T1: hypointense
  – T2: hyperintense
  – Extension into the foramen of Luschka commonly observed

• CT Head
  – Hyperdense with homogeneous enhancement

• MRI Total Spine
  – To rule out metastatic disease
Work Up/Diagnosis

• Histologic confirmation preferable with open surgery with gross total resection over stereotactic biopsy

• Most important prognostic factor is extent of resection
  – 7-year EFS GTR 77% vs STR 34%

• Postop MRI Brain to assess residual disease

• CSF cytology for staging
  – 10-14 days postop to reduce the risk of herniation and decrease the risk of false positives

Merchant et al. Lancet Oncol 2009
General Management

- Maximal safe resection followed by adjuvant radiation therapy
- Incompletely resected grade II or III tumors may benefit from short course of chemotherapy followed by second-look surgery then radiation therapy
  - Current protocol ACNS0831
- Complete resected grade II or III tumors should be followed by adjuvant radiation therapy
Radiation Treatment

• RT is local unless documented metastatic disease
  – CSI to 36Gy if ≥3 years old

• Volumes
  – GTV = tumor bed and residual disease or preop GTV
  – CTV = GTV + 1cm
  – PTV = CTV + 0.3-0.5cm

• Doses
  – Patterns of practice vary from 54-59.4Gy at 1.8Gy per fraction
When is CSI appropriate?

• Only with documented disseminated disease
  – Positive CSF or
  – Positive MRI neuroaxis and
  – ≥3 years of age

• Merchant et al. JNS 1997
  – Retrospective review of 28 anaplastic ependymomas
    • 12 received CSI in addition to primary site boost
    • 14 received focal RT only
    • No benefit from CSI as primary failure is local
Radiation Treatment Planning

• Simulate with thermoplastic mask and anesthesia if necessary
• Fuse pre- and postsurgical MRI brain to CT
• If CTV/PTV extends into the brainstem, consider cone-down after 54Gy to limit brainstem dose
Posterior Fossa Syndrome

• Occurs in 15-25% of patients s/p posterior fossa surgery, especially when brainstem invasion is observed
• Onset is 1-2 days postop and can last for up to several weeks
• Symptoms include
  – Mutism
  – Dysphagia
  – Truncal ataxia
  – Hypotonia
  – Increased mood lability
  – Gaze palsy
  – Occasionally respiratory failure
• RT should be not delayed but symptoms can persist throughout treatment
Long-Term Outcomes

• Toxicities
  – Neurocognitive deficits
  – Focal neurologic deficits
  – Sensorineural hearing loss
  – Growth abnormalities
  – Endocrine abnormalities
  – Secondary malignancies
Merchant et al. Lancet Oncol 2009

• Phase II ACNS0121

• 153 patients with localized ependymoma (80% infratentorial)
  – 85 with anaplastic ependymoma
  – All received adjuvant RT to 59.4Gy after resection
  – Median age 2.9 years; 78% <3 years old

• Outcomes
  – 7-year LC 87.3%
  – 7-year EFS 69.1%
  – 7-year OS 81.0%
Current Open Protocol: ACNS0831

• Phase III
• Arm 1: GTR of supratentorial WHO grade II -> observation
• Arm 2: WHO grade III or infratentorial, or most of the tumor removed (but not all)
  – Arm A: RT -> observation
  – Arm B: RT -> chemotherapy
• Arm 3: STR -> induction chemo
• Zhang RR, Kuo JS. Reduced H3K27me3 is a New Epigenetic Biomarker for Pediatric Posterior Fossa Ependymomas. Neurosurgery 2017; 1;81(1):N7-N8.
• Please provide feedback regarding this case or other ARRO cases to arrocase@gmail.com