ARROCase:
Pediatric Ependymoma

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Outline

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

Case Presentation

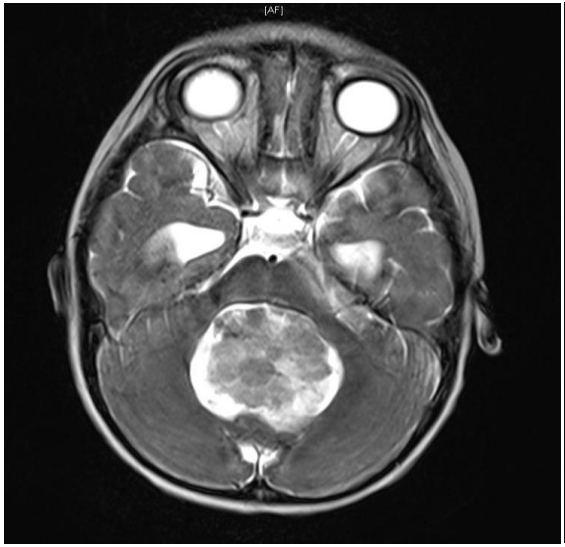
- CC: Unsteady gait worsening over a 2-month period
- HPI: 2yo boy born NSVD, FT with age appropriate milestones met, UTD immunizations and no significant medical history

Physical Exam

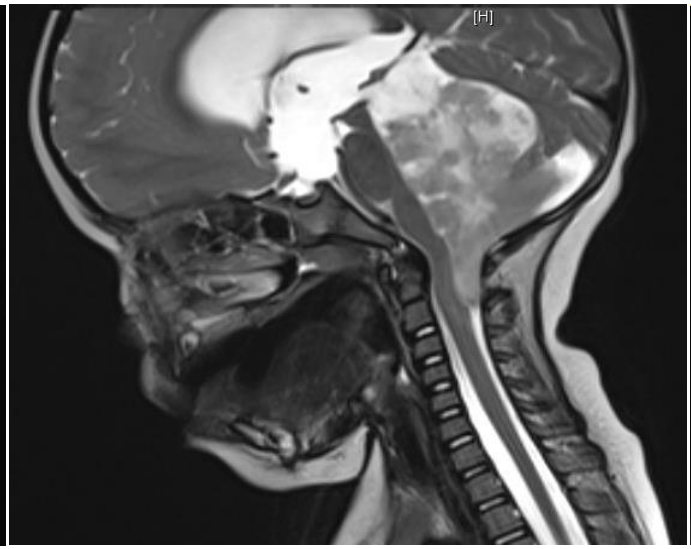
- Normocephalic with CN II-XII intact, muscle strength and tone normal in both arms and legs proximally and distally, no evidence of atrophy or fasciculations. Able to stand and can take a few steps with minimal ataxia.

Work Up

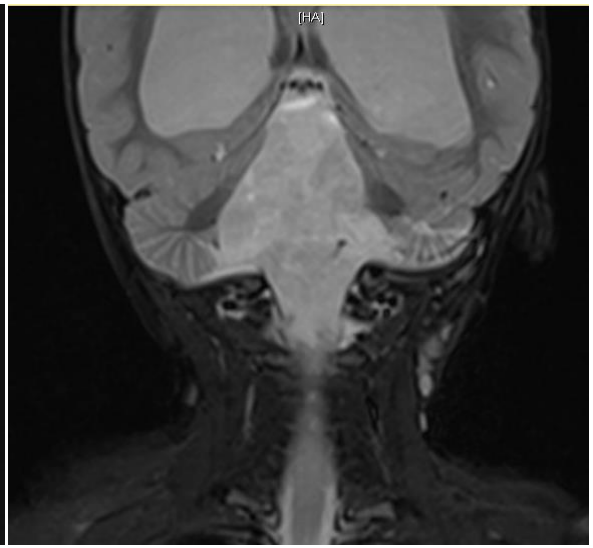
- MRI Brain & Spine
  - s/p VP shunt placement; expansile lobulated tumor filling the fourth ventricle, involving the prepontine and premedullary cisterns extending down to the posterior aspect of the foramen magnum
  - No evidence of metastatic disease in the spine
  - Likely representing ependymoma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



T2



T2



T1

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

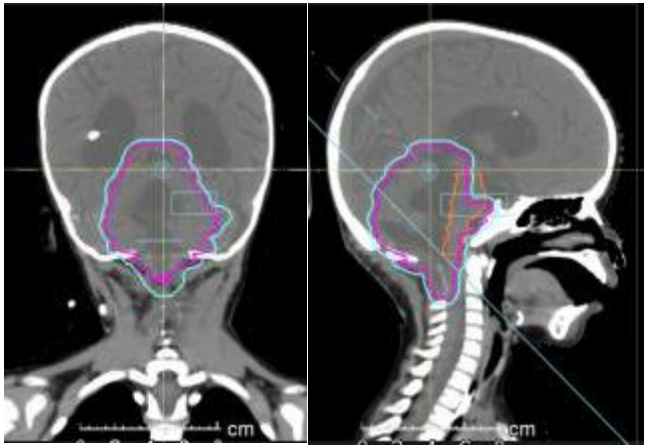
Further Work Up

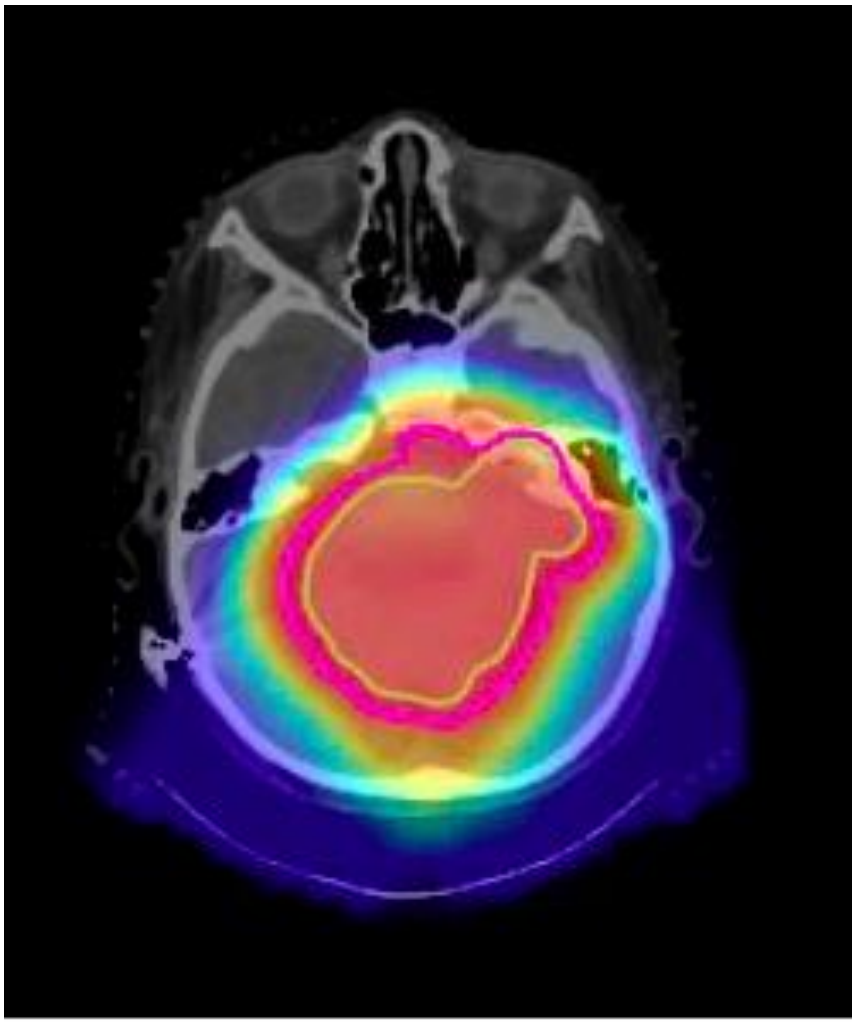
- MRI on POD #1 revealed no residual disease
- Lumbar puncture 14 days post-op showed CSF cytology was negative for any malignant cells
  - If positive, indication for chemotherapy as bridge treatment or CSI (the latter only if patient is ≥3 years old)

Adjuvant RT

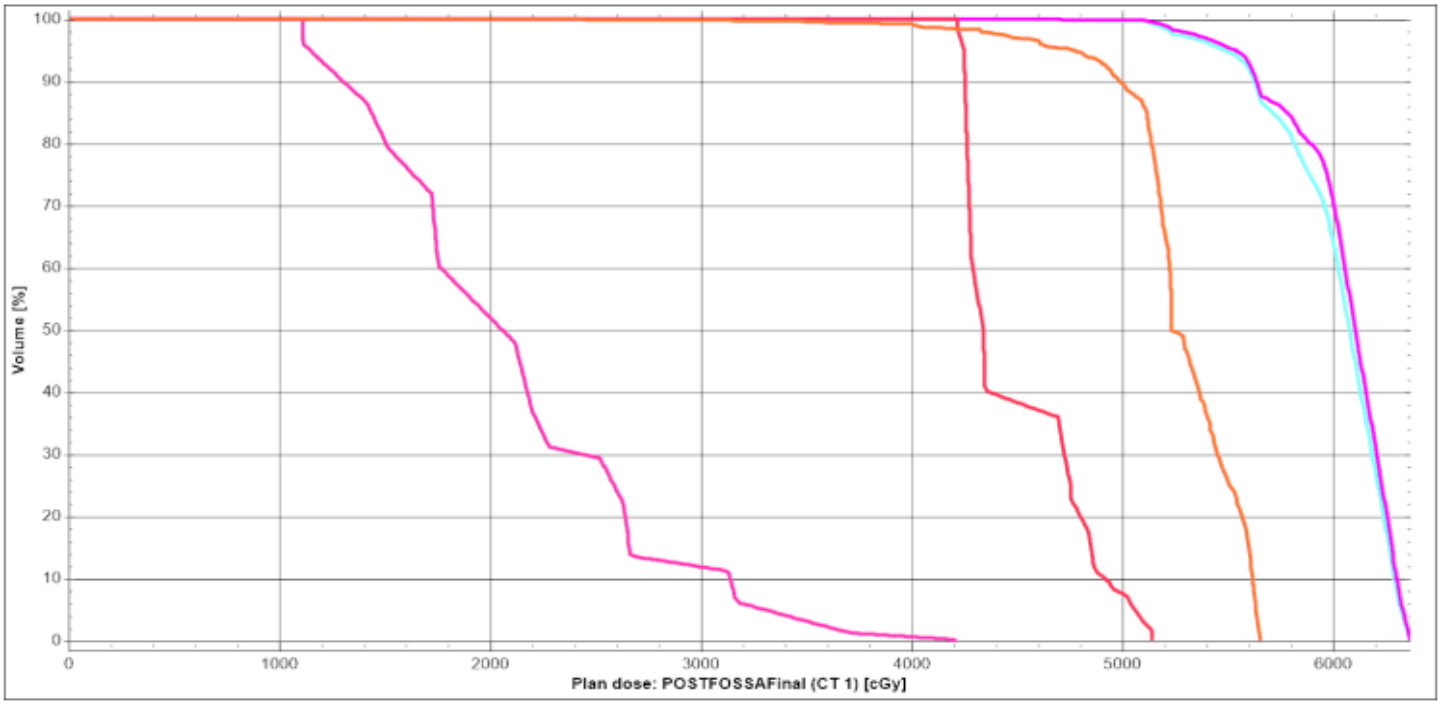
- Preop GTV (light green)
- CTV = Preop GTV + 1cm (pink)
- PTV = CTV + 0.3cm

- **Proton therapy (uniform scanning) with 5940cGy in 33 fractions**





Dose Volume Histogram (DVH)

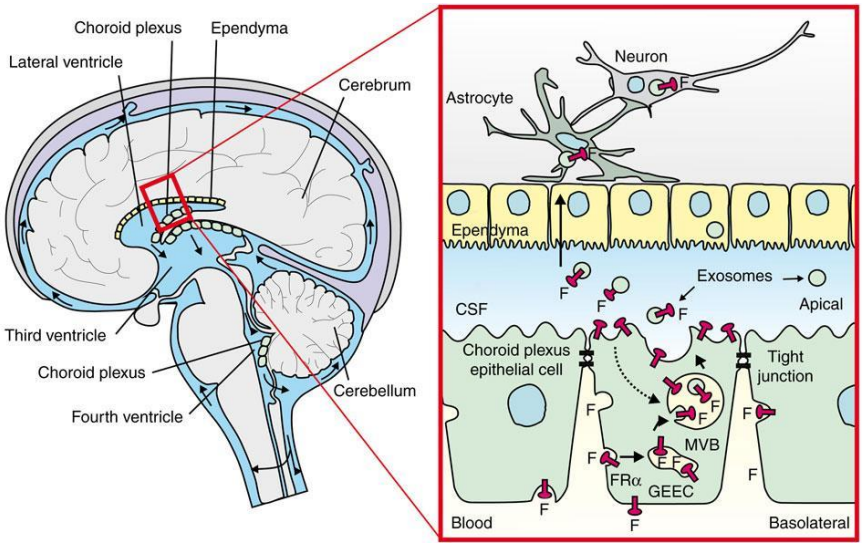


Name (from right to left)	Volume [cm³]	D99 [cGy]	D98 [cGy]	D95 [cGy]	Average [cGy]	D50 [cGy]	D2 [cGy]	D1 [cGy]	% outside grid
CTV5940	142.54	5206	5296	5540	6046	6105	6353	6358	0
PTV5940 3mm	200.21	5167	5228	5490	6013	6077	6350	6357	0
BRAINSTEM	13.24	4019	4329	4770	5276	5232	5644	5648	0
COCHLEA_L	0.08	4216	4221	4247	4492	4340	5129	5142	0
COCHLEA_R	0.12	1108	1108	1145	2096	2058	3629	3838	0

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



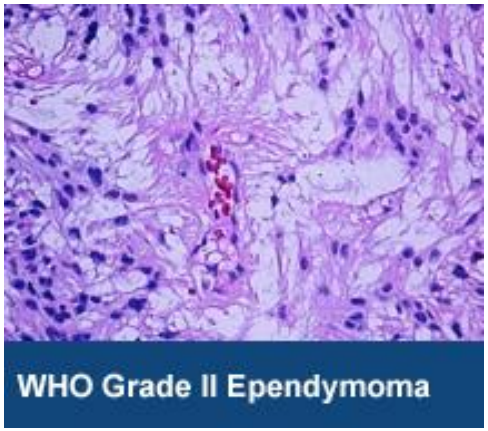
Epidemiology

- 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

WHO Grade I	Myxopapillary or Subependymoma
WHO Grade II	Classic
WHO Grade III	Anaplastic

Pathology

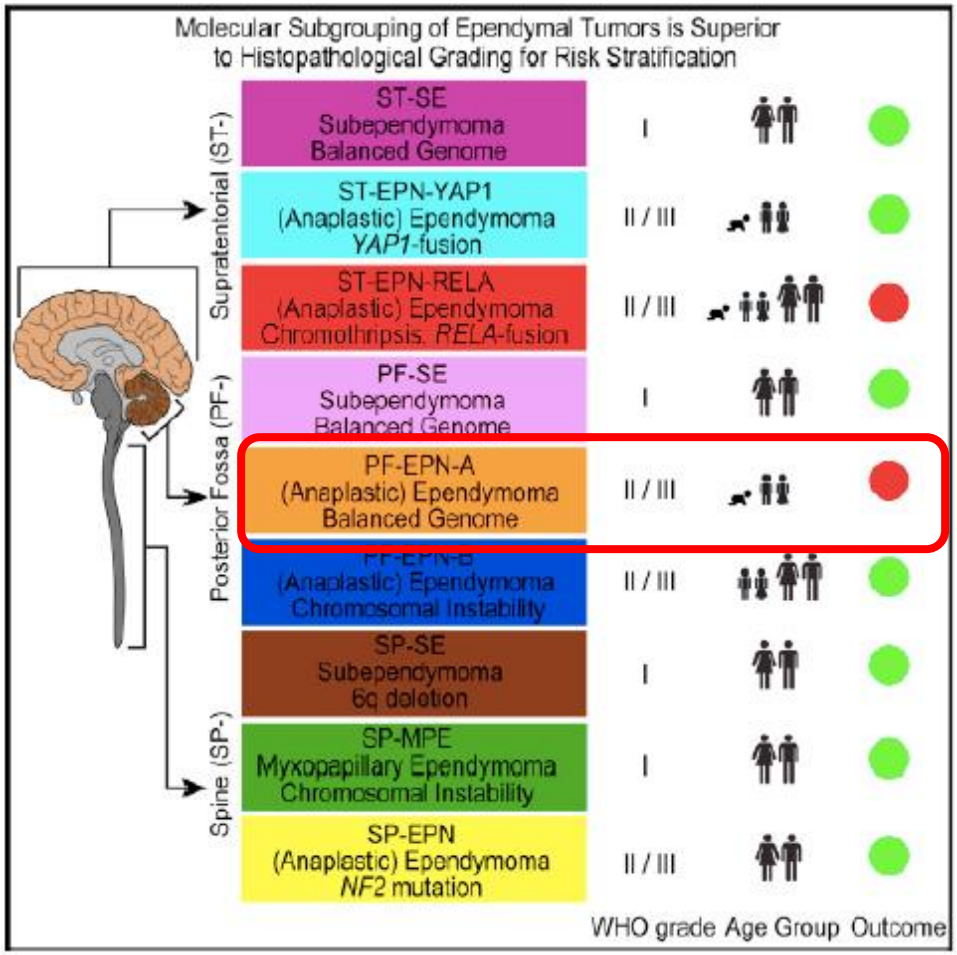

WHO Grade I Ependymoma (Myxopapillary)


WHO Grade II Ependymoma


WHO Grade III Ependymoma (Anaplastic)

- 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



our patient

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

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