ARRO Case: Diffuse Intrinsic Pontine Glioma

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Case Presentation

- 6 y/o F with no significant PMH
- **Late 11/2016:** patient noted to have a medially inverted right eye initially evaluated as a “lazy eye” by an optometrist
- **Early 12/2016:** development of progressive weakness of the left extremities, dysequilibrium, headache, and fatigue
- **12/23/16:** Presentation to the ED with asymmetric pupils, nystagmus, right hemi-facial weakness, left hemiplegia, asymmetric clonus, and dysequilibrium
Hyperdense mass 4 cm in size arising from the right pons and extending into the right CPA cistern, favoring a pontine glioma.
MRI

- A 4.3 cm mass arising from the right pons and extending into the CPA and cerebellopontine cistern with ill-defined margins.
- Radiographic characteristics included heterogeneous enhancement, restricted diffusion, partial effacement of the fourth ventricle and aquaduct with mild dilation of the third ventricle.
Differential Diagnosis by Imaging Findings

- Brainstem glioma
- Medulloblastoma
- Ependymoma
- Hamartoma
- Osmotic demyelination
- Langerhans cell histiocytosis
Pathology

• Stereotactic brain stem biopsy
  – Diffuse midline malignant glioma, H3K27M wildtype
  – WHO grade: III
  – Molecular markers:
    • IDH I wildtype
    • TP53 mutated
    • ATRX wildtype
    • H3K27M wild-type by IHC
    • BRAFv600E negative
  – Ki-67 labeling in the range of grade IV tumors
Complications

• Post-biopsy CT head showed increased prominence of the cerebral ventricles for which dexamethasone and acetazolamide were started.

• Seven days later, VP shunt placement was required to stabilize hydrocephalus.
Epidemiology

• In 2015, >3,000 new pediatric CNS tumors were diagnosed
  – Ten to 15 percent located in the brainstem
  – Of those in the brainstem, 80% are diffuse intrinsic pontine gliomas (DIPG)
• Peak ages of onset: 5-9 yr
• Median survival is about 12 months
• Most DIPGs (75%) are astrocytomas/high-grade
  – Both high- and low-grade histologies can be aggressive

Clinical Presentation

• Rapid symptom onset
• Common findings include cranial nerve palsies (VI and VII most commonly) and ataxia >50%
• Long tract signs (hemiplegia, clonus, muscle spasticity, hyperreflexia)
• Hydrocephaalus with elevated ICP <10%
(Favorable) Prognostic Factors

• Age < 3 yr at diagnosis
• Prolonged timespan between symptom onset and diagnosis
• Lack of pontine cranial nerve palsies
• Atypical radiologic characteristics
• NF-1
Work Up and Staging

• Work up includes H&P, labs, and MRI
  – Traditionally, biopsy has not been routinely indicated, but rather when the clinical course is atypical or when MRI findings are atypical (focal exophytic, strongly contrast enhancing, well circumscribed lesions)
  – Stereotactic brain biopsy has been increasingly pursued more recently

• Disease progression is predominantly local
• No formal disease staging exists
Typical Imaging Findings

- **CT**
  - Hypodense to isodense appearance
  - Variable contrast enhancement
  - Rarely calcified

- **MRI**
  - Expansile
  - Hypointense on T1
  - Hyperintense on T2
Treatment Paradigm

Steroids → ?Biopsy? → Radiation
Stereotactic Brainstem Biopsy

• First described by Roujeau 2007, in a prospective assessment of 24 children with diffuse pontine lesions using a suboccipital transcerebellar approach.

• Postop complications occurred in two patients:
  – Two with transient new cranial nerve palsy
  – One with exacerbation of preop hemiparesis

• Diagnostic yield: 100%
  – Two patients found to have non-malignant lesions, which affected management

• Similar outcomes seen in the largest single-institution series by Puget et al. Childs Nerv Syst 2015; 31:1773-80.

External Beam Radiation

- Commonly: 54-59.4 Gy using standard fractionation
- Hyperfractionation (70.2 Gy delivered 1.17 Gy/fx BID) offers no benefit per prospective randomized evidence from POG 9239 (Mandell et al. IJROBP 1999; 43:959-64)
Hypofractionation

• Janssens et al. *IJROBP* 2013; 85:315-20
  – Matched cohort analysis of 54 patients comparing 54 Gy/30 fx to 39 Gy/13 fx (prospective) and 44.8 Gy/17 fx (retrospective)
  – Comparable tumor control, overall survival, treatment completion rates between groups
  – No grade 3 or 4 toxicities observed, although those receiving hypofractionation uniformly experienced moderate skin erythema and dry desquamation (minority with moist desquamation about auricular skin folds)

• Randomized data of 71 patients by Zaghloul (*Radiother Oncol* 2014) showed similar results between 54/30 and 39/13, though they did not fulfill the non-inferiority assumption
Simulation and Planning (this case)

• Simulation
  – Position: supine
  – Immobilization: head mask
  – Other notes:
    • No general anesthesia

• Volume delineation
  – GTV
  – CTV = GTV + 0.5 cm
  – PTV = CTV + 0.5 cm
Dose Constraints
(Standard Fractionation)

• Brainstem
  – Point max: ≤60 Gy

• Optic chiasm
  – Point max: ≤56 Gy

• Optic nerve
  – Point max: ≤55 Gy

• Retina
  – Point max: ≤50 Gy

• Lens
  – Point max: ≤7 Gy
Radiation Treatment Plan

• 54 Gy in 30 fractions
• Started with 2D therapy to expedite initiation of therapy
• Re-simmed after VP shunt placed 1/1/17, IMRT planning utilized
Dose Distribution
## Dosimetry

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Max Dose [cGy]</th>
<th>Mean Dose [cGy]</th>
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<tbody>
<tr>
<td>Brain</td>
<td>5815.2</td>
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<tr>
<td>BrainStem</td>
<td>5751.8</td>
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<tr>
<td>Chiasm</td>
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<td>Cochlea_L</td>
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<td>Globe_L</td>
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<tr>
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<td>SpinalCord</td>
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<td>637.3</td>
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</table>
Systemic Therapy

• No meaningful survival benefit of chemotherapy has been demonstrated in a variety of settings:
  – Neoadjuvant
  – Concurrent
  – Adjuvant
  – Progression after radiation therapy
  – In combination with stem cell rescue

• Greater than 250 clinical trials have aimed to address this

Novel Molecular Targets

• Most (80%) of DIPGs are associated with a gain-of-function mutation in histone H3 (H3K27M) leading to loss of histone tri-methylation resulting in epigenetic aberrations

• Two recent preclinical studies have identified therapeutic targets to treat H3K27M-mutated DIPG
  – EZH2: the catalytic subunit of polycomb recessive complex 2 (PRC2), a protein whose role (oncogenic vs tumor-suppressive) is unclear
  – Bromodomain proteins that bind to acetylated H3K27 residues and participate in gene regulation

• Several other mutations are being studied, including ACVR1, TP53, PDGFRA, PIK3CA, and Myc.

Re-irradiation?

- Given rapid time to progression (5-8 months from initial treatment), attempt is for palliation and possible small survival benefit
- Handful of small retrospective studies since 2012 that have examined this approach
  - Heterogeneous study populations across studies
  - Median overall survival after re-irradiation about six months
  - Seemingly well tolerated

Epilogue

• Mental status and range of motion improved throughout the duration of her inpatient admission

• Completed radiation therapy without interruption, tolerated well

• MRI brain 3/2017 showed marked tumor growth with evidence of increased necrotic tissue

• Started adjuvant bevacizumab 3/20/17
Summary

• DIPG is a rare but aggressive pediatric neoplasm
• Stereotactic biopsy, while not standard, has been shown to be safe and effective in experienced hands and is likely to play a greater role in diagnosis and treatment
• Treatment centers around external beam radiation therapy with the goal of improving local control
  – Hypofractionation may be beneficial in shortening treatment time, but at the expense of normal tissue toxicity
  – Hyperfractionation has similar outcomes to standard fractionation, but requires BID general anesthesia
• Recent advances in tumor epigenetics have provided insight into disease mechanisms and identification of several putative molecular targets