ARRO Case:
Diffuse Intrinsic Pontine Glioma

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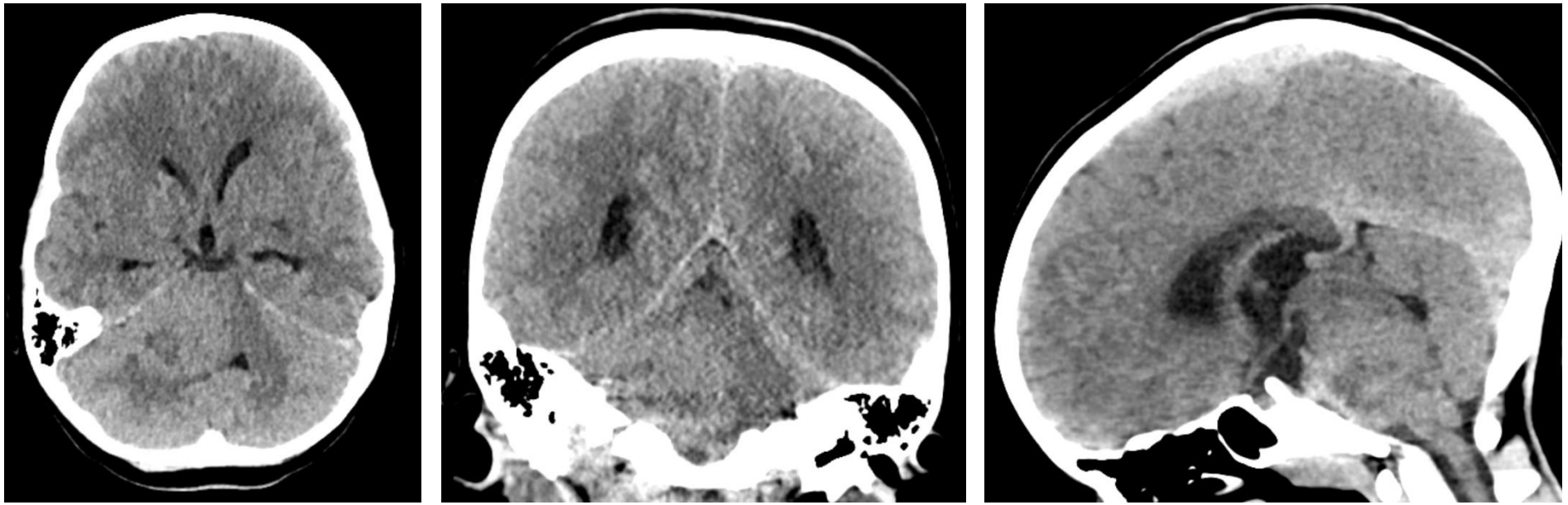
Case Presentation

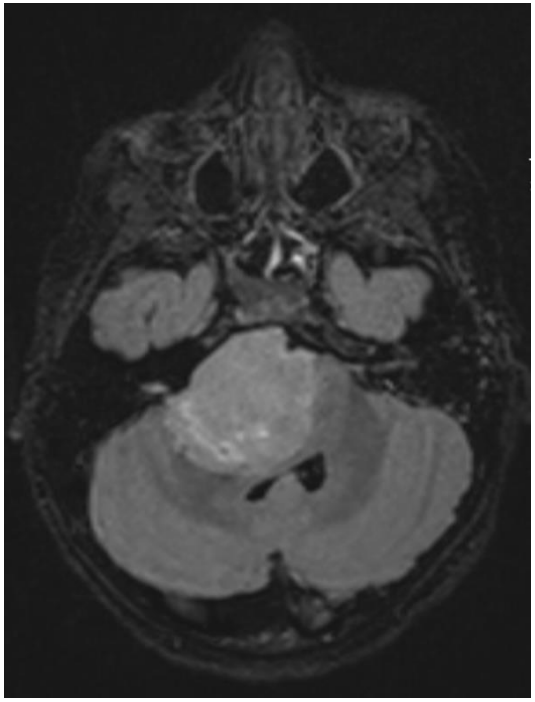
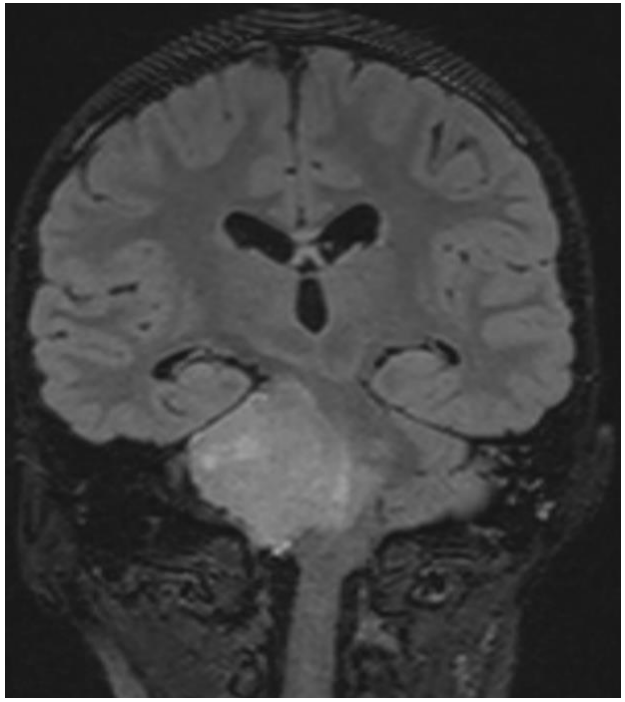
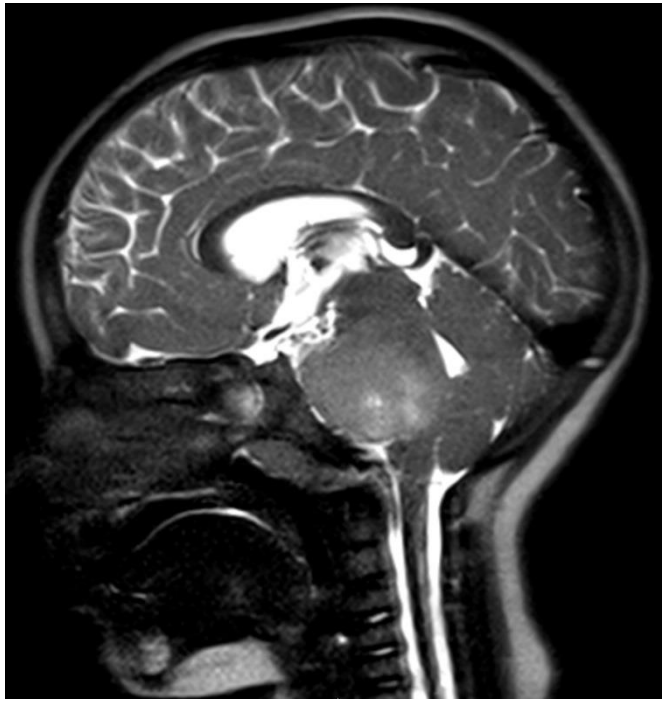
- 6 y/o F with no significant PMH
- **Late 11/2016:** patient noted to have a medially inverted right eye initially evaluated as a “lazy eye” by an optometrist
- **Early 12/2016:** development of progressive weakness of the left extremities, dysequilibrium, headache, and fatigue
- **12/23/16:** Presentation to the ED with asymmetric pupils, nystagmus, right hemi-facial weakness, left hemiplegia, asymmetric clonus, and dysequilibrium

CT



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

Ostrom et al. *Neuro-Oncol* 2015; 17(suppl 4):iv1-iv62.
Vanan et al. *Front Oncol* 2015; 5:237.

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 spacticity, hyperreflexia)
- Hydrocephalus 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.

Roujeau et al. *J Neurosurg* 2007; 107(1 Suppl):1-4.

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)

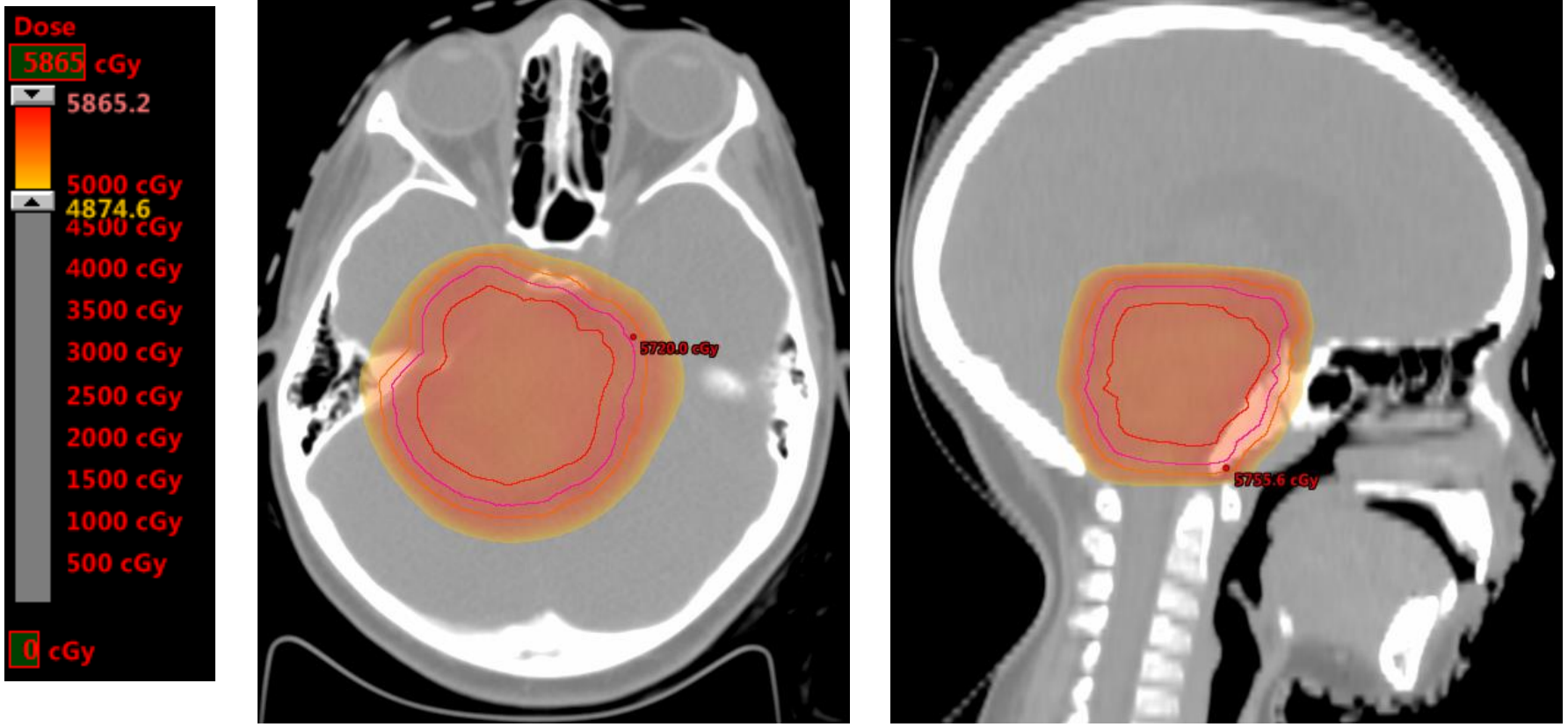
- Brainstem
  - Point max: ≤60 Gy
- Optic chiasm
  - Point max: ≤56 Gy
- Optic nerve
  - Point max: ≤55 Gy
- Retina
  - Point max: ≤50 Gy
- Lens
  - Point max: ≤7 Gy

RTOG 0825

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

	Max Dose [cGy]	Mean Dose [cGy]
Brain	5815.2	1639.8
BrainStem	5751.8	5592.6
Chiasm	5506.8	4940.3
Cochlea_L	4981.6	2721.5
Cochlea_R	5509.4	5240.5
Globe_L	1795.1	1047.3
Globe_R	1863.1	1201.8
LacrimalGland_L	1459.6	1121.7
LacrimalGland_R	1789.9	1573.0
Lens_L	626.6	500.0
Lens_R	595.6	488.7
OpticNerve_L	3090.9	2073.5
OpticNerve_R	3697.5	2336.5
PTV_54Gy_30fr	5865.2	5591.0
SpinalCord	5603.5	637.3

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

Cohen et al. *Neuro-Oncol* 2017 (in press).
Lapin et al. *Front Oncol* 2017; 7:57.

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.

Lapin et al. *Front Oncol* 2017; 7:57.
Ridler *Nat Neurol* 2017.

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

Freese et al. *Pract Rad Oncol* 2017; 7: 86-92.

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