ARRO Case: Low Grade Glioma (LGG)

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October 25, 2013
Case

- 44 F, h/o hypothyroidism
- Presentation:
  - While driving became drowsy, pulled over, passed out and had a seizure with bladder incontinence
  - No health insurance, so did not seek medical evaluation
  - Continued to have seizures 1-2x/month for approximately 5 months
    - Occurring at night, generalized tonic-clonic with loss of bladder function and occasional tongue lacerations
    - No numbness, weakness, nausea, vomiting or vision changes
  - Has frontal headaches, unchanged, present for years
Physical Examination

• Karnofsky Performance Status (KPS) 80%, Eastern Cooperative Oncology Group (ECOG) Grade 1

• Neurological:
  – She is alert and oriented to person, place, and time.
  – CN II-XII intact.
  – Motor 5/5 in all extremities.
  – Sensation to light touch intact.
  – No dysdiadochokinesia.
  – Normal heel-to-shin and finger-to-nose test.
  – Tandem, heel walk, toe walk, and normal gait.
  – Negative Romberg.
Workup

• Labs:
  – Hgb: 9.8
  – Hct: 30
  – WBC: 12.4

• EEG: normal

■ Imaging

■ CT
  • Low grade glioma (LGG) typically demonstrates ill-defined, diffuse, non-enhancing low-density region
  • Enhancement less common in LGG than high grade glioma (HGG) (21% vs. 57-96%)
    • Exception is pilocytic astrocytomas
Imaging

- MRI- Study of choice
  - T1- Hypointense and non-enhancing
  - T2- Hyperintense
  - Ill-defined tumor margins, best seen on T2-weighted MRI or FLAIR images
  - Calcification up to 20% of cases of astrocytomas and up to 90% of oligodendroglialomas
  - Mass effect, rim enhancement or vasogenic edema uncommon
Findings: Left parietal lobe and left parieto-occipital region. 2.3x2.0x1.8cm mass with effacement of sulci. No mass effect, midline shift or extra-axial collection.
Findings:
Expansile non-enhancing FLAIR hyperintensity centered in left medial posterior parietal region extending to the posterior aspect left parahippocampal gyrus which is similar to most recent prior exam. No associated elevated rCBV and overall unremarkable MR spectroscopy. Overall imaging findings favor a low-grade process, favor low-grade glioma.
Surgical Resection

- Left parietal craniotomy and inter-hemispheric microsurgical approach
- Stereotactic neuro-navigation was utilized for surgical resection due to proximity to corpus callosum
- Near total resection
- Final Diagnosis:
  - Infiltrating glioma, most consistent with diffuse astrocytoma, WHO grade II
Epidemiology

- 10% of primary intracranial tumors

- 20-25% of gliomas are low grade gliomas (LGG)
  - 2000 per year

- LGG found in younger patients (3rd-4th decade)
Low Grade Glioma (LGG)

- World Health Organization (WHO) Grading system
  - Atypia, Mitoses, Endothelial Proliferation, and Necrosis (AMEN)
- Types of low grade gliomas
  - WHO Grade 1
    - Subependymal giant cell astrocytoma
    - Pilocytic astrocytoma
  - WHO Grade 2
    - Pleomorphic xanthoastrocytoma
    - Diffuse astrocytoma
  - Oligodendroglial tumors
Presentation

• **Seizure-65%**
  – Higher incidence in LGG than GBM
  – Better prognosis
  – Start anticonvulsants
  – Median time to dx is 6-17 months after seizure

• **Headache-36%**

• **Weakness-30%**

• **Visual loss/change-15%**

• **Personality change-14%**

• **Nausea/vomiting-10%**
Oligodendroglioma (OD): 1p/19q deletion

• 50-80% of cases of low grade or anaplastic have loss of one entire 1p and one entire 19q chromosomal arm (Perry 2003)

• If both deletions are present (“co-deleted”), associated with prolonged survival and favorable response to PCV and/or radiation therapy

• Children (especially under 10 yrs) highly unlikely to have the deletions

• Should consider testing for deletions using FISH or CGH (comparative genomic hybridization)

T(1;19)(q10;p10) and prognosis

– Found that a t(1;19)(q10;p10) mediates the 1p/19q deletion in gliomas
– This translocation is associated with superior OS and PFS in LGG
  – Median OS 11.9 years for fusion vs. 8.1 years with no fusion
  – Median PFS 8.1 years with fusion vs. 3.3 years with no fusion

Isocitrate Dehydrogenase (IDH) Mutation: glioma-specific

• IDH1 Mutation
  – Ch 2q33, Arg→His
  – Inversely correlated with grade
  – Associated with and precedes 1p19q deletion and MGMT methylation
  – Mutually exclusive with EGFR ampl, loss of ch 10
  – Low incidence in primary GBM (5%); high in secondary (75%)

• IDH2 Mutation (less common): Oligodendroglioma (OD)
IDH1 Mutation and Response

- IDH1 mutation → better outcomes (compared to wild type)

- Progressive de-differentiated low-grade astrocytomas: response not differ based on IDH1 mutation (van den Bent MJ CCR 2010).

- Anaplastic OD RT vs RT+PCV: response not different based on IDH1 mutation (Dubbink Neurology 2009)
IDH/MGMT-driven molecular classification

• 210 adult LGGs screened for IDH1/2 mutation, MGMT methylation, 1p/19qLOH, and nuclear TP53 immuno-positivity

• Results
  – Molecular parameters better survival predictor than histology
  – IDHmut/MGMTmet favorable (HR=0.33, P<0.01)
  – IDHmut/MGMTmet/1p19qloh performed the best (HR=0.18, P<0.001)
  – IDHmut/MGMTmet/TP53pos combo significant RF for malignant transformation (HR=2.75, P<0.05)

Leu, et al. Neuro Oncol 2013
Prognostic Factors: Summary

- **1p/19q co-deletion**
  - Favorable response to PCV and/or radiation therapy
- **IDH mutation**
  - Overall better outcomes
  - Associated with and precedes 1p/19q co-deletion
  - With progressive LGG or anaplastic OD no difference in prognosis/response to RT +/- chemo.
- **p53**
  - More common among astrocytomas
  - Mutually exclusive with 1p/19q deletions
- **MGMT methylation**
  - Increased responses to alkylating agents
Treatment Algorithm

• **Maximally safe resection (GTR vs STR)**
  – Get postoperative MRI within 48-72 hours

• **S/P surgery offer observation if:**
  – Age <40
  – Oligodendroglioma
  – GTR
  – Good neurologic function
  – < 6 cm
  – Tumor does not cross midline
Radiation

• Timing of radiation therapy
  - EORTC 22845 ("Non-Believers Trial")
    • Postoperative RT to 54 Gy improves PFS (median 5.3 vs. 3.4 years, 5 year PFS 35% vs. 55%)
    • OS is NOT prolonged
    • Seizure control improved

• RT Dose
  - EORTC 22844 ("Believers Trial")
    - Low (45 Gy) vs. High Dose (59.4 Gy)
    - Increased adverse events including fatigue/malaise, worsened emotional functioning in high dose group.
  - NCCTG
    - Low (50.4 Gy) vs. High Dose (64.8 Gy)
    - Severe RT toxicity increased in high dose group
  - No difference in OS or PFS
Chemotherapy

- No role for chemo in newly diagnosed LGG

- **SWOG**
  - CCNU (lomustine) with radiation does not significantly improve OS in LGG

- **RTOG 9802**
  - RT (54 Gy) vs. RT+PCV: no OS difference but showed a trend for PFS. Increased toxicity.
  - 2 year survivors probability of OS for an additional 3 years was **84% vs. 72% (SS)**
Ongoing Studies

- **EORTC 22033 (closed to accrual):**

  - **ECOG E3F05 (RTOG 1072):**
    - **Eligibility:** Age ≥ 40, or radiographic progression, or uncontrolled symptoms/seizures
    - **Pre-study:** 1p testing
    - **Stratification:** 1p status
    - **1st endpoint:** Progression-free survival
    - **2nd endpoints:** Overall survival Quality of life Cognition

  - **Arm A (standard arm) RT (50.4 Gy/28 fx)**

  - **Arm B (experimental arm) RT + TMZ daily → TMZ × 12 cycles**

  - **N=466**

  - Schiff et al. Cancer Investigation 2007
Radiation Planning

Volumes

- GTV=T1 enhancement or FLAIR.
- CTV=GTV + 1-2 cm margin.
- PTV=CTV + 0.3-0.5 cm.

Dose Constraints

- Brainstem: 5500 cGy
- Optic Chiasm/nerves: 5000-5600 cGy
- Spinal cord: 5000 cGy
- Eye/Retina: 4500-5000 cGy
- Lens: 500-700 cGy
- Cochlea: 5500 cGy
5-Field IMRT Plan

2-Field Proton Plan
DVH Comparison of Proton and IMRT

Initial-P=Proton
Follow Up

• MRI q3-6 mo for 5 years then annually thereafter

• Anaplastic transformation from LGG to HGG (high grade glioma)

• Issues with follow-up
  – Slow growth until they undergo malignant transformation
  – No contrast enhancement
  – Poor correlation imaging and clinical status
References

• Leu et al. IDH/MGMT-driven molecular classification of low-grade glioma is a strong predictor for long-term survival. Neuro Oncol 2013.

• Chang et al. Multiinstitutional validation of the University of California at San Francisco low-grade glioma prognostic scoring system. Clinical article. J Neurosurg 2009.


