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Neuroradiology / Neuropathology
Conference

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C. Ryan Miller, MD, PhD
Case 1

• 56 year old female

• Presented with:
  – 3-4 weeks of visual symptoms (asymmetric vision loss, blurry & dark vision, photosensitivity & decreased peripheral vision) & optic disc edema.
Intensely enhancing, highly vascular (prominent flow voids) right posterior fossa mass and concomitant hydrocephalus.
Frozen: Hemangioblastoma
Inhibin

Negative markers:
GFAP – not a hypervascular glial tumor
EMA – not a meningioma (angiomaticous or clear cell)
RCC/CD10 – not a metastatic renal cell cancer
PAX8 – not a hemangioblastoma of renal origin
Hemangioblastoma

- Most common posterior fossa mass in young adults (30-60yo).
- Intracranial (87-97%) or spinal (3-13%).
  - 95% in posterior fossa (85% cerebellar hemisphere, 10% cerebellar vermis and 5% medulla). Rarely extend beyond the cerebellum into the CPA. 5% supratentorial (optic radiations and hemispheric VHL).
- From a macroscopic point of view:
  
  Type 1 - simple cyst form (6%)
  Type 2 - macrocystic form (65%)
  cyst of variable size with a mural nodule of approximately 1 cm.
  Type 3 - solid form (25%)
  Type 4 - microcystic form (4%)
- Highly vascular lesion with multiple flow voids, avid enhancement (solid portion) and high perfusion (CBV).

• The blood supply is usually received through the pia mater and rarely through the external carotid artery.

Intra-axial tumor with blood supply from dural arteries:

- Dural invasion
- Previous minor bleeding over the pia mater which causes adhesion of the tumor to the dura
- Recurrence of a tumor after surgical resection
- Extra-axial origin with intra-axial invasion
Case 2

- 37 year old male
- Presented with:
  - Multiple episodes of syncope.
- Past medical history:
  - Multiple epidural steroid injections for management of chronic neck and back pain.
Large right frontal mass with surrounding edema and brain compression: anterior skull base hyperdense mass with extra-cranial extension (soft tissue opacification of the frontal sinus) and right frontal heterogeneous hyperdense lesion.
Extra-axial lesion involving the right anterior skull base with intracranial and extracranial involvement. No restricted diffusion.

Heterogeneous intraparenchymal lesion in the right frontal lobe which does not appear to be contiguous with the skull base mass. Some areas of restricted diffusion.
The extra-axial lesion shows intense and homogenous enhancement, while the frontal intraparenchymal lesion shows heterogeneous enhancement after gadolinum administration.
Evidence of prior sinonasal surgery with soft tissue within the ethmoid cavity, frontoethmoidal recesses, and frontal sinuses. The internal carotid arteries bony canals are intact. Bilateral ethmoid and frontal roof dehiscence.
Fungal Infection - Exserohilum species
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Fungal Infection - Exserohilum species

- Exserohilum – dematiaceous fungus is ubiquitous environmental contaminant
- Most CNS infections associated with contaminated epidural corticosteroid injections
Fungal Infection - Exserohilum species

- LM inflammation
- Thrombosis + Infarction
- GMS
- Melanin
Postsurgical changes from right frontal approach biopsy of periventricular anterior right frontal lobe lesion with hemorrhage along the biopsy track.

MRI 01/13/2015
Same patient develops right cranial nerve III palsy.
Focal areas of restricted diffusion at the orbitofrontal aspect of the right frontal lobe. Asymmetry of the right cavernous sinus, best seen on post contrast coronal CISS images concerning for cavernous sinus invasion.
Fungal brain abscesses

- Ring-enhancing with restricted DWI as seen on non-fungal abscess.
- Irregular walls and irregular projections into the cavity with no contrast enhancement of these projections. The analysis of DWI images and ADC values showed restricted diffusion in these projections and in the wall of the fungal abscess, but the rest of the core of the abscess showed no restricted diffusion.
- MRS: Fungal lesions are known to show lipids (1.2–1.3 ppm), lactate (1.3 ppm), alanine (1.5 ppm), acetate (1.9 ppm), succinate (2.4 ppm), choline (3.2 ppm). The presence of multiple signals seen between 3.6 and 3.8 ppm assigned to the disaccharide trehalose have been reported in the wall of cryptococcosis and cerebral mucormycosis.
- In vitro studies of the fungal colony have shown paramagnetic elements with growth of hyphae resulting in increased magnetic susceptibility effects.

Fungal invasion of brain parenchyma was notably infrequent. CNS tissues of only one patient had evidence of fungus in the deep brain parenchyma.
Case 3

• 82 year old female
• Presented with:
  – New onset headache and right upper extremity weakness.
• Past medical history:
  – Mixed mullerian tumor of the uterus in 2005 treated with surgery (TAH/BSO) and 3 cycles of adjuvant chemotherapy
Brain mass with surrounding vasogenic edema in the left frontal lobe.
Left prefrontal mass lesion with vasogenic edema. Low T2 signal and restricted DWI.
Intense homogenous enhancement after gadolinium administration. The lesion does not show high perfusion on CBV or CBF on DSC perfusion maps.
• Small round blue cell tumor
• Initial IHC – CD45+, S100 neg, CK7/20 neg
• Dx - Lymphoid neoplasm
CD20

CD3

BCL2

BCL6 – activated (non-GCB subtype)
CD138
CD10 – activated (non-GCB subtype)
Cyclin D1
TdT
EBV ISH

CD5

Ki67
MUM1 – activated (non-GCB subtype)
Box 14-1. Classification of Hematopoietic Malignancies of the Nervous System

- Diffuse large B-cell lymphoma (DLBCL)
- Immunodeficiency-associated lymphoma
- Lymphomatoid granulomatosis
- Intravascular large B-cell lymphoma
- Marginal zone ("MALT") lymphoma of the dura
- Low-grade B-cell lymphoma
- Plasmacytoma
- Anaplastic large-cell lymphoma
- T-cell lymphoma
- Secondary lymphoma or leukemia
- Myeloid sarcoma

Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling

![Image of gene expression profiling](image_url)
Progress in central nervous system lymphomas

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Table I. High-dose methotrexate-based trials in PCNSL that yielded median progression-free survival ≥2-years.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Reference</th>
<th>Patients (n)</th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX 2.5 g/m², PCB, vincristine, IT-MTX, WBRT</td>
<td>DeAngelis et al (2002)</td>
<td>98</td>
<td>24</td>
<td>37</td>
</tr>
<tr>
<td>MTX 8 g/m², TMZ, rituximab, etoposide, ARA-C</td>
<td>Wieduwilt et al (2012)</td>
<td>31</td>
<td>24</td>
<td>66</td>
</tr>
<tr>
<td>MTX 3.5 g/m², rituximab, vincristine, PCB, ARA-C, rd-WBRT</td>
<td>Morris et al (2013)</td>
<td>52</td>
<td>39</td>
<td>79</td>
</tr>
<tr>
<td>MTX 8 g/m², TMZ, Ritux, etoposide, ARA-C</td>
<td>Rubenstein et al (2013b)</td>
<td>44</td>
<td>48</td>
<td>NR</td>
</tr>
</tbody>
</table>

PCNSL, primary central nervous system lymphoma; PFS, progression-free survival; OS, overall survival; MTX, methotrexate; PCB, procarbazine; IT-MTX, intrathecal methotrexate; WBRT, whole brain radiotherapy; TMZ, temozolomide; ARA-C, cytarabine; rd-WBRT, reduced dose whole brain radiotherapy; NR, not reached. [Response criteria according to Abrey et al (2005)].
Diffuse large B-cell lymphoma

- Primary CNS lymphoma (PCNSL) are uncommon, accounting for only 1% of malignant CNS tumors.
- Typically PCNSL are supratentorial (75-85%) and appear as a mass or multiple masses (11-50%) usually in contact with the subarachnoid/ependymal surfaces. They may cross the corpus callosum.
- Low grade tumors differ from the more common high-grade PCNSL:
  - Deep locations and spinal involvement is more common and contrast enhancement is absent, irregular or only mild.
- Disseminated meningeal/intraventricular disease is uncommon (1 and 7%) and usually seen in high grade cases.
- CT hyperdense; MRI T1 hypointense, T2 iso- to hypointense, pronounced and usually homogeneous enhancement, restricted diffusion.
- MR spectroscopy: large choline peak, reversed choline/creatinine ratio, lactate peak may be present.
- MR perfusion: shows only a modest increase in rCBV, much less marked than in high-grade gliomas, where angiogenesis is a prominent feature.
Case 4

• 59 year old male

• Presented with:
  – Blurred vision in the right eye with asymmetric optic disc edema (right greater than left).
Mass along the inferior aspect of the fourth ventricle, extending through the midline outlet foramen (Magenie) with intermediate signal on T1-WI and heterogeneous subtly increased signal on T2-WI. No restricted DWI. No evidence for obstructive hydrocephalus.
Slightly heterogenous enhancement after gadolinium administration.

Slightly increased fluid within the right optic nerve sheath compared to the left.
Subependymoma
## Subependymoma

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Clinical Presentation</th>
<th>Neuroimaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subependymoma (WHO grade I)</td>
<td>Often asymptomatic</td>
<td>Sharply demarcated nodular intraventricular lesions or arising eccentrically within the spinal cord; variable CT and MRI findings; enhancement uncommon, but many have calcification</td>
</tr>
<tr>
<td>Myxopapillary ependymoma (WHO grade I)</td>
<td>Back pain and/or sensory/motor deficits</td>
<td>Cauda equina/conus/fulum region well-circumscribed lesion, hyperintense on T1- and T2-weighted MRI with intense contrast enhancement</td>
</tr>
<tr>
<td>Ependymoma (WHO grade II)</td>
<td>Spinal: back pain and/or sensory/motor deficits Intracranial: hydrocephalus with signs/symptoms of increased intracranial pressure</td>
<td>Spinal: centrally situated intramedullary tumors with discreet margins; CT-hyperdense; MRI T1-iso- to hypointense, T2-hyperintense, with uniform enhancement postcontrast; rostral and caudal cysts Intracranial: sharply demarcated, often partially cystic, heterogeneous contrast-enhancing and similar T1 and T2 to spinal lesions</td>
</tr>
<tr>
<td>Anaplastic ependymoma (WHO grade III)</td>
<td>Similar to ependymoma but with more rapid onset</td>
<td>Similar to ependymoma, often with microinfiltration into surrounding tissues</td>
</tr>
</tbody>
</table>

**Table 6-1. Clinicopathologic and Neuroimaging Findings of Ependymal Tumors**

COX-2, cyclooxygenase-2; CT, computed tomography; EM, electron microscopy; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; IHC, immunohistochemistry; MRI, magnetic resonance imaging; NCAM, neural cell adhesion molecule; WHO, World Health Organization.
Subependymoma

- Uncommon, benign (slow growing and non-invasive).
- Subependymomas account for 0.2%–0.7% of intracranial neoplasms; however, this may be an underestimate, since often they are asymptomatic and found incidentally.
- Middle aged to older individuals (typically 50-60yo)
- Most commonly seen in the IV ventricle, but can arise anywhere where there is ependyma.
- Avascular or hypovascular with no enhancement, although at times may demonstrate mild enhancement.
- Cystic degeneration is common, and calcification may be present. Intratumoral hemorrhage may also occur.
- Prognosis is good; recurrence after surgical resection is rare.
Case 5

- 74 year old female
- Presented with:
  - Headaches for multiple weeks, memory loss, episodes of confusion and altered mental status.
Ill-defined right parieto-occipital mass lesions with vasogenic edema and brain compression with midline shift. The lesions show central necrosis, hemorrhage and no restricted diffusion.
Irregular enhancement with leptomeningeal, pachymeningeal, and ependymal enhancement.
Glioblastoma (WHO IV)
**Table 2. Molecular and metabolic alterations in GBM and their potential biomarker status.**

<table>
<thead>
<tr>
<th>Molecular/metabolic alteration</th>
<th>Possible biomarker status</th>
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</thead>
<tbody>
<tr>
<td>O(6)-methyguanine-DNA-methyltransferase (MGMT) promoter methylation</td>
<td>Prognostic, predictive [1]</td>
</tr>
<tr>
<td>Loss of heterozygosity chromosome 1p 19q</td>
<td>No prognostic significance [8]</td>
</tr>
<tr>
<td>Loss of heterozygosity 10q</td>
<td>Prognostic [9]</td>
</tr>
<tr>
<td>Isocitrate dehydrogenase (IDH) mutational status</td>
<td>Prognostic [10]</td>
</tr>
<tr>
<td>Epidermal growth factor receptor (EGFR)</td>
<td>Prognostic [11]</td>
</tr>
<tr>
<td>Epidermal growth factor, latrophilin, and 7 transmembrane</td>
<td>Diagnostic, potentially prognostic [12]</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (VEGF)</td>
<td>Potentially prognostic [13]</td>
</tr>
<tr>
<td>Tumor suppressor protein p53</td>
<td>Diagnostic [14]</td>
</tr>
<tr>
<td>Phosphatase and tensin homolog (PTEN)</td>
<td>Prognostic, possibly predictive [13]</td>
</tr>
<tr>
<td>p16INK4a gene</td>
<td>Inconsistent findings [13]</td>
</tr>
<tr>
<td>Cytochrome c oxidase (CcO)</td>
<td>Potentially prognostic [15]</td>
</tr>
<tr>
<td>Phospholipid metabolites</td>
<td>Potentially predictive [16]</td>
</tr>
<tr>
<td>Telomerase messenger expression (hTERT messenger ribonucleic acid [mRNA])</td>
<td>Potentially diagnostic [17], prognostic [18]</td>
</tr>
<tr>
<td>microRNAs (miRNAs)</td>
<td>Diagnostic, prognostic [19]</td>
</tr>
<tr>
<td>Cancer stem cell markers</td>
<td>Potentially prognostic [20,21]</td>
</tr>
</tbody>
</table>

- MGMT promoter methylation is an independent favorable prognostic factor;
- 1p and 19q is the most common genetic alteration in oligodendrogioma tumors and is associated with favorable response to chemotherapy, radiation and survival;
- For all gliomas, IDH mutations appear to have a prognostic advantage;
- Currently, there are no significant differences in the treatment of GBM based on any molecular or imaging prognostic biomarkers.
<table>
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<tbody>
<tr>
<td><strong>Classical</strong>—High <em>EGFR</em>, <em>TP53</em>, longest survival of subgroups in response to aggressive treatment.</td>
<td><strong>Proliferative</strong>—Enriched for neural stem cell markers, <em>PTEN</em> loss, <em>EGFR</em> amplified or normal, Akt (protein kinase B) cell signaling pathway activation, shorter survival than proneural subgroup.</td>
<td><strong>I-X glioma</strong>—GBM like; multiple molecular subgroups, distinct from <em>IDH1/ATRX/TP53</em> (I-A glioma) and <em>IDH/CIC/FUBP1</em> (I-CF glioma) tumors—prognosis approximately 1 year.</td>
</tr>
<tr>
<td><strong>Proneural</strong>—<em>TP53</em> mutated, <em>IDH1</em> gene mutated, <em>PDGFRA</em> mutated, patients significantly younger.</td>
<td><strong>Proneural</strong>—<em>PTEN</em> intact, <em>EGFR</em> normal, Notch activation, longer survival than proliferative and mesenchymal subgroup.</td>
<td></td>
</tr>
<tr>
<td><strong>Mesenchymal</strong>—<em>NF1</em> mutated, <em>TP53</em> mutated, <em>PTEN</em> mutated.</td>
<td><strong>Mesenchymal</strong>—Enriched for neural stem cell markers, <em>PTEN</em> loss, <em>EGFR</em> amplified or normal, Akt cell signaling pathway activation, shorter survival than proneural subgroup.</td>
<td></td>
</tr>
<tr>
<td><strong>Neural</strong>—mutations in many of same genes as the other 3 subgroups. Oldest patients on average.</td>
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</table>

EGFR, epidermal growth factor receptor; TP53, tumor suppressor protein 53; IDH1, isocitrate dehydrogenase 1; PDGFRA, platelet derived growth factor receptor A; NF1, neurofibromatosis type 1; PTEN, phosphatase and tensin homolog; ATRX, alpha thalassemia/mental retardation syndrome X-linked mutation; CIC, homolog of *Drosophila capicua*; FUBP1, far-upstream binding protein 1.
• The rCBVmax measurements could be used to predict patient overall survival independent of the molecular sub-classes of GBM.

• Verhaak classification provided additional information, suggesting that molecular markers could be used in combination with hemodynamic imaging biomarkers in the future.

• Phillips subclasses are not predictive of overall survival nor do they affect the predictive ability of rCBV measures on overall survival.
Purpose - determine if ADC histogram analysis can stratify progression-free and overall survival in patients with newly diagnosed GBM treated “up-front” (ie, before tumor recurrence) with Avastin.

Conclusion: Pretreatment ADC histogram analysis can stratify progression-free survival in bevacizumab-treated patients with newly diagnosed GBM. Tumors with MGMT promoter methylation had lower ADC values than unmethylated tumors.
• All IDH1 mutant tumors were non contrast enhancing and most were located in the frontal lobe with larger tumor size.

• Edema stratified survival in MGMT promoter methylated but not in unmethylated tumors with median survival for methylated tumors with little/no edema being 2,476 days compared with 586 days for unmethylated tumors or tumors with edema.
• IDH mutations result in a very high accumulation of D-2HG.
• D-2HG signals from Hβ (1.91 ppm) and Hγ (2.24 ppm) protons are superimposed by glutamate, glutamine, and γ-aminobutyric, while Ha (4.02 ppm) signals are obscured by myoinositol, phosphocreatine, and lactate.
• 2D correlation spectroscopy (COSY), J-difference spectroscopy, multiple-quantum filtering sequences and a variety of 2D spectroscopic methods.
J-difference spectroscopy: Applies a narrow-band radiofrequency pulse to selectively refocus the Hα-Hβ scalar coupling evolution, then removing the contribution of overlapping metabolites. Hα signal of D-2HG is detected at 4.02 ppm.

Spectral editing at a TE=97. In the case of D-2HG, a TE of 97 ms maximizes the contribution of Hγ protons (2.24 ppm) against the background of glutamate and glutamine. This approach has the advantage of simplicity because it uses sequences existing on all MR scanners and relies on the fitting to separate D-2HG from glutamate, glutamine, and other metabolites at TE of 97 ms.