Biomarkers in Neuro-Ophthalmic Tumors

Fausto J. Rodriguez  MD
Department of Pathology
Johns Hopkins University School of Medicine

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Biomarkers in Neuro-Ophthalmic Tumors

Outline

• I-Optic Nerve Glioma
  • NF1
  • BRAF alterations
  • Diencephalic gliomas
• II-Orbital Meningioma
  • Anatomic and molecular subtypes
  • III-Miscellaneous tumors

Optic Nerve Glioma

• Variable clinical presentation
• Visual loss, proptosis, disc swelling
• Fusiform expansion
• Confined by dural sheath
• Predominantly pilocytic astrocytoma histology
• Observation currently favored in many cases, particularly in NF1 setting
• May stabilize or even regress
Optic Nerve Glioma
Pilocytic Astrocytoma (PA) Histology

Neurofibromatosis type 1
- Genetic tumor-predisposing syndrome
- ~1/3000
- Caused by germline mutations in the NF1 gene located at 17q11.2
- Predisposed to peripheral and CNS tumors
- Distinctive predilection to involve the optic nerve, chiasm, and hypothalamus.

Pilocytic Astrocytoma
WHO Grade I
- "Piloid Area"
- Micronodular area

Pilocytic Astrocytoma
- Rosenthal Fibers
- EGBs
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Pilocytic Astrocytoma

**BRAF duplication**

- Tandem duplication of the BRAF kinase domain resulting in KIAA1549:BRAF fusion
- Multiple independent publications in 2008:
  - Bar, E.E., et al., JNEN 2008

Tandem duplication at 7q34 produces a fusion gene between KIAA1549 and BRAF.

KIAA1549-BRAF fusions in paraffin

**FISH strategy**

BRAF duplication in paraffin

**FISH strategy**
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- **BRAF duplication** in 11 (of 15) patients
- **Non duplicated:**
  - 1 GG
  - 3 NF1 patients

**BRAF** point mutations

- **BRAF** V600E
  - Frequent in papillary thyroid carcinoma and melanoma
  - Absent to extremely rare in GBM, oligodendrogial tumors, ependymomas
  - Present in a subset of low grade/pediatric gliomas (Schindler G et al. 2011)
  - 66% of pleomorphic xanthoastrocytomas
  - 18% of gangliogliomas
  - 9% of pilocytic astrocytomas

**BRAF** point mutation

- **BRAF** V600E Immunohistochemistry

  - **Ganglioglioma**

  - **Pleomorphic Xanthoastrocytoma**

**BRAF** point mutation

- **BRAF** p.V600E Immunohistochemistry

  - **Ganglioglioma**

  - **Pleomorphic Xanthoastrocytoma**
Diencephalic Glioma

Pilomyxoid Astrocytoma

- Pilocytic Variant
- Infants, hypothalamic region
- Higher propensity for aggressive behavior, CSF dissemination
- Grade II on past WHO (2007)
  - WHO update: no grade
- No Rosenthal fibers, EGBs rare to absent

Clinicopathologic Features of Diencephalic Pediatric Low-Grade Gliomas

- 56 Diencephalic pediatric low grade gliomas
- BRAF p.V600E mutation in 36%
- Predilection for infants and young children
- Nodular, yet infiltrative in neuroimaging
- Monophasic, compact, partially infiltrative
- 75% not classifiable upon initial review
- 5-year PFS lower than BRAF p.V600E wild type PA

Clinicopathologic Features of Diencephalic Pediatric Low-Grade Gliomas

Histologic Features of Diencephalic Pediatric Low-Grade Gliomas

<table>
<thead>
<tr>
<th>Feature</th>
<th>BRAF V600-mutant LGG</th>
<th>BRAF V600-WT PA</th>
<th>BRAF V600-WT PMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases (%)</td>
<td>19 cases</td>
<td>21 cases</td>
<td>14 cases</td>
</tr>
<tr>
<td>Monophasic pattern</td>
<td>17 (89.5)</td>
<td>2 (9.5)</td>
<td>8 (57.1)</td>
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<tr>
<td>Biphasic pattern</td>
<td>2 (10.5)</td>
<td>19 (90.5)</td>
<td>6 (42.9)</td>
</tr>
<tr>
<td>Pilomyxoid features*</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Microcysts</td>
<td>1 (5.3)</td>
<td>18 (86.2)</td>
<td>5 (35.7)</td>
</tr>
<tr>
<td>Oligodendrocytes</td>
<td>0 (0)</td>
<td>3 (14.3)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Rosenthal fibers</td>
<td>3 (15.8)</td>
<td>18 (85.7)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>EGBs</td>
<td>5 (26.3)</td>
<td>7 (35.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>5 (26.3)</td>
<td>5 (26.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mitotic activity</td>
<td>0 – 2/10 hpf</td>
<td>0 – 5/10 hpf</td>
<td>0 – 5/10 hpf</td>
</tr>
<tr>
<td>Ki67 (median)</td>
<td>3% (15 cases)</td>
<td>&lt; 1% (19 cases)</td>
<td>5% (11 cases)</td>
</tr>
</tbody>
</table>

Clinicopathologic Features of Diencephalic Pediatric Low-Grade Gliomas

- MEK and Akt pathways activated in Nfi1 deficient astrocytes and murine optic gliomas
- PI3K/AKT and MEK inhibitors
  - Decreased tumor volume and proliferation
  - Decreased optic glioma-associated retinal ganglion cell loss and nerve fiber layer thinning
- May become feasible therapies for optic nerve glioma

PI3K inhibition decreases optic nerve volume and glioma proliferation.

Aparna Kaul et al. Neuro Oncol 2015;17:843-853

PI3K and MEK inhibition attenuates retinal dysfunction in FMC mice in vivo.

Aparna Kaul et al. Neuro Oncol 2015;17:843-853
Orbital Meningioma

Meningiomas
General Molecular Pathology

- Cytogenetic abnormalities
  - Chr 22 loss (most common)
  - Also 1p, Chr 6, 10, 14, 18 and 19 losses
  - Additional alterations in atypical and anaplastic subsets

- Molecular genetic abnormalities
  - NF2 mutations frequent

- Syndrome associations
  - Meningiomas, commonly multiple, occur in majority of NF2 patients
  - Germline SMARCB1/INI1 mutations present in 30% of patients with familial schwannomatosis
  - Germline SMARCB1/INI1 mutation, and somatic NF2 mutations, in one family with multiple meningiomas
  - SMARCB1/INI1 mutations very rare in familial multiple meningiomas

Orbital Meningioma

Background

- Meningiomas account for ~4% of intraorbital tumors
- May be subclassified anatomically as optic nerve sheath, primary intraorbital ("ectopic"), or secondary (i.e. extensions of an intracranial/sphenoid wing primary)
- Most common tumors of the optic nerve sheath
- Most commonly identified in middle age women
- Painless progressive visual loss (optic nerve sheath) or proptosis (intracranial with secondary extension)
• 19 orbital meningioma
• WHO grade I (n=17) or grade II (n=2)
• NF2 associated (n=1)
• SNP array (Illumina 300K platform)
• Genomic alterations in 13/19 (68%)
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Genetic Profiling by Single-Nucleotide Polymorphism-Based Array Analysis Defines Three Distinct Subtypes of Orbital Meningioma

Brain Pathology
Volume 25, Issue 2, pages 193-201, 21 MAY 2014
DOI: 10.1111/bpa.12150

Orbital Meningioma

- Sphenoid wing meningioma
  - Monosomy 22/22q loss in 7 (70%)
  - 1p, 6q, 19p loss in 5 (50%)
  - 1p and 6q most frequent in progressive tumors
- Optic nerve sheath meningioma
  - Monosomy 22/22q loss infrequent, only 1 (20%)
- Ectopic meningioma
  - Monosomy 22/22q loss in 3 (75%)

Genomic architecture of meningiomas

Victoria E. Clark et al. Science 2013;339:1077-1080
Published by AAAS
Meningioma Recurrent Somatic Mutations

- Recurrent mutations in POLR2A in meningioma (6% of benign cases)
- Encodes catalytic subunit of RNA polymerase II
- Meningothelial histology, genomic stability
- Favor the tuberculum sellae region

Case Presentations

Case 1

- 23-year-old woman
- Followed for 4 years for presumptive optic glioma
- Recent decline in visual field exam and changing MRI
- Decreased vision on the right eye
- Incongruous left homonymous hemianopsia
Gangliogliomas of the Optic Pathways

- Present with progressive optic disturbance
- Total resection usually not feasible
- Progression in ~ 1/3
- NF1-association or BRAF p.V600E frequent

Case 2

- 29-year-old male
- Visual disturbances and hypopituitarism
Germinoma

- Relatively common in suprasellar region
- Associated with excellent prognosis in pure form
- Immunohistochemistry: OCT3/4+, SALL4+, KIT+, PLAP+
- Frequent KIT and RAS mutations (~60%)
- Rare as intrinsic optic nerve/chiasomatic tumors
- Young men, non-exophytic tumors

Case 3

- 48-year-old woman presented for a routine hysterectomy for adenomyosis
- Large pelvic masses identified intraoperatively
- Intractable headaches and nausea
- Atypical cells in CSF suggestive of metastatic carcinoma
- Progressive decline with altered mental status, hypotension and seizures
- Respiratory failure, died 1 month after presentation
Leptomeningeal Carcinomatosis

**Favor Gastrointestinal Tract Primary**

- Secondary optic nerve tumors more common than primary tumors
- Spread from intraocular tumors (melanoma, retinoblastoma), hematolymphoid neoplasms, metastatic carcinoma
- Metastatic carcinoma may involve optic nerve proper or leptomeninges
- Common types include lung, breast and stomach

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**Case 4**

- 42-year-old woman with right visual loss
- Blurred vision in right eye for several days
- Visual acuity 20/25 OU, mild right dichromatopsia
- Modest hyperemic optic disc edema on the right with a flat, normal-appearing optic disc on the left

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**Clinical History**

- History of anaplastic astrocytoma diagnosed 5 years prior
- Treated with surgery and chemotherapy
- Progression to glioblastoma, IDH1 mutant/ATRX lost, 1 year prior
- Treated with Avastin and PD1 inhibitor

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**Case 4**

- Extraocular motility and the remainder of her neurologic exam unremarkable
- A and B scan: dome-shaped lesion overlying the right optic disc
- Moderate to high internal reflectivity
- Maximal elevation ~3.1mm
- Right retrobulbar optic nerve enlarged posteriorly

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**Case 4**

- Worsening eye exam
- Vitreous opacity
- R vitrectomy
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Vitrectomy Specimen

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**Diagnosis:**
Involved by Glioblastoma, IDH1 mutant

**Vitreous involvement by tumor**
- LBCL lymphoma
  - Vitreous floaters, visual loss
  - Elderly patients or younger immunosuppressed patients
  - Bilateral 60-90%
  - Manifestation of CNS lymphoma (eye involved before CNS is 50-80%)
  - Vitreous usually spared in secondary lymphoma

**Vitreous involvement by tumor**
- Other tumors with vitreous involvement
  - Retinoblastoma
  - Metastatic melanoma
  - DDx infectious process
Intraocular Glial Lesions

- Astrocytomas
  - Syndrome associated (NF1, TSC) ~70%, sporadic ~30%
  - Astrocytic Hamartoma (NF, TSC)
  - Massive retinal gliosis (vasoproliferative tumors)

Tuberous Sclerosis

Glial Hamartoma
NF2
**IDH mutant Gliomas**

- "Isocitrate dehydrogenase" (IDH)
  - IDH1: cytosolic form
  - IDH2: mitochondrial form
- Converts isocitrate to α-ketoglutarate
- Mutation impairs normal function
  - Gains ability to convert α-ketoglutarate to 2HG
- Mutations frequent in diffuse gliomas, rare in non-CNS tumors

**IDH mutant Gliomas**

- IDH1 Immunohistochemistry
  - Recognizes most frequent mutation (R132H)
  - Works well in formalin fixed tissues
  - Useful diagnostically (gliosis vs. infiltrating glioma)
  - Useful prognostically (improved prognosis in positive high grade gliomas)
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Summary

• Testing for BRAF alterations is evolving as an important biomarker for optic pathway gliomas
  • BRAF duplication/fusion in gliomas of the optic nerve proper
  • BRAF duplication/fusion or p.V600E in diencephalic tumors
• Testing for relevant alterations in meningioma is currently feasible through a variety of next generation sequencing gene panels
  • Some of these alterations are targetable and being tested in clinical trials

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