CNS UPDATE 2: DIFFUSE GLIOMAS AND PA

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Distribution of Childhood Primary Brain and CNS Tumors by Histology and Age (Ages 0-14) (N = 15,398), CBTRUS Statistical Report: NPCR and SEER, 2006-2010.


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Want to Know My Future?

New genetic tests can point to risks—but not always a cure

BY BONNIE ROCHMAN
• Disease entities should be defined as narrowly as possible in order to establish highly biologically uniform groups (i.e., as previously undertaken by the hematopathology community)
• Molecular information will be incorporated into the definitions of some diagnostic entities
• For some diagnostic entities, histology will remain the basis for definition and diagnosis
ISN-Haarlem conclusions (2)

• Grade will reflect natural history and will be based on histological findings; for some diagnoses, avoiding a histological grade may be preferable

• Some pediatric tumor types will require the creation of entities independent of their adult histological “look-alikes”
  1. ‘Pediatric GBM’
  2. ‘Pediatric oligodendroglioma’
ASTROCYTOMAS

- **Diffuse**
  - Fibrillary
  - Gemistocytic
  - Giant Cell
  - Small Cell
  - Granular Cell
  - Others

- **Circumscribed / Favorable**
  - Pilocytic
  - PXA
  - SEGA
  - DIA
DIFFUSE ASTROCYTOMAS
DIFFUSE ASTROCYTOMA GRADING

Atypia

Mitoses

Endothelial Proliferation (MVP, EH)

Necrosis

WHO II=A; III=A+M; IV=A+M+(E or N)
ASTROCYTOMA (WHO GRADE II)
ANAPLASTIC ASTROCYTOMA, WHO III
GEMISTOCYTIC ASTROCYTOMAS
GLIOBLASTOMA (GBM), WHO GRADE IV

- WHO dropped “multiforme” in 2000
- Rapid onset and progression
- Rim (or ring)-enhancing, but can be less clear in kids
- Survival ~1-year, but highly variable
- More often brainstem and thalamus in kids, but also cerebral hemispheres
GBM, WHO IV
BRAINSTEM GLIOMA
‘BRAINSTEM GLIOMA’

• Diffuse intrinsic pontine glioma (DIPG): malignant

• Dorsal, exophytic cervicomedullary astrocytoma (pilocytic)

• Focal tectal glioma (pilocytic)

• NF1-associated (pilocytic)
PDGFRA Amplification is Common in Pediatric and Adult High-Grade Astrocytomas and Identifies a Poor Prognostic Group in IDH1 Mutant Glioblastoma

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Keywords
astrocytoma, FISH, IDH1, isocitrate dehydrogenase 1, PDGFRA, prognosis.

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Abstract
High-grade astrocytomas (HGAs), corresponding to World Health Organization grades III (anaplastic astrocytoma) and IV (glioblastoma; GBM), are biologically aggressive, and their molecular classification is increasingly relevant to clinical management. PDGFRA amplification is common in HGAs, although its prognostic significance remains unclear. Using fluorescence in situ hybridization (FISH), the most sensitive technique for detecting PDGFRA copy number gains, we determined PDGFRA amplification status in 123 pediatric and adult HGAs and found a significant association with worse overall survival. These findings may explain in part the adverse prognosis in the IDH1-mutant glioblastoma subset.
IDH1R132H mutant GBM maybe further subdivided based upon PDGFRA amplification

Log-rank test, p<0.05
Recurrent somatic mutations in ACVR1 in pediatric midline high-grade astrocytoma
GBM VARIANTS / PATTERNS

- Fibrillary (Classic)
- Gemistocytic
- Giant Cell
- Gliosarcoma
- Adenoid / Epithelioid / Metaplastic
- Lipidized
- Inflammation-rich

- Granular Cell
- Small Cell
- GBM with an oligodendroglial component
- GBM with PNET-like foci
- Rhabdoid / Epithelioid
GIANT CELL GBM
GIANT CELL GBM

19p13
19q14
GIANT CELL GBM/GS

- ~1-5% of GBMs and gliosarcomas
- Clinical DDx: Meningioma, pleomorphic sarcoma, or metastasis
- Pathology DDx: PXA (EGBs; BRAF V600E)
- Less infiltrative
- Clinically a primary GBM, but younger patients, TP53 mutations common and EGFR-AMP rare; Mostly IDH1-R132H-neg
- Small subset with better prognosis
- May be overrepresented in Turcot disease
RESEARCH ARTICLE

Malignant Gliomas with Primitive Neuroectodermal Tumor-like Components: A Clinicopathologic and Genetic Study of 53 Cases

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Keywords
- genetics, glioblastoma, gliosarcoma, metastases, MYC, neuroblastoma, oligodendroglioma, primitive neuroectodermal tumor, prognosis, small cell, stem cell.

Abstract

Central nervous system neoplasms with combined features of malignant glioma and primitive neuroectodermal tumor (MG-PNET) are rare, poorly characterized, and pose diagnostic as well as treatment dilemmas. We studied 53 MG-PNETs in patients from 12 to 80 years of age (median = 54 years). The PNET-like component consisted of sharply demarcated hypercellular nodules with evidence of neuronal differentiation. Anaplasia, as seen in medulloblastomas, was noted in 70%. Within the primitive element, N-myc or c-myc gene amplification could be detected in 75% and 15%, respectively.
GBM with PNET-like Features

PTEN
DMBT1
GBM with PNET-like Features

CEP2
N-myc
Table 3. Clinical features in 53 MG-PNETs. Abbreviation: FU = follow-up; MG-PNET = malignant glioma-primitive neuroectodermal tumor.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>12–80 years (median = 54 years)</td>
</tr>
<tr>
<td>Sex</td>
<td>30 male : 23 female (ratio = 1.3)</td>
</tr>
<tr>
<td>Survival Time (FU in 39; 27 dead)</td>
<td>&lt;1 month–3.3 years (median = 9.1 months)</td>
</tr>
<tr>
<td>Length of Symptoms (n = 29)</td>
<td>10 days–10 years (median = 3 months)</td>
</tr>
<tr>
<td>Gross Total Resection</td>
<td>12 of 19 (63%)</td>
</tr>
<tr>
<td>Adjuvant Radiation</td>
<td>18 of 23 (78%)</td>
</tr>
<tr>
<td>Adjuvant ChemoRx (n = 16)</td>
<td>Temozolomide (63%), Platinum-based (31%)</td>
</tr>
<tr>
<td>Prior Glioma Dx (n = 13; 25%)</td>
<td>8 months–10 years prior (median = 4 years)</td>
</tr>
<tr>
<td>Astrocytoma, World Health Organization grade II (n = 2)</td>
<td>eight of 20 cases (40%): eight CSF, one bone marrow</td>
</tr>
<tr>
<td>Oligoastrocytoma, World Health Organization grade II (n = 4)</td>
<td></td>
</tr>
<tr>
<td>“Low-grade glioma” (n = 1)</td>
<td></td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma, World Health Organization grade III (n = 1)</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma with oligo features, World Health Organization grade IV (n = 2)</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma, World Health Organization grade IV (n = 3)</td>
<td></td>
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</tbody>
</table>
GBM/GS WITH A PNET COMPONENT

• <1% of diffuse gliomas
• DDx: CNS PNET, lymphoma, metastatic small cell carcinoma
• Behaves locally like a GBM, but many develop CSF dissemination
• Can be either a primary or secondary GBM: PTEN-del in most cases, MYCN-AMP or MYCC-AMP in PNET-like area in >40%; IDH1-R132H in 16%
• Misdiagnosed CNS PNETs in kids?
Epithelioid Versus Rhabdoid Glioblastomas Are Distinguished by Monosomy 22 and Immunohistochemical Expression of INI-1 but not Claudin 6

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Epithelioid GBMs Show a High Percentage of BRAF V600E Mutation

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Clinicopathological characteristics and treatment of rhabdoid glioblastoma

Clinical article

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RHABDOID/EPITHELIOID GBM

• Younger patients
• Superficial and circumscribed
• -22 in more rhabdoid cases?
• Focal INI1 loss?
• IDH1-neg
• BRAF V600E in more epithelioid cases
• Subset with better survival
### Epigenetic and Biological Subgroups of Glioblastoma

<table>
<thead>
<tr>
<th>Mutations / Cytogenetics</th>
<th>DNA Methylation</th>
<th>Gene Expression</th>
<th>IHC Protein Marker</th>
<th>Age Distribution (years)</th>
<th>Tumor Location</th>
<th>Patient Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH</td>
<td>H3F3A&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>TP53&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>CIMP*</td>
<td>0-30</td>
<td>50-90</td>
<td>0-120</td>
</tr>
<tr>
<td>K27</td>
<td>H3F3A&lt;sup&gt;mut&lt;/sup&gt;K27</td>
<td>TP53&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>Proneural</td>
<td>0-30</td>
<td>50-90</td>
<td>0-120</td>
</tr>
<tr>
<td>G34</td>
<td>H3F3A&lt;sup&gt;mut&lt;/sup&gt;G34</td>
<td>TP53&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>Mixed</td>
<td>0-30</td>
<td>50-90</td>
<td>0-120</td>
</tr>
<tr>
<td>RTK I</td>
<td>PDGFRA ampl.</td>
<td>CDKN2A del.</td>
<td>Proneural</td>
<td>0-30</td>
<td>50-90</td>
<td>0-120</td>
</tr>
<tr>
<td>MESENCHYMAL</td>
<td>CNV&lt;sup&gt;&gt;&lt;sup&gt;&gt;&lt;&lt;/sup&gt;&lt;/sup&gt;</td>
<td>CNV&lt;sup&gt;&gt;&lt;&lt;/sup&gt;</td>
<td>Mesenchymal</td>
<td>0-30</td>
<td>50-90</td>
<td>0-120</td>
</tr>
<tr>
<td>RTK II</td>
<td>EGFR ampl.</td>
<td>CDKN2A del.</td>
<td>Classical</td>
<td>0-30</td>
<td>50-90</td>
<td>0-120</td>
</tr>
</tbody>
</table>
OLIGODENDROGLIOMA

- Rare in kids (2-3% of gliomas)
- Oligo mimics more common: DNT, pilocytic astrocytoma, central neurocytoma, clear cell ependymoma
- Series with long followup rare since often transfer care as adults
- Same biology as adults?
- Genetics appear to be different
OLIGODENDROGLIOMA, WHO GRADE II
ADULT TYPE OLIGODENDROGLIOMA

IDH1-R132H
ADULT TYPE OLIGODENDROGLIOMA
Pediatric Oligodendrogliomas: A Study of Molecular Alterations on 1p and 19q Using Fluorescence In Situ Hybridization

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Abstract. Oligodendrogliomas (OGs) are rare in children and have not been well characterized from a molecular viewpoint. In adults, losses on chromosomes 1p and/or 19q are common in “oligodendrogial” neoplasms and are highly associated with chemosensitivity and greater length of survival, especially in the anaplastic category. We have analyzed the 1p/19q status of pediatric OGs and compared it with similar alterations in adult OGs. Paraffin sections from 26 pediatric OGs (21 WHO Grade II OGs; 2 anaplastic oligodendrogliomas [AOGs]; and 3 mixed oligo-astrocytomas [MOA]) were retrieved. Fluorescence in situ hybridization (FISH) was performed using probes spanning the 1p32 and 19q13 regions. In tumors from children 0 to 9 years of age (n = 15), none had any deletions on 1p or 19q, but 2 had polysomies for 1p and/or 19q. All are alive and 4 have had recurrences. In tumors from children >9 years, losses were identified on chromosomes 1p (5/11; 45%) and/or 19q (3/11; 27%), but to a much lesser extent than that observed in adult OGs. Tumors from 6 older patients also had polysomies for 1p and/or 19q. Although the majority of the older children are alive, 4 had recurrences. Curiously, 2 of the older children with AOGs had combined losses and polysomies on 1p and 19q, but responded poorly to treatment and died within a year. We conclude that alterations on 1p or 19q are infrequent in pediatric compared to adult OGs and are virtually absent in OGs presenting in the first decade of life. Compared to adults therefore, different genetic pathways are likely involved in the pathogenesis of most pediatric OGs. Genomic screening on a larger series is clearly indicated to delineate the unique molecular characteristics of these rare pediatric tumors.

Key Words: Chromosome 1p; Chromosome 19q; Fluorescence in situ hybridization (FISH); Molecular genetics; Pediatric oligodendroglioma.
### TABLE 2

Deletions in Predominantly Adult Oligodendroglial Tumors from Studies Using FISH as an Analysis Tool: Comparison with Data from Pediatric OGs

<table>
<thead>
<tr>
<th></th>
<th>1p Del</th>
<th>19q Del</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Burger et al (23)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>8 (100%)</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td><strong>Smith et al (6)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>24 (72%)</td>
<td>24 (72%)</td>
</tr>
<tr>
<td>Absent</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td><strong>Perry et al (21)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>74 (74%)</td>
<td>76 (76%)</td>
</tr>
<tr>
<td>Absent</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>101</td>
<td>101</td>
</tr>
<tr>
<td><strong>Raghavan et al (current study)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>5 (20%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Absent</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>25</td>
</tr>
</tbody>
</table>
Adult (some teenagers) Diffuse Glioma

Histologic diagnosis

Oligodendroglioma phenotype
Astrocytoma phenotype
Glioblastoma phenotype
Diffuse glioma, indeterminate, “mixed” or ambiguous phenotype

Grade II, III, IV, ungraded
IDH, ATRX, 1p/19q

1) Histology and molecular concordant: Diagnosis, grade, molecular findings
2) Indeterminate or mixed histology: Diagnose and grade based on molecular profile
3) Histology and molecular discordant: Diffuse glioma, histologic phenotype, molecular profile
4) Molecular testing not performed: Histologic diagnosis, NOS

Integrated Diagnosis

Molecular information

IDH, ATRX, 1p/19q
Grade II, III, IV, ungraded
ADULT TYPE ASTROCYTOMA

IDH1

p53

ATRX
Adult Type Oligodendroglioma

Integrated diagnosis:

**Oligodendroglioma, WHO grade II, IDH-mut, 1p/19q codeleted**

Histological classification:

**Diffuse glioma, oligodendroglioma phenotype**

WHO grade:

**Grade II**

Molecular information:

**IDH-mut, 1p/19q codel, ATRX intact**
<table>
<thead>
<tr>
<th>Molecular Information</th>
<th>Diffuse astrocytoma</th>
<th>Oligodendroglioma</th>
<th>“Oligoastrocytoma” or ambiguous histology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDH-mut, 1p/19q-nondel, ATRX loss</strong></td>
<td>Diffuse astrocytoma, ATRX loss of expression</td>
<td>Diffuse glioma (oligodendroglioma phenotype), 1p/19q non-deleted, ATRX loss of expression</td>
<td>Diffuse astrocytoma, ATRX loss of expression</td>
</tr>
<tr>
<td><strong>IDH-mut, 1p/19q-codel, ATRX intact</strong></td>
<td>Diffuse glioma (astrocytoma phenotype), 1p/19q-codeleted</td>
<td>Oligodendroglioma, 1p/19q-codelleted</td>
<td>Oligodendroglioma, 1p/19q-codelleted</td>
</tr>
<tr>
<td><strong>IDH wild type</strong></td>
<td>Diffuse astrocytoma, IDH wild type*</td>
<td>Diffuse glioma (oligodendroglioma phenotype), IDH wild type</td>
<td>Diffuse astrocytoma, IDH wild type*</td>
</tr>
<tr>
<td><strong>Testing not performed</strong></td>
<td>Diffuse astrocytoma, NOS</td>
<td>Oligodendroglioma, NOS</td>
<td>“Diffuse glioma, NOS”</td>
</tr>
</tbody>
</table>
Pediatric AA/GBM

Primary GBM

Primary GBM

Diffuse astrocytoma

Anaplastic astrocytoma, GBM

Neural Progenitor Cell

IDH1-mutated infiltrating adult gliomas

Pediatric AA/GBM

Pilocytic astrocytoma (PXA)

Anaplastic astrocytoma, GBM

Anaplastic oligodendroglioma

Oligodendroglioma

TP53, ATRX

RB1, CDK4, CDKN2A, MDM2, PTEN

1p/19q
CIC, FUBP1
TERT promoter

BRAF

H3F3A, DAXX
TP53, ATRX

IDH1,2

EGFR, PDGFRA
PTEN, TP53
CDKN2A/B, NF1
TERT promoter

Courtesy of Dr. Dan Brat
PILOCYTIC ASTROCYTOMA

- Child / young adult
- Cerebellum, hypothalamus/3rd v., optic pathway, spinal cord
- NF1-associated OPG
- Insidious onset / slow growth
- Surgically “curable” (WHO I)
- 20-year survival = 80%
PILOCYTIC ASTROCYTOMA
PILOCYTIC ASTROCYTOMA
OPG-JPA
Recurrent somatic alterations of *FGFR1* and *NTRK2* in pilocytic astrocytoma

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LOWER-GRADE GLIOMA GENETICS

• **BRAF-KIAA1549 duplication/fusion**
  - pilocytic astrocytomas (~70% in cerebellum; less in other locations)
  - PMA (1/3rd to ½)
  - MEK inhibitors?

• **BRAF V600E mutation:**
  - PXA (~67%), GG (20-50%), DNET (20-30%), PA (~10%), GBM (5-10%)
  - BRAF inhibitors, especially in recurrent or disseminated cases?
VIRTUALLY ‘ALL’ PEDIATRIC BRAIN TUMORS

Did you order BRAF testing?

On this???
Really??

Pediatric Neuro-Oncologist

Pediatric Pathologist/Neuropathologist
OBJECTIVE: Pilocytic astrocytoma (PA) is a common type of pediatric brain tumor that can arise within the hypothalamic/chiasmatic region and typically has an excellent outcome. We identified a group of tumors, previously classified as PAs, with unique histological features and aggressive behavior. This article describes the clinicopathological features of these unusual neoplasms, which are currently known as pilomyxoid astrocytomas (PMAs), to better differentiate them from typical PAs.

METHODS: Medical information and surgical specimens were obtained for 42 PA cases and 21 PMA cases. Patient demographic features, treatment modalities, progression-free survival (PFS) times, overall survival (OS) times, and outcomes were compared between the groups with nonparametric tests.

RESULTS: The PMA group included 12 male and 9 female patients. The PA group included 27 male and 15 female patients. The mean ages at diagnosis for the PMA and PA groups were 18 months (range, 2–84 mo) and 58 months (range, 4–189 mo), respectively (P < 0.01). The mean PFS times for the PMA and PA groups were 26 and 147 months, respectively (P < 0.001). The mean OS times for the PMA and PA groups were 63 and 213 months, respectively (P < 0.001). Sixteen patients with PMAs (76%) experienced local recurrence, and three of those patients demonstrated evidence of cerebrospinal fluid dissemination. Twenty-one patients with PAs (50%) experienced local recurrence, none with evidence of cerebrospinal fluid dissemination. Within the follow-up period, seven patients with PMAs (33%) and seven patients with PAs (17%) died as a result of their disease. In an age-matched set, the mean PFS times for the PMA and PA groups were 25 and 163 months, respectively (P < 0.01), and the mean OS times for the PMA and PA groups were 60 and 233 months, respectively (P < 0.001).

CONCLUSION: Hypothalamic/chiasmatic PMAs occurred in a significantly younger population and were associated with substantially shorter PFS and OS times than were typical PAs. Increased recognition of these lesions could affect the prognosis and treatment of pediatric astrocytomas.

KEY WORDS: Astrocytoma, Hypothalamic, Optic chiasm, Pilocytic, Pilomyxoid
PILOMYXOID ASTROCYTOMA, WHO II
FIGURE 3. Kaplan-Meier curve comparing the PFS times for patients with PMAs and PAs in age-matched groups. The PFS times (mean ± SE) for the PMA and PA groups were 25 ± 6 and 163 ± 31 months, respectively (P < 0.01).

FIGURE 4. Kaplan-Meier curve comparing the OS times for patients with PMAs and PAs in age-matched groups. The OS times (mean ± SE) for the PMA and PA groups were 60 ± 10 and 233 ± 26 months, respectively (P < 0.001).
Spectrum of Pilomyxoid Astrocytomas
Intermediate Pilomyxoid Tumors

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Abstract: To define the spectrum of pilomyxoid morphology and to characterize the association between pilomyxoid astrocytoma (PMA) and pilocytic astrocytoma (PA), 84 cases of pediatric astrocytomas with pilomyxoid features were reviewed. Forty-two of these tumors had coexistent features of PMA and PA ("intermediate"). With the accumulation of more cytoplasm, fibrillar background, microcyst, and thickened blood vessels, these intermediate tumors were more PA-like and less like classic PMA. In the recurrent specimens, PMAs and intermediate tumors sometimes showed more prominent PA features. Both PMA and intermediate tumors involved sites outside the hypothalamus, optic chiasm, and the third ventricle. Both the existence of intermediate tumors and the finding that some PMAs and intermediate tumors mature into PA-like neoplasms over time, provided strong support for a biological relationship between PMA and PA. Additional evidence for a "maturational effect" was the finding that intermediate tumors occurred in patients with a median age of 36 months compared with the median age of 21 months for those with PMAs (P = 0.017). Features that were often assumed to be poor prognostic indicators in gliomas, that is, necrosis, mitotic figures, and vascular proliferation, were not uncommon in typical PMAs and intermediate lesions. Further follow-up is needed to more accurately determine the prognosis of intermediate tumors.

Key Words: pilomyxoid, pilocytic, tumor, astrocytoma, pediatric, suprasellar, brain

The lesion now known as pilomyxoid astrocytoma (PMA), was initially described as a pilocytic astrocytoma (PA) of infancy in 1996.4 Cytologic monomorphism, "cobweb" architecture, and abundant myxoid background were features that distinguished it from classic PA. Rosenthal fibers and eosinophilic granular bodies were scant or absent. The sites involved were, in general, those of PAs. An earlier publication had discussed diencephalic PMAs in infants, and, although it made no distinction between them and classic PAs, some may well have been PMAs.6

The issue was revisited in a 1999 study of 18 pediatric astrocytomas that had distinctive clinical and histologic characteristics.13 Although not discounting the possibility that these were variants of PA, the term "pilomyxoid astrocytoma" was coined. The rates of recurrence and cerebrospinal fluid dissemination were higher in these tumors compared with classic PA in the same age group and location. Subsequent experience has confirmed an overall, more aggressive biological behavior for this tumor category, but individual PMAs may not behave any differently than classic PAs, and PMAs can occasionally occur in elderly individuals and adults.5,9,10,11 The 2007 World Health Organization classification considers PMA as a grade 2 variant of PA.1,12

According to the 2007 World Health Organization classification, PA is defined as "a relatively circumscribed, slowly growing, often cystic astrocytoma occurring in children and young adults, histologically characterized by a biphasic pattern with varying proportions of compacted..."
QUESTIONS?