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Pilomyxoid Astrocytoma: Expanding the Imaging Spectrum

BACKGROUND AND PURPOSE: Pilomyxoid astrocytoma (PMA) is a recently described variant of pilocytic astrocytoma (PA) with unique clinical and histopathologic characteristics. Because the histopathology of PMA is distinct from that of PA, we hypothesized that PMAs would display distinctive imaging characteristics. We retrospectively reviewed the imaging findings in a large number of patients with PMA to identify these characteristics.

MATERIALS AND METHODS: CT and MR images, pathology reports, and clinical information from 21 patients with pathology-confirmed PMA from 7 institutions were retrospectively reviewed. CT and MR imaging findings, including location, size, signal intensity, hemorrhage, and enhancement pattern, were tabulated.

RESULTS: Patients ranged in age from 9 months to 46 years at initial diagnosis. Sex ratio was 12:9 (M/F). Twelve of 21 (57%) tumors were located in the hypothalamic/chiasmatic/third ventricular region. Nine (43%) occurred in other locations, including the parietal lobe (2/21), temporal lobe (2/21), cerebellum (2/21), basal ganglia (2/21), and fourth ventricle (1/21). Ten (48%) tumors showed heterogeneous rim enhancement, 9 (43%) showed uniform enhancement, and 2 (9%) showed no enhancement. Five (24%) masses demonstrated intratumoral hemorrhage.

CONCLUSION: This series expands the clinical and imaging spectrum of PMA and identifies characteristics that should suggest consideration of this uncommon diagnosis. One third of patients were older children and adults. Almost half of all tumors were located outside the typical hypothalamic/chiasmatic region. Intratumoral hemorrhage occurred in one quarter of patients. PMA remains a histologic diagnosis without definitive imaging findings that distinguish it from PA.

Pilomyxoid astrocytoma (PMA) is a rare primary central nervous system (CNS) tumor recently described as a histologic variant of pilocytic astrocytoma (PA).^{1,2} PMA differs from PA both clinically and histopathologically. PMA typically occurs at an earlier age and is associated with a significantly worse prognosis.³ Identifying an astrocytoma as PMA is important for patient management because its more malignant biologic behavior and shorter recurrence-free survival may justify more aggressive treatment.⁴

To date, there are only 3 small case series of PMA in the imaging literature.⁵⁻⁷ Unique imaging characteristics that distinguish PMA from PA have not yet been identified. Because the histopathology of PMA is quite distinct from that of PA, we hypothesized that PMAs would display imaging characteristics that might suggest the correct preoperative diagnosis. We retrospectively reviewed the imaging findings in 21 patients with pathologically proved PMA to identify any unique imaging characteristics. This article expands the clinical manifesta-

tions and imaging spectrum of these rare tumors. We report some features that—when present—may suggest PMA.

Materials and Methods

A retrospective review of images, pathology reports, and clinical information of 21 patients with pathology-confirmed PMA was collected from 7 different institutions. Five cases were previously published as case reports.⁷⁻⁹ Contributors searched their respective institutional teaching files, PACS archives, and pathology department data base archives. Pathology reports were available in all cases and documented the diagnosis of PMA. Original specimens were available in 5 cases and were reviewed by our neuropathologist. Patient demographics and clinical presentation were recorded. Age and sex were available in all cases. At least 1 presenting symptom was noted in all patients.

Noncontrast-Enhanced CT (NCCT) scans were obtained in 12/21 patients. Three patients had contrast-enhanced CT (CECT) studies. Tumor location, size (maximal diameter), hemorrhage, calcification, and attenuation characteristics, and contrast enhancement on CT were tabulated.

MR imaging was performed in all patients. Signal intensity relative to gray matter on multiple MR images, surrounding edema, presence or absence of diffusion restriction, MR spectroscopy signature, and presence and pattern of enhancement following contrast administration were noted. Standard precontrast T1-weighted spin-echo sequences (TR/TE = 400–700/8–20 ms) were available for review in 17/21 patients; T2-weighted fast spin-echo sequences, in 20/21 patients (TR/TE = 3000–7000/100–120 ms); and fluid-attenuated inversion recovery (FLAIR) fast spin-echo scans, in 15/21 (TR/TE = 8000–9000/110–150 ms). T2* (gradient recalled-echo [GRE]) sequences were performed in 2/21 cases (TR/TE = 500/26 ms; flip angle, 20°). Contrast-enhanced T1-weighted spin-echo sequences were performed in all patients. Echo-planar diffusion-weighted imaging

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Clinical, pathologic, and imaging characteristics of PMA and PA*		
	PMA	PA
Pathology	Monomorphous piloid cells with myxoid background angiocentric pattern Rosenthal fibers, eosinophilic granular bodies, and microcalcifications rare ^{1,2}	Heterogeneous/mixed piloid and protoplasmic cells Rosenthal fibers, eosinophilic granular bodies, and microcalcifications common ^{1,2}
Clinical	Infants, children, and adults ³ More aggressive Less progression-free and overall survival More recurrences ³ Most common location: hypothalamus/optic chiasm ¹⁷ May be associated with NF-1 ^{9,10}	Young children and, less commonly, adults ³ Less aggressive Greater progression-free and overall survival Fewer recurrences ³ Most common location: posterior fossa ¹⁷ May be associated with NF-1 ¹⁰
Imaging	Hypointense T1 Hyperintense T2/FLAIR ⁵ Variable contrast enhancement ⁵ Solid with central necrosis ⁵ Calcification (<10%) ⁵ Intratumoral hemorrhage common (12%–25%) ^{8,16,32,33}	Hypointense T1 Hyperintense T2/FLAIR ⁵ Variable contrast enhancement ⁵ Often cystic ⁵ Calcification (10%) ⁵ Intratumoral hemorrhage less common (~8%) ²⁹

* Although PMA is most commonly found in the hypothalamic/chiasmatic region, because of its rarity, an undiagnosed hypothalamic/chiasmatic tumor is most likely to be the more common PA.

(DWI) was performed in 11/21, and MR spectroscopy (TE = 135 and 30 ms), in 4/21 patients.

Results

Patient demographics, clinical presentation, and imaging findings in all 21 patients are summarized in on-line Table 1. Patient age ranged from 9 months to 46 years, with a mean of 7 years (median 5 years) at time of initial diagnosis. There were 12 males and 9 females. Presenting symptoms in order of frequency included headache, vomiting, visual changes, seizure, failure to thrive, and hemiplegia. Two patients had neurofibromatosis type 1 (NF-1).

Four patients with original pathology specimens initially diagnosed as PMA were confirmed by second-opinion review of our neuropathologist. A fifth patient (case 20) was originally diagnosed with PA in 1997, before the identification of PMA as a distinct tumor entity. Because imaging findings were so atypical for PA, the teaching file case had been noted as inconsistent with the pathologic diagnosis. The original slides were re-reviewed by our neuropathologist and found to be consistent with PMA.

Twelve of 21 (57%) tumors were located in the optic pathway/hypothalamus/third ventricle region, including those of both patients with NF-1. Nine (43%) occurred in atypical locations, including the parietal lobe (2/21), temporal lobe (2/21), cerebellum (2/21), basal ganglia (2/21), and fourth ventricle (1/21). Median tumor maximal diameter was 4 cm (range, 2–11 cm). One patient had a large bitemporal tumor (Fig 1).

NCCT scans showed uniform hypoattenuation in 7 of 12 patients. Hemorrhage was identified in 5 patients. Four tumors contained mixed hyperattenuations suggestive of intratumoral hemorrhage, and an additional 1 displayed gross fluid-fluid levels. Only 1 case demonstrated calcification, with a partial rim and central punctuate pattern. Contrast was administered to 3 patients. All 3 tumors showed rim enhancement.

MR signal intensity varied widely. Seventeen patients had T1-weighted scans available for review. Relative to gray matter, tu-

mors were uniformly hypointense in 12/17 patients (71%). Two of 17 (12%) showed uniform isointensity, 1/17 (6%) demonstrated mixed hypointensity-hyperintensity, 1/17 (6%) showed hypointensity-isointensity, and 1/17 (6%) showed intratumoral fluid-fluid levels suggesting hemorrhage.

T2 sequences were available for review in all except 1 patient. Fourteen of 20 (70%) showed uniform hyperintensity; 2 of 15 showed mixed iso- and hyperintense signal intensity. Three of 20 (15%) showed small areas of adjacent edema surrounding the tumor. None demonstrated extensive edema. Four patients had intratumoral hemorrhages, ranging from 1 to 3 cm in maximal diameter. One patient (case 20) also had subarachnoid hemorrhage adjacent to the tumor. All hemorrhages were hypointense on T2-weighted images (T2WI); 1 demonstrated fluid-fluid level (case 11). T2* (GRE) sequences were performed in 2 patients with hemorrhage. Both showed heterogeneous hyperintensity within the tumor and uniform hypointensity in the areas of hemorrhage.

FLAIR sequences were performed in 15 patients. Seven of 15 (47%) showed uniform hyperintensity, 5/15 (33%) showed heterogeneous hyperintensity, 2/15 (13%) showed an isointense center with a rim of hyperintensity, and 1/15 (7%) showed fluid-fluid levels. Three of 15 (20%) showed small areas of adjacent edema.

Contrast-enhanced T1 sequences were available for review in all patients and showed the following patterns: 8 of 21 (38%) showed solid uniform enhancement, 6/21 (29%) showed heterogeneous enhancement with rim enhancement, 5/21 (24%) showed rim enhancement alone, and 2/21 (9%) patients showed no enhancement. MR angiography performed in 2/5 patients with intratumoral hemorrhage showed no evidence of abnormal vascularity. No patients in whom DWI was performed (11/21) showed evidence of diffusion restriction. Proton MR spectroscopy was performed in 6 patients. All spectra revealed elevated choline (Cho) and lipids, with decreased creatine (Cr) and *N*-acetylaspartate (NAA). Quantitative data were available in 2 patients (mean Cho/Cr = 2.94 ± 1.71 at TE = 135 ms and 6.24 ± 0.86 at 30 ms).

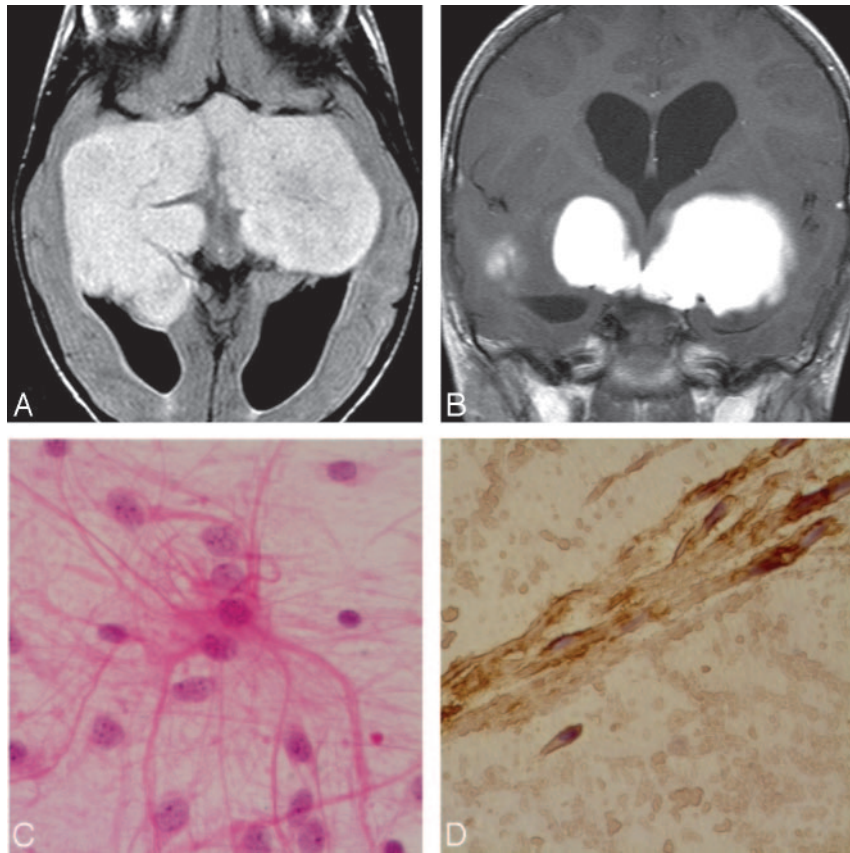


Fig 1. Case 9. *A*, Axial FLAIR sequence in a 3-year-old girl with progressive blindness shows a large solid lobulated suprasellar and bitemporal PMA, with uniform hyperintensity. *B*, Coronal contrast-enhanced T1-weighted image shows a homogeneously enhancing suprasellar and bitemporal PMA. *C*, Photomicrograph shows classic hairlike ("piloid") astrocytes in a myxoid background (hematoxylin-eosin, original magnification $\times 300$). *D*, Photomicrograph shows that the tumor is strongly positive for glial fibrillary acidic protein, confirming its astrocytic origin.

Discussion

The first reports of PMA described this lesion as a strictly pediatric tumor, occurring at a mean age of 18 months versus 58 months for PA.³ Early investigators thus suggested that PMA was a "juvenile" variant of PA.² However, review of all PMA cases subsequently reported in the literature reveals a larger age range (on-line Table 2). The mean age at presentation of patients in our series was 7 years (median, 5 years), with fully one third of tumors occurring in adolescents and young adults. The oldest patient in our series was 46 years old. Therefore, PMA is certainly not an exclusively pediatric tumor.

Before our series, the association of PMA with NF-1 had been reported 3 times.^{9,10} One of these previously reported cases, a 9-year-old girl, is included in our series. A second patient in our series, a 9-month-old girl, also has NF-1. These 4 cases of PMA in the setting of NF-1 suggest that PMA may be another NF-1-associated tumor.

PMA has a strong geographic predilection for the hypothalamic/chiasmatic region.^{2,11} The first case series reporting imaging findings in 4 patients with PMA described a solid hypothalamic tumor with homogeneous contrast enhancement and T2 hyperintensity extending into the adjacent deep white and gray matter.⁵ A large solid hypothalamic tumor in a very young patient (Fig 1) has been considered the classic pattern, with few tumors before 2004 being reported outside this region. Nearly half the PMAs in our series occurred in atypical locations (Figs 2 and 3), suggesting that this tumor may occur anywhere along the central neuraxis. This observation is sup-

ported by a number of recently reported cases found in atypical locations,^{2,3,8,11-13} including recent reports of 4 spinal PMA tumors (on-line Table 2).^{6,14}

Both our data and these most recent reports also suggest a relationship between atypical tumor location and age. Two of 3 hemispheric tumors recently reported were in adults,^{8,13} and 3 of the 4 spinal cord tumors occurred at 6, 8, and 29 years of age.^{6,14} In our series, 2 cortical tumors were found in 13- and 24-year-old patients. Cerebellar tumors ($n = 2$) and basal ganglia tumors ($n = 2$) were also found in patients older than 13 years. This finding confirms that atypical tumor locations are more common in older patients. Some investigators have commented on the recent increase in adult PMA diagnoses.^{15,16} One possible explanation is an increased awareness of the entity by pathologists and radiologists alike (eg, our case 20).

Size and morphology of PMA varies widely.¹⁷ The tumor size in our series was variable, with 5 tumors measuring ≥ 6 cm in maximal diameter.

The T1, T2, and FLAIR signal-intensity characteristics of our tumors are consistent with prior descriptions. However, enhancement patterns in our patients were highly variable. Only 8 (38%) tumors showed uniform enhancement. Eleven (52%) tumors displayed some rim enhancement (Fig 3), suggesting central necrosis or cystic degeneration, both of which have been described in some PMAs.⁵ Two tumors (9%) in our series showed no enhancement. Thus, we found a much broader spectrum of enhancement patterns.

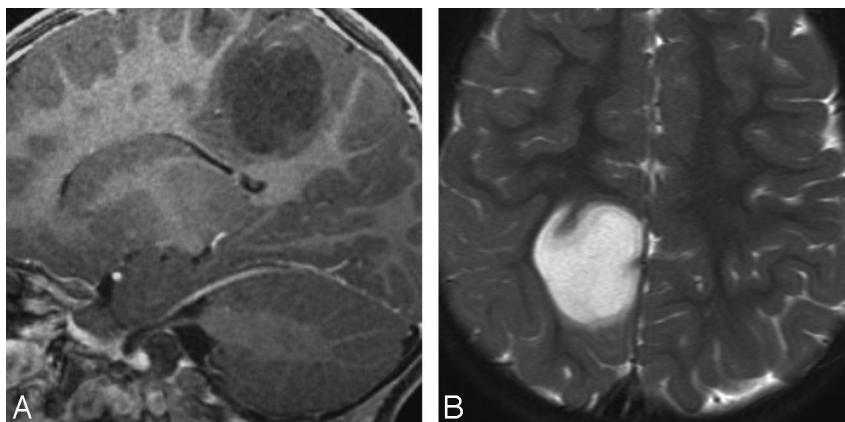


Fig 2. Case 6. *A*, Sagittal contrast-enhanced T1-weighted image in a 2-year-old boy with seizures shows a nonenhancing tumor in the posterior parietal cortex. *B*, Axial T2WI in the same patient shows homogeneous hyperintensity without surrounding edema. PMA was found at surgery.

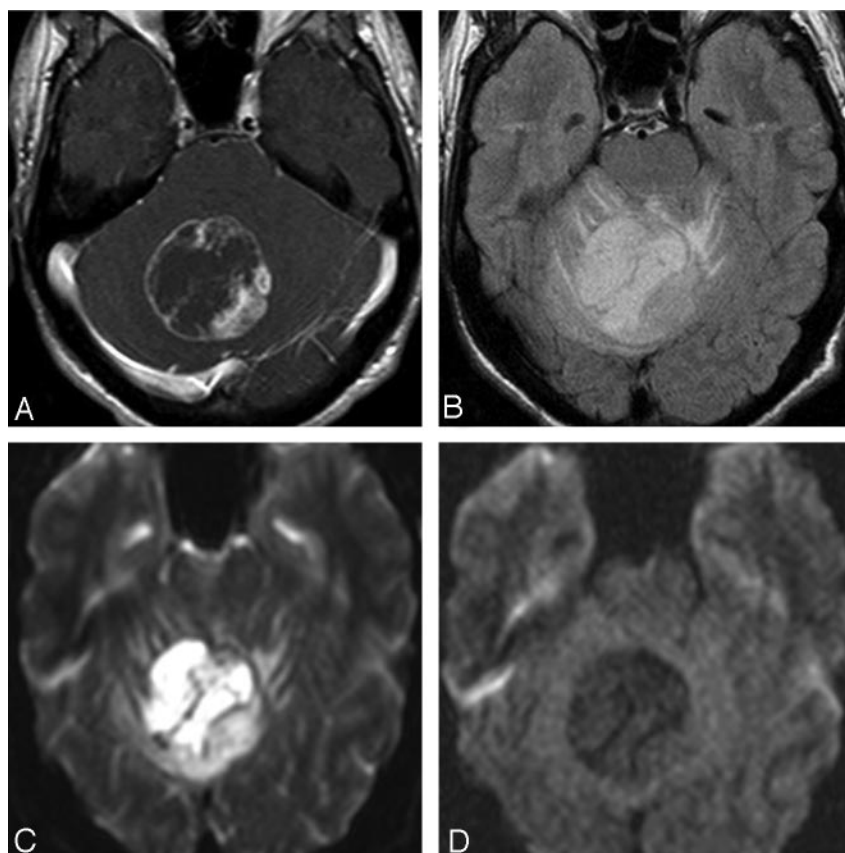


Fig 3. Case 13. *A*, Axial contrast-enhanced T1-weighted image in a 17-year-old boy with intractable headaches shows a rim-enhancing PMA of the cerebellar vermis. *B*, FLAIR image shows heterogeneous hyperintensity with extension into adjacent white matter of the cerebellar folia. *C* and *D*, DWI (*C*) and apparent diffusion coefficient map (*D*) show no restricted diffusion. This case demonstrates atypical age, location, and enhancement pattern.

Of particular interest are the 5 PMAs in our series that demonstrated spontaneous intratumoral hemorrhage. Nearly 25% of patients had evidence of hemorrhage (Fig 4). Our literature review of PMAs showed a 12% incidence of hemorrhage (on-line Table 2). In 1997, before the first description of PMA, 1 of our patients (case 20) was initially imaged for symptoms suggestive of subarachnoid hemorrhage (“worst headache of my life”). Emergency NCCT scanning at an outside hospital confirmed subarachnoid hemorrhage. An angiogram was obtained and was negative for aneurysm. When the patient was referred for further evaluation, MR imaging dis-

closed a hemorrhagic hypothalamic-optic chiasm tumor, which was subsequently diagnosed as a pilocytic astrocytoma. This tumor was re-examined in 2007 because of the unusual finding of hemorrhage on the initial MR image (Fig 5). On re-evaluation, it was found to have histologic features consistent with the diagnosis of PMA.

In contrast to PMA, hemorrhage is relatively rare in PAs, with mostly isolated case reports in the current literature.¹⁸⁻²⁸ Until recently the rate of hemorrhage in PA was estimated at <1%. However, a recent retrospective series of 134 patients with a tissue diagnosis of PA found an 8% spontaneous hem-

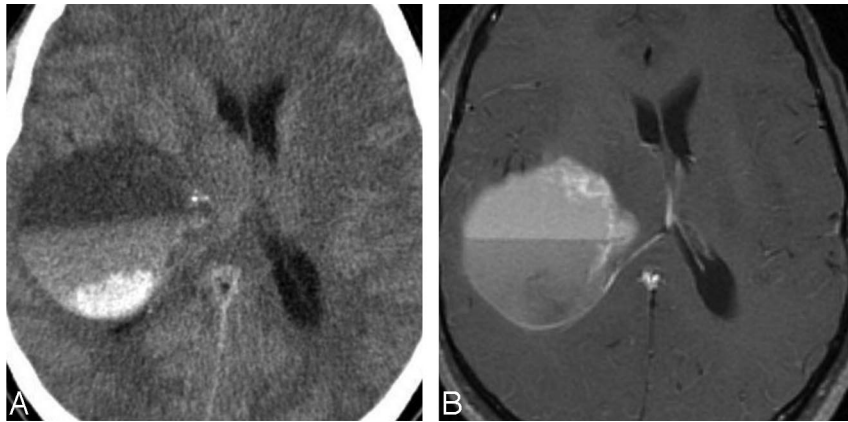


Fig 4. Case 11. *A*, Hemorrhage in PMA. Axial NCCT scan in a 24-year-old man with headache, confusion, and gait instability shows a right temporal lobe PMA with fluid-fluid levels and hyperattenuation consistent with hemorrhage. *B*, Axial contrast-enhanced T1-weighted image shows anteromedial rim enhancement and fluid-fluid levels.

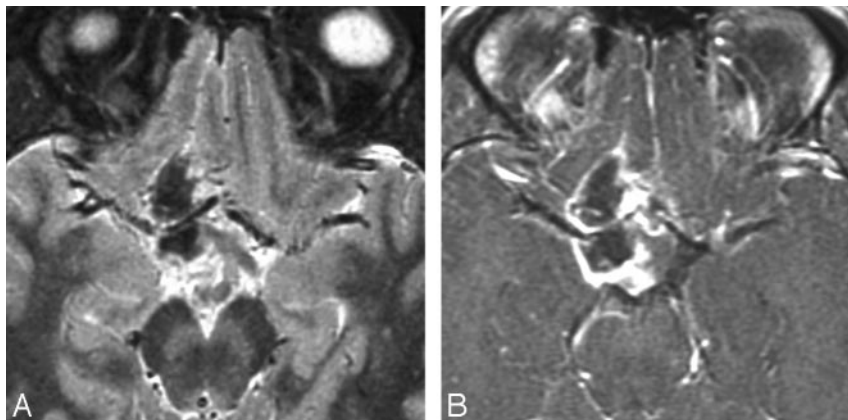


Fig 5. Case 20. *A*, Axial T2WI in a 21-year-old man with headache shows a heterogeneous supra- and juxtaseptal mass. The hypointense core suggests hemorrhage, which was confirmed at surgery. *B*, Axial contrast-enhanced T1-weighted image shows a rim-enhancing tumor surrounding a nonenhancing hemorrhagic core. Hemorrhagic exophytic hypothalamic/chiasmatic tumor was partially resected and originally diagnosed as PA in 1997. Re-examination of the specimen in 2007 showed features consistent with PMA.

orrhage rate, much higher than that previously reported.²⁹ Hemorrhagic PAs were found primarily in older patients, the average being 20 years of age (range, 5–58 years). Notably, none of the tumors with spontaneous hemorrhages occurred in the cerebellum, and only 1 was found in the hypothalamus, the typical locations for PA.²⁹ Could some of these tumors have been PMAs? The article is unclear, because some PAs included in this study had a tissue diagnosis established before the identification of PMA as a unique tumor entity. We hypothesize that at least some previously reported cases of PA in older patients with spontaneous intratumoral hemorrhage may indeed have been PMAs, which might be documented if re-evaluation of pathology specimens were possible, as occurred in our case 20. When present, intratumoral hemorrhage may be an important feature suggestive of PMA.

MR spectroscopy data in PMAs are similar to those described for PA. All 6 of our patients demonstrated elevated Cho and lipids and decreased Cr and NAA (Fig 6). These profiles are characteristic of aggressive tumors and are considered to be paradoxically elevated in low-grade astrocytomas (PA and PMA).^{7,30,31} Two recent articles evaluating MR spectroscopy in PMA also found that the Cho/Cr ratio was not appreciably different in PMA compared with PA. They did, however, find increased Cho/Cr in the peritumoral region, a

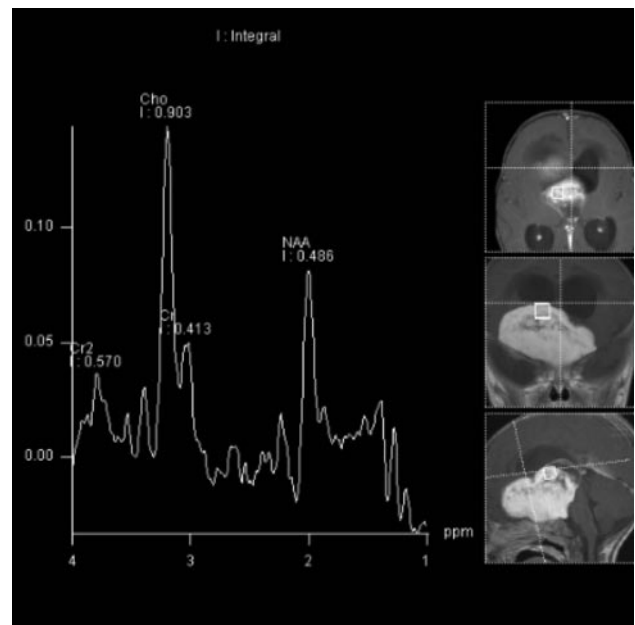


Fig 6. Case 7. MR spectroscopy (TE = 135 ms) in a 9-month-old boy with failure to thrive shows increased Cho and lipids with decreased Cr and NAA within the tumor. Multivoxel MR spectroscopy map showed Cho/Cr = 6.1.

finding consistent with the more infiltrative and aggressive nature of PMA.⁷

PA and PMA are difficult to distinguish on the basis of imaging findings alone (Table). Whereas PA is more commonly found in the posterior fossa,¹¹ its second most common intracranial location is the hypothalamus/optic chiasm, the most common location of PMA. The cerebral hemispheres are rare sites for PA, but 4 of our patients had hemispheric or cortical PMAs. The most prominent imaging characteristic that suggests PMA versus PA is the presence of intratumoral hemorrhage. Although hemorrhage can certainly occur in PAs, it is less common ($\leq 8\%$)²⁹ compared with PMA (nearly 25% in our series and 12% in previously reported cases).^{8,16,32,33}

When reported clinical outcomes of PA and PMA of the hypothalamic/chiasmatic region are compared, PMA is associated with shorter progression-free survival (26 versus 147 months), shorter overall survival (60 versus 233 months), and higher frequency of recurrence (76% versus 50%), often with prominent CSF dissemination.^{3,11} Hypothalamic/chiasmatic PAs are often treated conservatively without histologic confirmation.³⁴ We suggest that a neoplasm in this location, when it occurs either with intratumoral hemorrhage¹ or in patients outside the typical age for PA,² may be a PMA, not a PA. Some authors suggest a confirmed diagnosis of PMA versus PA might warrant more aggressive treatment.^{4,32}

Conclusion

We found a broader clinical and imaging spectrum of PMA than previously reported. One third of our patients were adolescents and young adults. Whereas PMA predominantly affects the hypothalamic/chiasmatic region, we demonstrate that it may be found anywhere along the central neuraxis, with nearly half of our patients having neoplasms outside this region. Intratumoral hemorrhage, if present, is a feature more frequently encountered in PMA. Although we suggest that an older patient with a hemorrhagic neoplasm in a location atypical for PA should be considered as having a possible PMA and thus warranting histologic confirmation for treatment planning, PMA remains a histologic diagnosis. There are no definitive pathognomonic imaging findings to distinguish it from PA.

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