

# Pilomyxoid astrocytoma: diagnosis, prognosis, and management

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Pilomyxoid astrocytoma (PMA) is a recently defined pediatric brain tumor; PMAs were previously classified within the pilocytic astrocytoma (PA) category. Nevertheless, PMA has different histological features and has been shown to behave more aggressively than PA. These findings indicate that PMA may be a unique entity that is distinct from PA, or it may be an unusual variant. To increase awareness of PMA within the neurosurgical community, the authors review the diagnostic criteria, prognostic implications, and current management of this recently described pediatric low-grade astrocytoma.

**KEY WORDS • pilocytic astrocytoma • pilomyxoid astrocytoma • diagnosis • management • prognosis • pediatric tumor**

Pilocytic astrocytomas are generally benign, typically showing 20-year survival rates of 70 to 80%, even when only a subtotal resection is achieved.<sup>30</sup> These highly treatable and potentially curable pediatric tumors are considered Grade I neoplasms according to the World Health Organization tumor classification system.<sup>3,22</sup> Prior to its recognition, PMA was grouped with PA, because the two display similar histological features. The PMA was first described by Tihan and colleagues<sup>27</sup> in 1999. Earlier reports pointed out unusual features of some pediatric astrocytomas, particularly those within the hypothalamic/chiasmatic region, but did not specifically use a term to distinguish them.<sup>7,11,17</sup>

Our group reported that PMA demonstrates a more variable clinical course and tends to behave more aggressively than PA, with a decreased duration of disease-free survival and higher mortality rates.<sup>27</sup> Their histological features distinguish PMAs from typical PAs.<sup>24,28</sup> In this paper we describe the clinicopathological characteristics of PMA, as well as its prognostic implications and management strategies. Increased awareness of this recently described neoplasm within the neurosurgical community is important for accurate diagnosis and treatment of low-grade astrocytomas in the pediatric population.

## DIAGNOSIS

### *Clinical Manifestations*

The original report on PMA consisted of tumors located exclusively in the hypothalamic/chiasmatic region. Subse-

*Abbreviations used in this paper:* GTR = gross-total resection; MR = magnetic resonance; PA = pilocytic astrocytoma; PMA = pilomyxoid astrocytoma.

quently, PMA was also described in the posterior fossa and in the spinal cord. Although the mean age at diagnosis for patients with PMA is 18 months, it may present throughout childhood.<sup>18,19,27</sup> This tumor typically causes focal neurological symptoms, such as visual disturbances and endocrine dysfunction. The clinical manifestations of PMA also parallel those of other pediatric brain tumors, and include failure to thrive, developmental delay, altered level of consciousness, vomiting, feeding difficulties, and generalized weakness.<sup>18</sup> If the tumor involves the posterior fossa, gait abnormalities, dysmetria, and nystagmus may be present, with tumor extension into the foramen magnum leading to neck stiffness or head tilt.

### *Radiographic Findings*

Radiographic findings for PMA appear similar to those for PA (Figs. 1 and 2); PMA tends to be well-circumscribed, demonstrates solid or cystic components, and has little to no calcification on computerized tomography scans. These lesions are commonly isointense on T<sub>1</sub>-weighted sequences, hyperintense on T<sub>2</sub>-weighted ones, and exhibit variable enhancement on MR images with addition of Gd. Furthermore, PMAs may exhibit peritumoral edema, mass effect, and necrosis.

No radiographic characteristics have yet been identified that reliably differentiate PMA from PA. Preliminary investigations with the use of proton MR spectroscopy in two cases of pediatric optic/chiasmatic PMA revealed decreased concentrations of total choline, creatine, and *N*-acetylaspartate.<sup>4</sup> In comparison, proton MR spectra of PAs revealed elevated choline and decreased creatine and *N*-acetylaspartate signals. Although larger studies are clearly

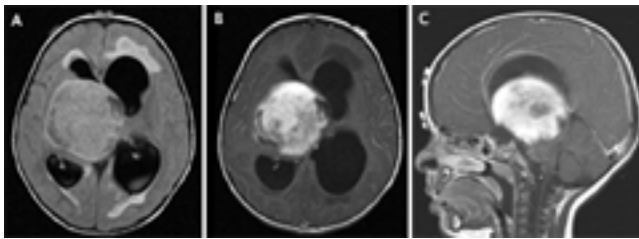


Fig. 1. Axial fluid-attenuated inversion-recovery (A), and axial (B) and sagittal (C) T<sub>1</sub>-weighted MR images with Gd contrast demonstrating a large hypothalamic/thalamic PMA. There is associated hydrocephalus with transependymal flow.

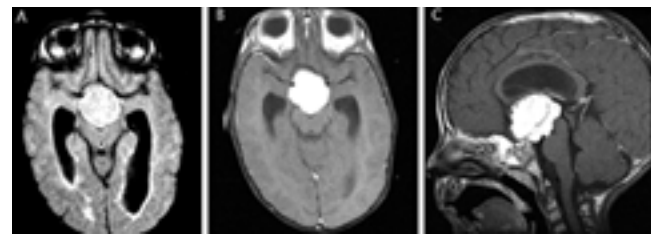


Fig. 2. Axial fluid-attenuated inversion-recovery (A), and axial (B) and sagittal (C) T<sub>1</sub>-weighted MR images of a PMA obtained with Gd contrast demonstrating a midline, suprasellar mass. Postcontrast images demonstrate homogeneous enhancement of this neoplasm. The mass fills the third ventricle, causing obstructive hydrocephalus.

needed, MR spectroscopy may prove to be useful in the future to help distinguish this tumor from PA.

*Histological Features*

The diagnosis of PMA is made predominantly on the basis of histological features (Fig. 3). Whereas classic PA is a compact neoplasm with biphasic architecture, PMA is composed of piloid and highly monomorphous cells. Even though myxoid change is commonly encountered in PAs, PMAs display a much more uniform and extensive myxoid background. A PMA often lacks Rosenthal fibers and only rare cases have eosinophilic granular bodies, both of which are characteristic of PA. In PMA, the neoplastic cells display an angiocentric pattern that remotely resembles the perivascular rosettes seen in ependyomas. The tumor cells can infiltrate into the surrounding neural parenchyma. In contrast with typical PA, mitoses can be readily seen in PMA and necrosis is not uncommon.

Recent anecdotal evidence has demonstrated that biopsy samples obtained in patients with PMA who underwent a repeated operation at a later date may resemble more typical PAs. These cases have initiated a discussion about the possibility of “maturation” of PMAs into typical PAs. Even

though there is very limited experience in this area, such cases underline the association between PMA and PA.

**PROGNOSIS**

Although limited clinical experience makes it difficult to generate conclusive prognostic data regarding this recently described pediatric tumor, PMA has been shown to behave more aggressively than PA.<sup>18</sup> A preliminary investigation addressed this topic by comparing the long-term clinical outcomes (mean follow-up duration 26 months) for 21 patients with hypothalamic PMAs with the outcomes in 42 patients with PAs in the same location. Patients with PMA had a higher rate of local recurrence than those with PA (76 and 50%, respectively), despite having undergone equal degrees of GTR. Notably, the PMA group had a substantial rate of dissemination (14%) in the cerebrospinal fluid, an event not recognized in the PA group. Patients with PMA also demonstrated significantly shorter progression-free (mean duration 26 and 147 months for those with PMA and PA, respectively; *p* < 0.001) and overall (mean duration 63 and 213 months, respectively; *p* < 0.001) survival times than those with PA (Fig. 4). Even when matched for age, patients with

Table 1.

**Typical Pilomyxoid and Pilocytic Histologic Features**

| Feature                      | Pilomyxoid  | Pilocytic  |
|------------------------------|-------------|------------|
| Architecture                 | Monophasic  | Biphasic   |
| Protoplasmic cells           | Rare        | Present    |
| Rosenthal fibers             | Absent      | Present    |
| Myxoid background            | Predominant | Infrequent |
| Calcification                | Uncommon    | Occasional |
| Eosinophilic granular bodies | Absent      | Present    |
| Angiocentric pattern         | Frequent    | Rare       |

Fig. 3. Diagnosis of PMA based on histological features. Table reprinted with permission from Komotar RJ, et al: Pilocytic and pilomyxoid hypothalamic/chiasmatic astrocytomas. *Neurosurgery* 54:72–80, 2004

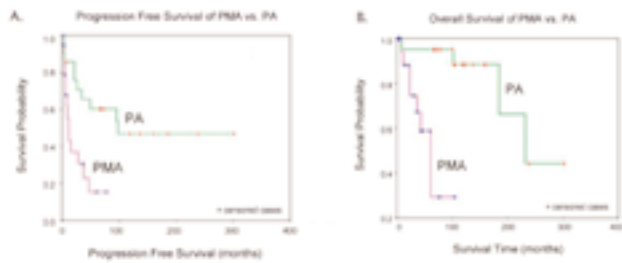


Fig. 4. A: Kaplan–Meier curve comparing the progression-free survival of patients with PMA and PA in age-matched cohorts. The mean progression-free survival duration for PMA and PA cohorts was  $25 \pm 6$  and  $163 \pm 31$  months, respectively (mean  $\pm$  standard error;  $p < 0.01$ ). B: Kaplan–Meier curve comparing the overall survival duration of patients with PMA and PA in age-matched cohorts. The mean duration of overall survival for PMA and PA cohorts was  $60 \pm 10$  and  $233 \pm 26$  months, respectively (mean  $\pm$  standard error;  $p < 0.001$ ). Figure reprinted with permission from Komotar RJ, et al: Pilocytic and pilomyxoid hypothalamic/chiasmatic astrocytomas. *Neurosurgery* 54:72–80, 2004

PMA continued to demonstrate significantly shorter progression-free (mean duration 25 and 163 months for those with PMA and PA, respectively;  $p < 0.01$ ) and overall (mean duration 60 and 233 months, respectively;  $p < 0.001$ ) survival times than those with PA. Furthermore, 33% of patients with PMA died of their disease, compared with 17% of those with PA.<sup>18</sup>

### MANAGEMENT

The management of pediatric low-grade astrocytomas, including PMA, remains controversial. Depending on the location of the lesion, surgery is often the primary treatment strategy.<sup>1,2,5,6,8,9,12,16,21–26</sup> Cerebellar tumors, for instance, are often cured by a complete resection, whereas hypothalamic and suprasellar tumors are usually not amenable to GTR. In low-grade gliomas, provided it can be performed without excessive morbidity, GTR is the most reliable predictor of favorable outcome in the pediatric population.<sup>8,12,15,16,21,22,26,29,30</sup> Consequently, the long-term biological behavior of residual neoplastic tissue impacts the use of adjuvant therapy in the management of these lesions.

The indications for adjuvant therapy in the treatment of low-grade astrocytomas vary, and PMA is no exception. Adjuvant therapy, either chemotherapy or radiotherapy, is frequently instituted in at least three situations: 1) tumor recurrence following initial GTR; 2) partially resected tumors that are causing neurological impairment; and 3) partially resected tumors that demonstrate growth on follow-up imaging, even in the absence of symptoms.

The use of chemotherapy in the pediatric population is currently expanding. Chemotherapy is often used now to treat infants and very young children.<sup>10</sup> The careful administration of chemotherapy in this patient population may serve to delay the need for radiotherapy, which has been shown to have severe and irreversible side effects when applied to the developing nervous system.<sup>13,14</sup> To this end, chemotherapy appears to be an effective postoperative treatment for brain tumors during early childhood, with higher doses occasionally being administered to treat pa-

tients with malignant lesions.<sup>20,28,30</sup> Adjuvant radiation therapy in low-grade astrocytomas is generally limited to patients older than 3 to 5 years of age whose disease progresses after an initial resection.<sup>14</sup>

Currently, there is no standard of care in treating patients with PMA. A recently described tumor, PMA was initially treated similarly to PA. Surgical intervention remains the first step, with complete resection the goal. Unfortunately, however, the location of these lesions usually prevents a GTR. Once a diagnosis is made, an MR image of the spine should be obtained (if this was not done preoperatively), given the significant rate of dissemination in the cerebrospinal fluid in children with PMA.<sup>18</sup>

### CONCLUSIONS

Because PMA generally exhibits more aggressive biological behavior, physicians have been inclined to implement adjuvant therapy earlier in the course of treatment. At our institution and others, unless a GTR is achieved, adjuvant therapy is started immediately after surgery, without waiting for tumor growth or recurrence. Chemotherapy is most often used because of the young age of patients at diagnosis, and it can delay the need for radiation. For older children, radiotherapy administered concomitantly with chemotherapy may prove to be a more effective method of treatment for PMA, although side effects can be severe in certain cases.<sup>29</sup> Given the uncertainties about the prognosis of PMA overall and the possible maturation of some tumors into typical PA, it is not possible to provide strict management guidelines at this stage. More definitive guidelines are certain to emerge as clinicians gain more experience with PMA in the future.

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Manuscript received February 28, 2005.

Accepted in final form May 16, 2005.

Dr. Ricardo J. Komotar was supported by a National Institutes of Health Research Training Fellowship, Dr. J Mocco was supported by the Congress of Neurological Surgeons Wilder Penfield Fellowship, and Jess E. Jones was supported by an American Heart Association Research Fellowship.

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