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REVIEW ARTICLE

Pilomyxoid astrocytomas: a short review

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Abstract
Pilomyxoid astrocytoma is a variant of pilocytic astrocytoma and the clinical, histological and molecular data point to a very close relationship as well as a more aggressive biological behavior for the former. WHO 2016 classification does not provide a specific grade for these neoplasms, but there is sufficient evidence in the literature that pilomyxoid astrocytoma has slightly worse prognosis than typical pilocytic astrocytoma. There is increasing evidence that in addition to the MAPK pathway alterations, pilomyxoid astrocytomas harbor genetic alterations that distinguish them from typical pilocytic astrocytoma

Keywords Astrocytoma · BRAF · Pediatric glioma · Pilocytic · Pilomyxoid

Introduction

Pilomyxoid astrocytoma (PMA) has been recognized as a variant of pilocytic astrocytoma (PA), and was originally classified as a WHO grade II neoplasm in the 2007 WHO classification scheme. The WHO 2016 classification still recognizes PMA as a variant of PA, but a specific grade has not been assigned [1, 2]. Although these two entities share plenty of similarities clinically and morphologically, they have significant differences. This brief review will focus on distinct features of PMA, emphasizing the molecular findings of the recent studies and our experience.

Clinical, demographic and radiologic features

PMA is often seen at early stages of life [3, 4], and because of this finding this group of tumors were once suggested to represent the "infantile form" of PA [5]. Early studies reported these tumors primarily in infants and the diencephalic region, but failed to recognize their histological distinction from typical PA. Although PMA could be seen anywhere in the central nervous system, the most common site is hypothalamic/chiasmatic region [1, 3–5]. The tumors are less common in the spinal cord and cerebellum, with only a handful of cases reported to date [6, 7].

Radiologically, PMAs look very similar to PAs but they are more commonly solid rather than cystic, and they tend to have more prominent enhancing components [8, 9]. PMAs also have a higher incidence of leptomeningeal dissemination compared to PAs [10].

Histological features of PMAs and differences from PAs

Pilomyxoid astrocytomas are often well-demarcated, solid tumors that have a uniform morphology in a diffusely myxoid background. Like PAs, focal areas of infiltration into surrounding parenchyma can be seen. PMAs tend to be more cellular and monomorphic compared to pilocytic astrocytomas. The cytological features are similar to PA, with neoplastic cells having fibrillary processes and hyperchromatic, elongated nuclei. Significant pleomorphism is not a common finding. Neoplastic cells of PMA have prominent angiocentric arrangement. When solid, PMAs often do not demonstrate the linear-type microvascular proliferation seen in the cystic components of PAs, and they tend to harbor more mitoses. The overwhelming majority of PMAs do not have Rosenthal fibers, and a rare example may show eosinophilic

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granular bodies. Both formations are much less common compared to typical PAs.

Tumors with hybrid features of PA and PMA (the so-called "intermediate tumors") were reported by Johnson et al. in 2010 [11]. This and other studies suggested a biological link between these neoplasms. In addition, PMAs have been reported to "mature" into typical PAs on recurrence or following treatment. The patients with hybrid tumors often have an older median age at presentation when compared to PMAs, which may also support the notion that PMA and PA are very closely related [11].

Clinical course and outcome

PMA is a rare tumor and only accounts for a small percentage of pilocytic neoplasms, and because of its rarity, clinical studies with sufficiently long follow-up periods and comprehensive prognostic studies are exceedingly rare. One of the earlier studies demonstrated that age and location matched-series of PMAs and PAs have significantly different outcomes. There was a striking difference on progression-free survival (PFS) times in between these two groups (median progression-free survival 25 months for PMA as opposed to 163 months for PA) in favor of PAs [4]. Other studies also supported these findings [5, 12, 13]. The major caveat of all these studies was the limited number of cases.

Molecular features

Similar to PAs, PMAs also have a relatively simple genomic structure. They tend to have limited number of genomic alterations [14]. The most commonly altered pathway for both tumors is the MAPK pathway followed by the FGFR signaling pathway. By far the most common alteration is the BRAF fusion with a series of partner and tandem duplications resulting in activation of the MAPK pathway. The most commonly altered genes are BRAF, NF1, FGFR1 and PTPN11. Other rare mutations were also described [15, 16]. Limited copy number variations are seen both in PAs and PMAs. A study by Jeon et al. showed that PA and PMA have different copy number changes. While PAs showed chromosomal gains more frequently, PMAs had chromosomal losses [17]. Another study by Kleinschmidt-DeMasters compared gene expression profiles of PAs and PMAs. PMAs had overexpression of mitosis-related genes and extracellular matrix genes, whereas PAs had weak overexpression of plasma membrane and collagen-related genes [18]. Especially, the finding on mitosis-related gene overexpression in PMAs was suggested as a reason for the adverse clinical course of these tumors.

In recent years, increasing number of PMAs and PAs have been studied using high-throughput genetic analysis, allowing the identification of both common and rare alterations as well as chromosomal copy number alterations. In addition, molecular and genetic differences emerged between PA and PMA in recent studies. We analyzed one such case using the capture-based NGS platform as previously described [19]. There was a distinct boundary between the PMA and the PA patterns and material could be procured separately for analysis. Both regions had focal copy number gains on 7q34 locus containing the 3′ end of the BRAF gene with accompanying KIAA1549–BRAF gene fusion. However, the different areas had different copy number alterations: PMA component had trisomy 11 and was diploid for chromosomes 5 and 7, but the pilocytic component had focal gains in chromosomes 5 and 7, and was diploid for chromosome 11 (Fig. 1).

In addition to the hybrid tumor characterized using the NGS platform, we have analyzed 3 PMAs during the last 3 years. One of these tumors demonstrated K656E point mutation in the FGFR1 gene and E76 K mutation in the PTPN11 gene. Copy number analysis of this tumor demonstrated gain of chromosome 8 (containing FGFR1) and gain of chromosome 12 (containing PTPN11). The second tumor had BRAF V600E mutation and showed no copy number changes. The third case had the classical BRAF-KIAA1549 fusion with no additional chromosomal copy number alterations.

In summary, there is strong evidence that PMA is a variant of PA and the clinical, histological and molecular data point to a very close relationship as well as a more aggressive biological behavior for the former. It has been an unfortunate change for the WHO classification to eliminate the WHO grade designation, leaving no clear suggestion to the clinician that these tumors have a more aggressive clinical course. Main reasons for this reversal may have been: the belief that the same genetic alteration virtually justifies the same grade; and the fact that PMA still has a much better prognosis compared to diffuse gliomas in the same age group and location. In the opinion of the authors, there is sufficient evidence in the literature to suggest that PMA behaves more aggressively than PA [4, 12, 13], and the subsequent versions of the WHO classification may actually reverse this reversal to consider these tumors locally aggressive (i.e., WHO Grade II).

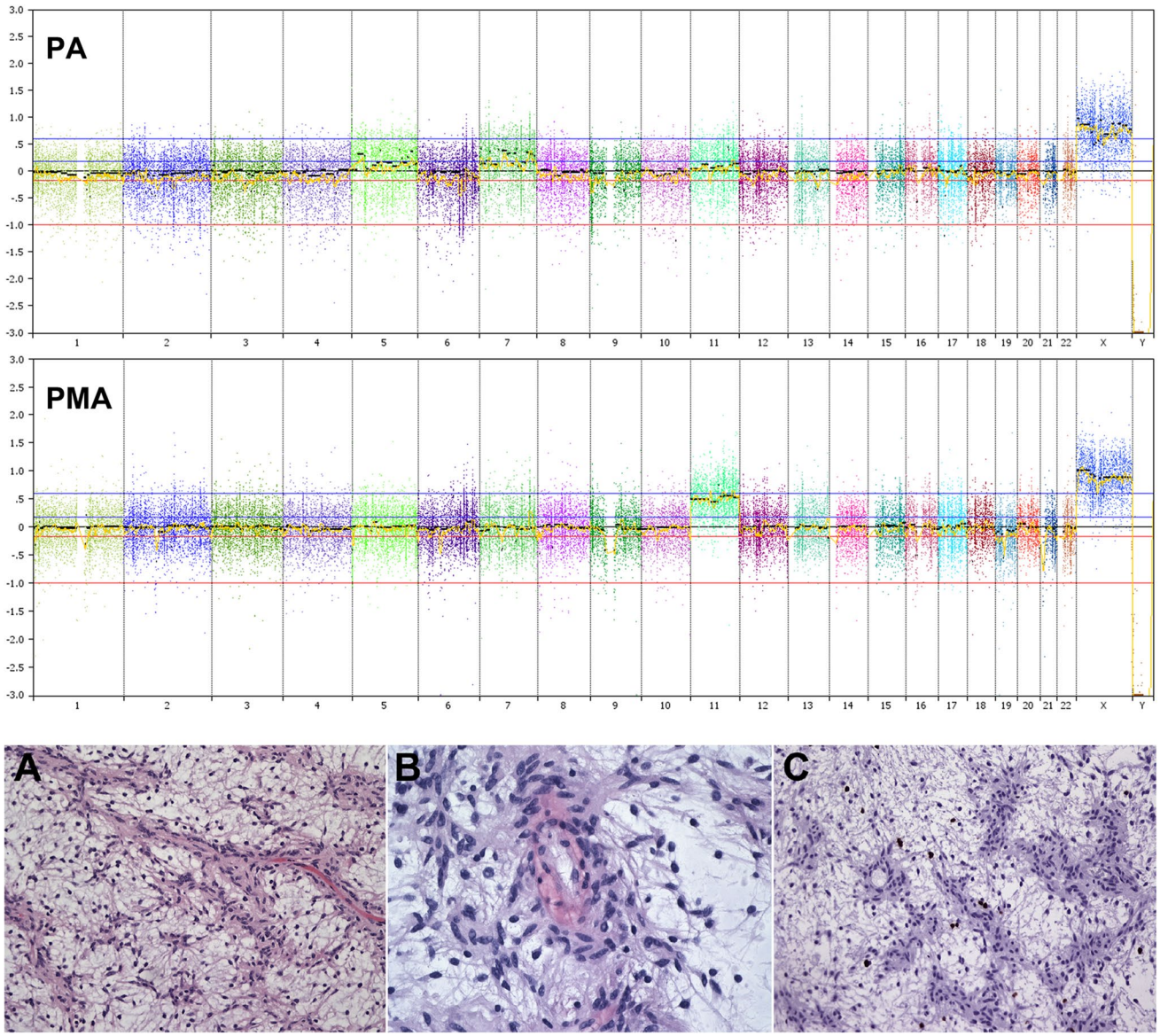

Fig. 1 Copy number plots of PA (top) and PMA (bottom) components of a hybrid PA + PMA case. PA component showed focal gains in chromosomes 5 and 7, otherwise diploid; PMA component showed only gain of chromosome 11 (trisomy)

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