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Pleomorphic Xanthoastrocytoma: MRI Characteristics and Clinicopathological Analysis

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Abstract

Background: Pleomorphic Xanthoastrocytoma (PXA) is a rare astrocytic tumor, occurring primarily in childhood and adolescence, with relatively favorable prognosis.

Objective: We compared MRI findings and clinical characteristics of PXA with histopathology diagnosis to better understand the diagnosis and prognosis of the tumor.

Material and Methods: MRI findings of 17 patients with histopathologic diagnosis of PXA were retrospectively analyzed and matched with clinical and pathological features.

Results: The clinical presentation of 17 patients generally occurred in children and youths and included epilepsy (n=11), headaches and dizziness (n=7), with bradykinesia (n=6). All tumors were solitary lesion, located in the superficial cerebral cortex. Thirteen tumors were in temporal lobes, with 2 each in the junction between the right parietal and occipital lobe and the junction between the right frontal and parietal lobe. MRI revealed superficial lumps in the brain: 4 were a solid nodule, 8 were a cystic lesion with a nodule, and 5 were a mixed cystic-solid lesion. The tumor margins were well-defined (n=14) or poorly-defined (n=3), with mild (n=5) or no (n=12) peritumoral edema. The tumors were hypointense or isointense on T1-weighted images, and hyper intense or of mixed signal intensity on T2-weighted images. There was moderate (n=5), marked (n=9) or no (n=3) contrast enhancement in the solid components and mural nodules, with a meningeal "tail sign" (n=0), and the capsule wall of the cyst was either mildly or not enhanced. The solid portions showed slightly hyper intense, isointense in DWI scanning of 6 cases, whereas the Apparent Diffusion Coefficient (ADC) displays slightly hypointense, isointense. The ADC values of the solid portions were higher than contralateral tissue. Histologically, all tumors were classified as World Health Organization grade 2, comprising spindle, multiform giant cells, and foamy cells. No tumor showed necrosis. Irregular mitosis was seen in 2 cases (<5 mitoses per 10 HPF). Immunohistochemistry demonstrated positive staining for Glial Fibrillary Acidic Protein (GFAP), vimentin, and S-100 protein, and 13 cases also showed positive staining for CD34.

Conclusion: Superficial location, solitary and cystic lesion with enhanced solid components and mural nodules were typical MRI features of PXA. MRI is able to well reveal its morphologic features and have important diagnostic value for PXA, combined with advanced imaging technology, such as DWI, and distinctive clinicopathological features as well as positive reaction of GFAP and CD34, which will contribute to improve the diagnosis and prognosis prediction.

Keywords: Pleomorphic xanthoastrocytoma; Magnetic resonance imaging; Diagnosis; Pathology

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Introduction

Pleomorphic Xanthoastrocytoma (PXA) is a rare and special type of astrocytoma. Proposed as a distinct entity in 1979 [1], it occurs mostly in childhood and adolescence [2]. Seizures are the most common presenting symptom, and it also occurs in patients with a long history of headaches and dizziness. It is characterized by superficial growth and a predilection for supratentorial locations in the cortex. The temporal lobe is the most common site of PXAs. Pathologically, PXA is an astrocytic tumor, based on its immunohistochemical phenotype, with positive reaction for Glial Fibrillary Acid Protein (GFAP) [1]. Moreover, expression of neuronal and glial markers has also been reported before [3]. PXAs are generally considered to be relatively favorable and indolent tumors [2,4]. The tumor was recognized by the World Health Organization (WHO) as a grade 2 tumor in 2007 [5].

However, PXA is associated with increased recurrence and malignant transformation [6,7].

PXA is a rare and special type of astrocytoma, clinical understanding for PXAs is still inadequate, and the misdiagnosis rate is very high. This study aim to analyze MRI characteristics in a series of patients diagnosed with PXA, and combined with MR diffusion weighted imaging technology as well as distinctive clinicopathological features of PXA.

Materials and Methods

Clinical data collection

This study was approved by the institutional review board of our hospital. MR images, clinical manifestations, diagnostic pathology of 17 patients diagnosed with PXA at our institution between January 2005 to October 2014 were retrospectively analyzed.

MRI procedure

For MRI imaging, we used a 1.5T or 3.0T superconductive MR unit (Avanto, Magnetom Trio Tim, Siemens, Medical Systems, Erlangen, Germany) with a standard head coil. MRI acquisition parameters were standard axial spin-echo T1-weighted (TR/TE=330-500/8.1-13 ms), axial turbo spin-echo T2-weighted (TR/TE=3000-4000/90-101 ms), and axial T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR) images (TR=9000 ms, TE=87 ms, TI=2500 ms). Other parameters were: Field of View (FOV) =250 × 250 mm, 5.5 mm thickness, an interslice gap of 2 mm, and 160 of lip angle. T1-weighted gadolinium-enhanced images were obtained in the axial, sagittal and coronal planes after intravenous injection of gadopentetate dimeglumine (0.1 mmol/kg, Bayer Schering Pharma AG, Guangzhou, China). A high-pressure syringe was used to inject the Gd-DTPA into the cubital vein (flow rate: 3.0 ml/s), then an equivalent volume of saline water was injected in the same stream. Diffusion weighted imaging (DWI) involved the SE-EPI technique (TE=99 ms, TR=5000 ms, matrix =192 × 192, b values=0 s/mm^2, 1000 s/mm^2).

Data analysis

MRI data were evaluated by two roentgenologists who have extensive clinical experience. The location, signal intensity characteristics, contrast enhancement, and edema of the tumor on MR images were analyzed and matched with clinicopathological features.

Results

Clinical characteristics

We recruited 17 patients (9 males, 8 females, mean age at 27.6 years [range 7 to 54 years]) for the study. The 17 PXA cases accounted for about 1% of the 1,828 pathologically confirmed astrocytoma cases presenting over the same period in our hospital. Most PXA cases occurred in children and adolescents: 12 patients (70.6%) were younger than 35. The patients had a long course of disease, with slow development (range 2 to 5 years). The diagnosis for all cases before surgery was glioma (n=5), hemangiopericytoma (n=2), hemangioblastoma (n=2), and unknown origin (n=8). The main clinical presentation in the 17 patients were epilepsy (n=11), headaches and dizziness (n=7), with bradykinesia (n=6).

MRI features

All cases were supratentorial tumors, with round or irregular lumps. Some showed irregular and accumulational mural nodules. The tumors were located in right (n=6) or left (n=7) temporal lobe, junction of the right parietal and occipital lobe (n=2), and junction of the right frontal and parietal lobe (n=2). The tumors were all solitary lesion, located in the superficial brain, with well-defined (n=14) or poorly defined borders (n=3). Peritumoral edema was mild (n=5) or not obvious (n=12). The maximal tumor size was about 5.0 cm × 5.5 cm and minimal size about 3.5 cm × 3.5 cm.

Four lesions were solid masses (Figure 1). Eight tumors were cystic lesions with mural nodules (Figure 2). Five tumors were mixed cystic-solid lesions (Figure 3). The cystic components of the tumors were hypointense on T1-weighted images and hyperintense on T2-weighted images. The solid-components and mural-nodule lesions were hypointense or isointense on T1-weighted images and hyperintense or with mixed signal intensity on T2-weighted images, with marked (n=9), moderate (n=5) or no (n=3) contrast

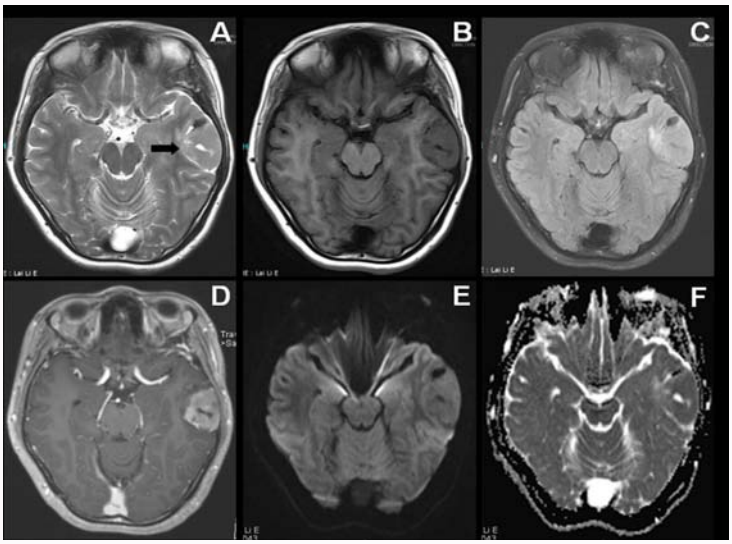

Figure 1: Female, 21 years-old, admitted to the hospital after sudden limb twitching for 2 weeks. Solid pattern of Pleomorphic Xanthoastrocytoma (PXA). MRI shows a solid mass in the subcortical area of the left temporal lobe. (A) Unenhanced axial T2-weighted image of an isointense, slightly hyperintense lesion. (B) Unenhanced axial T1-weighted image of a hypointense lesion. (C) Axial FLAIR-weighted image of a slightly hyperintense lesion. (D) Moderate contrast enhancement of solid components on enhanced T1-weighted imaging. (E) Diffusion-Weighted Imaging (DWI) of the mass showing cystic hypointense and solid slightly hyperintense regions. (F) Apparent Diffusion Coefficient (ADC) of the cystic hyper-intense lesion.

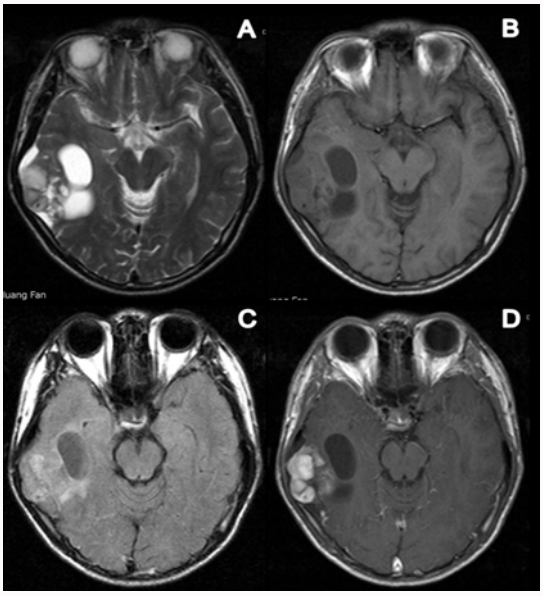

Figure 2: Male, 16 years-old, admitted to the hospital after repeated mouth convulsions for 3 months. Cystic lesion with a nodule pattern of PXA. The lump located in the right temporal lobe shows several cystic lesions with large mural nodule. (A) Unenhanced axial T2-weighted image of slightly hyperintense lesions with a mural nodule adjacent to the leptomeningeal surface. (B) Unenhanced axial T1-weighted image of isointense, hypointense lesions. (C) FLAIR-weighted images of slightly hyperintense lesions. (D) Obvious contrast enhancement of mural nodule, no enhancement of the capsule wall on the axial enhanced T1-weighted image, and the mural nodule is significantly enhanced compared with the solid components of the previous case.

enhancement, and without meningeal "tail signs" (n=0). The solid portions showed slightly hyperintense, isointense in DWI scanning of 6 cases, whereas the Apparent Diffusion Coefficient (ADC) displays slightly hypointense, isointense. The ADC values of the solid portions were higher than contralateral tissue (Figure 1E, 1F).

Surgical results and pathology findings

All 17 cases underwent craniotomy to remove the tumor. Macroscopically most tumors were gray or brown, and gelatinous. The tumor texture was soft or firm, and featured a general blood supply with, in general, a complete envelope. All tumors were commonly cystic, with a glossy surface and gray or taupe cyst fluid. Mura nodules were grayish red and attached to the cyst wall or partially adhered to the leptomeninges, with well-defined boundaries. Only a few nodules tightly adhered to surrounding tissues.

Histologically, all tumors were WHO grade 2. On microscopy, the tumors were a mixture of spindle cells, pleomorphic giant cells or foamy cells (Figure 4), with dense reticulated fibers and infiltration of lymphocytes, and lipid deposition seen in some cells, occasionally in some vacuoles. No significant microvascular proliferation and necrosis was seen. No tumors showed anaplastic features of pleomorphic polygonal cells with high mitotic activity (≥ 5 mitoses per 10 High-Power Fields [HPF]). Mitotic activity was only seen in 2 cases (<5 mitoses per 10 HPF). Histological examination of tumors revealed immunopositivity for glial fibrillary acidic protein (GFAP+ to +++) (Figure 5) and CD34 (+) (Figure 6). Other immunohistochemistry results were for S-100 (+ to ++), vimentin (+), O-6-methylguanine-DNA methyltransferase (+ to +++), Ki-67 (5%+), epithelial membrane antigen (-), CD57 (-), creatine kinase (-), desmin (-), p53 (10%+), and CD68 (+).

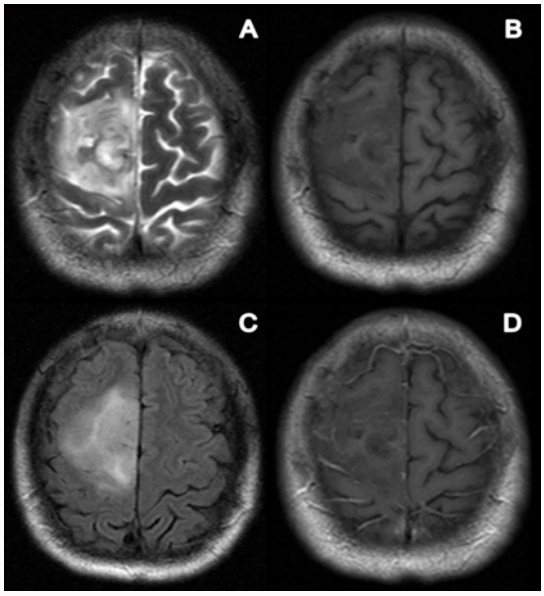

Figure 3: Male, 31 years-old, admitted to the hospital because of frequent dizziness and headache. Mixed cystic-solid PXA pattern. MRI mainly demonstrates several mixed cystic-solid lesions in the junction of the right frontal and parietal lobe. (A) The lesion is slightly hyperintense, hyperintense with mild peritumoral edema on unenhanced T2-weighted images. (B) Unenhanced axial T1-weighted image shows hypointense, isointense lesions. (C) FLAIR-weighted image show slightly hyperintense lesions. (D) No contrast enhancement of the lesion on enhanced T1-weighted image.

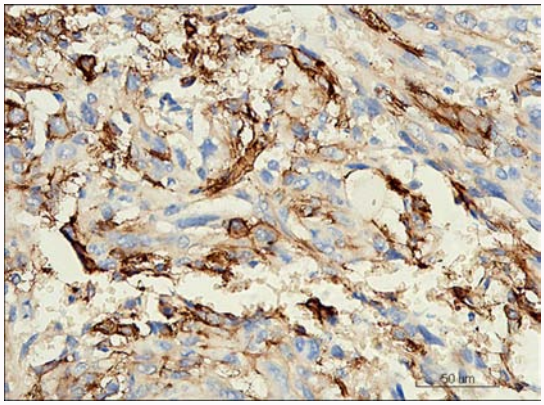

Figure 4: Histological features of selected PXA tumors.
Tumor cells are markedly pleomorphic with nuclear staining and demonstrate cytoplasmic vacuoliza-tion (black arrow) and mitosis. Photomicrography (H&E, 400x magnification) shows multinucleated giant cells (red arrow), foamy cells (blue arrow) and spindle cells (yellow arrow).

Discussion

PXA is a rare neoplasm, and the incidence is low, accounting for less than 1% of astrocytic neoplasms [6]. It was considered an independent central-nervous-system tumor for the first time in 1993 in the WHO classification system [8]. PXA originates in pluripotent neural ectoderm neuron or astrocyte precursor cells, and has a pleomorphic appearance on histology. PXA tumors contain pleomorphic cells and xanthoma cells, with expression of GFAP of tumor cells [9], so it has been called pleomorphic xanthoastrocytoma. Here we compare MRI findings and clinical characteristics of 17 cases of PXA with histopathology diagnosis to further understand the diagnosis and prognosis of the tumor.

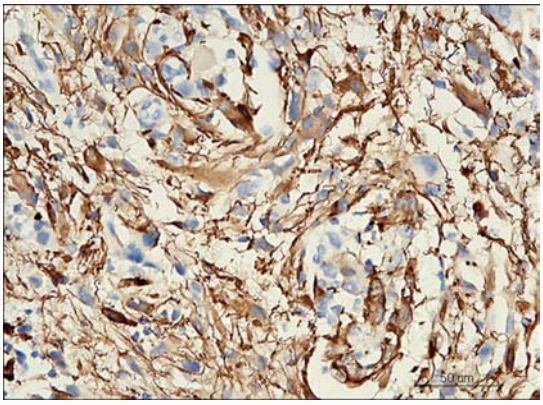

Figure 5: Immunohistochemistry for glial fibrillary acidic protein (GFAP) x400, which demonstrates pleomorphic tumor cells with cytoplasmic positivity for GFAP, confirming their astrocytic lineage.

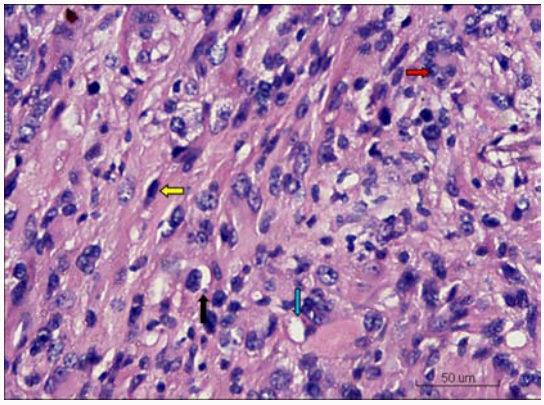

Figure 6: Immunohistochemistry for CD34 x400, which reveals areas with strongly immunoreactive tumor cells and processes.

Analysis of MRI findings

The morphological and histological features of PXA are well demonstrated on MRI [2]. PXA is categorized as a cystic, mixed cystic-solid, or solid lesion according to MRI findings. Typical PXA often shows cystic-solid masses on MRI. The lesions presented here are mainly solid tumors (Figure 1), cystic lesions with nodules (Figure 2) or mixed cystic-solid lesions (Figure 3). PXA has been previously found to be completely solid or cystic lesions [2], but we did not find such lesions. Tumors show hypo-or isointense signals on T1-weighted images and isointense or slightly hyperintense signals on T2-weighted scans. Signal characteristics of PXA in our sample were almost consistent with the literature. Uneven Signal characteristics may owe to the pathological components of tumor tissue or be associated with cystic degree. All tumors were commonly cystic, with a central or ambient location, and cystic areas were almost equal to the cerebrospinal fluid area. Sometimes lesions were accompanied by mural nodules that were mostly close to the leptomeningeal surface in the superficial brain, accompanied by partial invasion or adjacent bone compression and displacement. Gadolinium-enhanced T1-weighted images markedly enhance the mural nodules and solid components of tumors. The cystic areas do not show contrast enhancement, the capsule walls are mildly or not enhanced. The capsule wall of the cyst was mildly enhanced in 2 cases of our sample. This showed cystic wall was tumor tissue of tumor cyst necrosis rather than reactive proliferation of glial cells. A meningeal "tail sign" around lesions is considered an important feature of PXA [10]. Imaging of tail signs occurs because the location of the tumor is superficial, and tumors often invade the surrounding leptomeningeal area, causing meningeal thickening. Enhancement rate of leptomeninge is only 14% in report before we did not find tail signs in this study [11].

There was usually mild or no peritumoral edema in PXA. This index remains controversial for judging prognosis. Tien et al. [12] believe that peritumoral edema may be a symbol of poor tumor prognosis. However, Yu et al. [13] did not find sufficient evidence to support the use of edema for judging prognosis. According to our clinical studies and observations, peritumoral edema may be associated with growth rate of the tumor. There were only 5 cases of mild peritumoral edema in our study (Figure 3). Consequently, we could not determine the prognosis or malignancy of the tumor simply from edema.

Diffusion-Weighted Imaging (DWI) has increasingly gained in importance in cancer imaging for differentiation of malignant and benign lesions. Tumor cell density was well associated with ADC value, which can guide the tumorous grading [14]. The higher the degree of malignant of tumor becomes and the more tumor cell number are, the smaller the intercellular space will be, all these factors will lead to the more limited the diffusion of water molecules are, DWI of solid portions will showed hyperintense, ADC displays obvious hypointense, the ADC values are lower, *vice versa*. In our sample, solid portions of PXA appeared slightly hyperintense or isointense on DWI, and the diffusion of water molecules were not obviously restricted, meaning cell density was lower, which indicate that these tumors were close to benign tumors. This also agrees with pathological results in our sample. Therefore, DWI can guide grading of PXA according to the degree of diffusion of water molecules.

Clinical and pathological features of PXA

PXA most commonly occurs in children and young adults [2], as we found; there are few reports of older adults with PXA. Gender differences are not obvious and the tumor tends to occur on the right side of the brain. In our study, 10 cases (58.8%) occurred on the right side. The most common site was the temporal lobe, followed by the parietal, occipital and frontal lobes. PXA cases are seldom reported to occur in special locations [2], such as the thalamus, cerebellum, deep frontal lobe and sellar region. As seen with other series, all cases occurred in the superficial location of the brain in our study, 13 cases (76.5%) of which were located in the temporal lobe. Moreover, almost all cases located in the temporal lobe occurred with epilepsy. Previously, 1% to 6.9% of tumors causing epilepsy have been to be found associated with PXA [9,15], and PXAs with epilepsy seizures represent 71% to 79% of all cases [16]. Therefore, almost 70% to 80% of patients visit the physician with epileptic seizures as the initial symptom. Therapeutic drug control for associated epilepsy is poor according to our clinical observations.

Before immunohistochemistry, PXA was considered a tumor of the meninges and mesenchymal tissue of brain [17]. However, GFAP positivity with PXA definitely demonstrates an astrocytic origin. So the diagnostic feature of PXA is pleomorphic and xanthic tumor cells positive for GFAP. Similarly, microscopically, our tumors also agree with the above pathological feature. On histology, the tumors were all positive for GFAP and 13 cases showed positive staining for CD34, consistent with CD34 immunoreactivity being previously found to be associated with tumor cells in more than 80% of WHO grade 2 PXAs and 44% of PXAs with anaplastic features [18]. Moreover,

distinguishing anaplastic PXA from glioblastoma is difficult in the presence of active mitosis, especially extensive necrosis. However, we can differentiate PXA from glioblastoma according to CD34 expression, which is commonly positive in PXA, whereas CD34-immunoreactive giant cell glioblastoma is rare [18]. So GFAP and CD34 are important indicators for PXAs, their positive reaction will have important diagnostic value and differential diagnosis contribute to improve the diagnosis.

About 15% to 20% of PXAs have aggressive biological behavior [2], and the degree of malignancy is lower in terms of biology than histology, which is highly pleomorphic, for most PXAs. For benign PXA, cell division, infiltration of vascular endothelial cell and cell necrosis in most cases is rare. Anaplastic PXA features a mitotic index or tumor cell necrosis, with infiltration of vascular endothelial cells, both aggressive prognostic indicators. Some authors consider that tumor necrosis is a moderate reliable indicator of prognostic long-term seizure and morbidity outcomes [19], whereas others believe that the mitotic index is a better indicator [20,21]. However, according to our clinical studies and experience, each case should be analyzed comprehensively under the specific circumstances in terms of the value of the indicators or even other indicators. Necrosis is present only during transformation to anaplastic PXA [22]. We found no significant necrosis in our cases, possibly because none of our tumors showed anaplastic features of cells with high mitotic activity (≥ 5 mitoses per 10 HPF), although we observed mitotic activity in 2 tumors (<5 mitoses per 10 HPF).

Differential diagnosis

The typical imaging features of PXAs were cystic and cystic-solid lumps with mural nodules in the superficial location of brain. Ganglioglioma typically shows mural nodules, which are not adjacent to the meninges, usually with calcification, whereas PXA seldom calcifies. Hemangioblastomas often show shadows of blood vessels with a "flow void signal", the most important trait distinguishing hemangioblastomas from PXAs. Meningioma, with the appearance of typical extra-axial tumors, with pseudocapsule signs, middle-age onset, rare necrosis, and cystic degeneration, should be differentiated from solid PXAs. The main difference between pilocytic astrocytomas and PXAs is the position of occurrence. The tumor usually occurs in the infratentorial area of the cerebellum, fourth ventricle and brain stem, with a solid lump, whereas PXA often occurs in the cerebral hemispheres. Oligodendroglioma often occurs in the frontal lobe, and has a larger lesion scope and less cystic lesion shapes, with striped calcifications. Contrast enhancement, edema and the mass effect of most cases are not obvious.

In conclusion, PXA is a rare tumor occurring in childhood and adolescence with a usually favorable prognosis. Epilepsy, headache and dizziness are the most common clinical symptoms. MRI findings in this series corroborated a typical description of PXA. MRI is able to reveal its morphologic features, combined with advanced MR diffusion-weighted imaging technology as well as positive reaction of GFAP and CD34, which will provide important diagnostic and differential diagnosis value and contribute to improve the diagnostic accuracy and prognosis prediction for PXA.

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