Clinical Features and Surgical Results of Pediatric Pleomorphic Xanthoastrocytoma: Analysis of 17 Cases with a Literature Review

Wenhao Wu, Pengcheng Zuo, Chunde Li, Jian Gong

BACKGROUND: **Pediatric pleomorphic xanthoastrocytoma (PXA) is a rare brain tumor. To date, there are few studies dedicated to this kind of pediatric tumor. The aim of this study was to investigate the clinicopathologic characteristics of pediatric PXA.**

METHODS: **We retrospectively analyzed 17 pediatric patients diagnosed with PXA histologically between July 2009 and December 2018. We also reviewed the relevant literature.**

RESULTS: **The majority of pediatric PXAs had cystic components and peritumoral edema, and approximately 40% of the tumors had calcifications. All large tumors (≥5 cm) were located in the nontemporal lobes except 1 ($P = 0.05$). Furthermore, the large tumors were primarily solid-cystic or cystic with mural nodules radiologically, while tumors measuring <5 cm were mainly solid or solid with cystic changes ($P = 0.02$). All patients underwent surgery, and 15 patients experienced complete tumor removal. Histologically, 11 patients had grade II PXAs and 6 patients had grade III PXAs. After the operation, most of the patients recovered uneventfully and the seizures were well controlled. The mean follow-up time was 43 months. Five patients received radiotherapy or chemotherapy. One patient had tumor recurrence 5 years after the first operation and underwent repeat surgery.**

CONCLUSIONS: **Cystic components and peritumoral edema could be seen in most pediatric PXAs, and calcification was also not uncommon. The size of the tumor was correlated with the tumor site and radiologic subtype. Maximal safe resection of pediatric PXA is recommended and was shown to be beneficial for seizure control and survival.**

INTRODUCTION

Pleomorphic xanthoastrocytoma (PXA) was first identified by Kepes et al[1] in 1979. PXA is a relatively rare brain tumor comprising <1% of all astrocytic tumors and has approximately one-tenth the incidence of pilocytic astrocytomas.[2] PXA usually affects young patients, especially in their second decade of life. Most of the tumors are superficially located, involving the cortex and meninges. The most common location of PXAs is the temporal lobe, and seizures are the most common presenting symptom. Histologically, the tumors can be classified into PXA and anaplastic PXA, which represent different histologic grades, malignancies, and prognoses. Surgical operation is the most effective treatment for PXA, and complete resection is usually associated with a favorable outcome.

At present, most of the literature regarding PXA includes both pediatric and adult patients, who were analyzed together. The clinical features of glioma may be significantly different among different age groups. Therefore the conclusions drawn by the studies on the combined populations may be unable to reflect the real disease characteristics of pediatric PXA. However, because of the low incidence of pediatric PXA, studies concentrated on pediatric PXA are rare, and most of the studies included only a few patients. To our knowledge, our cohort represents the largest

Key words
- Characteristic
- Children
- Pleomorphic xanthoastrocytoma
- Surgery

Abbreviations and Acronyms
CT: Computed tomography
MRI: Magnetic resonance imaging
PXA: Pleomorphic xanthoastrocytoma
T1WI: T1-weighted image
T2WI: T2-weighted image
WHO: World Health Organization

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series of pediatric PXA. The aim of this study was to investigate the clinical characteristics, radiologic features, and surgical and prognostic results of pediatric PXA.

PATIENTS AND METHODS

This study was approved by our institutional review board. A total of 17 patients (<16 years old) with a histologic diagnosis of PXA were identified in our pediatric department between July 2009 and December 2018. The diagnosis was made and reviewed by our neuropathologists. Clinical data including age, sex, symptoms, surgery, and radiologic and histologic findings were collected. The patients were followed up regarding their clinical manifestations, radiologic changes, adjuvant therapy, and survival data.

The extent of resection was defined according to postoperative magnetic resonance imaging (MRI). If the tumor was totally removed, it was considered gross total resection. Subtotal and partial resection was defined as an extent of resection >90% and 50%–90%, respectively. The size of the tumor was defined as the maximal diameter of the lesion in 3 dimensions on MRI. The extent of peritumoral edema was classified as obvious, mild, and absent. Peritumoral edema was defined as hyperintense around the tumor on T2-weighted imaging (T2WI). If the length from the tumor surface to the outer edge of the edema measured >1 cm, the peritumoral edema was classified as obvious. If this length was <1 cm, the peritumoral edema was classified as mild. If there was no high signal surrounding the tumor, the peritumoral edema was classified as absent.

Continuous data are described by means and standard deviations or medians and ranges. The normality of all continuous variables was examined using the Kolmogorov-Smirnov test before statistical inference. The comparison of age between the temporal and nontemporal PXA groups was performed using the Student's t-test. Categorical variables (sex, symptoms, grade, tumor size, and peritumoral edema) were compared using the Fisher exact test. Statistical analyses were performed using the statistical software package SPSS 17.0. $P < 0.05$ was considered significant.

RESULTS

Patient Demographics

Demographic and tumor characteristics and treatment information are shown in Table 1. The 17 patients included 6 males and 11 females, with a median age of 10 years (range, 5–15 years). All the tumors were located in the supratentorial regions. Eight patients had tumors involving the temporal lobe (47.1%), followed by 3 involving the frontal lobe and another 3 involving multiple lobes. Seizures, the most common symptom, occurred in 10 patients (58.8%), followed by headache in 5 patients, limb weakness in 3 patients, and visual disturbance in 1 patient. In addition, 1 patient had no obvious symptoms and was diagnosed following an accidental finding. Of the 8 patients with temporal PXA, 6 of them (75.0%) suffered from seizures, while only 4 patients (44.4%) among the remaining 9 with nontemporal PXA had seizures.

Table 1. Characteristics of Pediatric Pleomorphic Xanthoastrocytoma

Characteristics	
Age (years)	
Mean (SD)	9.5 (2.5)
Median (range)	10 (5–15)
Gender, number (%)	
Male	6 (35.3)
Female	11 (64.7)
Symptoms, number (%)	
Epilepsy	10 (58.8)
Headache	5 (29.4)
Visual disturbance	1 (5.9)
Limb weakness	3 (17.6)
Incidental finding	1 (5.9)
Tumor location, number (%)	
Frontal	3 (17.6)
Temporal	8 (47.1)
Frontoparietal	2 (11.8)
Parietooccipital	1 (5.9)
Multiple lobes	3 (17.6)
Surgical approach, number (%)	
Frontal	2 (11.8)
Frontotemporal	8 (47.1)
Frontoparietal	2 (11.8)
Temporooccipital	3 (17.6)
Parietooccipital	2 (11.8)
Extent of resection, number (%)	
Total	15 (88.2)
Subtotal	1 (5.9)
Partial	1 (5.9)
Histologic grade, number (%)	
WHO grade II	11 (64.7)
WHO grade III	6 (35.3)
Adjuvant treatment, number (%)	
Radiotherapy	4 (23.5)
Chemoradiotherapy	1 (5.9)
Follow-up (months), number (%)	
Mean (SD)	43.0 (31.0)
Median (range)	32 (8–112)

SD, standard deviation; WHO, World Health Organization.

Radiologic Findings

Computed tomography (CT) scans were available from 12 patients. Seven patients showed isodense lesions, and 5 patients showed hyperdense tumors. Compression of the skull (inner table scalloping) and calcification of the tumor were observed in 4 (33.3%)

and 5 (41.7%) patients from CT scans, respectively. On T1-weighted imaging (T1WI), a hypointense mass was identified in 5 patients and an isointense mass was identified in 12 patients. On T2WI, isointense lesions were indicated in 10 patients and hyperintense lesions were indicated in 7 patients. Radiologically, the tumors could be divided into 4 subgroups: solid masses (11.8%), solid masses with cystic changes (41.2%), solid-cystic masses (23.5%), and cystic lesions with mural nodules (23.5%). The solid parts of the tumor were all identified with different degrees of enhancement. Enhancement of the cystic wall was seen in 4 patients (4/8 patients, 50%). Notably, these 4 patients all showed cystic lesions with mural nodules. In addition, cystic lesions with mural nodules could only be seen in the nontemporal PXA group. On T2WI, 7 patients showed obvious peritumoral edema. Another 7 patients showed mild peritumoral edema, and 3 patients had no edema (Table 2; Figures 1–3).

Comparison of Temporal and Nontemporal Pleomorphic Xanthoastrocytomas

Eight tumors were located in the temporal lobe, which accounted for 47.1% of the cohort. Of these 8 temporal PXAs, only 1 was identified with a size >5 cm (12.5%), while 6 of the 9 nontemporal PXAs showed tumors measuring >5 cm (66.7%). Large pediatric PXA tumors (≥5 cm) appeared to be more frequently seen in nontemporal areas ($P = 0.05$). In addition, PXAs with tumors measuring >5 cm were mainly solid-cystic or cystic with mural nodules (85.7%), while tumors measuring <5 cm were mainly solid or solid with cystic changes (80%). Tumor size significantly correlated with tumor subtype ($P = 0.02$). All nontemporal PXAs showed obvious or mild peritumoral edema, while 3 patients (37.5%) from the temporal group had no peritumoral edema. However, the incidence of peritumoral edema between the 2 groups was not significantly different ($P = 0.08$). There were also no differences in age, sex, seizure, or histologic grade between temporal and nontemporal PXA patients ($P > 0.05$) (Table 3).

Treatment and Prognosis

After preoperative evaluation, all the patients underwent surgery. The frontotemporal approach was used for 8 patients (47.1%), followed by the temporooccipital approach for 3 patients. Gross total resection was achieved for 15 patients (complete removal of the solid part of the tumor; the cyst wall was subtotally resected in 1 case). Subtotal resection and partial resection were achieved in 1 patient each. Histologically, 11 patients were diagnosed with PXA grade II and 6 patients were diagnosed with PXA grade III. One of the 11 patients had collision tumors with a combined subependymal giant cell astrocytoma. After surgery, most of the patients recovered well. One patient had limb weakness and blepharoptosis, and 1 patient demonstrated weakness of the right arm. Vision and the visual field improved after the operation for a patient with visual disturbance. All the patients were followed up except for 1 patient who withdrew from the study. The mean follow-up period was 43 months, with a median time of 32 months (range 8–112 months). The seizures were well controlled and did not recur for most of the patients (9/10 patients, 90%). One patient suffered from epileptic seizures twice during follow-up, and 1 patient occasionally had tremors of his left hand. Adjuvant treatment was administered to 5 patients (29.4%). Four patients received radiotherapy alone, and 1 patient received radiotherapy and chemotherapy. One patient with a grade II PXA had tumor recurrence 5 years after the operation and received a second operation. Other patients underwent periodic magnetic resonance imaging examinations and showed no sign of relapse.

Table 2. Radiologic Features of Pediatric Pleomorphic Xanthoastrocytoma

Parameters	Number (%)	Total
Computed tomography		12
Isodensity	7 (58.3)	
High density	5 (41.7)	
MRI T1-weighted image		17
Hypointense	5 (29.4)	
Isointense	12 (70.6)	
MRI T2-weighted image		17
Isointense	10 (58.8)	
Hyperintense	7 (41.2)	
Enhancement		
Solid mass	17 (100)	17
Cystic wall	4 (50)	8
Peritumoral edema		17
Obvious	7 (41.2)	
Mild	7 (41.2)	
No	3 (17.6)	
Calcification		12
Yes	5 (41.7)	
No	7 (58.3)	
Inner table scalloping		12
Yes	4 (33.3)	
No	8 (66.7)	
Tumor type		17
Solid	2 (11.8)	
Solid with cystic changes	7 (41.2)	
Solid cystic	4 (23.5)	
Cystic with mural nodules	4 (23.5)	
Tumor size		17
≥5 cm	7 (41.2)	
<5 cm	10 (58.8)	
Tumor border		17
Clear	7 (41.2)	
Unclear	10 (58.8)	

MRI, magnetic resonance imaging.

DISCUSSION

Clinical Characteristics

PXA can affect every age group, with a predominance among young people. The mean age at time of diagnosis is approximately 26 years old.[3,4] PXA in children is relatively rare. The mean age in our group was 9.5 years, and the male-to-female ratio was 1:1.8. Our series demonstrated a female preponderance, which is different from previous reports on pediatric PXA.[5,6] This difference should be validated by a large cohort of patients. Most of the PXAs were located in supratentorial areas and involved the cerebral hemispheres. However, cases of cerebellar, brainstem, spinal, and hypothalamic involvement in children have also been reported. Yu et al[7] reported 19 patients with PXA, with a mean age of 29.4 years. Most of the tumors (17 cases) were superficially located on the brain surface, and the other 2 tumors were located in the thalamus or deep area of the frontal lobe. In our series, all the tumors were hemispheric and approximately half of the tumors were located in the temporal lobe, followed by the frontal lobe and multiple lobes. Given the

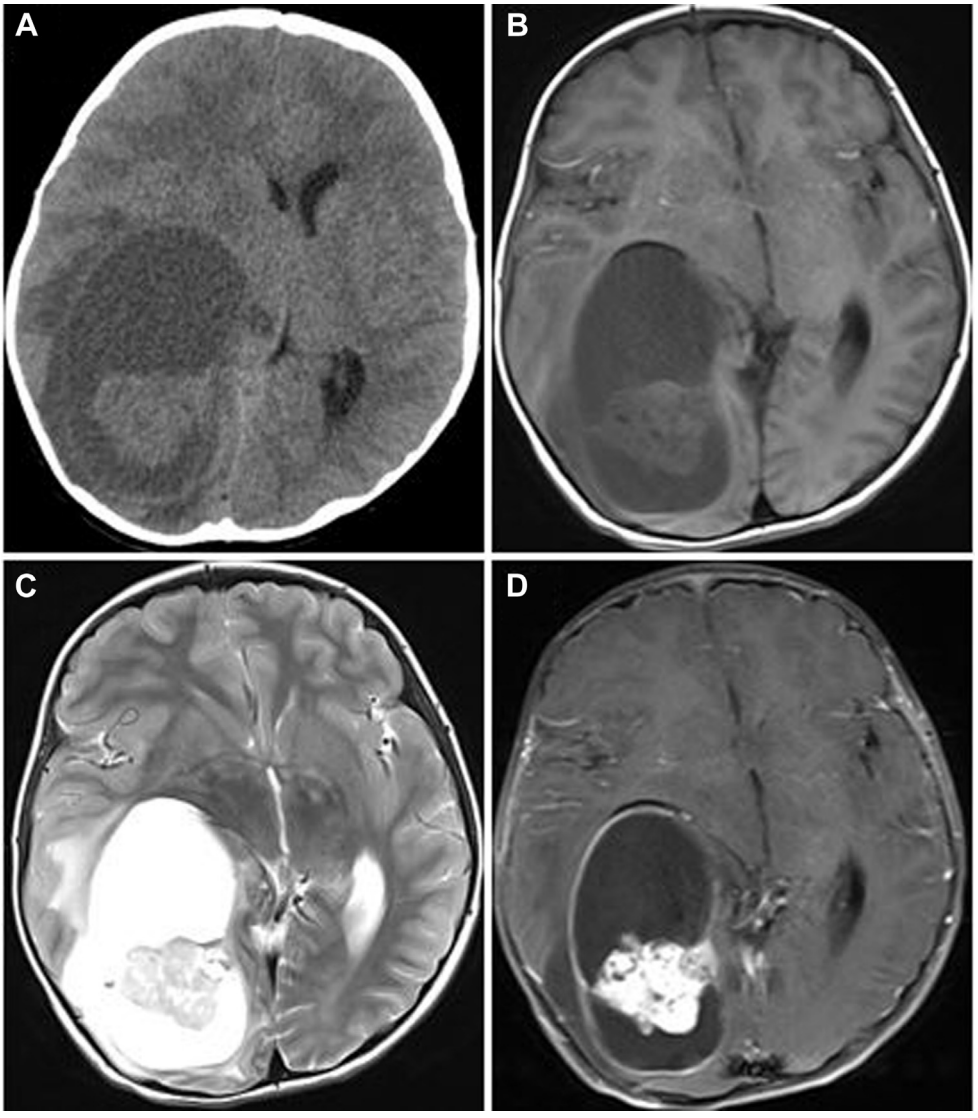

Figure 1. Radiologic characteristics of cystic tumors with mural nodules. (**A**) An isodense solid lesion on computed tomography. (**B** and **C**) The solid mass shows slightly hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging. The tumor is cystic with a mural nodule and is located in the right parietooccipital lobe. Peritumoral edema is obvious, and the midline is pushed to the left. (**D**) Both the solid mass and the cyst wall show contrast enhancement.

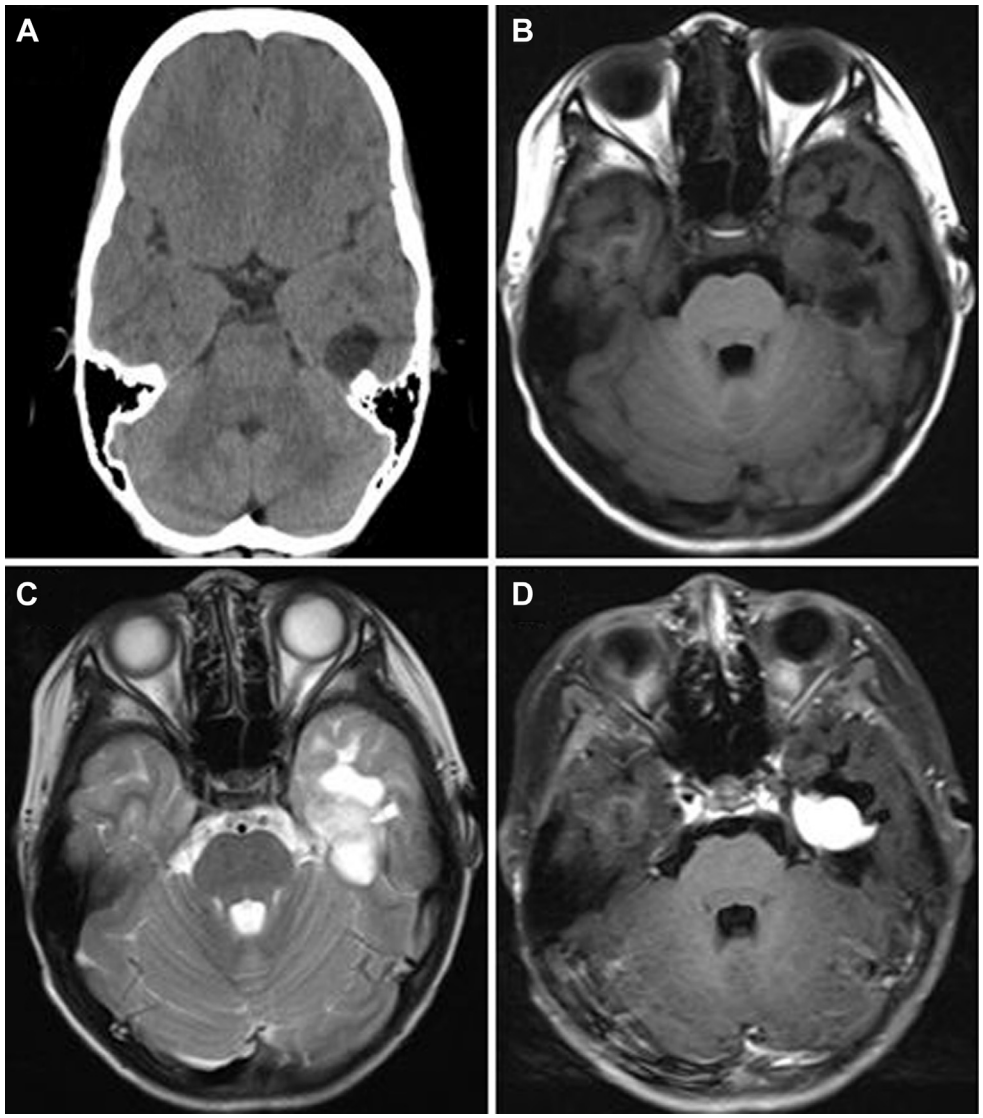

Figure 2. Radiologic characteristics of solid-cystic tumor. (**A**) On computed tomography scan, a cystic lesion can be seen at the left temporal lobe. (**B** and **C**) The tumor is solid cystic, and the solid part of the tumor shows isointense on T1-weighted imaging and hyperintense on T2-weighted imaging. There is no obvious edema around the tumor. (**D**) The solid mass is obviously enhanced, and there is no enhancement of the cyst wall.

superficial location, the most common symptom of PXA was seizures, occurring in 58.8% of patients in our series. This proportion reached up to 75% among the temporal PXA patients. This may be because the temporal lobe is the most common area for brain tumors causing epilepsy.[8] Other presenting features included headache, limb weakness, and visual disturbance.

Radiologic Findings

The radiologic features of PXA may vary, which hinders a definite diagnosis preoperatively. On computed tomography scan, the tumor was isodense or hyperdense. The solid part of the PXA mainly showed isointense on T1WI (70.6%), while the tumor usually showed isointense (58.8%) or hyperintense (41.2%) on T2WI. This is different from adult PXA; according to a recent report, 88% of adult PXAs showed hypointense on T1WI, whereas 96% of tumors showed hyperintense on T2WI.[9] This may be the result of the differences in the tumor types between children and adults. Radiologically, pediatric PXAs can be divided into 4 subtypes, and solid tumors with cystic changes are the most common. Byun et al[9] reported that 48% of adult PXAs were solid, while in our pediatric cohort, solid tumors only accounted

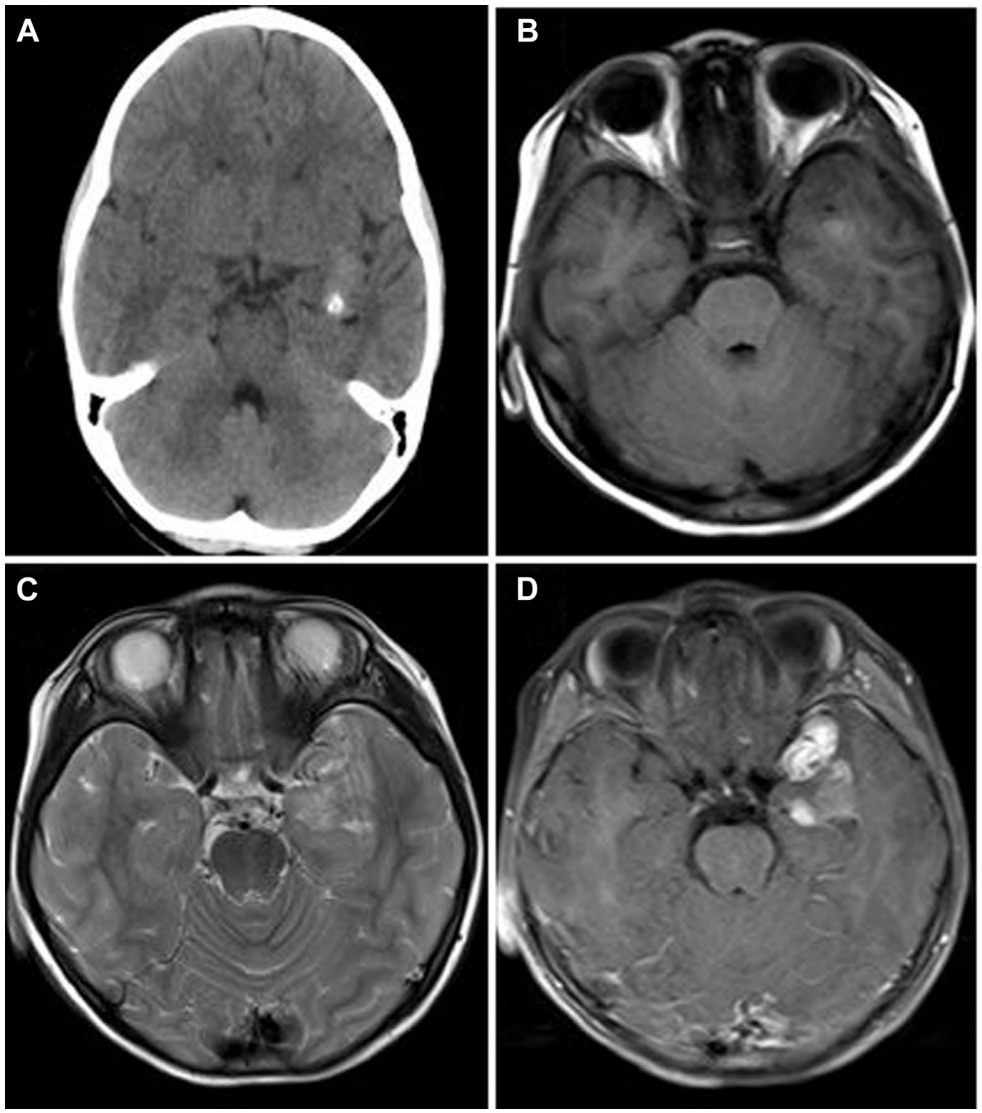

Figure 3. Radiologic characteristics of a solid tumor with cystic changes. (**A**) The tumor is isodense with calcification and is located in the left temporal lobe. (**B** and **C**) The tumor shows isointense on T1-weighted imaging and T2-weighted imaging, and there is mild edema around the tumor. (**D**) The tumor shows high enhancement and contains multiple cystic changes.

for 11.8%. On the other hand, PXAs with cystic changes or cystic lesions accounted for 88.2% in our patient group. This is consistent with previous reports, in which 8 of 11 pediatric patients with PXA had tumors with cystic components.[5] Peritumoral edema was common in pediatric PXA, with an incidence of 82.4% among our patients. In a study on the MRI characteristics of pediatric PXA, all 9 patients showed perilesional edema, classified as marked in 7 patients and mild in 2 patients.[6] Inner table scalloping was seen in one third of our patients. This is the result of the extrusion effect caused by the slow-growing, superficial nature of the tumors. Calcification was also not uncommon in our group (41.7%). Compared with grade II PXA, anaplastic PXA is often associated with high-grade features such as a large tumor diameter, obvious contrast enhancement, and extensive peritumoral edema.[10] Of our 6 anaplastic PXAs, there were 4 tumors measuring >5 cm and there were also 4 tumors with marked peritumoral edema.

We also compared temporal and nontemporal PXAs. We found that large tumors (≥5 cm) were usually located in the nontemporal lobe, and most of the tumors arising from the temporal lobe measured <5 cm. We thought this was because seizures, which can be examined and diagnosed in the early tumor stages, are the most common symptom for temporal PXA. In contrast, mass effects, which can be seen only for relatively large tumors, are

Table 3. Comparison of Temporal and Nontemporal Pleomorphic Xanthoastrocytoma (PXAs)

Variables	Temporal PXA (n = 8)	Nontemporal PXA (n = 9)	*P* Value
Age (mean ± SD)	9.38 ± 2.92	9.56 ± 2.13	0.89
Gender			1.00
Male	3	3	
Female	5	6	
Seizure			0.34
Yes	6	4	
No	2	5	
WHO grade			1.00
II	5	6	
III	3	3	
Tumor size			0.05
≥5 cm	1	6	
<5 cm	7	3	
Peritumoral edema			0.08
Obvious	2	5	
Mild	3	4	
None	3	0	
Tumor type			0.15
Solid	1	1	
Solid with cystic changes	5	2	
Solid cystic	2	2	
Cystic with mural nodules	0	4	

SD, standard deviation; WHO, World Health Organization.

common in nontemporal PXA. In addition, the tumor size was significantly associated with tumor subtype. Most of the PXAs located in nontemporal lobes had obvious peritumoral edema, while tumors located in the temporal lobe usually had mild or no edema. The different extents of peritumoral edema between the 2 groups may be correlated with tumor size.

Pathologic Features

PXA is regarded as a benign neoplasm with a generally favorable outcome after gross total resection. However, anaplastic features, recurrence, and malignant progression have been observed in some PXA patients. It can transform into anaplastic astrocytoma and glioblastoma and even undergo leptomeningeal dissemination.[11] We speculate that there may be genetic changes during the growth of the tumor that cause histologic transformation. Marton et al[12] reported a malignant progression rate of 37.5% and a mean recurrence time of 5.7 years. Therefore the latest 2016 World Health Organization (WHO) classification categorized PXA into histologic grade II and grade III tumors. In our cohort, 6 patients were defined as having WHO grade III PXA and no patients have presented with tumor recurrence. The relatively short follow-up time may be the influencing factor. Regular MRI examination is necessary for these patients. PXA can occur in the form of collision tumors. PXA combined with ganglioglioma or oligodendroglioma has been previously reported.[13,14] In our cohort, 1 patient was identified as having PXA associated with subependymal giant cell astrocytoma. This may indicate the multiple differentiation potential of the precursor cells of the tumor.

Treatment of Pediatric Pleomorphic Xanthoastrocytomas

Treatments for pediatric PXA include surgery, radiotherapy, chemotherapy, and targeted therapy. Surgical excision is the first choice for the treatment of PXA, and maximal safe resection is recommended. Surgery can not only remove the tumor but also control seizures. Intraoperative electrocorticography is necessary for patients with epilepsy. Electrocorticography-guided epilepsy surgery for pediatric patients with brain tumors is highly effective, and long-term seizure freedom can be achieved.[8] For patients with grade II PXA, if the tumor was completely resected, simple observation was recommended. When the tumor progressed, second surgery was attempted, if possible, followed by radiotherapy.[15] For anaplastic PXA, radiotherapy or chemotherapy should be considered after surgery. In our cohort, 15 patients underwent total resection and the other 2 patients separately underwent subtotal and partial resection. Five patients received radiotherapy or chemotherapy. However, given the rarity of patients and the little knowledge about their molecular biological characteristics, there is no standard adjuvant treatment regimen for pediatric PXA. PXAs are often accompanied by a high frequency of *BRAF V600E* mutations, and targeted therapy using BRAF inhibitors has been explored in several studies. BRAF inhibitors such as vemurafenib and dabrafenib have shown favorable results in a single case of relapsed anaplastic PXA.[16-18] Notably, acquired resistance could occur in a majority of patients due to reactivation of the MAPK pathway. The combination of BRAF inhibitors and MEK inhibitors could solve this problem and achieved sustained response in some reported cases.[19-21] Most recently, BRAF inhibition with concurrent tumor treatment fields for progressive PXA was shown to be well tolerated and was associated with radiographic partial response.[22]

Prognosis of Pediatric Pleomorphic Xanthoastrocytomas

Previously, PXA was regarded as an indolent tumor with a favorable prognosis; however, with an increasing number of cases reported, we have gradually recognized that PXA can have a high recurrence rate and undergo malignant transformation. For children, the mean time to progression has been reported to be 3.2 years (range, 0.2–8.6 years) and the 5-year progression-free survival rate was 49.2%.[6] Another report showed that the estimated 5-year progression-free survival and overall survival (OS) rates were 49% and 85.7%, respectively, similar to those of other reported series.[5] Perkins's study included 214 PXA patients stratified by age. For young patients (age 0–20 years), PXA had a significantly worse prognosis than pilocytic astrocytoma and oligodendroglioma and a better OS than ependymoma and glioblastoma.[3] The extent of

surgical resection and histologic grade may be associated with the prognosis of PXA, which has been reported in children and adolescents.[23,24] A larger tumor size (>4 cm) and evident peritumoral edema were considered adverse prognostic factors in adult PXA, and the latter may be correlated with disease progression in PXA grade II patients.[9] There were 7 patients with larger tumor sizes and marked peritumoral edema in our cohort. Whether these are also risk factors for pediatric PXA remains to be determined with a larger cohort size. The preoperative symptoms (whether or not the patient presents with seizure) and length of symptoms had no correlation with survival; radiologic features such as calcification or scalloping also had no correlation with prognosis.[24] In addition, the role of adjuvant therapy and mutational status of BRAF V600E in the survival of PXA patients are currently unclear. The exact prognostic factors of pediatric PXA need to be studied with a larger patient cohort and longer follow-up durations.

CONCLUSIONS

Pediatric PXA is rare and usually arises from the temporal lobe. Radiologically, the majority of tumors were accompanied by cystic components and peritumoral edema. Calcification was also not uncommon in pediatric PXA. Large PXA tumors were usually located in the nontemporal lobes, and tumor size was significantly associated with radiologic subtype. Surgery was the first choice of treatment even for recurrent PXA. The role of adjuvant therapy remains controversial and requires further investigation.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Wenhao Wu: Writing - original draft, Conceptualization. **Pengcheng Zuo:** Formal analysis, Investigation. **Chunde Li:** Methodology, Resources. **Jian Gong:** Writing - review & editing, Supervision.

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