Int J Clin Exp Med 2016;9(10):20145-20150
www.ijcem.com /ISSN:1940-5901/IJCEM0026947

Original Article

Clinical manifestations and outcomes of typical versus atypical pleomorphic xanthoastrocytoma: a single-institution experience

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Received February 29, 2016; Accepted August 19, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: Pleomorphic xanthoastrocytoma (PXA) are rare, low-grade, intracranial tumors of glial origin, classified by the World Health Organization (WHO) as central nervous system grade II tumors. Typical PXA are relatively benign neoplasms that affect children and young adults and carry favorable prognoses. However, the age of PXA onset and tumor location in some patients differ from typical PXA cases. Indeed, atypical PXA patients usually display a range of clinical manifestations and have poor prognoses. Moreover, the clinical course, prognostic factors and optimal treatment strategies for atypical PXA patients has not been extensively evaluated. Therefore, in the current study, we aimed to describe the clinical features, prognosis and treatment strategy of ten PXA cases from the Department of Neurosurgery at the First Affiliated Hospital of Soochow University, China. Between 1999 and 2013, we retrospectively analyzed the clinical manifestations, imaging findings, extent of resection, recurrence rate and a 12-162 months follow-up data from these patients. In a group of six typical PXA patients, results demonstrated that the PXA was a relatively benign neoplasm with a clear tumor boundary and favorable prognosis. However, in a group of four patients with atypical PXA, the invasiveness of the tumor and recurrence rates were higher than in the typical group, leading to increased mortality due to the difficulty in tumor excision. Therefore, successive adjuvant radiochemotherapy should be offered to patients with PXA in atypical sites or with postoperative residual PXA.

Keywords: Pleomorphic xanthoastrocytoma, treatment, prognosis, atypical

Introduction

According to the WHO classification, pleomorphic xanthoastrocytoma (PXA) is a rare, low-grade, intracranial, glial origin grade II tumor of the central nervous system affecting children and young adults. Histological characteristics of the tumor show significant cellular and nuclear pleomorphism with a mix of glial pleomorphic nuclei, single or multinucleated cells, fusiform cells in fascicles and lipidized cells. PXA usually develop within the supratentorial region with preference towards the temporal lobe (49% of the reported cases) [1, 2] PXA can be classified into typical or atypical neoplasm according to the patient's age, location, invasiveness, recurrence and prognosis of the tumor [3, 4]. Typical PXA is usually seen in adolescents, and has a favorable prognosis [2] with a five-year survival rate of >80% [1]. Atypical PXA carry a less favorable prognosis and high recurrence rate [3-6]. In this study, we analyzed and discussed the clinical features, relapse and prognosis of atypical versus typical PXA based on 10 cases from the Department of Neurosurgery at the First Affiliated Hospital of Soochow University. We aimed to examine the clinical outcome in patients with atypical PXA upon undergoing routine PXA treatment.

Materials and methods

Patients

Ten patients (six males and four females) diagnosed with PXA were enrolled in this study from

Table 1. Clinical summary of the two types of PXA

	Gender	Age (Years)	Location	Diagnosis	Recurrence	Follow-up (Months)
Typical PXA	f	18	L F	PXA	N	24, NED
	m	69	R TP	PXA	Y	6, DOD
	m	66	R TP	PXA	N	80, DOC
	f	19	R FT	PXA mix gliosarcoma	N	72, NED
	f	17	R T	PXA	N	162, NED
	m	55	L P	PXA	N	60, NED
Atypical PXA	f	49	D F	PXA	Y	62, DOD
	m	61	R Ce	PXA	Y	22, DOD
	m	56	IV V	PXA	Y	6, DOD
	m	20	Ce (vermis)	Anaplasia PXA	Y	24, DOD

f, female; m, male; T, temporal; F, frontal; P, parietal; V, ventricle; Ce, cerebellum; R, right; L, left; D, double; NED, no evidence of disease; DOD, died of disease; DOC, died of other cause.

1999 to 2013. The enrollment criteria were: 1. PXA or anaplastic PXA cases as confirmed by pathological analysis. 2. Patients who were able to be followed up for more than one year postoperatively. The exclusion criteria of this study were: 1. Patients who were diagnosed with any other forms of cancer. 2. Patients with additional intracranial tumors. Six patients with supratentorial unilateral lesion were assigned to the typical group and the other four patients were assigned to the atypical group, according to the aforementioned criteria.

Methods

Over a period of fourteen years, between 1999 and 2013, 1458 glioma patients were treated in the Department of Neurosurgery at the First Affiliated Hospital of Soochow University, China. Amongst these patients, ten cases were identified as PXA patients by histopathological examination. The data of these PXA patients were retrospectively retrieved from paper-based medical records between 1999 and 2007, and an electronic medical record system from 2007 to 2013 to collect the following information; age, disease course, imaging information, pathology results and photographic images. Postoperative follow-up duration ranged between one and fourteen years.

Statistical analysis

Survival time was calculated as the time from surgical resection of the tumor to death, and differences between the typical and atypical groups were compared by Student's t-test and Fisher's exact test. A survival curve was obtained by Kaplan-Meier analysis and the difference between both groups was estimated with log-rank test. Sigmaplot 12.0 (Systat Software Inc., Chicago, IL, USA) was used for analysis and mapping.

Results

The morbidity rate of PXA was 0.7% among the glioma cases (10/1458 cases) as confirmed by pathological examination. The age of PXA patients ranged from 17 to 69 years, 40% of cases were ≤20 years old (four cases). 20 and 65 years were the two peak stages of PXA development, and the onset of symptoms ranged from one week to four years (**Table 1**).

Tumor location

In four of the PXA patients, tumors were located in the right temporal lobe. The fifth patient suffered from a tumor in left occipital region and the sixth patient developed the tumor in left parietal lobe. The tumor was located in the anterior fossa of the seventh patient, in the cerebellum of eighth patient, in left ventricle of the ninth patient, and finally, in the IV ventricle of the tenth patient. Six patients with supratentorial unilateral lesions were included in the typical group, and the remaining four patients were included in the atypical group (**Table 1**).

Clinical manifestations

Four patients suffered from epilepsy, another four patients developed intracranial hypertension, one patient developed focal neurological signs, and the final patient had blurred vision. No obvious differences in age were observed between the two groups (P=0.704), although the age of the atypical group was slightly higher (46.5 vs 40.6). In the typical PXA group, five patients suffered from epilepsy, while all of the atypical PXA patients developed intracranial hypertension (**Table 2**).

Table 2. Demographic characteristics of patients in both PXA groups

Characteristics	Typical PXA (n=6)	Atypical PXA (n=4)	*p* value
Age			
Mean	40.6	46.5	0.704[a]
Range	18-69	20-61	
Gender			
Male	3	3	0.571[b]
Female	3	1	
Tumour grade			
WHO II	5	3	1[b]
WHO III	1	1	
Ki67	5.1±3.2%	6.5±3.5%	0.522[a]
Tumour Size	30.2±12.1 cm^3	24.1±10.4 cm^3	0.395[a]
Symptoms			
Seizure	5	0	0.048[b]
Other	1	4	
Extent of resection			
GTR	4	1	0.524[b]
STR	2	3	
Recurrence	1	4	0.048[b]

GTR, Gross total removal; STR, subtotal removal; [a]Student's t-test. [b]Fisher's exact test.

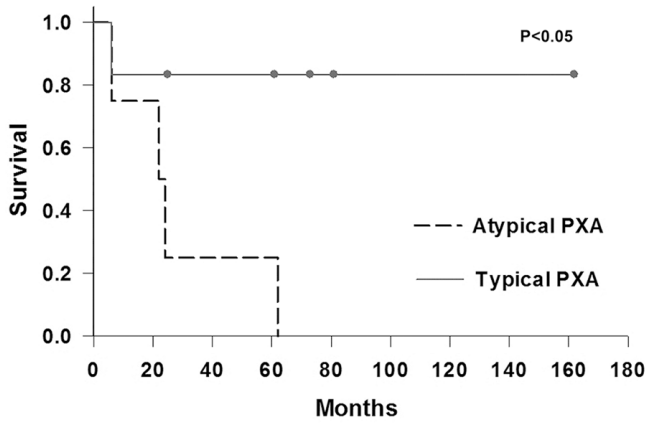

Figure 1. Overall survival curves (Kaplan-Meier method) based on the type of PXA.

Magnetic resonance imaging (MRI) and computed topography (CT) scans

MRI revealed cystic-solid lesions in five patients, two patients had cystic lesions and three patients had solid lesions (**Figure 2**). CT scans demonstrated heterogeneous low density or isodense lesions with clear borders, without calcification, and strengthened parenchymatous areas were observed. MRI scans demonstrated lesions with irregular shadows, clear margins and cystic degeneration. Four cases had typical wall nodules, and minimal or moderate edema at the periphery of tumors (**Figure 2**). No differences were seen between the typical and atypical groups by iconography.

Surgery

Tumor resection under microscopic guidance was performed in all patients. Five of the six patients in the typical group exhibited a clear tumor margin, and one patient exhibited an indistinct tumor border. Therefore, total resection was possible in five patients in the typical PXA group. The final patient underwent subtotal resection. In the atypical group, two patients had tumors with unclear margins and invasion into the brain parenchyma. Complete removal of the tumor was performed in one patient and subtotal resection in three patients (**Table 2**).

Pathology and prognosis

In the typical PXA group, one patient showed PXA mixed with a glioma. However, in the atypical group, one case went on to develop anaplastic PXA (**Table 1**). Histological and immunohistochemical features did not differ significantly between the two groups. However, Ki67 labeling indices were slightly higher in the atypical 6.5±3.5% versus the typical group 5.1±3.2% (**Table 1**). In the follow-up period (24-162 months), all patients in the atypical group relapsed, while only one patient in the typical group had relapsed. The survival time in the typical group patients was longer, with more than the five years follow up period. Among the six typical PXA patients, five patients survived, and one died. In the atypical group, all patients died, the survival time was shorter, and survival analysis showed significant differences between groups (**Figure 1**, *P<0.05*). In summary, the prognosis of PXA in the atypical group was poor, and the survival time was distinctly shorter, compared to the typical PXA patients (**Figure 1**, *P<0.05*).

Discussion

PXA is rare grade II astrocytic neoplasm that was first described by Kepes et al. in 1979 [7].

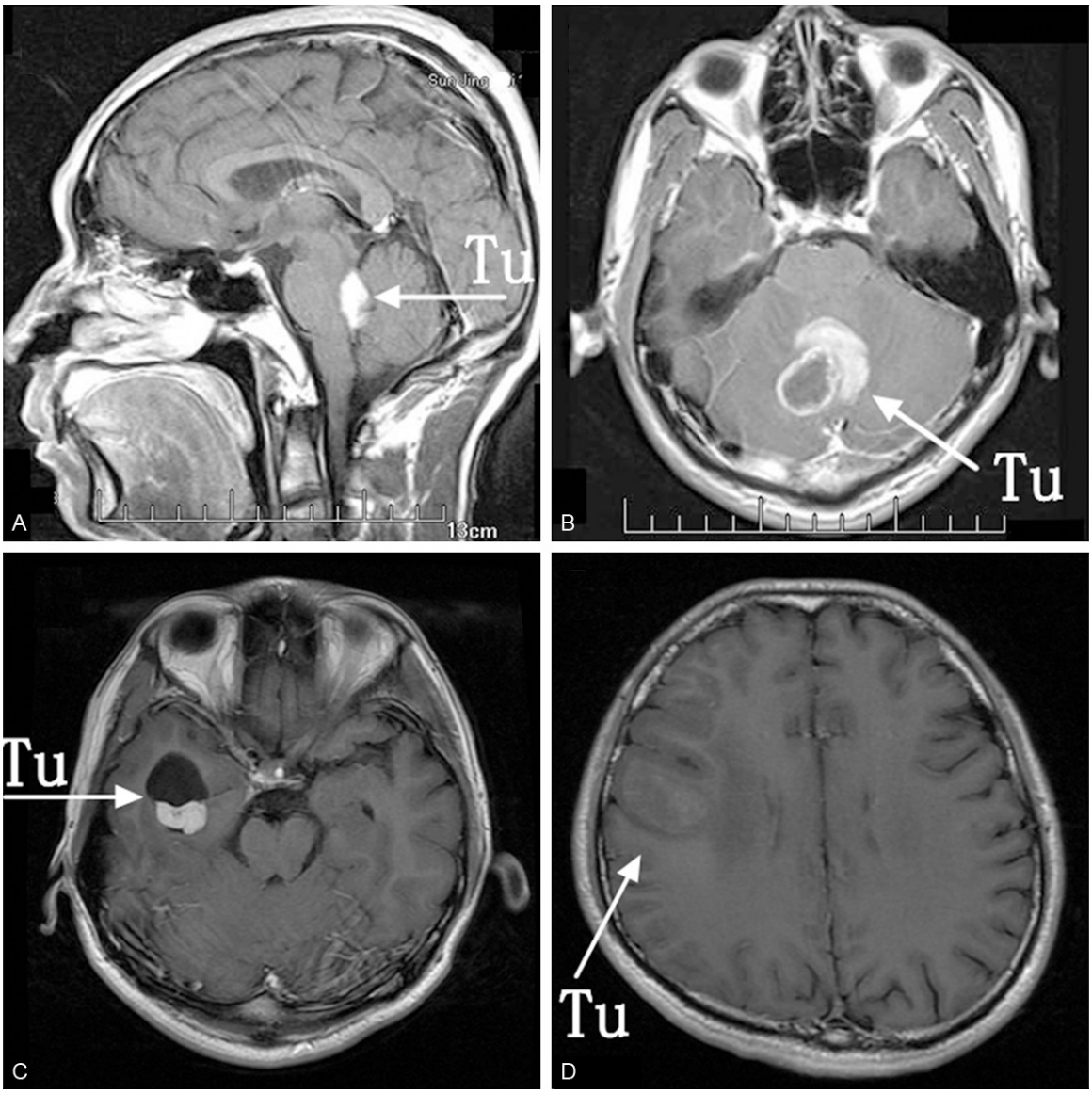

Figure 2. Representative MRI scans of two patients with atypical PXA (A, B) and two patients with typical PXA (C, D). Arrows show the tumor mass. Tu (tumor). (A) IV ventricle PXA; (B) Cerebellum vermis PXA; (C) Temporal lobe PXA show enhance tumor mass with cyst; (D) Parietal lobe mass with weak enhance.

Incidence in the temporal lobe is twice as high as the incidence in frontal, parietal, and occipital lobes [1]. Epilepsy and headaches are common clinical symptoms of PXA [2]. Most PXAs display a relatively favorable outcome, however, some PXAs show rapid progression unlike typical low-grade gliomas. Furthermore, the location of some atypical tumors include the cerebellum, thalamus, hypothalamus, callosum, pineal body, and/or multicentric distribution [8-11]. Therefore, it is clinically important to identify patient subpopulations with poor prognosis and establish effective therapeutic modalities.

In the current study, according to the tumor location, we classified PXA into typical and atypical groups. Supratentorial unilateral PXA was included in the typical group, while subtentorial and deep bilateral frontal lobes were included in the atypical group. The First Affiliated Hospital of Soochow University is an adult hospital, therefore, patients below 16 years old were not enrolled in this study. The lack of pediatric patients led to an average age of 40.5 and 46.5 years old in the typical and atypical PXA groups, respectively, which was higher than that reported in literature (26.3 years) [2]. In the atypical PXA group, tumors

were observed in rare pathogenic sites such as the IV ventricles and cerebellum. Tumor size and Ki67 labeling showed no significant differences between the two groups. Conversely, the recurrence rate of tumors was statistically different between the two groups (100% [atypical group] vs 17% [typical group]; *P<0.048*). Lim et al. previously reported that with tumors in atypical sites, peritumoral edema and tumor size were prognostic factors for recurrence [12]. We observed similar findings in our study. The atypical PXA group had a poor prognosis and the survival time was significantly shorter compared to the typical group.

Surgery is the main treatment for PXA. Patients who undergo total tumor resection often show good prognosis [2, 13, 14]. The typical group was easier to treat with complete tumor removal. Moreover, the total resection rate was higher in patients with supratentorial unilateral lobe lesions. Nonetheless, in the atypical group, cerebellum tumors were observed in two cases and IV ventricle lesions in one case. These tumors could not be completely removed especially tumors in the IV ventricle. Another case showed a bilateral frontobasal lesion that invaded the median line, with postoperative residue. Hence, gross total removal was lower in the atypical group. In this study, we observed that patients displaying an atypical feature of PXA (atypical PXA group) have a poor prognosis and hence, we recommend that those patients should undergo adjuvant radiotherapy or chemotherapy to increase their odds of survival. Adjuvant radiotherapy were considered effectiveness when there is postoperative residual tumor and/or anaplastic features [15].

In conclusion, we examined the incidence and prognosis of PXA in adults. In typical PXA patients that undergo full tumor excision, adjuvant radiotherapy is unnecessary but long-term follow-up and reexamination is recommended. Conversely, successive adjuvant radio/chemotherapy should be offered to patients whom PXA develops at atypical sites or with postoperative residual PXA as well as anaplastic PXA patients to extend their survival time. Given the slow growth of the tumor and its rarity, more cases and longer follow-up periods will be needed to confirm our findings.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (Grant No. NSFC81372689), the Foundation of Health Department in Jiangsu Province (Grant no. K201106). Also, we would like to thank Medjaden Bioscience Ltd [http://www.medjaden.com/index.html] for providing English language editing services.

Disclosure of conflict of interest

None.

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