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Malignant progression in pleomorphic xanthoastrocytoma: Personal experience and review of the literature

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Abstract

Pleomorphic xanthoastrocytoma (PXA) is a rare primary low-grade astrocytic tumor, recently classified as a neuroglial tumor. It generally occurs in children and young adults and shows benign behaviour (WHO II), although an anaplastic variant and malignant potential have been described. Pleomorphic xanthoastrocytomas with malignant transformation have been reported in three out of eight patients operated on for this type of tumor in our department in the last 15 years. The three patients were two adult women and a child, the primary tumors were located in the cortex of the right temporal lobe, and treatment consisted of complete surgical resection. Histological examination revealed simple PXA in two patients and a PXA with anaplastic foci in the other. Mean recurrence time was 5.7 years, with the original xanthoastrocytoma evolving to glioblastoma in two cases and anaplastic astrocytoma in the third. All three patients underwent a second operation, followed by adjuvant therapies. Two died from tumor progression and one from brain edema after intracerebral haemorrhage.

A review of the available PXA literature dating back to 1979 revealed 16 cases of primary anaplastic astrocytoma and 21 cases of PXA with malignant transformation. Our experience adds three more cases of malignant transformations, outlining once again the potential malignancy of pleomorphic xanthoastrocytomas and the fact that prognosis in these cases is the same as for primary anaplastic astrocytoma and glioblastoma. Analysis of glioneuronal markers, Ki67 and p53 in all pleomorphic xanthoastrocytomas did not prove to be a discriminating factor to identify a subgroup of xanthoastrocytomas prone to malignancy. Accordingly, these tumors demand close long-term clinical and radiological follow-up.

Keywords: Xanthoastrocytoma; Low-grade glioma; Malignant transformation

1. Introduction

Pleomorphic xanthoastrocytoma (PXA) is a rare low-grade glial tumor described for the first time in 1979 by Kepes [1]. This tumor is superficially located, involves the cortex and leptomeninges but not the dura, and generally occurs in children and young adults. The temporal lobe is the predominant site of location and seizures are the main manifestation. PXAs are generally supratentorial, but cerebellar lesions have also been described [2,3]. They tend to be cystic with a mural nodule. Histological features include marked cellular pleomorphism, variable lipidization, abundant reticulin and perivascular inflammatory cells, with no necrosis. PXA is classified as a low-grade astrocytic tumor (WHO II), but recent studies have demonstrated the presence of both neuronal and glial markers in the tumor cells, and the presence of neuroglial differentiation suggests that they may derive from multipotential precursor cells [4]. The tumor is generally associated with long survival after complete surgical excision and has a favourable prognosis. However, cases of PXA with primary anaplastic features and malignant potential are less uncommon than previously reported [3,5–33].

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2. Materials and methods

Over the last 15 years, 8 cases of pleomorphic xanthoastrocytoma have been referred to our institution for surgery. Three of them evolved into malignant gliomas in a mean time of 5.7 years. The aim of this report is to describe these latter three cases, highlighting their clinical features, pathological findings and the therapeutic approaches adopted.

2.1. Case 1

A 40-year-old Caucasian female presented with a sudden episode of hypersomnia followed by a generalized epileptic seizure. During anamnestic interview, she reported occasional difficulty in remembering names or object definitions. Neurological examination at admission was normal.

Cerebral computerized tomography (CT-scan) and magnetic resonance imaging (MRI) showed the presence of a small solid lesion at the anterior pole of the right temporal lobe, without clear dural attachment, inhomogeneously hyperdense/hyperintense, with irregular enhancement after contrast injection (Fig. 1).

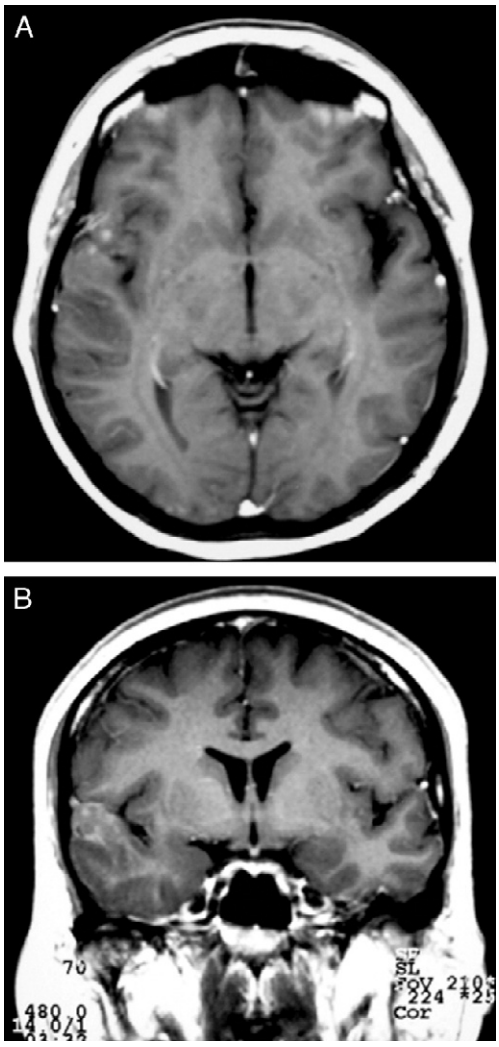

Fig. 1. Case 1: pleomorphic xanthoastrocytoma in the right temporal lobe.

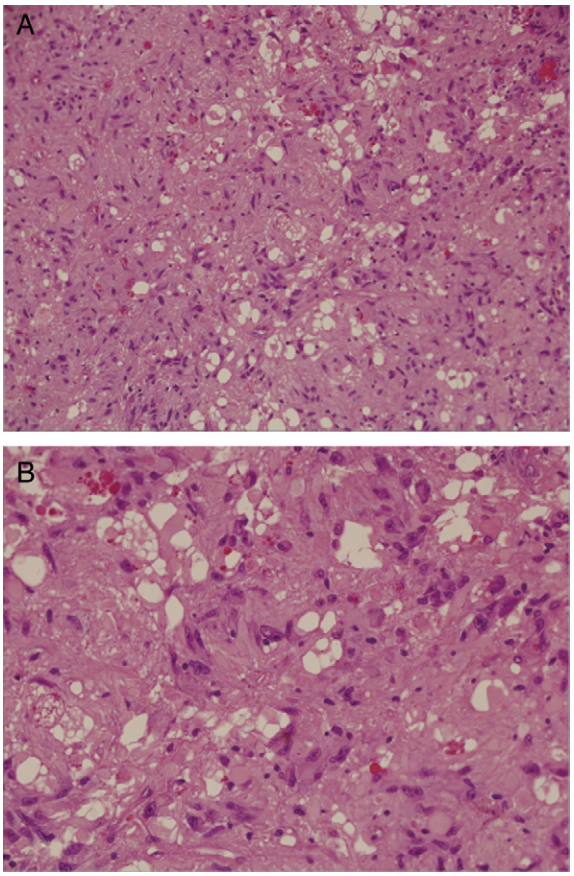

Fig. 2. Case 1: histological features of a pleomorphic xanthoastrocytoma include marked cellular pleomorphism, variable lipidization, abundant reticulin and perivascular inflammatory cells, without necrosis (A: EE, 200× and B: EE, 400×).

The patient underwent craniotomy with macroscopically complete excision of the mass, which was focally attached to the dura mater. The post-operative course was free of complications.

Histological examination revealed a lesion with multinucleated giant cells, rare xanthic cells, nuclear inclusions and perivascular lymphocytes, without necrosis or endothelial proliferations. Mitoses were 6/10 high power fields (HPFs). Immunohistochemical analysis identified positivity for glial fibrillary acidic protein (GFAP), p53 (++) and S-100 protein; synaptophysin and neurofilaments were not represented. The Ki67 (MIB1) labelling index was 12% (Fig. 2). The diagnosis was pleomorphic xanthoastrocytoma, with anaplastic foci.

Two years later, the patient presented new symptoms, as headache, asthenia, memory impairment, followed by stuporous state. CT-scan and MRI revealed a relapse of the tumor, located in the right temporal lobe, which was irregular in shape, with a hypointense central core, an enhancing ring, and surrounding edema (Fig. 3). The patient underwent a second operation in order to remove the new lesion. Histology determined the new tumor to be a giant-cell glioblastoma

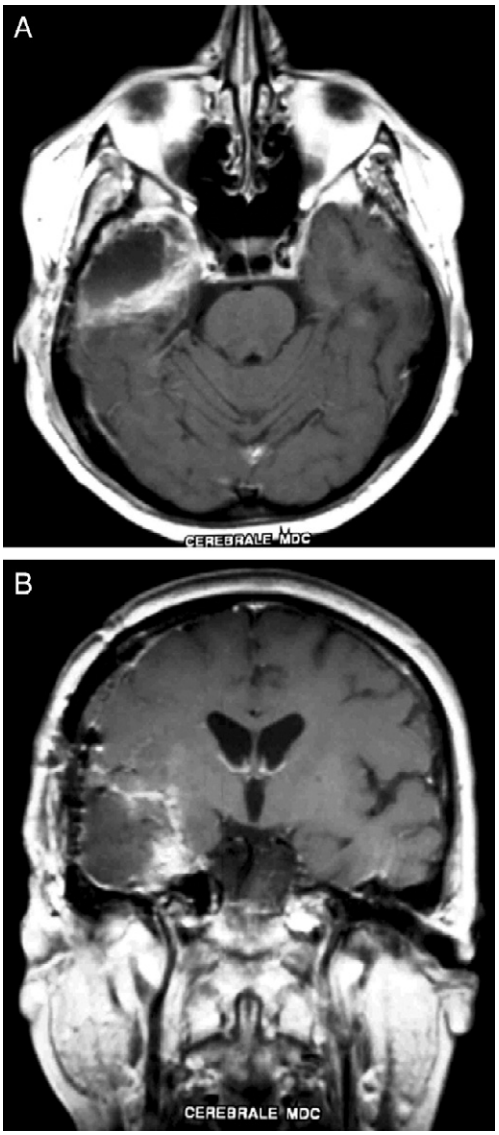

Fig. 3. Case 1: local recurrence of a necrotic lesion with ring enhancement 4 years after the first diagnosis. Pathological examination revealed a glioblastoma multiforme.

multiforme (Fig. 4), prompting radiotherapy and chemotherapy with temozolamide.

Three years later, a new recurrence was detected. The lesion appeared as a solid enhancing nodule in the hippocampus with a cystic portion in the temporal lobe (Fig. 5). A third operation was performed, and histological examination confirmed the presence of a high-grade fibrillary astrocytoma (grade IV, WHO). GFAP and S-100 protein expression was detected, synaptophysin was absent. The patient died from tumor progression 8 months after the third craniotomy.

2.2. Case 2

An 8-year-old Caucasian girl presented with a history of progressive headache and generalized fatigue. CT-scan and MR imaging showed the presence of an expansive cystic lesion with an enhancing mural nodule in the right temporal lobe, with no dural attachment. At admission, neurological examination was negative. The neoplasm was surgically removed. Histological examination revealed the presence of multinucleated giant cells, with rare xanthic cells, granular bodies and calcifications. No necrosis, no endothelial proliferation and no perivascular lymphocytes were detected, with 3 mitoses per 10 HPFs. Immunohistochemistry yielded positivity for GFAP, Ki67 of 2% and negativity for synaptophysin and neurofilaments; S-100 and p53 were not analyzed. There was no necrosis and no mitosis. All these elements supported a diagnosis of pleomorphic xanthoastrocytoma.

Fourteen years later, the patient was hospitalized because of drowsiness, severe headache, complete impairment of the right 3rd cranial nerve, left hemiparesis, and diplegia. A new craniotomy was performed to remove a recurrence of the lesion, which heterogeneously enhanced on MRI with an important surrounding edema and midline shift. Histological examination revealed an anaplastic astrocytoma (WHO III) with clear signs of malignant progression, focal necrosis and mitosis, expressing GFAP and S-100 protein; neurofilaments and synaptophysin were absent. The Ki67 labelling index was expressed at 10% (Fig. 6). The patient died 10 days after

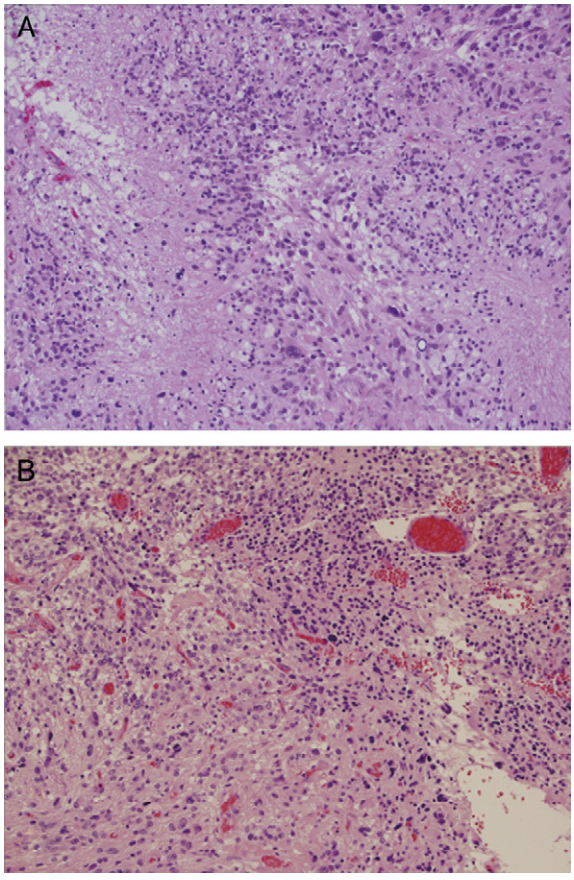

Fig. 4. Case 1: histological features of glioblastoma multiforme include necrosis and neovascularization (EE, 200×).

surgery from untreatable intracranial hypertension and hemispheric ischemia.

2.3. Case 3

A 56-year-old female presented with a 6-month history of worsening headache, defect of short-term memory and alteration of mood. CT-scan and MR imaging showed a cystic lesion in the right temporal lobe with a slight ring enhancement and no dural attachment (Fig. 7). The patient underwent surgical removal of the tumor, which was identified as a pleomorphic xanthoastrocytoma (grade II, WHO) on histological examination. The tumor was composed of multinucleated giant cells, xanthic cells, Rosenthal fibers, granular bodies and nuclear inclusions, perivascular lymphocytes and glomeruloid vessels. Necrosis and mitosis were absent, and the Ki67 labelling index was 1% (Fig. 8).

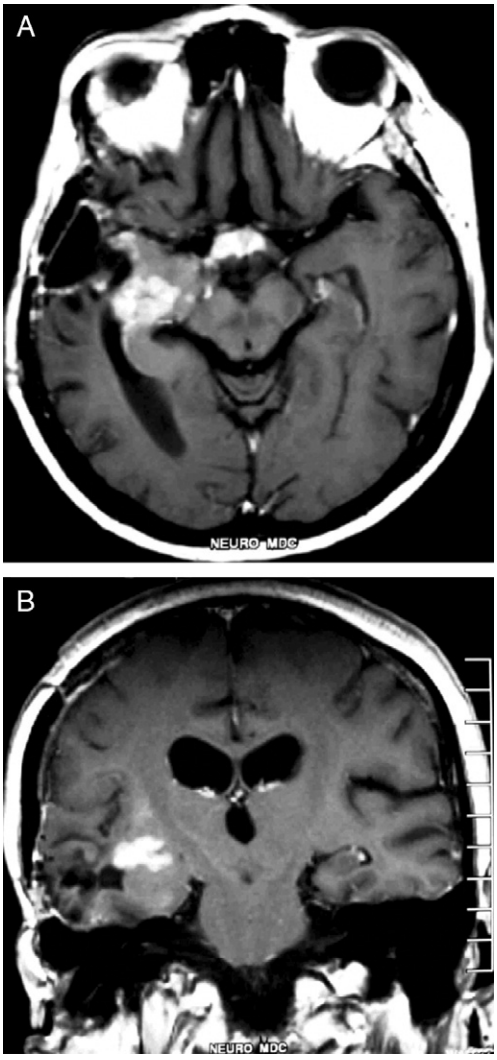

Fig. 5. Case 1: recurrence of glioblastoma multiforme 8 months after the second craniotomy and after radiotherapy and chemotherapy with temozolamide.

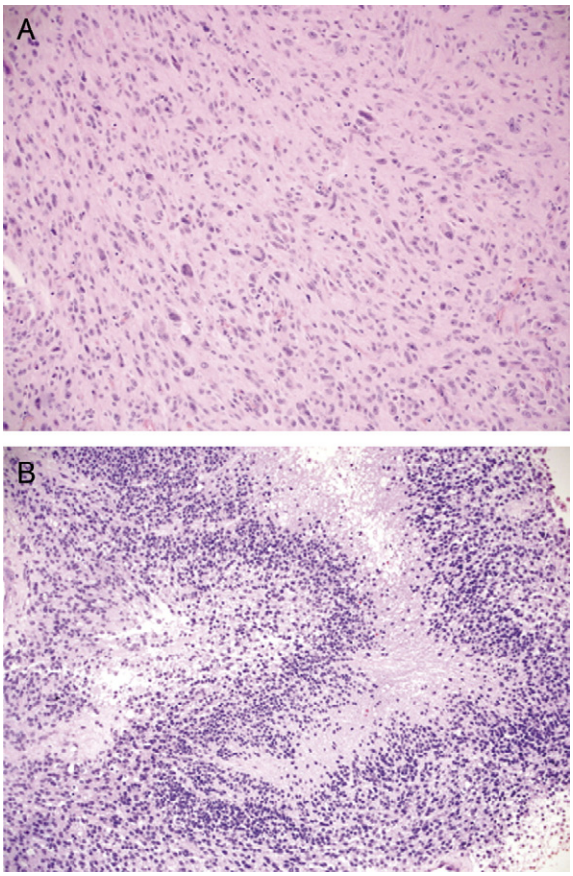

Fig. 6. Case 2: (A) Astrocytic tumor with pleomorphic and multinucleated cells (EE, 200×). (B) The lesion evolved into a high-grade astrocytoma with necrosis (EE, 200×).

Immunohistochemistry yielded positivity for GFAP, p53 and S-100 protein, but neurofilaments and synaptophysin were not expressed. The patient declined radiotherapy after surgery.

One year later, the patient was newly admitted to our hospital because of severe headache and progressive asthenia; MRI demonstrated a relapse of the lesion in the right temporal lobe, consisting of an enhancing nodule and a small satellite cyst (Fig. 9). A second craniotomy was performed and the tumor removed. In this case too, histological examination revealed a malignant progression of the neoplasm towards glioblastoma, with necrosis and mitosis 5/10 (400×), expressing GFAP, p53 (10%) and S-100 protein; neurofilaments and synaptophysin were absent. The Ki67 labelling index was expressed at 15%, +CD138. The patient underwent radiotherapy and chemotherapy with temozolamide, and died 15 months after completing adjuvant therapies.

In summary, all three cases harboring pleomorphic xanthoastrocytomas with subsequent malignant progression were positive for GFAP and negative for neurofilaments and synaptophysin; S-100 and p53 were analyzed and found to be present in two; Ki67 ranged from 1% to 12%.

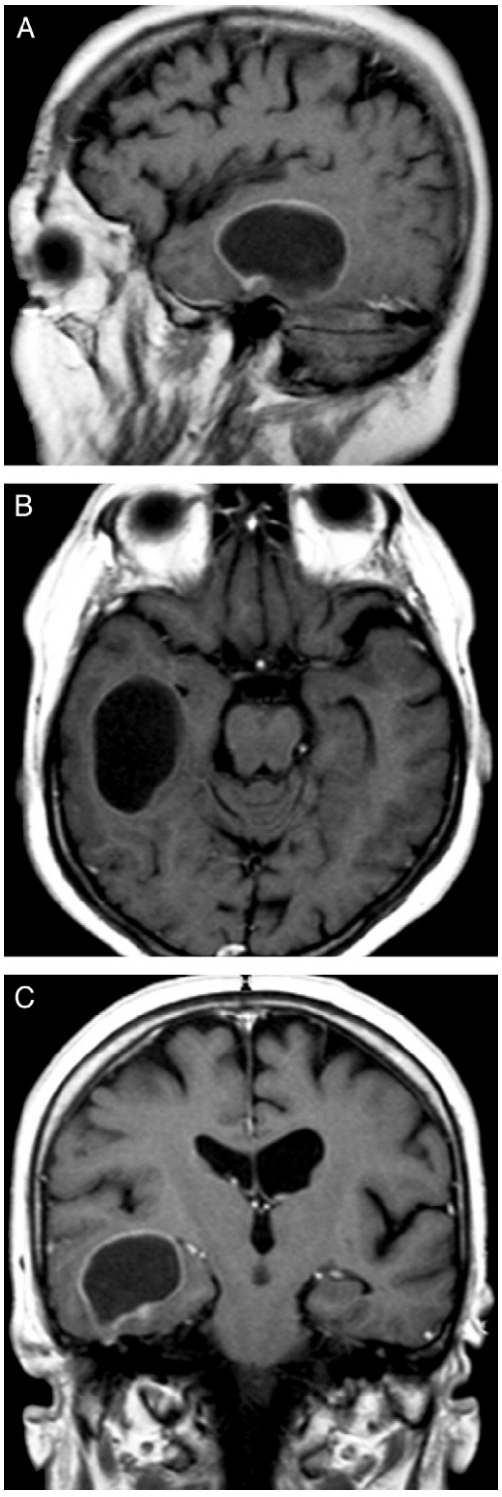

Fig. 7. Case 3: RMI image of a right temporal pleomorphic xanthoastrocytoma: local recurrence 3 years after the first craniotomy. The pathological examination revealed a glioblastoma multiforme.

For the purposes of comparison, we then reviewed all pathological samples of non-evolving PXA. All of them expressed multinucleated giant cells, xanthic cells, Rosenthal fibers, and granular bodies. Nuclear inclusions and perivascular lymphocytes were present in 3 out of 5 cases; necrosis, calcifications and endothelial proliferation were all absent. Mitosis ranged from 1 to 2 per 10 HPFs. All were positive for GFAP and S-100, synaptophysin and neurofilaments were absent, Ki67 ranged from 2% to 10%.

Substantially, neither histological elements nor immunohistochemistry constitute a distinctive factor to identify a potentially evolving PXA at onset (Table 1).

3. Discussion

3.1. Histogenesis and behaviour

Pleomorphic xanthoastrocytoma is a rare, usually low-grade, astrocytic tumor, with a generally good prognosis, although anaplastic features and potential malignant transformation have been described.

The histogenesis of PXA is less clear: recent studies have suggested that it might derive from bipotential precursor cells [29,34]. Previous analysis also proposed mesenchymal precursors [35] or a subclass of astrocytes origin [36]. The existence of complex PXA with components of neuronal differentiation has been described, as composite PXA-ganglioglioma or PXA-oligodendroglioma. One of our patients presented a mixed PXA-ganglioglioma.

Recurrence and malignant progression of PXA have been repeatedly reported, with progressions to high-grade PXA, malignant astrocytomas, or glioblastoma multiforme.

PXA was first described in 1979 [1], and in 1999 a total of 121 cases of PXA had been published [37]. In 2004, Tekkok [38] reported a total literature review of less than 200 cases, collected over a 25-year period. In particular he revealed the presence of 11 cases of primary anaplastic PXA and 16 cases of PXA with secondary malignant transformation.

After the review of Tekkok [38], we could collect a further 37 new cases of PXA in the literature. In particular, 26 typical PXAs [2,30,31,39–48], 2 typical PXAs with dissemination at diagnosis [49,50], 5 anaplastic PXAs [3,24–27] and 5 PXAs with subsequent malignant progression [28–31]. We have added two more cases of PXA with malignant transformation and one case of anaplastic PXA evolving to glioblastoma. Hence, the review of the entire PXA literature including our three cases has revealed a total of 17 anaplastic PXAs (Table 2) and 23 PXAs with malignant transformation (Table 3).

We describe our experience of one case of progression to anaplastic astrocytoma and two cases of progression to glioblastoma multiforme, with a malignancy progression rate of 37.5% and a mean recurrence time of 5.7 years. In particular the case of anaplastic PXA (case 1) recurred as a glioblastoma after 2 years. Our two cases of PXA with malignant progression recurred after 14 years (case 2) and 1 year (case 3), respectively.

In the literature the time required for such transformation varies from 7 months to 15 years, with a malignant transformation rate of 10–20% [5,28].

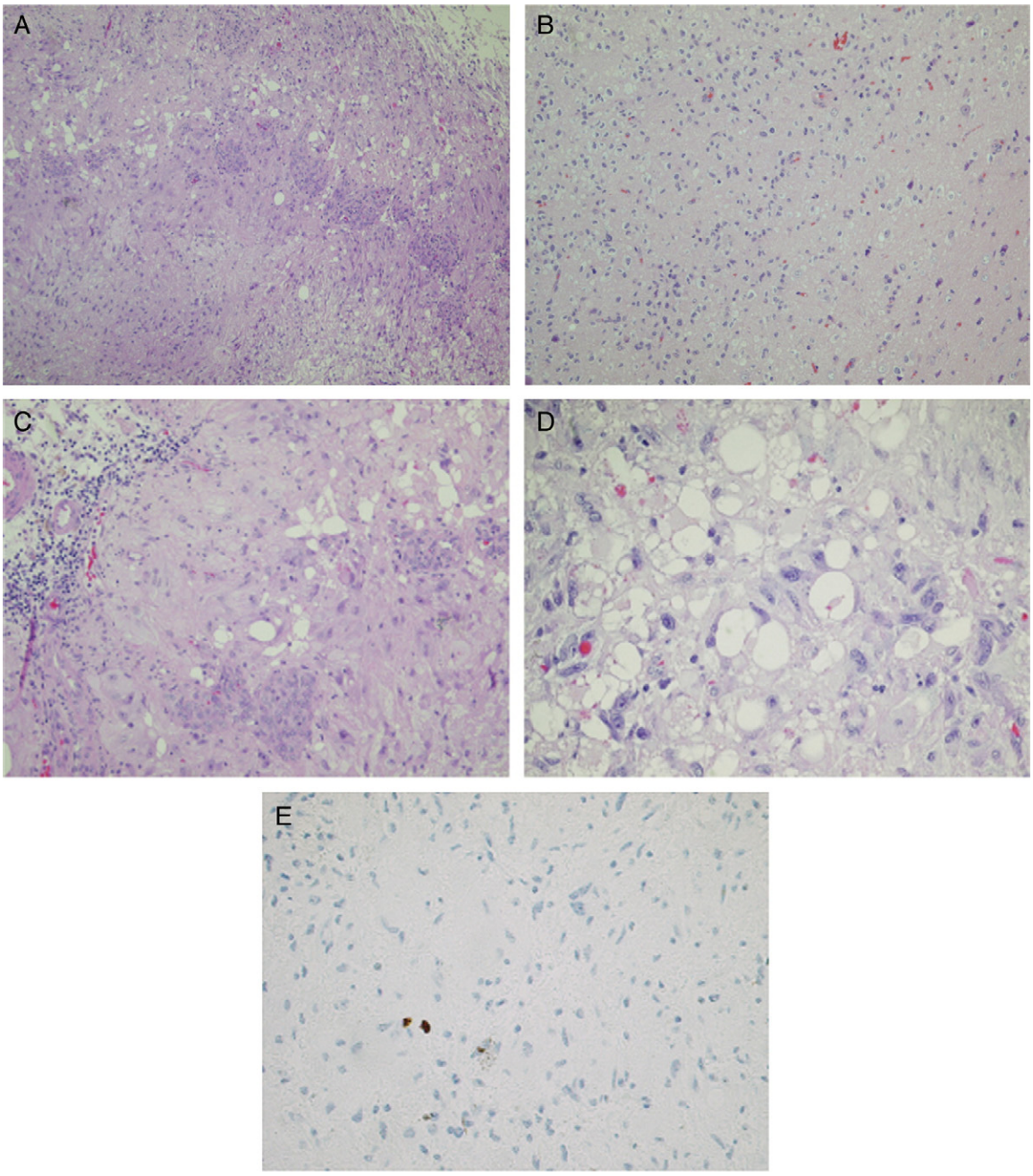

Fig. 8. Case 3: Pleomorphic xanthoastrocytoma with infiltrative aspect (A, B: EE, 100×), where xantic cells, glomeruloid vessels and perivascular lymphocytes are visible (C: EE, 200×). Particulars of xantic cells (D: EE, 400×) and of MIB1 (E: antibodies Ki67, 400×) which show a labelling index of 1%.

Malignancy recurrence time varies considerably. Mean malignancy progression time in the group of anaplastic PXAs (Table 2) is 12.8 months (1–36 months).The malignancy progression time for simple PXA varies from 1 month to 18 years [15].

3.2. Diagnosis

PXAs are characterized by the presence of spindle-shaped cells with elongated nuclei, arranged in bundles or in a storiform pattern. They present bizarre giant cells that are multinucleated or have multilobulated nuclei, with intracytoplasmatic lipid-containing vacuoles (xanthic), and are generally organized in alveolar structures, with an abundant surrounding reticulin network and perivascular lymphoid infiltrates. Mitosis is usually absent or rare and there is no necrosis. Conversely, atypical PXAs show high mitotic activity with marked hypercellularity and necrosis: the differential diagnosis with glioblastoma is based on reticulin staining, the absence of endothelial proliferation, vascular hyperplasia and pseudopalisading.

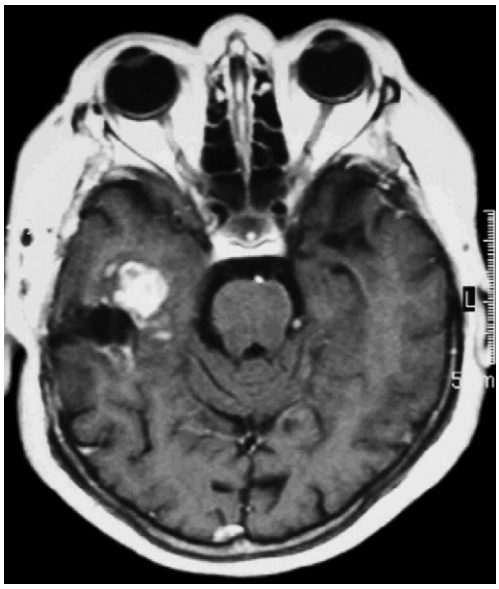

Fig. 9. Case 3: local recurrence 3 years after the first craniotomy (axial T1+ gadolinium image). The pathologic examination revealed a glioblastoma multiforme.

Recently, immunohistochemical and cytogenetic analyses have sought to avoid misleading diagnoses in the differential diagnosis of PXA with atypical or anaplastic features and to understand whether malignant transformations of previously normal PXA can be distinguished from primary high-grade gliomas.

Immunocytochemical patterns include the presence of GFAP, which may be faint or focal. Complete lack of GFAP has not been described [4,27]. While GFAP and S-100 are generally present, neuronal markers like synaptophysin, class III beta-tubulin and NF proteins have also been described [4,48,51], with different distribution rates. Ultrastructural analyses have demonstrated neuronal features as microtubules, dense core granules and clear vesicles [4]. PXA is usually reported for at least focal staining of individual tumor cells for most of the neuronal antigens tested [51]. The underlined double pattern of histological markers could be useful in differential diagnosis in difficult, anaplastic cases or in limited samples of PXA.

On the other hand, analysis showed the p53 mutation [51] to be negative or focally positive in PXA, and strongly represented in high-grade tumors. In 2001, Giannini and colleagues [52] concluded that the p53 mutation was an uncommon genetic event in PXA formation and did not seem to be involved in tumor progression.

In our three cases of malignant progression of pleomorphic xanthoastrocytoma, histochemical analysis exhibited GFAP positivity in 100% of cases. S-100 and p53 were clearly expressed in two out of three patients (67%), while synaptophysin and NF proteins were absent (0%). Ki67 (MIB1) was differently expressed (1%, 2%, 12%, respectively).

Table 1
Histologic and immunohistologic features in PXA specimens

Patient	PXA with malignant progression			PXA				
	1	2	3	4	5	6	7	8
Multinucleated giant cells	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Xantic cells	Rare	Rare	Yes	Yes	Yes	Yes, rare	Yes	Yes
Granular bodies	No	Rare	Yes	Yes	Yes	Yes	Yes	Yes
Rosenthal fibers	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Nuclear inclusions	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Reticulum	Rare	Rare	Rare	Yes	Rare	Yes	Rare	Rare
Perivascular lymphocytes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Calcifications	No	Yes	No	Yes	No	No	No	No
Mitosis × 10 HPF	6	3	No	1	1	1	2	1
Endothelial proliferations	No	No	Glomeruloid vessels	No	No	No	No	No
Necrosis	No	No	No	No	No	No	No	No
MIB-1	12%	2%	1%	2%	4%	10%	7%	6%
GFAP	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
S-100	Yes	Not analyzed	Yes	Yes	Yes	Yes	Yes	Yes
NF	No	Not analyzed	Not analyzed	Not analyzed	Not analyzed	Not analyzed	Not analyzed	Not analyzed
Synaptophysin	Not analyzed	No	No	No	No	No	Yes in the gangliar component	No
p53	++	Not analyzed	+	Not analyzed	No	Not analyzed	+	Not analyzed
First diagnosis	PXA with anaplastic foci	PXA	PXA	PXA	PXA	PXA	PXA-ganglio-glioma	PXA
Second diagnosis	GBM	Anaplastic astrocytoma	GBM					

Patients 1–3 are the cases of PXA with malignant progression.

Table 2
Literature primary anaplastic PXA cases

Reference, year	Age/Sex	Location	Treatment	Recurrence interval	Total survival
Jones et al. [17]	14/F	P	S+RT	15 months	24 months
Goldring et al. [18]	24/F	T	S+CT	Fatal 12 months	
Grant and Gallagher [19]	17/f	P	S		1 month
Iwaki et al. [23]	30/M	PO	S (×2)+RT	6 months	Alive/10 months
Gaskill et al. [6]	10/F	TP	?	?	?
Perry et al. [20]	18/M	T	S (×4)+RT+CT	3 recurrences in 4 years	4 years
	82/M	F	S		?
Tonn et al. [12]	18/M	TO	S (×2)+RT+CT	8 months	Alive/2.5 years
Chakrabatry et al., 1999 [21]	49/M	TP	S+RT		Alive/3 months
	40/M	T	S+RT		Alive?
Bucciero et al., 1999 [24]	65/M	Thalamic	S+RT	22 months	Died
Abdullah et al., 2003 [26]			?	?	?
Zhuang et al. [25]	53/F	F+F	S+RT+CT		Alive/24 months
Lubansu et al. [22]	7/F	T	S+CT	4 weeks	Alive/26 months
Gelpi et al. [27]	43/F	O	S+RT	3 years	Alive/7 months
Chang et al. [3]	4/F	Cerebellar	S	12 years	Alive
Marton et al. [Present article]	40/F	T	S	2 years/3 years	Died

The malignant tumors derived from PXA transformation showed characteristics similar to normal high-grade tumors, with greater mitosis and necrosis, with expression of GFAP, S-100 and p53 (++). The Ki67 index was 15% and 8% in the two glioblastomas and 10% in the anaplastic astrocytoma, respectively. It is interesting at this point to focus on these tumors: one PXA evolved in 14 years and one anaplastic PXA evolved in 2 years, confirming data in the literature. The case of PXA that degenerated in 1 year was analyzed several times in an attempt to identify a single distinguishing element that could explain this strange behaviour. The only distinct factors we found were the presence of glomeruloid vessels and an infiltrative aspect.

3.3. Treatment

Surgical excision seems to be the therapy of choice for PXA, since the survival rate in patients with complete resection is 85% at 5 years and 70% at 10 years [37]. In any event, PXA do not behave like other low-grade glial tumors (pilocystic astrocytoma and subependymal giant cell astrocytoma), as the recurrence rate after total removal is around

Table 3
Literature PXA with malignant transformation

Reference, year	Age/Sex	Location	Interval recurrence	Histologic Progression	Total Survival
Weldon-Line et al. [5]	32/M	T		MG	21 months
Gaskill et al. [6]	2/F	T	3 months	GBM	5 months
Kepes et al. [7]	16/F	P	7 years	MG	7 years
	16/F	O	15 years	MG	15 years
	7/F	TP	7 months	MG	7 months
Allegranza et al. [8]	13/F	FTP	8, 9, 11 years	AnPXA>GBM	??
Macaulay et al. [9]	7/M	FP	4 years	GBM	Alive/6 years
Van Roost et al. [10]	15/F	T	9 months	AnPXA	Alive/17 months
Bayindir et al. [11]	9/F	T	7, 17 months spinal 12 months	AnPXA>AnPXA	18 months
Tonn et al. [12]	3?	TPO		AnPXA>GBM	5 years
	19/F	TO	2, 4 years	GBM>GBM	Alive/5.5 years
Charbel [13]	9F	TP	8 months	GBM	Alive/10 months
Leonard et al. [14]	11/F	TP	7 months	AnPXA	11 months
Prayson and Morris [15]	17/F	T	18 years	AnPXA	??
	8/F	PO	1 month	AnPXA	Alive/7 months
De Tella et al. [16]	26/F	FT	5 months	AnPXA	??
Klein et al. [30]	18	Hypothalamus	1 year/8 years/11, 5 years	MG	12 years
	14	TP	1 month	MG	9 months
Tan et al. [31]	21/F	P	3 years	AnPXA	Alive/6 months
Saikali et al. [29]	30/F	O+cerebellar	6 months/1 year/10 months	An Oligo	3 years
Nakajima et al. [28]	31/F	T	13 months	GBM	Alive/36 months
	56/F	T	1 year	GBM	30 months
Marton et al. [Present article]	8/F	T	14 years	AnPXA	14 years

F=frontal, P=parietal, O=occipital, T=temporal, AnPXA=anaplastic PXA, An Oligo=anaplastic oligoastrocytoma, MG=malignant glioma, GBM=glioblastoma.

15–20%, with a mean delay of 6 years after total excision [22]. Surgery is also the therapy of choice in recurrences without malignant transformation. Radiotherapy and chemotherapy do not seem to have a significant role. Recurrences with malignant transformation (10–15% of PXA) must be treated as primitive malignant gliomas.

3.4. Prognostic factors

Immunocytochemical analysis of a representative group of pleomorphic xanthoastrocytomas with malignant transformations has not previously been reported in the literature.

All analyzed cases of anaplastic features and malignancy are sporadically reported [3,5–33]. Analysis of neuronal and glial markers is performed on heterogeneous groups of "benign" and "malignant" xanthoastrocytomas (considering "malignant" to be the ones recurring with malignant transformation). In this heterogeneous population, neuronal markers are generally described as being positive, even focally in individual tumor cells.

No analysis is currently available on a significant number of "malignant" xanthoastrocytomas at first presentation or on the differential immunostaining of a population of benign xanthoastrocytomas or xanthoastrocytomas recurring with malignant transformation.

Immunohistochemically, there was no difference between the malignant transformations of PXA observed by us (complete lack of neuronal markers, p53 positivity and moderately high Ki67) and PXA without malignant transformation, suggesting that immunohistochemistry is unable to identify a subgroup of PXA that may evolve into a high-grade glioma.

4. Conclusions

PXA is classified as a low-grade astrocytic tumor (WHO II), but recent studies have demonstrated the presence of both neuronal and glial markers in the tumor cells, suggesting that they derive from multipotential precursor cells. The tumor is generally associated with long survival after complete surgical resection and has a favourable prognosis. The potential malignancy of pleomorphic xanthoastrocytomas must be considered, and the prognosis in these cases is the same as primary anaplastic astrocytomas and glioblastomas.

Analysis of the glioneuronal markers, of p53 and of the Ki67 labelling index in a heterogeneous group of xanthoastrocytomas, is not a discriminating factor by which to identify a subgroup of xanthoastrocytomas, for which close long-term clinical and radiological follow-up is mandatory.

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