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CASE REPORT

A rare clinical presentation: a pleomorphic xanthoastrocytoma presenting with intracerebral haemorrhage and metastasizing vigorously—case report and review of the literature

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Abstract

Metastasis of an intracranial tumour is not a common situation in our daily neurosurgical practice. Pleomorphic xanthoastrocytoma is also a rare glial tumour with relatively a favourable prognosis among other CNS pathologies. Here, we present an anaplastic pleomorphic xanthoastrocytoma case which shows both haematogenous and lymphatic metastasis which is described first time in the up-to-date literature. Our case is a 17-year-old male operated for a right occipital intra-axial lesion with a diagnosis of anaplastic pleomorphic xanthoastrocytoma which recurs 5 years later and metastasize vigorously through haematogenous and lymphatic routes. A rare-presenting symptom for this pathology is also intracerebral haemorrhage. This is the ninth case report in the literature which presents initially with this entity.

Keywords Pleomorphic xanthoastrocytoma · Haemorrhage · Anaplastic PXA · Lesion

Introduction

Pleomorphic xanthoastrocytoma (PXA) is an uncommon (< 1%) central nervous system tumour most commonly seen in children and young adults that undergo anaplastic transformation in 15 to 20% of cases [1]. Kepes et al. [2] first described it in 1979 as a type of distinct astrocytic tumour. Most of these tumours are located in the supratentorial area, mainly in the temporal lobes. Therefore, the most common initial-presenting symptom is seizures [3]. The prognosis is favourable for this tumour, with a 30% recurrence rate in 5 years and 40% in 10 years following gross total resection and an overall survival rate of 80% and 70% in 5 and 10 years, respectively [2, 4]. Intracerebral haemorrhage is also a rare-presenting symptom for this pathology. PXA with anaplastic features, which display increased mitotic activity with or without accompanying necrosis, is defined as grade III tumours according to WHO classification [5].

To date, there has been only one case report that shows scalp and sacral metastasis via a haematogenous route [6], and here, we present the first case in the literature of a PXA that has metastasized via lymphatic and haematogenous ways to the mediastinum and extracranial skeleton. This case is the ninth reported case in the literature with intracerebral haemorrhage as an initial-presenting symptom.

Case

The seventeen-year-old male patient was admitted to our clinic with a complaint of headache with no neurologic deficit that had been present for the previous 2 years. Cranial magnetic resonance imaging (MRI) showed that he had a right occipital intra-axial lesion that was 2.5 × 3 cm in diameter after diffuse enhancement with an IV gadolinium injection. The lesion had a 6- to 7-mm haemorrhagic component in the central portion. MR spectroscopic investigation was consistent with a glial tumour (Fig. 1), and a gross total resection was performed via a right occipital craniotomy.

Under haematoxylin and eosin staining (Fig. 2a), the tumour cells exhibited classic features with pleomorphic and

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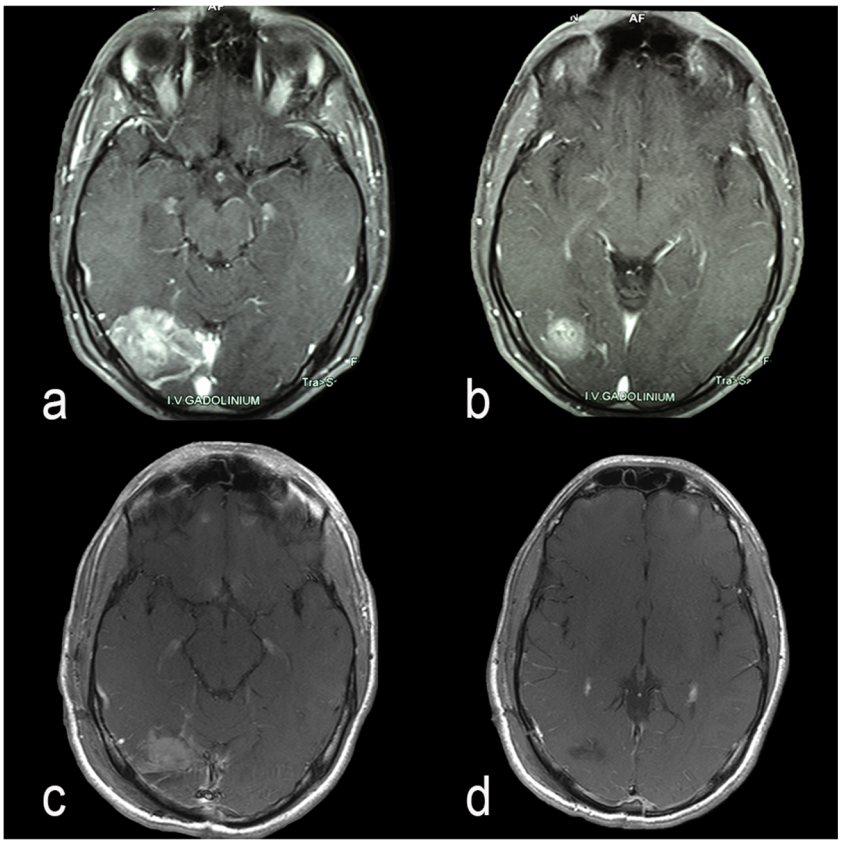

Fig. 1 Preoperative (**a**, **b**) and postoperative (**c**, **d**) axial MR images with IV gadolinium injection of first craniotomy

xanthomatous cells. Frequent multinucleated and enlarged cells with giant, oddly-shaped nuclei with occasional nuclear inclusion were seen. Brisk mitotic activity and necrosis were identified, and perivascular lymphocytic cuffing and scattered

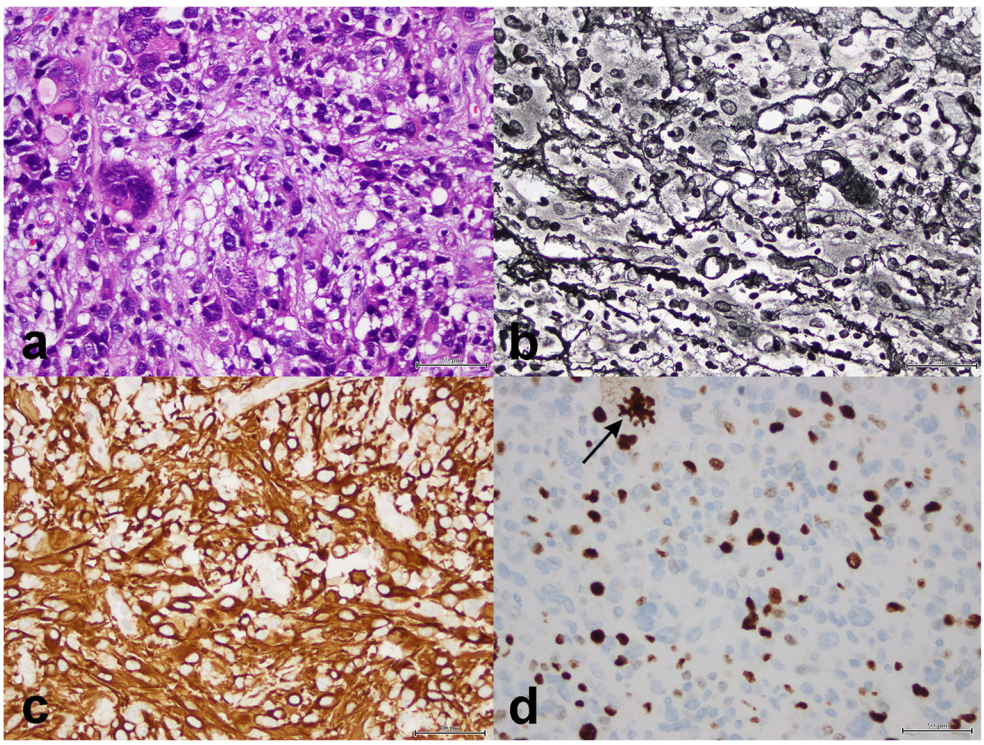

Fig. 2 **a** H + E, X400, bizarre giant cells and a smaller population of tumour cells with occasional cytoplasmic lipidization. **b** Reticulin, X400, pericellular reticulogenesis. **c** GFAP, X400, cytoplasmic positivity of glial fibrillary acidic protein in tumour cells. **d** Ki67, X400, nuclear immunoreactivity for Ki67 in tumour cells associated with an atypical mitosis at the upper left (arrow)

eosinophilic granular bodies were also seen. A reticulin rich network was identified throughout the tumour under reticulin staining (Fig. 2b). Immunohistochemically, both glial fibrillary acidic protein (GFAP) (Fig. 2c) and synaptophysin expressions in the large pleomorphic and xanthomatous cells revealed the biphenotypic glioneuronal appearance of the tumour cells. The Ki67 proliferation index was 30% (Fig. 2d). The final diagnosis was consistent with anaplastic pleomorphic xanthoastrocytoma (PXA) (WHO 2016) [5] infiltrating the dura. The patient received 5940-cGy adjuvant radiotherapy by the intensity-modulated radiation therapy (IMRT) method. He was seen under follow-up with no complaint and no radiologic progression.

Five years later, he was admitted to hospital with sudden onset of headache and loss of consciousness. Cranial computerised tomography (CT) investigation showed a left frontal acute intracerebral hematoma of 5 cm in diameter (Fig. 3a, b). The patient had a cranial MR (Fig. 3c, d), 4D dynamic MR angiography and conventional cerebral angiography investigations. A capillary haemangioma was present in the central portion of the hematoma with no other specific features. The patient then underwent a left frontal craniotomy and hematoma evacuation. A postoperative CT investigation showed no residual hematoma and no additional neurologic deficit.

During routine preoperative workups, a PA chest x-ray showed that bilateral intraparenchymal and hilar lesions had appeared. A thorax CT was performed, and bilateral hilar and mediastinal lesions were seen, with the lesion on the right side having a maximum diameter of 9.5 cm and the one on the left side having a diameter of 6.5 cm at its widest (Fig. 4a). Bilateral intraparenchymal nodules were present, and the largest of these had a diameter of 2.2 cm; this was consistent with the metastatic appearance of the left side. The patient underwent a mediastinal lymph node biopsy via mediastinoscopy. Histopathological examination showed a metastatic astrocytic tumour invading one of the two lymph nodes. The histomorphological features of this material and the initial tumour tissue, as taken in the first craniotomy, were similar, so this recurrence was considered to be metastatic anaplastic PXA. The tumour was composed of oval and fusiform astrocytic-like cells, and while these oval cells had hyperchromatic nuclei with ample cytoplasm, the fusiform cells had bipolar nuclei and cytoplasm. Pleomorphism and mitosis were present, though necrosis was not seen. Immunohistochemical study showed positive results for GFAP, olig2, synaptophysin and VEGF. IDH, NeuN, NFP, p53 and EGFR were negative in the tumour cells. MGMT was positive in 40 to 60% of tumour cells. The pathological samples which were taken from the hematoma border were

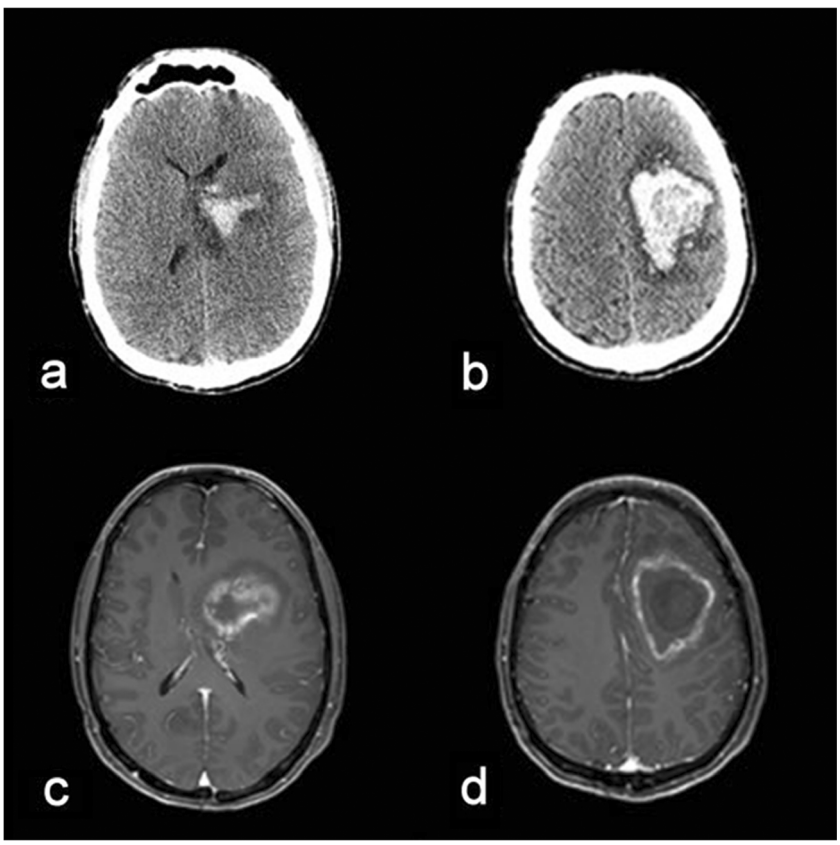

Fig. 3 Preoperative CT (**a**, **b**) and axial MR (**c**, **d**) images with IV gadolinium injection of second craniotomy

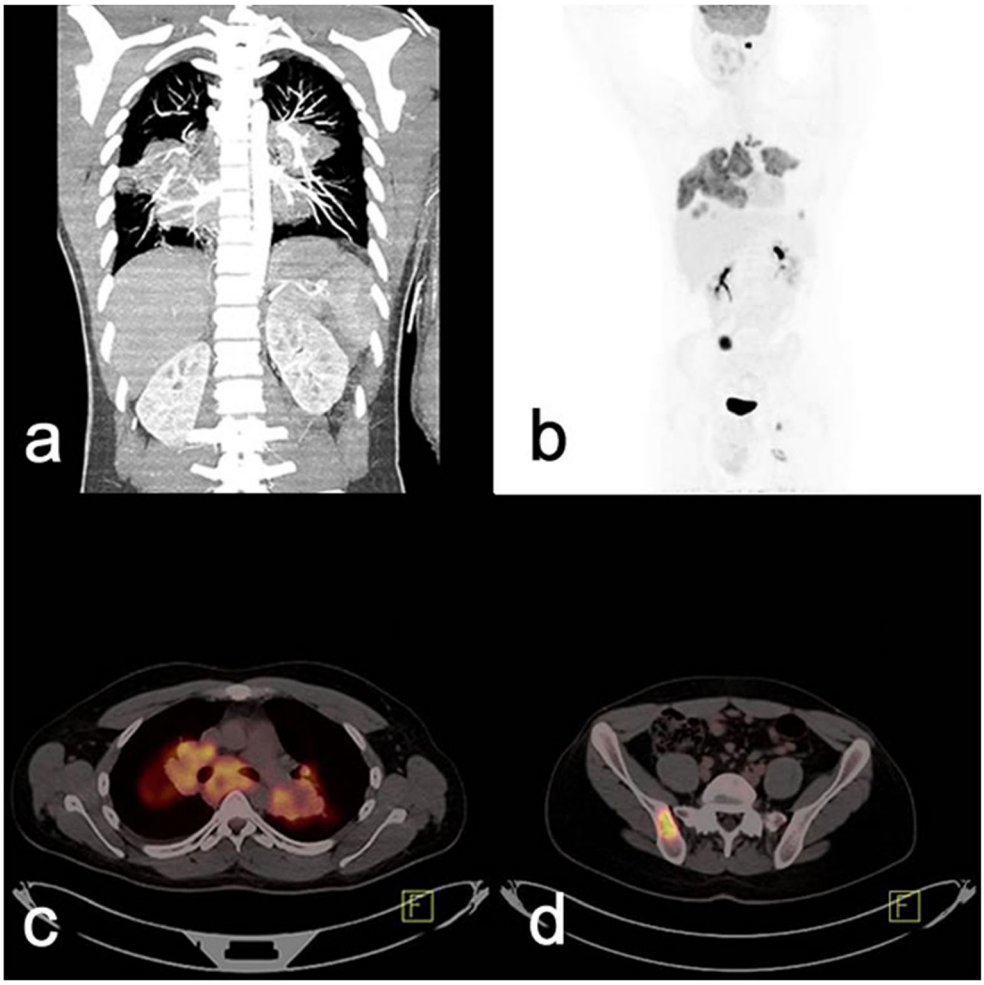

Fig. 4 Thorax CT (**a**) and PET-CT images (**b**, **c**, **d**) of the patient after second craniotomy showing metastasis to the hilar lymph nodes and ischium

also consistent with anaplastic PXA, with a Ki67 proliferative index of 30%.

A whole body PET–CT was performed to grade the disease; during this, mediastinal and intraparenchymal lung lesions above a new right frontal, C1 left arcus, right iliac bone and left ischium settled hyper metabolic lesions were seen (Fig. 4b, c, d). A cranial MR investigation using an IV gadolinium injection was performed, and a right frontal lesion was reported that was identified as a hematoma. One month later, this MR investigation was repeated, and a small resorption of the hematoma was seen.

The patient consulted with the medical oncology department, and systemic chemotherapy (zoledronic acid and temozolomide) was started. After two cycles of chemotherapy, a cranial MR investigation was performed again, and the right frontal hematoma had progressed, showing increased contrast enhancement and perilesional oedema with midline shift (Fig. 5a, b). MR spectroscopic evaluation could not be performed due to the increased blood component in the lesion [7]. Additionally, at the first operation site, ring contrast enhancement was seen, which was reported as tumour progression. The patient had a right frontal craniotomy, and the pathology was again consistent with anaplastic PXA (WHO 2016) [5].

Two months after his third craniotomy, the patient underwent a control MRI that showed multicentric contrast-enhancing lesions. The lesions were accepted as high-grade glioma, and he was referred to whole brain radiation therapy. Despite WBRT and chemotherapy, the patient died due to tumour progression 6 months after the final operation. His overall survival time was 72 months.

Discussion

The WHO defines PXA as a rarely seen (< 1%) grade III tumour [5]. Gross total resection of the tumour constitutes the majority of treatment [8], and radiologic follow-up and re-surgery are recommended if recurrence is detected. Anaplastic PXA was first described in 1999 [9] as having high mitotic activity with or without accompanying necrosis. To date, 55 PXA patients with anaplastic features have been presented in the literature as an initial diagnosis [4, 10–17].

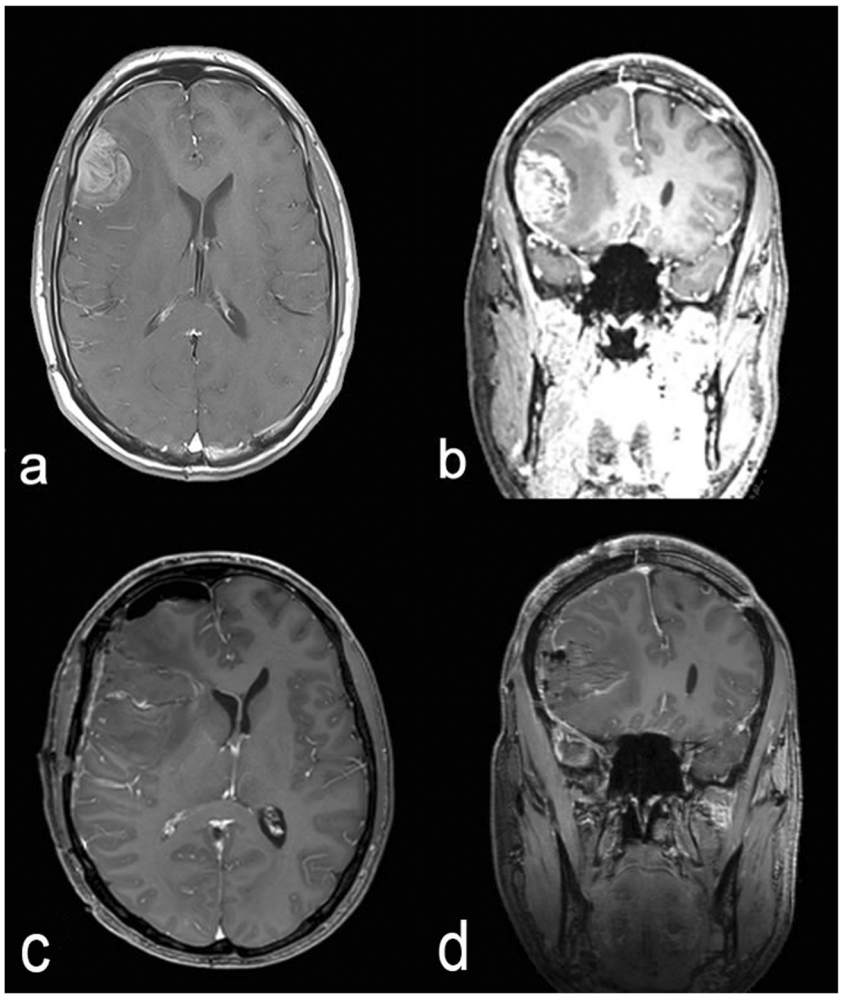

Fig. 5 Preoperative axial (**a**) and coronal (**b**) and postoperative axial (**c**) and coronal (**d**) MR images with IV gadolinium injection of the third craniotomy

Thirty-one PXA patients with malignant transformation (to anaplastic PXA or high-grade glial tumours) have been featured in the literature (Table 1).

Spontaneous intratumoural bleeding as seen in our case is rarely seen in PXA patients as an initial-presenting symptom. There have been only eight cases presented with haemorrhage in the literature so far [17–24] (Table 2). This has been linked to meningeal involvement in one of the cases [23], and a pseudoaneurysm formation due to vascular invasion by the tumour was seen in another case [18]; however, the exact mechanism is still unclear in our case and several others.

To date, there is only one case reported in the literature showing haematogenous metastasis to the sacrum and lumbar vertebrae with scalp metastasis 4 years from initial diagnosis; this was seen in a 27-year-old man [6]. The first diagnosis was PXA, and after a second recurrence, it transformed into anaplastic oligodendroglioma. The patient had repeated surgeries and radiotherapy but was lost in follow-up. Overall survival could not therefore be observed. Our case is the first one in the literature showing both haematogenous and lymphatic metastasis, as proved by lymph nodule biopsy of the mediastinum and whole body PET–CT investigation.

There is no approved treatment protocol for PXA with anaplastic features. According to the literature, adjuvant radiotherapy [6, 14, 25–27] is applied to those patients who have anaplastic PXA as an initial diagnosis. The tumour board of our institution therefore recommended radiation treatment in our case.

Adjuvant chemotherapy with temozolomide, which is an alkylating agent used in glioblastoma patients, has been tried in some cases [25, 27]. When using temozolomide, MGMT methylation status is an important prognostic factor of better response to treatment with better outcomes [28]. Marucci et al. [16] looked at the MGMT methylation status of 11 PXA patients, nine of whom had a diagnosis of PXA, and two of whom had a diagnosis of PXA with anaplastic features; this showed that only two PXA patients had a methylated MGMT gene. Neither of these patients recurred, but one patient with PXA with anaplastic features had recurred 3 years later, and the other was in follow-up when the paper was submitted. We tried temozolomide in our case after the second craniotomy, along with zoledronic acid to address the patient's bone metastasis. Before chemotherapy started, a right frontal lesion was detected and initially reported as a haematoma; this had

Table 1 Literature PXA with malignant transformation

Reference, year	Age, sex	Treatment	Recurrence interval	Histologic progression	Overall survival
Weldon-Linne et al. [29]	32, m	Surgery	Not mentioned	Malignant astrocytoma	21 months
Gaskill et al. [10]	2, f	Surgery + CT + RT	3 months	Glioblastoma	5 months
Kepes et al. [30]	16, f 16, f 7, f	Surgery + RT Surgery Surgery + RT	6 years 15 years 6 months	Malignant astrocytoma	7 years 15 years 7 months
Allegranza et al. [31]	13, f	Surgery + RT	8 years/2 years/1 year	Glioblastoma	Not mentioned
Macaulay et al. [32]	7, m	Surgery + CT + RT	4 years	Glioblastoma	Alive-6 years
Van Roost et al. [33]	15, f	Surgery	9 months	Anaplastic PXA	Alive-17 months
Bayindir et al. [34]	9, f	Surgery + RT	6 months/10 months	Anaplastic PXA	18 months
Tonn et al. [11]	19, f	Surgery + CT + RT	2 years/2 years	Glioblastoma	5.5 years
Charbel et al. [35]	9, f	Surgery + CT + RT	8 months	Glioblastoma	Not mentioned
Leonard et al. [36]	11, f	Surgery	8 months	Anaplastic PXA	11 months
Prayson et al. [37]	17, f 8, f	Surgery Surgery + RT	18 years 1 month	Anaplastic PXA	Not mentioned
De Tella et al. [38]	26, f	Surgery	5 months	Glioblastoma	Not mentioned
Klein et al. [39]	18 14	Surgery + RT	1 year/8 years/11.5 years 1 month	Glioblastoma Glioblastoma	12 years 9 months
Tan et al. [40]	21, f	Surgery	3 years	Anaplastic PXA	Alive-6 months
Saikali et al. [41]	30, f	Surgery + CT + RT	10 months/1 year/6 months/5 months	Anaplastic oligodendroglioma	3 years
Nakajima et al. [42]	31, f	Surgery+ CT + RT	13 months	Glioblastoma	Alive-3 years
Marton et al. [13]	8, f	Surgery	14 years	Anaplastic astrocytoma	14 years
Lim et al. [24]	40, f	Surgery + RT	21 months	Anaplastic PXA	Alive-32 months
Rodriguez-Mena et al. [43]	54, m	Surgery	9 months	Anaplastic PXA	9 months
Binesh et al. [25]	13, f	Surgery + CT + RT	5 months/4 months	Anaplastic PXA	Not mentioned
Alexiou et al. [27]	3, m	Surgery + CT + RT	1 year/9 months	Glioblastoma	Alive-29 months
Asana et al. [17]	59, f	Surgery	5 months/16 months	Glioblastoma	36 months
Frank et al. [44]	28, m	Surgery + CT + RT	14 months	Gliosarcoma	Not mentioned
Harada et al. [45]	25, f	Surgery + CT + RT	7 years/2 years	Anaplastic PXA	Not mentioned
Vu et al. [26]	50, m	Surgery + CT + RT	6 months	Glioblastoma	Alive-30 months
Tanaka et al. [46]	12, f	Surgery + CT + RT	13 years	Glioblastoma	165 months
Foo et al. [6]	27, m	Surgery + RT	3 years/1 year	Anaplastic oligodendroglioma	Not mentioned

regressed 1 month later. Chemotherapy was started, but after two cycles, the lesion progressed and a third surgery was performed. The patient's MGMT status was methylated, but despite this favourable condition, chemotherapy was ineffective for the intracranial portion.

Conclusion

PXA is a rare low-grade astrocytoma with a generally favourable prognosis. However, anaplastic PXA shows more aggressive behaviours in terms of recurrence intervals and

Table 2 Literature presenting with haemorrhage

Reference, year	Age, sex	Location	Treatment	Initial diagnosis
Asano et al. [17]	59, f	Temporal	Surgery	PXA with anaplastic features
Yoshikawa et al. [18]	60, f	Temporal	Surgery	PXA
Wind et al. [19]	5, f	Temporal and basal ganglia	Surgery	PXA
Lee et al. [20]	64, m	Frontal	Surgery	PXA
Abe et al. [21]	41, f	Hypothalamus	Surgery	PXA
Yoshida et al. [22]	61, f	Fronto-temporal	Surgery	PXA
Levy et al. [23]	41, f	Temporal	Surgery	PXA
Lim et al. [24]	7, m	Parietal	Surgery	PXA

ability to metastasize. Therefore, PXA with anaplastic features requires more aggressive or more specifically targeted therapy; nevertheless, despite such aggressive therapy, this type of tumour can metastasize in both lymphatic and haematogenous ways, and may present with intracerebral haemorrhage.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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