Pleomorphic xanthoastrocytoma: a brief review

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Pleomorphic xanthoastrocytoma (PXA) is a rare primary CNS tumor. Recent advances in the molecular characterization are helping to define subtypes of tumor. The discovery of *BRAF* mutations within a substantial percentage of PXA fosters a clearer understanding of the pathophysiology of these tumors with clear prognostic and therapeutic implications. These findings are expected to provide insight into the spectrum of clinical behavior observed in PXA, ranging from cure with surgery to diffuse dissemination throughout the neuraxis. This review details the clinical presentation including radiographic appearance of PXA. Pathology, including molecular pathology is discussed. Therapeutic management including surgical resection, radiotherapy and systemic therapies are reviewed.

Pleomorphic xanthoastrocytoma (PXA) is an astrocytic tumor thought to originate from subpial astrocytes or their precursors. It is rare and accounts for <1% of all astrocytomas. First described in 1973 [1] the term PXA was coined by Kepes in 1979 [2]. In 1993, it was formally incorporated in the WHO classification system of tumors of the central nervous system (CNS) as a WHO grade 2 tumor. Subsequent descriptions include anaplastic grade 3 variants. It is likely that the term PXA while describing a single histologic entity may represent more than one tumor type as defined molecularly. A similar evolution of thought has been seen with respect to other glial tumors. The varying descriptions of the natural history of this disease appear to support this hypothesis.

The epidemiologic perspective on PXA is limited. While listed as its own distinct entity in Surveillance, Epidemiology, and End Results (SEER), in the Central Brain Tumor Registry of the United States (CBTRUS), PXA is classified under the umbrella term 'unique astrocytoma variants' [3]. In SEER only 214 cases had been reported between 1981 and 2007 in the USA [4]. This is approximately one-tenth the incidence of pilocytic astrocytomas, another rare CNS tumor.

Clinical presentation

PXA is most commonly diagnosed in the second decade of life [5–7]. Mean age at diagnosis is 29 ± 16 years [5–7]. But cases as young as 2 and as old 68 have been reported [5,6]. The majority of large case series have reported no gender predilection. Presenting symptoms can be broadly classified as localizable or nonlocalizable. Localizable symptoms correlate directly with the neuroanatomy involved with tumor. These include seizure, the most frequent initial presenting symptom. Nonlocalizable symptoms are related to elevation of intracranial pressure and include
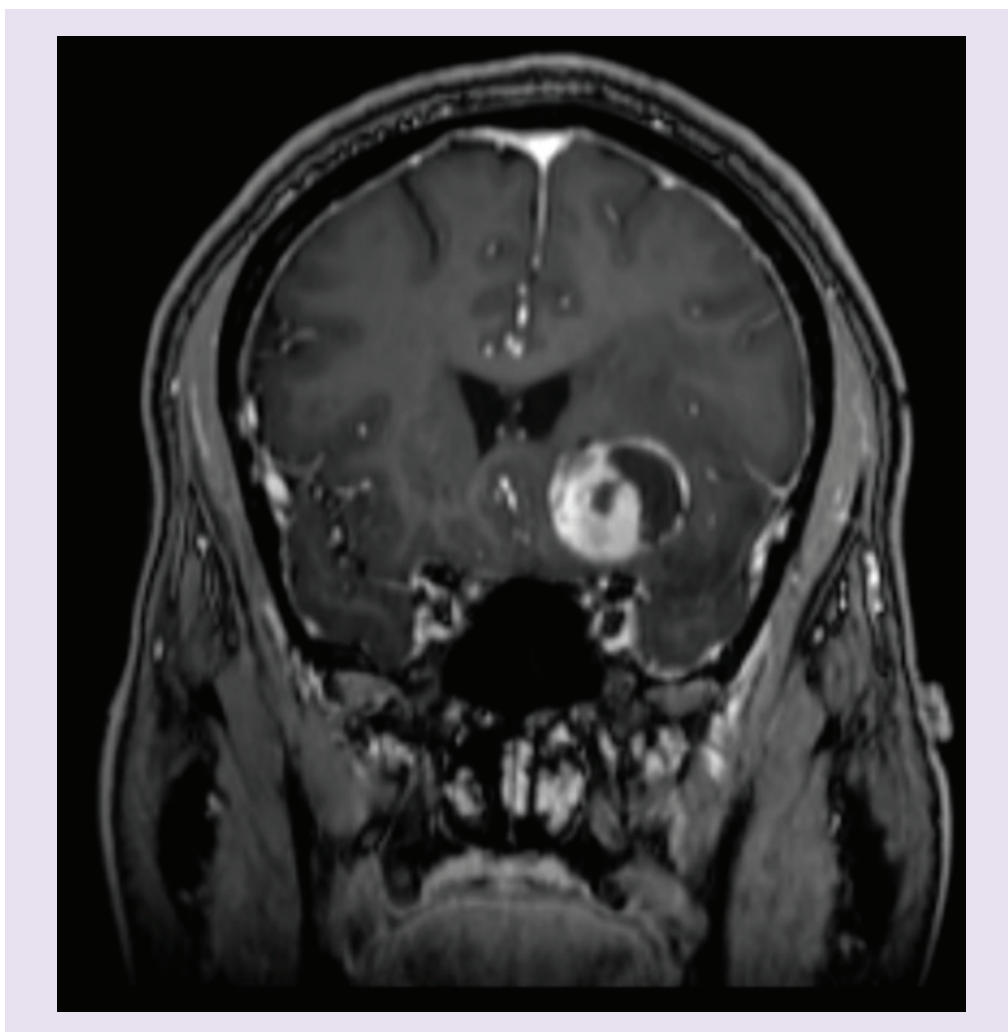
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Figure 2.   Coronal T1 postcontrast magnetic resonance imaging revealing a left frontal enhancing lesion with cystic components. A distinct delineation between tumor and surrounding brain parenchyma is noted.

headaches, nausea, vomiting, diplopia and somnolence. The mean duration of symptomatology prior to diagnosis is a few months. Rarely, these tumors are incidentally found when imaging is performed for other indications.

While described throughout the CNS, the temporal lobe is the most common location of PXAs, even when they occur in a multifocal fashion [5,7–11]. These tumors have the potential to spread via the cerebrospinal fluid (CSF). This is most commonly seen in the progressive/recurrent disease setting. Only a limited number of patients present with CSF disseminated disease at their initial diagnosis. Tumor grade and the potential for dissemination are not consistent across studies [12–15].

Imaging

Despite their generally favorable natural history, PXA appears ominous on imaging with some features reminiscent of high-grade gliomas. They occur most commonly as well circumscribed superficial masses with leptomeningeal contact. These tumors often consist of solid and cystic components. On contrast enhanced computed tomography imaging, the cystic component is hypodense. The solid component typically appears hypo to isodense, but can occasionally be hyperdense, with areas of calcification seen in the solid component. The solid component as well as the wall of the cyst often enhances. MRI reveals T1 isointense, T2 hyperintense and T1 post gadolinium heterogeneously contrast enhancing solid component with peripheral rim enhancement of the cyst (Figure 2). The cystic fluid is either isointense or hyperintense as compared with CSF depending on the imaging sequence. A minimal amount of vasogenic edema around the lesion can be seen at times. Leptomeningeal enhancement is seen
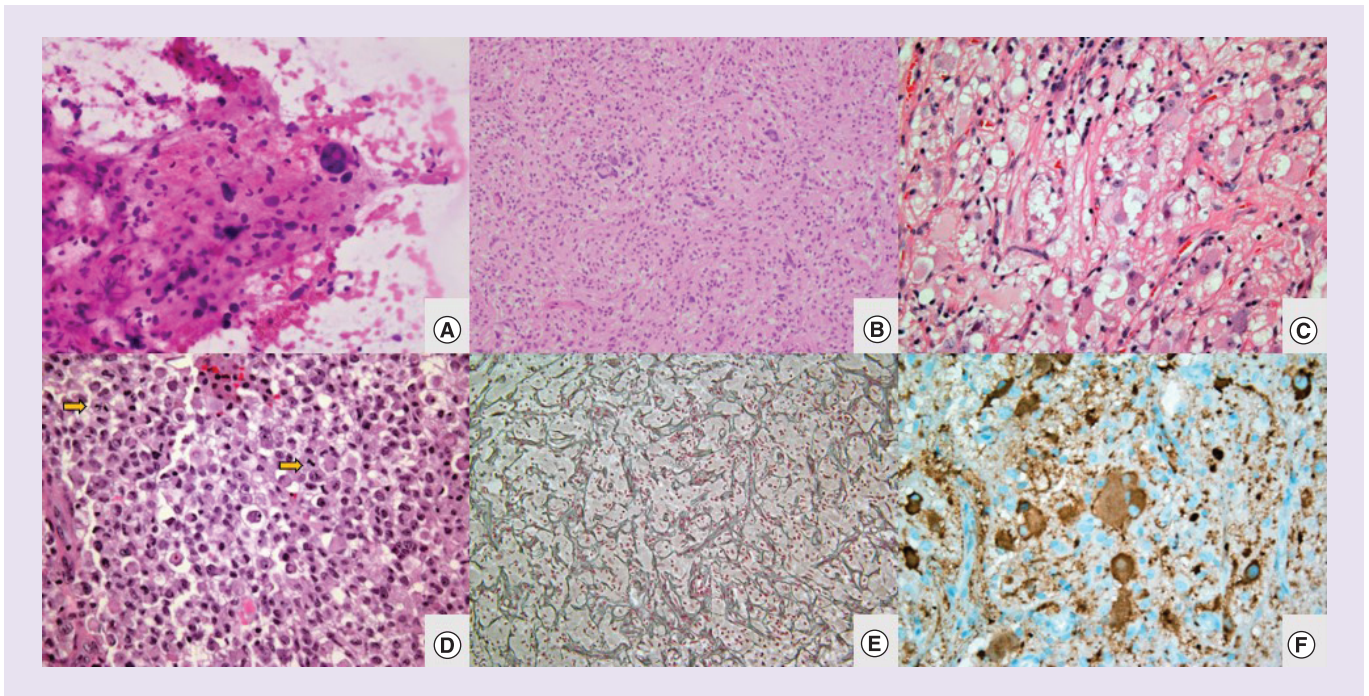
Figure 1.   Histopathology of pleomorphic xanthoastrocytoma. (A) The smear preparation shows highly pleomorphic tumor cells with occasional bizarre-looking nuclei (H&E, ×400). **(B)** There is an admixture of spindelled neoplastic and neoplastic cells with bizarre nuclei or multinucleation (H&E, ×200). **(C)** The neoplastic cells show multivacuolated cytoplasm (H&E, ×400). **(D)** An anaplastic pleomorphic xanthogranuloma showing paradoxically monomorphic tumor cells with increased cellularity. Scattered mitotic figures (arrows) are noted (H&E, ×200). **(E)** Reticulin stain shows a rich reticulin network surrounding nests of tumor cells. Occasional pericellular reticulin deposition is also noted (reticulin stain, ×200). **(F)** Synaptophysin immunohistochemical stain highlights pleomorphic tumor cells (synaptophysin, ×400).
H&E: Hematoxylin and eosin stain.

IHC stain	GFAP	S100	Vimentin	Reticulin	PAS	EMA	Synaptophysin
Table 1. Immunohistochemical characteristics of pleomorphic xanthoastrocytoma.							
PXA	+++	+++	+++	+++	+++	–	–

EMA: Epithelial membrane antigen; GFAP: Glial fibrillary acidic protein; IHC: Immunohistochemistry; PAS: Periodic acid-Schiff; PXA: Pleomorphic xanthoastrocytoma.

in a subset of patients [9–11,16]. PXA is hypovascular on angiography [17]. On fluorodeoxy glucose (FDG) positron emission tomography (PET), it has shown high glucose metabolism and hypoperfusion on SPECT perfusion scans [18].

Pathology
As with other primary CNS tumors, molecular characterizations have a growing role in the classification of PXA. This has not yet been formalized in the WHO classification system. However, in contemporary practice, PXA can now be divided into *BRAF* mutated and *BRAF* wild-type. This has both diagnostic and potential therapeutic implications.

Gross & histologic description
PXA (WHO grade II) is an astrocytic tumor that grossly appears as a superficial solid and cystic mass with involvement of the leptomeninges common. This tumor is most frequently located in the temporal lobe. Its histopathology was first described after microscopic review of 12 almost identical appearing cases [1]. It is a moderately cellular, predominantly pleomorphic tumor with foci of lymphoplasmacytic infiltration without any necrosis and rare mitoses (Figure 1 & Table 1) [1,2,5,7,11,13,14,15,20]. The tumor cells are either spindle shaped with elongated nuclei or large round cells with a single or multilobulated nucleus or multiple nuclei (bizarre multinucleate

giant cells) that invade the brain parenchyma directly or at the perivascular spaces. There is also evidence of external basal lamina on electron microscopy, which consists of reticulin fibers produced and present around the tumor cells. This finding points toward the potential origin of PXA from subpial fibrous astrocytes [19–21]. The cytoplasm of the tumor cells is eosinophilic and contains varying amounts of hyaline protein and lipid droplets. The cytoplasm is positive for glial fibrillary acidic protein (GFAP) on immunohistochemistry, a marker also positive in other glial neoplasms. GFAP positivity varies depending on the lipid content of the cytoplasm [2]. Unique histopathology with abundant clear cell component and focal papillary appearance has also been reported [22]. The varying morphologies within tumors highlight the pleomorphic nature of the tumor.

Anaplasia

In 1983 the first case of recurrent PXA with malignant (WHO grade III) transformation was described [19]. Both *de novo* presentation as a grade III tumor and progression of grade II–III have been described [23]. PXA in earlier WHO classification systems was categorized strictly as a grade II tumor, but the 2016 update of the WHO classification now also includes grade III anaplastic PXA (aPXA). aPXA is primarily defined by the presence of necrosis accompanying high mitotic activity usually >5 mitoses/10 high powered fields (HPF), and increased cellularity. Pseudorosette formation resembling ependymomas and focal endothelial proliferation has been reported [12,23,24]. MIB-1 labeling index cutoff is generally considered to be >4% [25–30]. aPXA has the potential of CSF spread, higher chance of recurrence and hence shorter progression-free and overall survivals (PFS and OS, respectively) [5,18,19,31–33].

Molecular features

The most frequently found mutated gene in PXAs is *BRAF*, which encodes an intracellular component of the MAPK pathway. BRAF is one of the three RAF (rapidly accelerated fibrosarcoma) kinases that is most commonly mutated and has the highest oncogenic potential [34–37]. BRAF mutations can be found in 70% of typical PXA, but appears less common in aPXAs, with a variable range reported (17–65%) [34,38–40]. Mutations that have been described in PXAs include activating BRAF p.V600E mutations, in frame deletions within BRAF exon and less often BRAF fusions [41]. *BRAF* mutation may divide these tumors into two clinically relevant subgroups, both with regards to natural history and response to therapy. *BRAF*-mutated PXA exhibits superior survival when compared with the *BRAF*wt [38]. The *BRAF*-mutated PXA also exhibits responses to BRAF targeting therapies [42] although no comparative prospective trials have been conducted in this patient population.

There have been reports of *EGFR* amplification found in glioblastoma (GBM) arising from malignant transformation of PXA. However, this is not common and may represent initial misdiagnosis of glioblastoma. Aberrations in p53 and p16, loss of heterozygosity of chromosome 10 are thought to be contributing to PXA formation and progression [21,41,43–45]. Mutations in p53 can occur in up to 25% of patients with PXA [43].

With the advent of immuno-oncology and its active investigation within the field of neuro-oncology, an interest exists in potential predictive biomarkers for response to immunotherapies in glial tumors. A number of candidate biomarkers have been suggested in glial tumors, including expression of programmed death 1 and its ligand [46], tumor mutational burden [47] and microsatellite instability [48]. However, programmed death 1/programmed death ligand 1 expression, tumor mutational burden and microsatellite instability in PXA have not been reported thus far, to our knowledge. Recent studies demonstrating MAPK pathway (including BRAF) alterations in glioblastoma can confer benefit with immunotherapies [49] may have direct relevance to PXA. This will require further study.

Prognosis

PXA is a rare glial tumor with relatively favorable prognosis. There are several retrospective studies evaluating potential intrinsic and modifiable prognostic biomarkers. Tumor intrinsic factors such as elevated mitotic index (>5 mitosis/10 HPF) and presence of necrosis, features consistent with aPXA, are associated with decreased OS and PFS on multivariate analyses [2,50]. In contrast, the presence of BRAF V600 mutations is associated with longer OS rates [38]. While clear radiographic responses have been seen in these patients when BRAF inhibition is utilized, the mutational status has not yet been validated as a predictive factor for response to BRAF inhibitors.

OS of PXA is favorable with 3- and 5-year survival rates of >80 and >75%, respectively [5,51]. PFS rates at 3 and 5 years are >60% [5,51]. This diminishes with increasing grade/anaplasia. aPXA has 5-year OS rate of 57% and PFS of 49% [32,52]. It must be kept in mind that a subset of patients with PXA is deemed to be cured of disease, even with surgical resection alone. This distinguishes PXA from other infiltrating gliomas.

Therapeutic management

Due to the rarity of the tumor there are no formal guidelines published on management. Optimal management is guided by case reports and case series. We highlight key concepts below.

Surgery

Conflicting reports exist on the importance of extent of resection (EOR) [50,51,53]. However, multiple groups have reported it as a reliable prognostic factor for OS and PFS [5,54], with a gross total resection correlating with 10-year OS of 82% [55]. As a routine practice, gross total resection (GTR), if feasible and safe, should be the goal of the surgeon.

Radiotherapy

Scant data exist to guide the utilization of radiotherapy (RT) in PXA. Some reports have noted an association with use of postoperative RT and improved PFS [2,26,51,53], but no definitive improvement in OS has been demonstrated. A recent meta-analysis of 167 patients with grade II PXA did not demonstrate an association between adjuvant therapy with improved oncologic outcomes; the majority of patients (76%) had RT utilized as a salvage treatment upon recurrence [56]. Given the paucity of data, using RT doses in the range of 45–54 Gy for either adjuvant or salvage treatment appears reasonable, with or without concurrent temozolomide. Earlier incorporation of radiation for subtotal resection and/or aPXA may be considered given the poorer outcomes associated with these factors. Craniospinal RT may be warranted for leptomeningeal dissemination on recurrence or at initial diagnosis [20,27,57].

Systemic therapy

Limited data exist on systemic chemotherapeutic agents from PXA tumors. Traditional chemotherapy has been generally considered minimally effective or ineffective for the treatment of PXAs (Table 2) [2,5,51]. However, in progressive disease when surgery or RT is not always a viable option, systemic treatments are often considered and employed.

Molecular markers are increasingly utilized to aid diagnosis and to subclassify glial tumors. In PXA where there is a high incidence of targetable mutations this is of particular importance. There have been a number of reports utilizing BRAF inhibitor monotherapy or BRAF+MEK inhibitors. Favorable responses have ranged from stable disease to complete responses [58–64]. In the largest published nonrandomized trial over 40% of patients with PXA treated with BRAF-inhibiting monotherapy exhibited radiographic response. More than half were noted to have a confirmed clinical benefit [63]. The addition of bevacizumab to this regimen at time of progression may prolong survival [64]. The utilization of BRAF inhibitor in conjunction with tumor-treating fields (TTFields) has also been reported [65].

Conclusion

PXA is a rare tumor ranging from WHO grade II to III, which has the potential to recur and to disseminate throughout the CNS. A broad range of outcomes can be seen ranging from cure of disease with single modality treatment (i.e., surgery) to rapid progression with CSF dissemination. This underlines a point seen in other infiltrating gliomas; while the histologic phenotype may be the same, molecular phenotypes may define distinct subtypes or types of disease. Our understanding of the molecular characteristics of the disease is of particular importance as they influence not only prognosis but also our therapeutic management. Notable radiographic responses have been seen with BRAF inhibitor-centered regimens. While the rarity of the disease will make definitive therapeutic studies difficult, we would anticipate that our clinical management for patients with this disease will evolve rapidly in the near future.

Future perspective

It is anticipated that the molecular neuropathology will play an increasingly important role in defined CNS tumors, including PXA [66]. The presence of BRAF driver mutations in a subset of PXA may be a more unifying feature tying them both pathophysiologically and in turn therapeutically to other relatively low-grade glial tumors. The value of these molecular features may supersede the identical histologic features of *BRAF*-mutated and *BRAF* wild-type PXA in the way clinicians and investigators conceptualize these tumors. It is likely that while level 1 evidence may be lacking, BRAF pathway-directed therapies will become standard treatments for *BRAF*-mutated PXA. The optimal future therapies for *BRAF* wild-type PXA are less clear. While complete surgical resection and RT will continue to

Table 2. Systemic therapies evaluated in pleomorphic xanthoastrocytoma.

Year	Study	N	RT	Systemic regimen	Setting	PFS	OS	Ref.
1979 and 1989	Kepes and Whittle *et al.*	4	Adjuvant 45 Gy WBRT; 55 Gy WBRT	NA	On initial presentation of typical PXA but STR; on first recurrence of PXA	11–14 years; 8 months	NA	[2,39]
1983	Weldon Linn *et al.*	2	65 Gy in 7 weeks	NA	On initial presentation of typical PXA	1.5 years; 18 months	Close to 2 years; 21 months	[3]
1985	Bukeo *et al.*	1	Adjuvant focal RT 59.6 Gy	NA	On initial presentation of aPXA and STR	5 years	NA	[36]
1987	Iwaki *et al.*	3	40; 50; 60 Gy focal RT	NA	On initial presentation as it was aPXA. One on recurrence of aPXA	6 years; 17 years; 4 months	NA	[32]
1988	Gaskill *et al.*	1	Spinal RT	CCNU, vincristine, prednisone	On recurrence and re-resection	8 months	11 months	[29]
1988	Stuart *et al.*	1	Adjuvant focal RT	NA	On initial presentation of typical PXA	3 years	NA	[38]
1989	Kepes *et al.*	5	Adjuvant 30–40 Gy or 46.3 Cobalt focal RT; 36.8 Cobalt WBRT to resection cavity on first recurrence	NA	On initial presentation of typical PXA and GTR. For last case, adjuvant RT was on recurrence of PXA with GBM component	7–8 months; 6 years; 4.5 years; 17 years; 3 years	Unknown; 6 years and few months; unknown; unknown; >6 years	[37]
1991	Allegranza *et al.*	1	Adjuvant RT to resection cavity	NA	On first recurrence aPXA	2 years	NA	[41]
1992	Zorsi *et al.*	2	Adjuvant 30 Gy; 60 Gy focal RT	NA	On initial presentation and on recurrence of PXA	16 years; unsure	NA	[40]
1993	Macaulay *et al.*	1	Concomitant RT 54 Gy in 30 fractions over 6 weeks	Eight cycles of ifosfamide, carboplatin and etoposide after re-resection	On recurrence of anaplastic pleomorphic xanthoastrocytoma (APXA) now with GBM component	2 years	NA	[22]
1997	Perry *et al.*	1	RT to resection cavity	Adjuvant chemotherapy	On initial presentation as there was a ganglioglioma component		4 years	[30]
1997	Perry *et al.*	1	RT to resection cavity	Adjuvant chemotherapy	On initial presentation as it was an STR and had ganglioglioma component	1 year	NA	[30]
1998	Leonard *et al.*	1	50 Gy in 30 fractions to resection cavity	Temozolomide	On first recurrence	4 months	11 months	[25]
1999	Chakrabarty *et al.*	2	Focal RT	NA	On initial presentation as it was aPXA		NA	[31]
2001	Primavera *et al.*	1	60 Gy in 30 fractions focal RT after re-resection	Adjuvant five courses of chemotherapy with procarbazine, CCNU and vincristine	On recurrence of APXA	1.5 years	NA	[33]
2001	Perry *et al.*	1	54 Gy focal RT in 30 fractions	NA	First recurrence of mixed PXA and oligodendroglioma	17 months	NA	[21]
2001	Cartmill *et al.*	1		Neoadjuvant chemotherapy with the goal of antiangiogenesis comprising of vincristine and cisplatin two cycles over 6 weeks followed by resection	On initial presentation of PXA	2 months	NA	[42]
2004	Lubansu *et al.*	1		Alternating cycles of carboplatin/VP-16, cyclophosphamide and vincristine. POD refractory to further chemotherapy including temozolomide, thiotepa and daily VP-16	On initial presentation	7 months	NA	[18]
2004	Tan *et al.*	1	60 Gy focal RT over 6 weeks after second resection	NA	On recurrence of PXA into aPXA	6 months	NA	[23]

aPXA: Anaplastic pleomorphic xanthoastrocytoma; CSI: Craniospinal irradiation; GBM: Glioblastoma; NA: Not applicable; OS: Overall survival; PCV: Procarbazine; PFS: Progression-free survival; POD: Progression of disease; PXA: Pleomorphic xanthoastrocytoma; RT: Radiotherapy; SRS: Stereotactic radiosurgery; STR: Subtotal resection; TMZ: Temozolomide; WBRT: Whole brain radiotherapy.

Year	Study	N	RT	Systemic regimen	Setting	PFS	OS	Ref.
2005	Nakajima *et al.*	1	30 Gy CSI with 30 Gy boost to resection cavity	Adjuvant ACNU	On second recurrence of GBM transformation of typical PXA	3 years	NA	[34]
2005	Saikali *et al.*	1	60 Gy focal RT on first recurrence	4 cycles TMZ on second recurrence APXA – no response treated with re-resection. PCV for third recurrence	On first recurrence of PXA	1 year; contd. Progression on second recurrence with TMZ; 4 months with re-resection	NA	[35]
2008	Koga *et al.*	1	SRS to first recurrence then to multiple lesions	NA	On first recurrence of PXA; on second recurrence	6 months; 44 months	NA	[43]
2018	Byun *et al.*	4	Adjuvant focal RT	NA	On initial presentation of aPXA	6 months	NA	[20]

Table 2. Systemic therapies evaluated in pleomorphic xanthoastrocytoma (cont.).

aPXA: Anaplastic pleomorphic xanthoastrocytoma; CSI: Craniospinal irradiation; GBM: Glioblastoma; NA: Not applicable; OS: Overall survival; PCV: Procarbazine; PFS: Progression-free survival; POD: Progression of disease; PXA: Pleomorphic xanthoastrocytoma; RT: Radiotherapy; SRS: Stereotactic radiosurgery; STR: Subtotal resection; TMZ: Temozolomide; WBRT: Whole brain radiotherapy.

be the components of the standard of care for both PXA subtypes, novel therapeutics may be of interest for the less treatment responsive *BRAF* wild-type tumors.

There are ongoing studies, in both adult and pediatric populations, focused on glial tumors, which have enrollment open to patients with PXA. These include trials of targeted therapeutics such as BRAF inhibitor (dabrafenib) in combination with MEK inhibitor (rametinib) (NCT02684058), a cyclin D1/CDK4/CDK6 inhibitor (ribociclib) in combination with an MEK inhibitor (rametinib) (NCT03434262), the antiparasitic mebendazole in conjunction with traditional cytotoxic chemotherapies (NCT01837862) and intratumoral injection of an oncolytic recombinant polio virus/rhinovirus (PVSRIPO) (NCT03043391). Results of these studies may help confirm suspected therapeutic targets or provide new avenues for further investigation. The speed of progress will likely be limited by the relative rarity of these tumors and the associated difficulty of clinical investigations in this patient population.

Executive summary

- Pleomorphic xanthoastrocytoma (PXA) is a rare astrocytic tumor with the potential for cerebrospinal fluid dissemination.
- Over two-thirds of PXA harbor mutations in *BRAF*.
- Presence of *BRAF* mutation confers a more favorable natural history and the potential for response to BRAF inhibition.
- The 5-year survival with PXA is >75%; however, tumors with anaplastic features exhibit less favorable outcomes.
- Complete surgical resection is a cornerstone of the management of these tumors.
- Radiotherapy may play a role for residual or recurrent disease.
- Traditional systemic therapies have proven of limited benefit in treating PXA.
- BRAF inhibition, alone or in combination with other treatments including MEK inhibition, has been associated with marked radiographic responses in *BRAF*-mutated PXA.
- Novel treatment strategies are under clinical investigation for PXA typically within the context of basket trials. However, they are hampered by the relative rarity of this tumor.

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