Pleomorphic Xanthoastrocytoma

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Pleomorphic xanthoastrocytoma (PXA) was recognized as a distinct entity in 1979 [1)]

General Information

Key concepts

● Low-grade astrocytoma (WHO grade II), possibly from subpial astrocytes → superficial location, > 90% supratentorial, most common in children or young adults

● mural nodule with a cystic component in 25%, meninges involved in > 67%

● pathology: pleomorphic cells (xanthomatous (lipid-laden) cells, fibrillary and giant multinucleated astrocytes). Usually circumscribed, occasionally invasive

● WHO grade II (if ≥ 5 mitoses per HPF it qualifies as anaplastic (WHO grade III))

● treatment: maximal safe resection

A low-grade glioma thought to arise from subpial astrocytes, which may explain their superficial location and abundance of reticulin fibers. Over 90% are supratentorial. The predilection for temporal

lobes (50%), followed by parietal, occipital & frontal lobes. Most have a cystic component (may be multiloculated, but > 90% have a large, single cyst).

Single-cell analysis shows high B7H3+ tumor cell prevalence in glioblastoma (GBM) and pleomorphic xanthoastrocytoma (PXA), while most gliomas, including pediatric cases, express targetable tumor antigens in less than 50% of tumor cells, potentially explaining trial failures [2)].

Classification

Pleomorphic xanthoastrocytoma (PXA) is a astrocytic tumor that occasionally progresses to a higher grade.

see Anaplastic Pleomorphic Xanthoastrocytoma.

see Pigmented variant of pleomorphic xanthoastrocytoma.

Tumor Name	WHO Grade	Key Characteristics
Pleomorphic Xanthoastrocytoma (PXA)	**Grade 2**	- Typically affects children and young adults - Frequently located in the temporal lobe - Often presents with seizures - Usually indolent with good prognosis after gross total resection - **BRAF V600E** mutation common
Anaplastic Pleomorphic Xanthoastrocytoma	**Grade 3**	- Progression or transformation from Grade 2 PXA - **≥5 mitoses/10 HPF**, possible necrosis - More aggressive behavior and worse prognosis - May retain BRAF mutation, often **IDH-wildtype** - Requires close follow-up and adjuvant treatment

🧬 Molecular Characteristics

- **BRAF V600E mutation**: present in ~60–70% of cases
- **IDH status**: typically **IDH-wildtype**
- **CDKN2A/B deletion**: associated with worse outcomes
- **TERT promoter mutations**: rare but possible in high-grade tumors
- **Ki-67 index**: variable, higher in anaplastic forms (>5-10%)

🧠 Diagnostic Criteria for Anaplastic PXA (Grade 3)

1. Mitoses ≥5 per 10 high-power fields (HPF)
2. Tumor necrosis (focal or geographic)

3. Elevated Ki-67 (often >10%)
4. Marked pleomorphism with xanthomatous cells and eosinophilic granular bodies

Epidemiology

≈ 1% of astrocytomas. Usually occurs in children or young adults (most are < 18 years of age). No gender difference.

They usually arise supratentorial > 90 % and superficially from the cerebral hemispheres (upper most sections) of the brain and in contact with the leptomeninges, rarely they arise from the spinal cord.

Pathology

Histopathological features

Histologically, they can be associated with inflammatory cell infiltration and reticulin deposits.

A rich reticulin network surrounds individual cells and small cell nests. Verification of a rich reticulin network is helpful in differentiating PXA from High-grade gliomas.

Pilocytic astrocytomas also tend not to display the extent of pleomorphism or reticulin network found in PXA, and are usually less compact in their architecture, frequently exhibiting loose microcystic areas containing cells with typical piloid processes.

MIB-1 index is usually < 1 %.

The term “PXA with anaplastic features” is reserved for those tumors with > 5 mitoses/10 high power fields, and/or necrosis.

Although histology may not reliably predict aggressive behavior in pleomorphic xanthoastrocytomas, the presence of increased mitosis, necrosis, and increased cell proliferation labeling indices may be indicative of a higher grade tumor [3)]

They have certain morphological similarities to fibrous histiocytoma (or fibrous xanthoma) of the meninges and brain, namely the occurrence of lipid-laden neoplastic cells and, frequently, a dense reticulin fiber network. The detection of glial fibrillary acidic (GFA) protein in the tumor cells helped to establish its astrocytic derivation, but it has been advanced that, in spite of this agreed observation, the tumor should still be regarded as a fibrous xanthoma of meningeal origin. Although many patients have a long symptom-free postoperative survival, local recurrences at varying intervals after surgery have been noted in some instances. Weldon-Linne et al. first reported that such a recurrence had the morphology of a small-cell glioblastoma. We are reporting three further examples of locally recurrent neoplasms in patients whose original meningocerebral tumors had the typical features of PXA; the recurrences (developing 7 months, 7 years and 15 years, respectively, after surgery) were small-cell glioblastomas. The rich reticulin network present in the initial tumor was mostly lost in the recurrences. This anaplastic evolution further confirms the astrocytic nature of the PXA [4)].

Immunohistochemistry

PXAs are notable for their biphenotypic glial and neuronal staining pattern.

They are consistently positive for S100 and GFAP, though the latter may be patchy.

Expression of neuronal markers, including synaptophysin, neurofilament, MAP2, and Class III b-tubulin, may be detected in individual pleomorphic cells; these markers will also highlight any true ganglion cell component.

CD34 expression is also frequently encountered.

CDKN2A deletions were detected in exons 1 and 2 in 1 (pleomorphic xanthoastrocytoma) sample of 9 samples analyzed [5].

BRAF V600E point mutations are occasionally observed in pilocytic astrocytoma; the mutations are also observed in nonpilocytic pediatric low-grade gliomas, including ganglioglioma, desmoplastic infantile ganglioglioma, and approximately two-thirds of pleomorphic xanthoastrocytomas [6].

Clinical

Usual presentation: seizures. May also produce focal signs or increased ICP.

Given their superficial “meningo-cerebral” localization, patients typically present with a history of sudden onset seizures, often of a longstanding nature.a Headaches may also occur.

Diagnosis

70% arise as a cyst with solid mural nodule, the remainder being predominantly solid with variable small cystic areas.

Their solid component is iso to hypodense on CT.

Intratumoral hemorrhage or calcifications are uncommon; peritumoral edema may be present, but is typically minimal.

They may rarely show multifocality or leptomeningeal dissemination.

MRI

Pleomorphic Xanthoastrocytoma MRI

Differential diagnosis

Pleomorphic Xanthoastrocytoma differential diagnosis.

Treatment

Pleomorphic Xanthoastrocytoma Treatment.

Prognosis

Prognosis depends on WHO grade, surgical resection, and molecular markers.

Classic PXA (WHO Grade 2)

- **Prognosis:** Generally **favorable**
- **5-year overall survival (OS):** ~75–90%
- **Progression-free survival (PFS):** ~60–70%
- **Key prognostic factors:**
  1. Gross total resection (GTR)
  2. BRAF V600E mutation (positive prognosis)
  3. Location in non-eloquent cortex (e.g. temporal lobe)
  4. Low Ki-67 (<5%)

Anaplastic PXA (WHO Grade 3)

- **Prognosis:** More aggressive and unpredictable
- **5-year OS:** ~40–60%
- **Median OS:** 2–5 years
- **Key negative prognostic factors:**
  1. Mitoses ≥5/10 HPF
  2. Tumor necrosis
  3. High Ki-67 index (>10–15%)
  4. CDKN2A/B deletion
  5. Incomplete resection

Molecular Prognostic Markers

Marker	Prognostic Impact
BRAF V600E	Better prognosis; targetable
IDH-wildtype	Common in PXA; no clear impact
CDKN2A/B deletion	Associated with early recurrence, poor OS
TERT promoter	Rare; may suggest aggressive behavior
High Ki-67 index	Correlates with tumor aggressiveness

Summary Table

Type	WHO Grade	Behavior	5-Year OS	Notes
Classic PXA	Grade 2	Indolent	75–90%	Often curable with complete resection
Anaplastic PXA	Grade 3	Aggressive	40–60%	Requires surgery + adjuvant therapy

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Pleomorphic xanthoastrocytoma (PXA) has characteristic histologic features and is regarded as a WHO grade II lesion. Overall survival is reported to be >60%, but published series usually consist of a range of ages and treatment modalities. Gross total resection is associated with superior survival, but recurrence rates after gross total resection are not well described, particularly in a pediatric population.

Perioperative neurological complications are relatively common, but do not affect long-term functional outcome or mortality.

Pleomorphic xanthoastrocytomas (PXA) may recur and demonstrate aggressive clinical behavior with a mortality rate between 15% and 20%, and a new concept of anaplastic PXA has been proposed.

No histopathologic features currently are known to reliably predict recurrence or tumor progression.

Malignant PXAs are higher risk for perioperative complications and, ultimately, death from tumor progression, despite increased use of adjuvant radiation and chemotherapy.

Gross total resection without adjuvant therapy provides prolonged disease control, as seen in 6 of 7 patients (85%) in the series of Fouladi et al. [7].

Extent of resection, mitotic index, and necrosis appear to be the best predictors of outcome [8) 9)].

BRAF mutation may potentially identify specific subgroups with distinct prognoses [10].

Complications

Both pediatric and adult PXAs may be resected with good functional outcomes. Perioperative neurological complications are relatively common, but do not affect long-term functional outcome or mortality. Malignant PXAs are higher risk for perioperative complications and, ultimately, death from tumor progression, despite increased use of adjuvant radiation and chemotherapy [11].

Literature review

1996

A literature review of 79 patients with PXAs is described and confirms a favorable prognosis in 80% of patients. The sex ratio in the reported cases was almost equal, and the median age at time of diagnosis was 14 years. Seventy-nine percent of the patients presented with seizures. Nine of the 15 deaths from PXA are associated with histological evidence of necrosis at initial presentation or in a recurrent tumor, confirming the poor prognosis associated with the presence of necrosis in these neoplasms. Survival curves confirm that the optimal treatment for PXAs without necrosis is primary surgical resection with subsequent operation for recurrent tumor. The roles of surgery or radiotherapy in necrotic PXA are not clear from the literature [12].

Retrospective cohort studies

Sullivan et al. identified 17 patients with pathologically confirmed PXA. Two patients were excluded due to incomplete treatment information or <6 months of follow-up; 15 patients were analyzed (median follow-up 4.4 years). Six patients had grade 2 PXA, and 9 had grade 3 anaplastic PXA. The 2- and 5-year PFS for the cohort was 57% and 33%, respectively; 2- and 5-year OS was 93% and 75%, respectively. Patients with grade 2 tumors exhibited superior PFS compared to those with grade 3 tumors (2-year PFS: 100% vs. 28%, 5-year PFS: 60% vs. 14%), hazard ratio, 5.09 (95% CI: 1.06-24.50), P = .02. Undergoing a gross total resection was associated with numerical longer survival but this was not of statistical significance (hazard ratio: 0.38, P = .15). All but one (89%) of the grade 3 patients underwent RT.

The poor survival of the cohort, especially with grade 3 tumors, suggests the need for more aggressive treatment, including maximal resection followed by intensive adjuvant therapy. Better prognostics of tumor recurrence are needed to guide the use of adjuvant therapy [13].

Patients who had PXAs surgery between 2000-2021 were retrospectively analyzed for demographics and radiological characteristics. Initial and salvage treatment outcomes were recorded. Overall, 40 and 9 patients had grade 2 and 3 PXAs; their 5-year progression-free survival (PFS) rates were 75.8% and 37.0%, respectively ($p = 0.003$). Univariate analysis revealed that strong T1 enhancement ($p = 0.036$), infiltrative tumor margins ($p < 0.001$), peritumoral edema ($p = 0.003$), WHO grade ($p = 0.005$), and gross total resection ($p = 0.005$) affected the PFS. Multivariate analysis revealed that the WHO grade ($p = 0.010$) and infiltrative tumor margins ($p = 0.008$) influenced the PFS. The WHO grade ($p = 0.027$) and infiltrative tumor margins ($p = 0.027$) also affected the overall survival (OS). Subgroup analysis for grade 2 PXAs revealed no significant associations between adjuvant radiation therapy and the PFS and OS. This study highlighted the heterogeneous nature of PXAs and their impact on patient prognosis. Infiltrative tumor margins emerged as a key prognostic factor. Our findings have emphasized the prognostic relevance of radiological features and the need for larger studies on comprehensive management [14].

Case series

Pleomorphic xanthoastrocytoma case series.

Case reports

Pleomorphic Xanthoastrocytoma case reports.

Recurrent Anaplastic Pleomorphic Xanthoastrocytoma Involving the Thalamus: A Case Report with Long-Term Clinical and Radiological Follow-up

Abstract

A 40-year-old male with a history of pleomorphic xanthoastrocytoma (PXA) initially diagnosed at age 28 presented with progressive neurological decline and recurrent seizures. The tumor, originally WHO grade 2, progressed to an anaplastic PXA (grade 3) with thalamic involvement. He underwent multiple surgical resections and radiotherapy. Despite partial control with steroids and antiepileptics, clinical deterioration prompted a third surgery in 2025. Intraoperative pathology confirmed high-grade glial neoplasm. This case highlights the long-term management challenges and the role of multimodal therapy in recurrent anaplastic PXA.

3. Introduction Pleomorphic xanthoastrocytoma (PXA) is a rare astrocytic tumor, accounting for <1% of all gliomas, often presenting in young individuals with seizures. While typically indolent (WHO grade 2), some PXAs undergo anaplastic transformation (grade 3), particularly in cases of recurrence. Anaplastic PXAs behave more aggressively and may require complex multimodal strategies.

4. Case Presentation Patient: Male, 40 years old

Initial Diagnosis: PXA (Grade 2, WHO) after left insular lesion resection in 2013

Symptoms at onset: Focal seizures and absence episodes

Histopathology 2013: PXA grade 2; Ki-67 <1%, no necrosis or mitoses

5. Disease Progression 2014–2018: Stable residual lesion on MRI; occasional seizures

2021: Neurological worsening; second surgery confirms anaplastic transformation (Grade 3)

2022: Post-radiotherapy pseudoprogression vs. recurrence on MRI

Spectroscopy: Cho/Cr ratios >2.5 indicating active tumor metabolism

Persistent right hemiparesis, diplopia, fatigue, and bradipsychia

6. Recent Intervention (April 2025) Symptoms: Progressive hemiparesis, seizure recurrence, diplopia

Decision: Multidisciplinary tumor board recommended surgical rescue

Surgery (14/04/2025): Left parietal craniotomy with subtotal resection (~50%)

MRI Post-op: Residual enhancing lesion in anterior thalamus/capsule interna

Intraoperative Pathology: High-grade glial tumor with necrosis

Final Histopathology: Pending

7. Discussion This case illustrates the chronic nature and therapeutic complexity of anaplastic PXA. While initially low-grade, transformation to grade 3 required escalation of care. Advanced imaging (spectroscopy) was essential for distinguishing true progression from post-radiation effects. Subtotal resection was performed due to deep-seated thalamic involvement, prioritizing neurologic function.

8. Conclusion Anaplastic PXA may recur and progress even years after initial diagnosis. Long-term monitoring, advanced imaging, and a multidisciplinary approach are crucial. Future management will depend on final histological results and molecular markers.

9. Learning Points PXA can transform into an anaplastic variant over time.

Spectroscopy aids in differentiating recurrence from treatment effects.

Deep-seated lesions (e.g., thalamic) often require subtotal resection to preserve function.

Multidisciplinary tumor boards play a key role in decision-making.

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