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Pediatric Pleomorphic Xanthoastrocytoma with Neoplastic Meningitis: A Case Report with Cytopathological Evidence with Literature Review

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Abstract

Pleomorphic xanthoastrocytoma (PXA) was regarded as grade II tumor and considered to be associated with favorable outcome. The World Health Organization Central Nervous System 5 (WHO CNS5) has classified PXA under circumscribed astrocytic gliomas and graded 2 or 3 depending on histology. Cerebrospinal fluid (CSF) and leptomeningeal spread are observed rarely in these tumors. The present case report describes a PXA, grade 3 tumor in a young male with neoplastic meningitis. This 17-year-old male child presented with history of seizure, signs of raised intracranial pressure, and meningeal irritation. Well-defined, T2 heterogeneously hyperintense lesion (5.5*4.8 cm) was seen in right frontal lobe with mild heterogenous contrast enhancement and adjacent pachy-meningeal enhancement. Right frontal craniotomy and near total excision were done. Postoperative hydrocephalus was treated with CSF diversion. Histopathology showed epithelioid and rhabdoid morphology with significant cellular pleomorphism and atypical mitosis consistent with the PXA, grade 3. The CSF cytology showed numerous tumor cells with marked nuclear and cytoplasmic pleomorphism. PXA is a rare malignancy of children and young adults, commonly seen in the temporal lobes. BRAF point mutations of V600E type are most common in PXA, grade 2. Meningeal dissemination is uncommon in PXA and its presence marks poor outcome. PXA, grade 2 tumors could be followed with serial imaging following gross total resection. PXA, grade 3 tumors are managed with maximal-safe resection, radiotherapy, and/ or chemotherapy. PXA, grade 3 with CSF spread tends to have rapid decline in the clinical course and it is advisable to get routine baseline and follow-up craniospinal screening and needs aggressive management.

Keywords

- neoplastic meningitis
- other astrocytic tumors
- pleomorphic xanthoastrocytoma

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Introduction

Pleomorphic xanthoastrocytoma (PXA) and anaplastic PXA were classified as grade II and III tumors under the category of "Other astrocytic tumors" in the World Health Organization (WHO) 2016 classification.[1] The WHO Central Nervous System 5 (CNS5) (2021 classification) has classified gliomas, glioneuronal, and neuronal tumors into six different families and the PXA has been listed under circumscribed astrocytic gliomas referring to their more solid growth pattern and graded 2 or 3 depending on histology.[2]

Since long time, PXA was regarded as low-grade tumor of young adults and thought to be associated with favorable outcome.[3] Anaplastic PXA can have a de novo origin or it can result from high-grade transformation of PXA grade II and portends a poor outcome.[3,4]

Cerebrospinal fluid (CSF) and leptomeningeal spread are considered uncommon in PXA tumors. Although there are some radiologically reported cases of leptomeningeal spread,[5] the cytopathological evidences are sparse.[6] Here we are describing a case of PXA, grade 3 who presented with neoplastic meningitis.

Case Report

This 17-year-old male child with a history of seizure for 1 year on irregular medications presented to us with blurring of vision, diplopia, altered sensorium, and neck stiffness. On examination, patient was conscious, drowsy, and irritable. Child had bilateral papilledema, lateral rectus palsy, and signs of meningeal irritation.

Magnetic resonance imaging brain has shown a 5.5*4.8 cm well-defined, intra-axial, T1 heterogeneously iso to hypointense, T2 heterogeneously subtle hyperintense lesion with few flow voids and focal hemorrhages in right frontal lobe at para-median location showing mild heterogenous contrast enhancement and diffusion restriction with adjacent pachy-meningeal enhancement displacing the genu of corpus callosum and left frontal lobe causing mass effect (►**Fig. 1**).

Right frontal craniotomy and near total resection of the tumor were done, Tumor was soft to firm, vascular, and brain parenchyma was invaded at some areas. A thin layer of tumor, which was densely adherent to anterior cerebral arteries, was left behind. Postoperatively, the child regained sensorium but continued to have headache. Computed tomography scan revealed hydrocephalus, hence ventriculoperitoneal shunt was done (►**Fig. 2**).

Histopathology of the tumor revealed a lesion with variable morphology. Part of the tumor showed papillary morphology and majority of the areas showed cells in sheets. The cells were polygonal with vesicular nuclei and prominent nucleoli. Epithelioid and rhabdoid morphology was seen with significant cellular pleomorphism with giant cells. Atypical

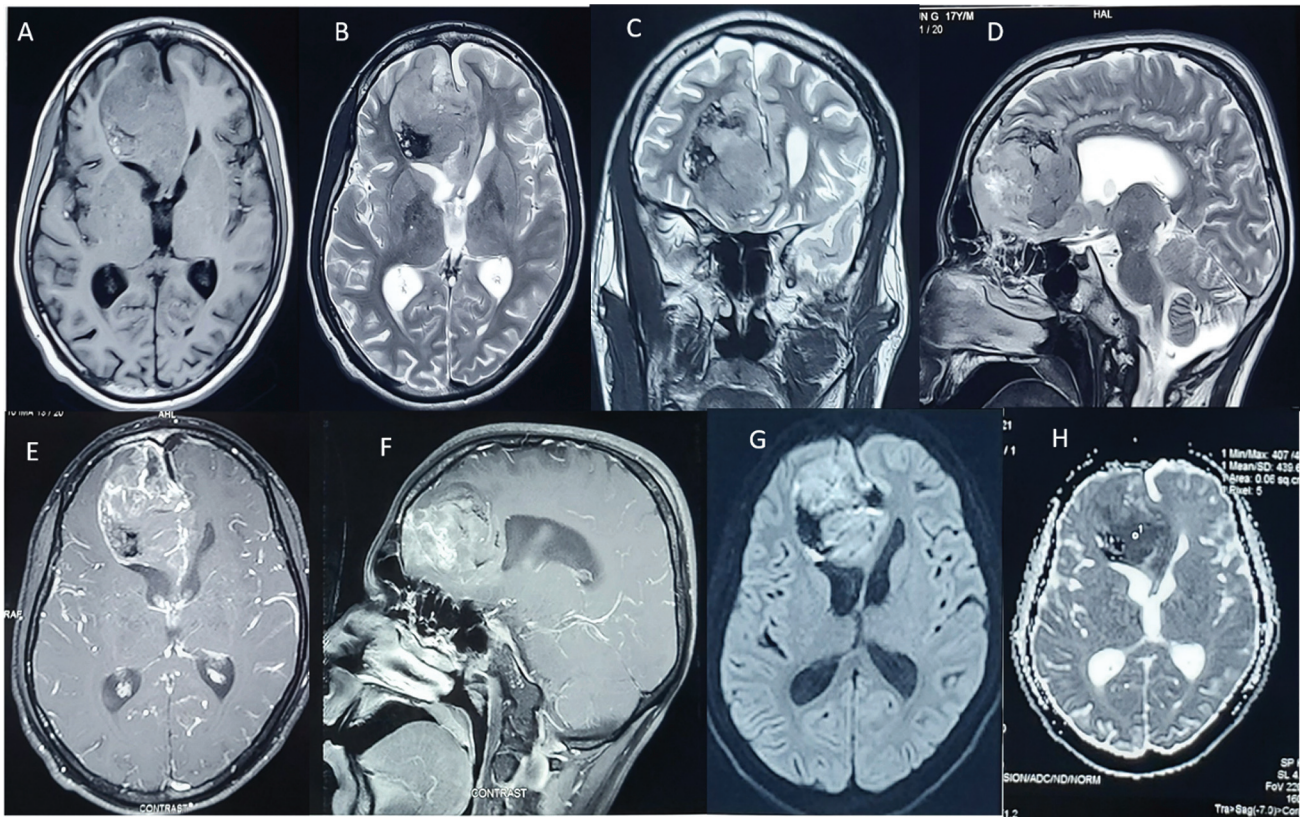

Fig. 1 Well-defined, intra-axial, T 1 heterogeneously iso to hypointense (**A**), T2 heterogeneously subtle hyperintense lesion (5.5*4.8 cm; **B–D**) with few flow voids and focal hemorrhages in right frontal lobe at para-median location showing mild heterogenous contrast enhancement (**E**, **F**) and diffusion restriction (**G**, **H**) with adjacent pachy-meningeal enhancement displacing the genu of corpus callosum and left frontal lobe causing mass effect.

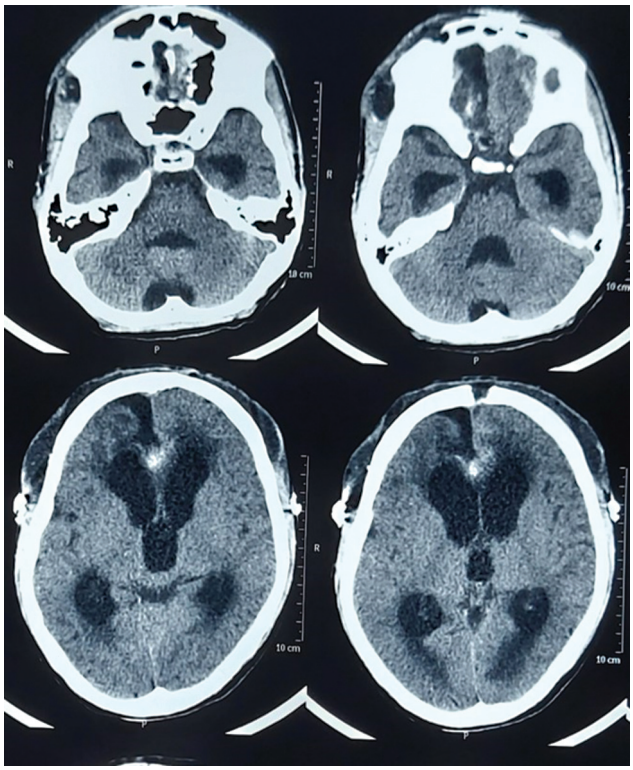

Fig. 2 Postoperative noncontrast computed tomography scan showed dilatation of bilateral lateral, third and fourth ventricles, suggestive of communicating hydrocephalus.

mitosis was observed along with occasional xanthoma cells and large areas of necrosis. These findings were suggestive of diagnosis of PXA, grade 3 (WHO, 2021;►**Fig. 3**). The dural sample collected was infiltrated by tumor cells, which was suggestive of neoplastic meningitis.

The immunohistochemistry panel of the tumor has shown positivity for GFAP, synaptophysin, BRAF V600E. Pancytokeratin was focally positive, integrase interactor 1 (INI-1) was retained, and Neu N was negative. All of which again confirmed the diagnosis of PXA, grade 3.

A CSF collected during shunt was studied, and found to have PMNs—1/µL, sugars—56mg/dL, and proteins—17mg/dL. The CSF cytology revealed plenty of tumor cells with characteristic nuclear and cytoplasmic pleomorphism. There were many large cells with fine vacuolated foamy cytoplasm and numerous multinucleated giant cells. These findings were suggestive of PXA, grade 3 and neoplastic meningitis.

Discussion

PXA is an uncommon malignancy, occurring mainly in children and young adults and constitutes less than 1% of all gliomas.[4] It is commonly seen in supratentorial location, involving the temporal lobe.[4]

Criteria for diagnosis of PXA include a relatively solid growth pattern, pleomorphic tumor cells, and foam cells intermingled in a fibrillary background. The cells tend to have prominent nucleoli and intranuclear inclusion. These tumors consistently have multinucleated xanthomatous cells with intracellular granular bodies and lipids. Histological findings of anaplastic tumors include high mitotic index ($\geq$5/10) and endothelial proliferation with or without necrosis.[1,4] In the absence of markers of anaplasia, tumors are classified as PXA, grade 2 and anaplastic tumors are regarded as PXA, grade 3 in the WHO CNS5 (2021 classification).[2]

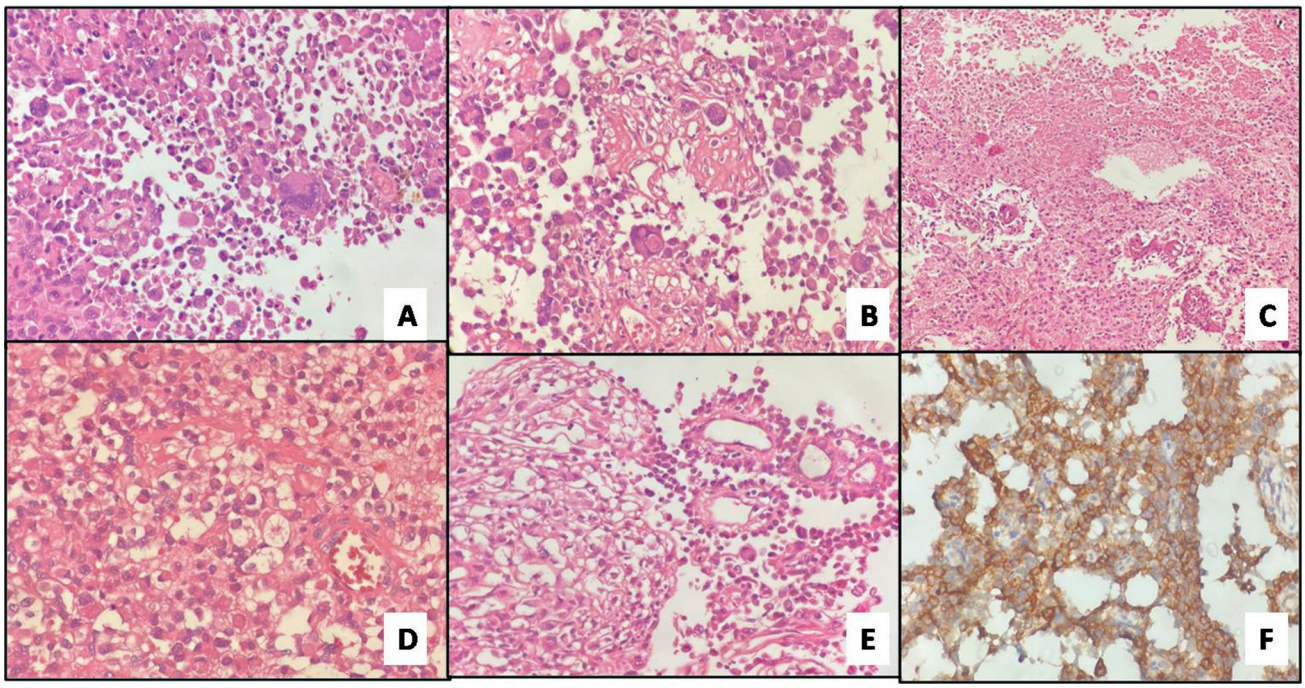

Fig. 3 Histopathologic features: (**A** and **B**) Tumor cells showing marked pleomorphism with bizarre giant cells, (**C**) foci of necrosis and (**D** and **E**) xanthoma cells, and (**F**) strong immunopositivity for BRAFV600E immunohistochemistry.

Table 1 Reported cases of pediatric PXA with dissemination

Sl. no.	Author and year of publication	Age (years)/ gender	Primary location	Dissemination pattern	Tumor histology	Surgery	Adjuvant therapy	Final outcome and follow-up period
1	Lubansu et al, 2004[5]	7/F	Left temporal	Simultaneous	Anaplastic PXA	GTR	CT	Relapse, alive, 26 months
2	McNatt et al, 2005[10]	13/F	Multiple lesions B/l cerebral	Simultaneous	PXA	Excisional biopsy	RT	No progression, 3 years
3	Passone et al, 2006[11]	9/F	Left temporal	Simultaneous	PXA; anaplastic at recurrence	Biopsy	CT and RT	Progressive, death, 5 years
4	Okazaki et al, 2009[12]	5/M	Basi-frontal	Simultaneous	Anaplastic PXA	Biopsy	CT	No progression, alive, 3 years
5	Alexiou et al, 2010[13]	3/M	Right parietooccipital	Delayed	Anaplastic PXA; GBM at recurrence	GTR; Redo GTR for recurrence	CT + RT after recurrence	No recurrence, alive, 29 months
6	Gardiman et al, 2012[14]	14/F	Fourth ventricle, left cerebellum	Simultaneous	PXA	Biopsy		
7	Amayiri et al, 2018[15]	16/F	Left parietal	Delayed	Anaplastic PXA	STR; NTR for recurrence	RT, CT BRAF targeted therapy	No progression, 30 months
8	Thomas et al, 2019[8]	16/F	Left frontal	Delayed	Anaplastic PXA	STR	RT, CT, bevacizumab, BRAF targeted therapy	Death, 23 months
9	Karthigeyan et al, 2021[6]	8/M	Left temporoparietal	Delayed	Anaplastic PXA	NTR	RT	Death, 5 months

Abbreviations: CT, chemotherapy; GBM, Glioblastoma multiforme; GTR, gross total resection; NTR, near total resection; PXA, pleomorphic xanthoastrocytoma; RT, radiotherapy; STR, subtotal resection.

Although BRAF point mutations, mostly V600E type, are common (50-78%) in PXA, grade 2,[7] they are not specific. It can also be observed in ganglioglioma and sone pilocytic astrocytomas. Presence of BRAF point mutations, in the absence of IDH mutation, are highly diagnostic of PXA. Mitotic index has shown corelation with the outcome,[3] but BRAF mutations did not show consistent corelation.[7]

Meningeal dissemination is uncommon in PXA and its presence marks poor outcome (►**Table 1**).[5,8] Spinal metastasis can present during the initial diagnosis or may be diagnosed at later stage. The patients who had leptomeningeal spread at the time of diagnosis have shown a rapidly worsening course.

Previous studies have shown that progression-free survival was better with gross total resection (GTR) compared to STR and biopsy but type of excision had no influence on the overall survival.[4] PXA, grade 2 tumors could be followed with serial imaging to avoid chemoradiotherapy following GTR. Whereas recurrences or less than GTR necessitates adjuvant focal radiotherapy.[4]

Although PXA, grade 3 tumors are managed with maximal-safe resection, and chemo-radiotherapy,[3] it tends to progress in many cases. Disseminated diseases are treated with multimodal therapies including surgical resection for reducing the tumor bulk, followed by craniospinal radiotherapy and chemotherapy.

An in vitro study has shown that temozolomide effectively reduces viability of cells in PXA, grade 3.[9] Targeted therapy against BRAF mutations is also adopted.[8] BRAFV600E-mutated PXA, grade 3 tumor has shown response with vemurafenib and dabrafenib.

In summary, present case of PXA, grade 3 has shown an aggressive clinical course with rapid deterioration and CSF dissemination, awareness of which would help to prognosticate and counsel the parents. It is also advisable to get routine baseline imaging of entire neuraxis and aggressively manage such case at the earliest. Reporting a greater number of such cases in the literature will reveal natural course of the disease and may help to reconsider its grading in the future.

Conflict of Interest
None declared.

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