

Rare clinical presentations of pleomorphic xanthoastrocytoma with a high proliferative index

Two case reports

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Abstract

Introduction: Pleomorphic xanthoastrocytomas (PXA) are rare, typically benign, slow-growing tumors that commonly occur in the cerebral hemispheres. We describe two cases of clinically aggressive PXA with uncommon locations; one was in the tectal plate, and the other had simultaneous multicentric lesions.

Patient Concerns: The both cases presented with severe headache with no significant past medical history.

Diagnosis: PXA World Health Organization grade II were histopathologically diagnosed from surgically resected specimens, and immunohistochemical and sequence analysis revealed a high Ki-67 proliferative index and BRAF V600E mutation in both the cases.

Interventions: The first case presented with multicentric lesions and underwent partial resection, whereas the second case presented with a tectal plate tumor that was managed by gross total surgical resection. Strong 5-aminolevulinic acid (5-ALA)-induced fluorescence was observed in both the lesions. Postoperative radiotherapy plus concomitant and adjuvant temozolomide was administered to both the patients.

Outcomes: Despite completing adjuvant chemo-radiotherapy, both the patients had local tumor recurrence at 2 and 5 months after the operation, respectively.

Conclusion: The progressive clinical courses in our cases suggest that additional postoperative therapy should be considered during the treatment of PXA with a high Ki67 index, and that temozolomide with radiotherapy, followed by temozolomide maintenance therapy, may not prevent recurrence in such tumors. Importantly, our experience implies that unlike other subtypes of low grade gliomas, 5-ALA fluorescence is useful for intraoperative visualization of PXA.

Abbreviations: 5-ALA = 5-aminolevulinic acid, FDG = ¹⁸F-fluorodeoxyglucose, MRI = Magnetic resonance imaging, PET = Positron emission tomography, PXA = Pleomorphic xanthoastrocytomas, WHO = World Health Organization.

Keywords: 5-aminolevulinic acid, glioma, multicentric, pineal, pleomorphic xanthoastrocytoma

1. Introduction

Pleomorphic xanthoastrocytoma (PXA) are a rare, low-grade glioma subtype that account for less than 1% and are characterized by a unique histopathological pattern.^[1] They most commonly affect children and young adults, typically originate from the supratentorial compartment, and are most

frequently observed in the temporal lobe with very a few lesions in other areas.

Very few reports have described simultaneous multicentric PXA.^[2,3] PXAs are associated with a favorable prognosis, and the current 5-year recurrence-free survival rate after surgical resection is 70.9%. In contrast, the 5-year recurrence-free survival rate is significantly shorter (48.9%) in PXAs with anaplastic features; this type of lesion is now classified as anaplastic PXA (Grade III) in the 2016 World Health Organization (WHO) classification of Tumors of the Central Nervous System.^[4] Anaplastic PXA is defined as PXA with a mitotic index ≥ 5 per 10 high-power fields and/or necrosis.^[5] Although proliferative activity does not affect tumor grading in PXA, some authors have emphasized the use of the Ki-67 index as a prognostic factor.^[6,7] Here, we describe two cases of clinically uncommon PXA with aggressive clinical courses, both with a high Ki67 index, wherein one patient presented with a multicentric lesion and the other, a tectal plate tumor.

2. Case presentations

2.1. Case 1

A 19-year-old female presented with severe headache. A neurological examination revealed no significant findings.

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Gadolinium-enhanced magnetic resonance imaging (MRI) revealed a distinct and enhanced mass lesion in the medial temporal lobe and the right orbital gyrus, both of which showed slight growth on a follow-up MRI at 1-month after initial presentation (Fig. 1A). Neither cyst formation nor calcification was detected in the mass lesions. Positron emission tomography (PET) revealed high ^{18}F -fluorodeoxyglucose (FDG) uptake in both the lesions (Fig. 1B). She underwent right front-temporal craniotomy with tumor resection, and strong 5-aminolevulinic acid (5-ALA)-induced fluorescence was detected intraoperatively. The tumor in the right orbital gyrus was totally resected, but that in the temporal lobe could only be partially resected because of tumor invasion of the cerebral penetrating branch (Fig. 1C). While the temporal lesion was an intra-axial tumor, the tumor of the right orbital gyrus was located in the subpial space. The residual tumor was treated with radiotherapy (54Gy/30fr) and concomitant (75 mg/m²/day, 7 days/week for 6 weeks) and adjuvant (150 mg/m²/day, 5 days/month) temozolomide following surgery. The reduction in size of residual tumor was not observed by adjuvant therapy. She remained stable without deterioration in her clinical symptoms, however, MRI at 3 months after the operation revealed tumor regrowth (Fig. 1D).

2.2. Case 2

A 47-year-old woman presented with progressive headaches and disturbance of consciousness. Neurological examination confirmed disorientation and recent memory impairment. Computerized tomography revealed hydrocephalus caused by a single

cystic tumor with calcification in the tectal plate, and the mural nodule exhibited gadolinium enhancement on T1-weighted MRI (Fig. 1E). She underwent surgery for a suspected low grade glioma, and the tumor was totally resected via a right occipital transtentorial approach (Fig. 1F). Intraoperative findings demonstrated a reddish purple tumor with strong 5-ALA-induced fluorescence. She was administered radiotherapy (54Gy/30fr) with concomitant (75 mg/m²/day, 7 days/week for 6 weeks) and adjuvant (150 mg/m²/day, 5 days/month) temozolomide following the surgery, despite which tumor recurrence was detected on follow-up MRI at 5 months after the operation (Fig. 1G). She was admitted to hospital with progressively worsening level of consciousness due to tumor invasion, and began treatment with bevacizumab (10 mg/kg every 2 weeks).

2.3. Pathological findings

Microscopic analysis of the resected tumors from both the patients revealed highly cellular tissue comprising atypical astrocytic tumor cells, including bizarre multinucleated cells and xanthomatous cells (Fig. 2A). Mitosis was rarely observed, and both the cases were devoid of microvascular proliferation and necrosis. Immunohistochemistry demonstrated GFAP and CD34 expression in both the cases (Fig. 2B, C). The Ki-67 labeling index (LI) values for cases 1 and 2 were 20% and 8.7%, respectively, (Fig. 2D). Sequence analysis revealed *BRAF V600E* mutation in both the cases, but no mutations in *IDH1/2* genes or the *TERT* promoter. Quantitative reverse-transcription PCR confirmed the absence of *KIAA1549-BRAF* fusion. Thus, both

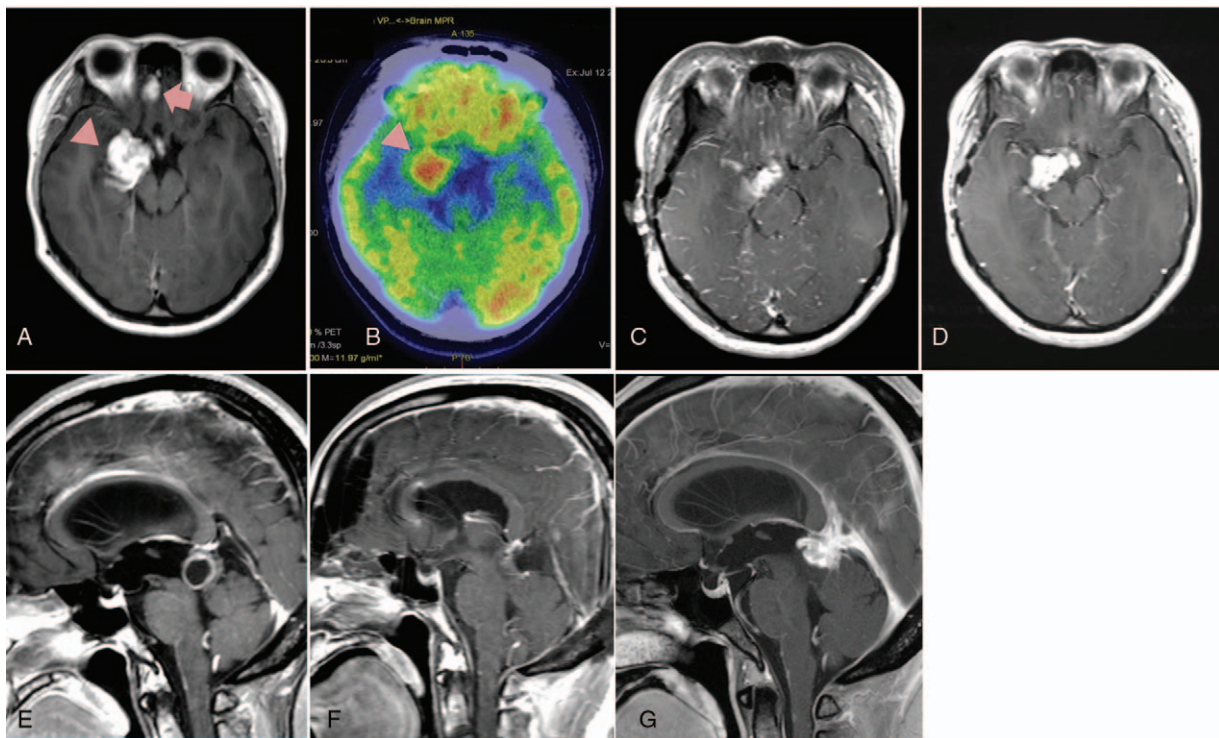


Figure 1. PET and gadolinium-enhanced MR imaging in case 1 (A–D) and case 2 (E–G). Case 1: Preoperative MRI shows two enhancing lesions in the frontal (A, arrow) and temporal lobes (A, arrow head), and PET imaging demonstrates high fluorodeoxyglucose (^{18}F) uptake in the temporal lesion (B, arrow head). Partial removal of the tumors was confirmed by postoperative MRI (C), and MRI after adjuvant therapy revealed regrowth of the residual tumor (D). Case 2: Preoperative MRI shows a cystic tumor in the tectal plate (E). Complete resection of the tumor was confirmed by postoperative MRI (F). MRI after adjuvant therapy indicated local recurrence of the tumor (G).

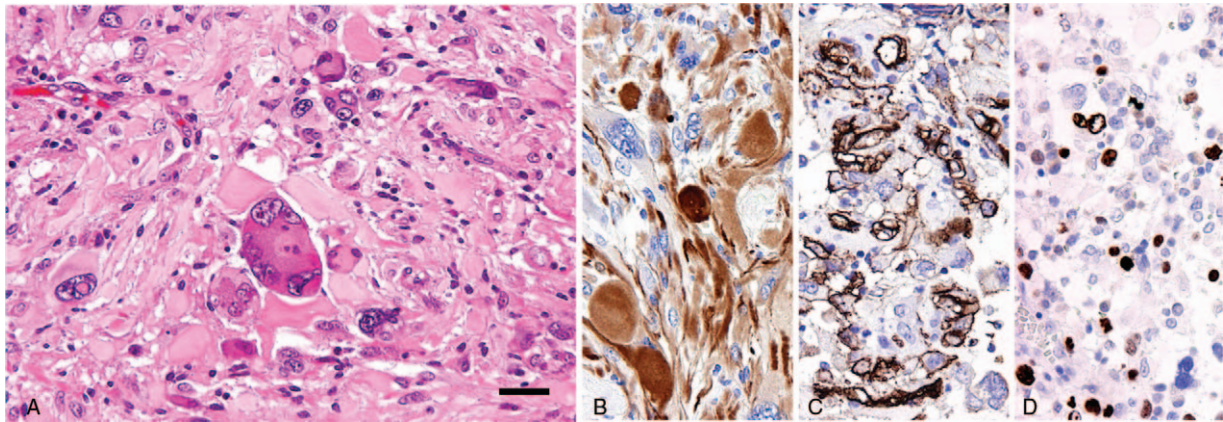


Figure 2. Micrographic findings in case 2. Micrography revealed a highly cellular tumor composed of bizarre glial cells with prominent nuclear atypia and xanthomatous cells (HE, A). Tumor cells showed high expression levels of GFAP (B), CD34 (C), and Ki-67 (D). The scale bar in (A) indicates 50 μ m for A–D.

the cases were histopathologically diagnosed as PXA WHO grade II. Patients have provided informed consent for publication of the cases.

3. Discussion

Few cases of PXA with simultaneous multicentric lesions have been previously described. In the first case of the present report, intraoperative finding of a subpial mass in the orbital gyrus was consistent with cerebrospinal fluid dissemination. PXA commonly displays leptomeningeal dissemination or malignant transformation during long-term follow-up but rarely exhibits dissemination at initial presentation. Our second patient had an extremely rare PXA tumor location, the tectal plate. Tectal gliomas are relatively noninvasive and slow-growing tumors that are have a less aggressive clinical course.^[8] Histopathologically, tectal gliomas are predominantly low grade gliomas, and pilocytic astrocytomas are the most frequent type.^[9] Nonetheless, a few cases of pineal or tectal region PXA have been reported,^[10,11] and as most of these tumors are involved in both the pineal and the tectal region, the site of tumor origin remains unclear. In our case, preoperative MRI and intraoperative findings confirmed tumor location as distal to the normal pineal body, with the tumor predicating as a tectal PXA.

It is difficult to assess the malignancy of PXA based on histopathological appearance alone, even though malignant PXA is diagnosed if necrosis and a high mitotic index are observed. Previous reports have indicated that a high Ki67 LI index and *BRAF* status also correlate with malignancy in PXA.^[7] The presence of *BRAF V600E* mutation, which is observed in 65% of PXA cases, is a predictor of favorable prognosis.^[4,12,13] Tabouret et al. have reported that the *BRAF V600E* mutation is associated with lower Ki67 LI values,^[13] however, both the cases described here exhibited a progressive clinical course despite the presence of the *BRAF V600E* mutation and absence of high mitotic activity, necrosis, or microvascular proliferation. Thus, our experience suggests that additional therapy following curative resection should be considered during treatment of PXA with high Ki67 LI values.

Recurrence and overall survival of PXA with anaplastic features are significantly lower than those of PXA without anaplastic features,^[4,14] and additional chemo/radiotherapy is commonly recommended in patients with anaplastic PXA. However, the

paucity of clinical studies hampers the selection of appropriate postoperative therapy, and the benefits of radiotherapy and chemotherapy with temozolomide or vemurafenib remain controversial. Importantly, both our patients did not respond to this combination of radiotherapy and chemotherapy.

High FDG uptake is commonly observed in recurrent and anaplastic PXA, but is rarely seen in typical PXA.^[15] However, we assumed that the hypermetabolic state observed in case 1 was associated with tumor aggressiveness, and FDG-PET may be a useful preoperative assessment tool for tumor aggressiveness in PXA.

The intraoperative use of 5-ALA fluorescence for guidance is an established practice for the visualization of gliomas. Positive fluorescence is generally observed in high grade gliomas, ependymoma, and medulloblastoma, but is less frequently seen in WHO grade II gliomas, including astrocytomas and oligodendrogliomas (15.8%), and is rarely seen in pilocytic astrocytomas and gangliogliomas.^[16,17] Only few cases have reported the use of 5-ALA fluorescence for PXA and Jaber et al have also indicated that ¹⁸F-FET PET uptake can predict 5-ALA-induced fluorescence.^[16] Interestingly, contrary to other WHO grade II gliomas, all the reported cases of PXA, including those reported here, displayed 5-ALA enhancement.^[18,19] Therefore, we propose the use of intraoperative 5-ALA fluorescence guidance in all the patients with PXA.

4. Conclusion

We describe 2 cases of PXA with unusual clinical presentations and the case reports suggest that high Ki-67 LI in PXA can be used as a predictive marker of an adverse clinical course and that a combination of radiotherapy and chemotherapy with temozolomide may not be beneficial for patients with PXA with high Ki-67 LI values. Conversely, 5-ALA fluorescence is potentially beneficial for intraoperative tumor visualization in PXA.

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