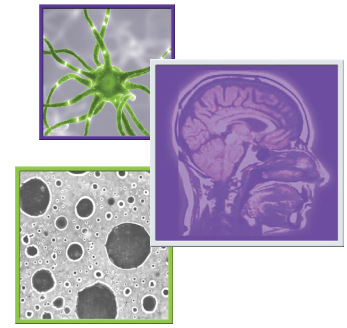
CASE REPORT

CNS Oncology



Dabrafenib in BRAFV600-mutated anaplastic pleomorphic xanthoastrocytoma

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Practice points

- Pleomorphic xanthoastrocytoma (PXA) is an uncommon brain tumor.
- Anaplastic PXA (20–30%) has recently been reclassified as a WHO grade III tumor (previously grade II).
- Typical treatment is with gross total resection, radiotherapy and cytotoxic chemotherapy.
- BRAFV600 mutation status should be determined for all patients with PXA.
- BRAF inhibitors such as dabrafenib and vemurafenib may be effective in the treatment of BRAFV600-mutated PXA.
- Due to well-recognized acquired resistance mechanisms, combining BRAF and MEK inhibitors may be more effective.

Pleomorphic xanthoastrocytoma (PXA) is a rare brain tumor. Anaplastic features are found in 20–30% of cases of PXA and are associated with poor outcomes. Typical treatment is with gross total resection, followed by radiation therapy and cytotoxic chemotherapy at relapse. BRAFV600 mutations have been identified in 38–60% of patients with PXA. Several case reports and small case series have identified clinical benefit with BRAF inhibition in patients with BRAFV600-mutated PXA. We report the second published case of successful treatment with the BRAF inhibitor dabrafenib in a female patient with relapsed anaplastic PXA with a BRAFV600 mutation, and the first published case of dabrafinib treatment following intolerance to vemurafenib.

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KEYWORDS
• anaplastic • BRAF inhibitor • BRAFV600 mutation • dabrafenib • pleomorphic xanthoastrocytoma • PXA • vemurafenib

Background

• Pleomorphic xanthoastrocytoma

Pleomorphic xanthoastrocytoma (PXA) is a rare brain tumor, with an incidence of fewer than 0.07 cases per 100,000. It most commonly affects children and young adults, with a median age of diagnosis of 20.5–30.5 years. There is no significant gender difference [1–4]. A total of 97–99% of tumors are supratentorial, most frequently occurring in the temporal lobe. The most common initial symptom is seizures, occurring in 64–75% at presentation [1–3]. Other frequent clinical features include focal neurological deficits, visual disturbance, raised intracranial pressure and rarely, intracerebral hemorrhage [5].

PXA have a typical MRI appearance of a cystic mass with a prominent solid component that is isointense to gray matter on T1-weighted views, mildly hyperintense in T2-weighted views,

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enhancing with gadolinium and with variable surrounding edema [6]. Purely solid and cystic forms also exist. PXAs are histologically distinct with pleomorphic giant cells with xanthomatous change, presence of eosinophilic granular bodies and dense deposition of intracellular reticulin [7].

Anaplastic features are found in 20–30% of cases and include a high mitotic index (≥5/10 high-powered fields) with or without necrosis [2,3]. Anaplasia confers a poorer progression-free and overall survival, although less reliably than in astrocytomas [7]. This aggressive variant of PXA has been recognized as a separate clinical entity in the recently published 2016 WHO Classification of Tumors of the CNS, termed 'anaplastic PXA', and now classed as a grade III tumor, having previously been categorized as a grade II tumor in the 2007 edition [8,9].

Typical treatment is gross total resection if feasible, followed by radiotherapy and cytotoxic chemotherapy at recurrence. Five-year overall survival is 76–80% in all patients with PXA, and 57% in those with anaplasia [1,3].

• BRAFV600 mutations

A seminal study investigating the MAPK signal-transduction pathway identified mutations in BRAF as a key driver of oncogenesis in a number of human cancers, most notably melanoma [10]. More than 95% of BRAF mutations are a substitution of valine by glutamate at amino acid position 600 (BRAF V600) that initiates constitutive and proneoplastic activation of the MAPK pathway [10,11]. The BRAFV600 mutation is found in 38–60% of patients with PXA [1,12–15]. It is unclear whether a BRAF mutation alone affects prognosis [1]. In glioma mouse models, BRAF mutation alone is insufficient to initiate tumorgenesis. However, the combination of cyclin-dependent kinase inhibitor 2A loss with mutated BRAF generates malignant transformation [16]. Concomitant cyclin-dependent kinase inhibitor 2A deletion and BRAF mutation have been frequently identified in PXA [11].

• BRAF inhibition

The introduction of drugs that inhibit mutant BRAF has dramatically changed the clinical outcomes of patients with BRAF-mutated tumors. The most robust data of efficacy are from large clinical trials in patients with metastatic melanoma.

A pivotal Phase III randomized trial compared the BRAF inhibitor vemurafenib with dacarbazine (standard therapy) in 675 patients with BRAFV600-mutated metastatic melanoma [17]. There were superior response rates (48 vs 5%), progression-free survival (5.3 vs 1.6 months [HR: 0.26 95% CI: 0.2–0.33, $p < 0.001$]) and 6-month survival (84% [95% CI: 78–89%] vs 64% [56–73]) in the vemurafenib arm. A further large Phase III randomized trial compared the BRAF inhibitor dabrafenib with dacarbazine in 250 patients with previously untreated BRAFV600 mutant metastatic melanoma with improved response rates (50% [42.4–57.1] vs 6% [1.8–15.5]) and progression-free survival (5.1 vs 2.7 months [HR: 0.3, 95% CI: 0.18–0.51, $p < 0.001$]) in the dabrafenib arm [18]. The most frequent side-effects of BRAF inhibitor therapy were arthralgia, rash, fatigue, cutaneous squamous cell carcinoma and keratoacanthoma. Comparing the two trials, dabrafenib appeared to be better tolerated than vemurafenib, with a lower incidence of skin toxicity. Treatment of melanoma patients with brain metastases demonstrated the efficacy of BRAF inhibitors in the CNS, with similar responses in intracranial and extracranial disease [13].

There is some evidence for the use of BRAF inhibitors in BRAFV600 mutant PXA. A Phase II 'basket' study of vemurafenib in 122 patients with nonmelanoma cancers with BRAFV600 mutations included four patients with PXA [19]. Of these, 3/4 patients had a partial response and 1/4 patient had a best response of stable disease. In a case series of four patients with PXA (one with anaplasia) with BRAFV600 mutations treated with salvage vemurafenib, best response assessments were partial response in one patient, stable disease in two patients and progressive disease in one patient [20]. The median overall survival was 8 months (range: 4–14 months), and median progression-free survival was 5 months (range: 2–10 months). All patients previously had surgical resection, radiotherapy and chemotherapy (PCV or temozolomide). Three case reports describe treatment with vemurafenib in three separate patients with anaplastic PXA [21–23]. All of these patients had been previously treated with surgical debulking, radiotherapy and chemotherapy. Two cases report tumor regression on MRI (1 near complete response) and the third case reported stable disease on follow-up imaging. The reported toxicities are consistent with those characterized in clinical trials in patients with melanoma described above.

There is a single published case report of dabrafenib use in PXA. A patient with primary meningeal PXA with anaplastic features was commenced on dabrafenib following surgery and radiation, with subsequent significant improvement in tumor-related symptoms and reduction in disease on imaging [24]. The patient developed progressive disease 3.5 months later (although therapy was withheld for several weeks due to an intracranial hemorrhage) and died a few weeks later.

Case

A 21-year-old university student initially presented in June 2014 with a 1 month history of crescendo headache, vomiting, blurred vision and somnolence. MRI of the brain demonstrated a large mass with a pleomorphic appearance within the right middle cranial fossa. There was a large enhancing soft tissue nodule at the medial inferior aspect, a large cystic component and surrounding vasogenic edema with midline shift **(Figure 1)**.

The patient had an emergency drainage of the large temporal cyst with initial histology reported as glioblastoma. Eleven days later she underwent a right temporal craniotomy and gross total resection. Final histology was reported as PXA with anaplastic features, and a BRAFV600 mutation was identified. Her symptoms resolved. The patient received adjuvant RapidArc intensity modulated radiotherapy (54.9 Gray in 33 fractions), completed in August 2014. In September and October 2014 she had several stereotypical episodes which "felt like being washed over with hot and cold water", with a "feeling" in her abdomen. These were diagnosed as temporal lobe seizures and she was commenced on lamotrigine.

An MRI scan in November 2014 **(Figure 2)** identified an increase in the volume of enhancing tissue in the surgical bed, suspicious for disease progression. The patient had a second right temporal craniotomy and complete resection. Histology was consistent with tumor recurrence. She was subsequently commenced on vemurafenib 960 mg twice daily in December 2014. Eleven days later she developed a widespread macular rash throughout her trunk and limbs. She stopped vemurafenib, commenced hydrocortisone cream and her rash subsequently resolved. Vemurafenib was recommenced at a 25% dose reduction 17 days later. The following day she developed a similar widespread rash. Vemurafenib was stopped and the rash again resolved. An MRI in February 2015 showed slight thickening in enhancement in the floor of the right middle cranial fossa. At this point

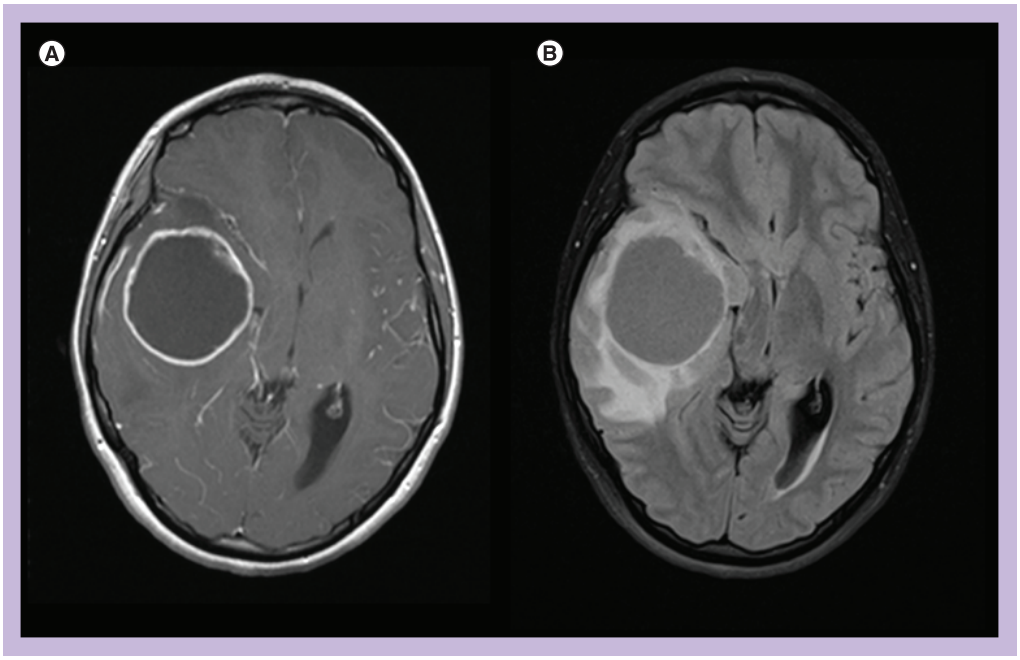

Figure 1. MRI performed at initial presentation. (A) Axial T1 sequence with Gadolinium. **(B)** Axial T2 sequence.

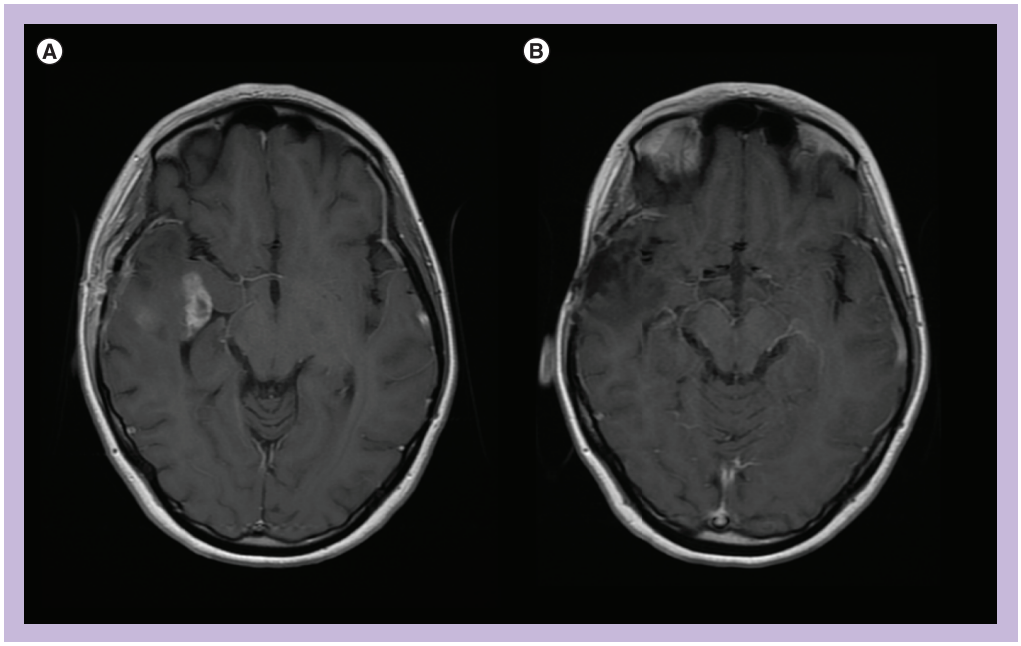

Figure 2. Axial MRI with gadolinium. (A) Enhancing tissue within surgical bed, suspicious for tumor recurrence. **(B)** No evidence of recurrence after resection and 18 months of BRAF inhibitor therapy.

she was commenced on dabrafenib 150 mg twice daily which she continues to take. In her last review in June 2016 she was well, with mild fatigue, but no other toxicities of dabrafenib or symptoms of her tumor. Serial MRI has shown no recurrence of her PXA.

Discussion

Our case is the second report of dabrafenib treatment in PXA, the first of successful treatment in PXA with dabrafenib following intolerance to vemurafenib and adds to the growing literature on the successful use of BRAF inhibitors in patients with PXA.

In clinical trials of BRAF inhibitors in metastatic melanoma while initial response rates are impressive, acquired resistance to BRAF inhibitors occurs in a significant proportion of patients. One of the most frequent causes of acquired resistance is reactivation of the MAPK pathway [25,26]. Furthermore, paradoxical activation of the MAPK pathway in cells without BRAF mutations has been implicated in the development of secondary skin tumors in patients treated with BRAF inhibitors [27,28]. MEK is an essential component of the MAPK pathway [29]. Trametinib, a MEK inhibitor, in combination with dabrafenib was superior to BRAF inhibition alone in two Phase III clinical trials in metastatic melanoma, with similar toxicity profiles [30,31]. Combination BRAF and MEK inhibition is now the standard treatment in BRAFV600 mutant metastatic melanoma [32].

Conclusion

In conclusion, all patients with PXA should be tested for the BRAFV600 mutation. If present we advocate that they should be commenced on combination BRAF and MEK inhibition with dabrafenib and trametinib.

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