

Successful Treatment of a Progressive *BRAF* V600E–Mutated Anaplastic Pleomorphic Xanthoastrocytoma With Vemurafenib Monotherapy

Introduction

Pleomorphic xanthoastrocytoma (PXA) is a rare brain tumor that most commonly affects children and young adults. PXA undergoes anaplastic transformation in 15% to 20% of patients.¹ Although the prognosis is relatively favorable for patients with a WHO grade 2 PXA, data suggest that the prognosis for anaplastic PXA is significantly worse.^{1,2} Maximal resection is generally recommended, but the role of radiation or chemotherapy in the management of these tumors remains unclear.

Alterations in the *BRAF* gene have been described in several pediatric low-grade gliomas.^{3–6} Approximately 70% of pilocytic astrocytomas contain *BRAF* fusions, resulting from a tandem duplication and rearrangement on 7q34 between *BRAF* and a gene centromeric to *BRAF*. This is in contrast with PXA, in which the described *BRAF* alteration is instead a *BRAF* mutation that results from an amino acid substitution replacing valine (V) with glutamic acid (E) at position 600. This *BRAF* V600E mutation is found in approximately 60% to 65% of WHO grade 2 and 3 PXAs,^{7,8} and is the same mutation that is found in approximately 50% of melanomas.⁹

Vemurafenib is a *BRAF* inhibitor that is approved for the treatment of *BRAF*-mutated metastatic melanoma in the United States and the European Union.¹⁰ There are several case reports of CNS melanoma metastases that were responsive to vemurafenib,^{11,12} and preliminary results from an open-label pilot study of vemurafenib for patients with melanoma and brain metastases suggest some activity.¹³ This evidence indicates that vemurafenib may penetrate CNS tumors. In addition, *BRAF* inhibition represses the growth of intracranial *BRAF* V600E pediatric malignant astrocytoma xenografts in mouse models.¹⁴ Hence, vemurafenib may have a role in the treatment of intracranial neoplasms with *BRAF* mutations. In support of this, we now present a case of a progressive *BRAF* V600E–mutated anaplastic PXA that was successfully treated with vemurafenib monotherapy.

Case Report

A 41-year-old, right-handed man with an anaplastic PXA with a *BRAF* V600E mutation developed radiographic progression despite surgery, radiation, and treatment with temozolomide. His neurologic history dates to his early twenties, when he presented with seizures. This was not further investigated until 2009, when he also developed headaches. Magnetic resonance imaging (MRI) of the brain revealed a right frontotemporal mass with solid and cystic components and focal areas of intense enhancement within the solid portion. The patient underwent a near gross total resection with pathology demonstrating a PXA (WHO grade 2). *BRAF* mutational status was assessed by

polymerase chain reaction–based amplification of exon 15, followed by pyrosequencing of polymerase chain reaction products using a commercial assay (Qiagen, Valencia, CA). This demonstrated a *BRAF* V600E (c.1799T>A) mutation. The patient was observed with serial imaging until 2011, when MRIs demonstrated increased surrounding enhancement. He was treated with temozolomide but developed radiographic progression after two cycles.

The patient underwent another resection in February 2012. Review of the pathology showed an anaplastic PXA (WHO grade 3). The histology had markedly changed since his 2009 resection and showed increased cellularity, mitoses, and a Ki-67 labeling index of 20%. He received involved field radiation to a total dose of 59.40 Gy in 47 fractions of 1.8 Gy, as well as concurrent temozolomide as a radiation sensitizer. He completed radiation and concurrent temozolomide in May 2012; thereafter, observation with serial imaging was planned. The initial postradiation brain MRI demonstrated some improvement radiographically with decreased enhancement, but then the lesion began to develop increasing nodular enhancement, as noted on subsequent scans. Because of the possibility of so-called pseudoprogression, the patient continued to undergo observation with close monitoring for 6 months. However, the abnormality continued to expand, with an increase in nodular enhancement (Fig 1A) and surrounding edema (Fig 1B) that was concerning for progressive disease. Despite these radiographic changes, the patient remained clinically asymptomatic, neurologically intact, and seizure free, without corticosteroids. We addressed management options, including repeat surgery for pathology to confirm progression. However, given the patient's comorbid nonischemic dilated cardiomyopathy and his preference to avoid surgery, no further biopsy or resection was performed.

Because the patient's tumor was known to harbor a *BRAF* V600E mutation, we appealed to his health insurer, who agreed to cover the cost of vemurafenib. The patient began receiving treatment with vemurafenib at a dose of 720 mg twice per day in early February 2013. He developed a grade 2 diffuse morbilliform eruption with xerosis and follicular prominence 10 to 14 days after starting treatment. A punch biopsy was obtained from his thigh and revealed a superficial and deep perivascular lymphocytic infiltrate with rare eosinophils that was suggestive of a hypersensitivity reaction. He had a concomitant grade 1 transaminitis without other evidence of systemic hypersensitivity. He was managed with liberal topical corticosteroids and antihistamines, with eventual improvement in his skin eruption and transaminitis. Other adverse events that may have been related to vemurafenib included grade 1 alopecia and grade 1 diarrhea. He remained neurologically intact and without systemic corticosteroids. A restaging brain MRI with contrast after approximately 3 weeks of vemurafenib treatment demonstrated an interval decrease in the amount of nodular enhancement. This was confirmed by another brain MRI with contrast after approximately 12 weeks of vemurafenib, which showed minimal residual enhancement (Fig 1C) and improvement in edema (Fig 1D) that was consistent with a nearly complete response.

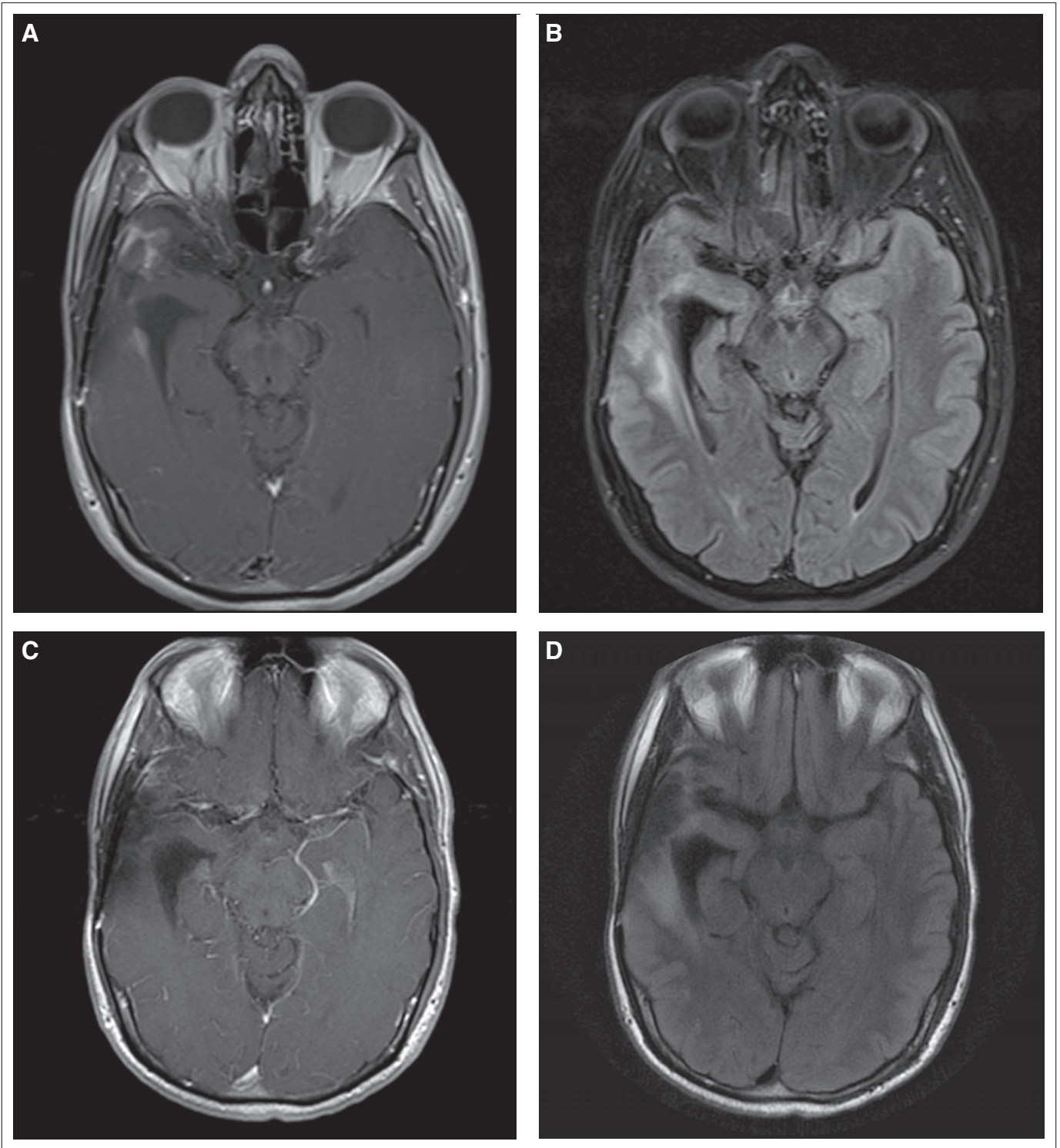


Fig 1.

Discussion

This is the first report, to our knowledge, of vemurafenib monotherapy used in the treatment of a *BRAF* V600E–mutated glioma. A recent case report describes the successful treatment of a brainstem *BRAF* V600E–mutated ganglioglioma with vemurafenib in combination with vincristine.⁵ Although those results are encouraging, the

relative contributions of vemurafenib and vincristine to the response are unknown.

In our patient, it is possible that the increased enhancement that was seen on imaging before initiation of vemurafenib was related to pseudoprogression, and that the subsequent improvement is unrelated to vemurafenib. Pseudoprogression after radiation and

concurrent temozolomide is a well-described phenomenon in high-grade glioma and is attributed to a transient increase in the permeability of the tumor vasculature from irradiation, which may be enhanced by temozolomide.^{15,16} However, we consider this unlikely in our patient because the increased nodularity developed more than 6 months after the completion of radiotherapy (that would be a late time frame for pseudoprogression on the basis of the high-grade glioma literature¹⁷). Notably, the extent of enhancement initially improved in the months after radiation and subsequently worsened and developed a more nodular appearance.

In most patients with melanoma who are treated with BRAF inhibitor monotherapy, resistance develops with disease progression within 6 to 8 months of therapy initiation.¹⁸ Although a variety of intrinsic and acquired pathways of resistance are being studied, combination MEK and BRAF inhibition is one method of attempting to overcome this resistance. Whether this patient's anaplastic PXA will become resistant to vemurafenib remains to be seen.

In summary, we successfully treated a *BRAF* V600E anaplastic PXA with vemurafenib, and an excellent radiographic response was achieved. Further investigation of BRAF inhibitors for the treatment of *BRAF*-mutated primary brain tumors is warranted, and a clinical trial testing the efficacy and safety of dabrafenib (a BRAF inhibitor) and trametinib (an MEK inhibitor) in patients with *BRAF* V600E-mutated rare cancers, including gliomas (clinicaltrials.gov NCT02034110), is in development.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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