Cranioopharyngiomas are locally aggressive lesions of the suprasellar space that occur in two distinct histopathological subtypes. Adamantinomatous craniopharyngiomas tend to occur in a bimodal distribution, with peaks in childhood and middle age, while papillary craniopharyngiomas develop in adults.11,12 Papillary craniopharyngiomas represent a distinct minority of cases, as few as 11% in some series.11 Both histologies exhibit a similar clinical course, with frequent recurrences despite aggressive local resection and subsequent radiation.6 These lesions can present with a morbid clinical picture due to compression of the optic chiasm, pituitary stalk, and hypothalamus. Adherence to these critical structures can limit the ability of the surgeon to completely resect the lesion, placing patients at risk for recurrence.

In circumstances in which there is a persistent lesion despite aggressive resection and subsequent radiation treatment (the current standard of care), there is a need to explore additional therapeutic avenues to improve long-term disease control while minimizing treatment-related morbidities. Papillary craniopharyngiomas frequently carry a mutation in the BRAF gene, of which the V600E mutation is a common alteration, affecting as many as 95% of tumors.2,8 This mutation results in constitutive activation of the gene and the associated downstream MAP kinase pathway, leading to increased cellular proliferation.2,7 The biological importance of the BRAF V600E mutation and targeted therapies directed toward the mutant protein have been pioneered in melanoma,3 and one reported case of treatment of a papillary craniopharyngioma with inhibitors...
of BRAF V600E (dabrafenib) and MAP kinase pathway (trametinib) resulted in an 85% reduction in tumor volume following treatment. In this report we present a case of a patient with a recurrent papillary craniopharyngioma who previously underwent surgery and radiotherapy, which was salvaged with dabrafenib and led to a radiographic response that was sustained through 1 year of therapy. The patient has remained free of tumor progression for more than 1.5 years since discontinuing dabrafenib.

Case Report

History and Examination

A 47-year-old man with a remote history of non-Hodgkin lymphoma presented with visual loss and color blindness, as well as symptoms of diabetes insipidus. Magnetic resonance imaging revealed a cystic suprasellar lesion concerning for a craniopharyngioma (Fig. 1A and B). He underwent resection of the lesion through a right pterional craniotomy at an outside institution. Histopathological analysis at the time confirmed the lesion to be a papillary craniopharyngioma. He suffered panhypopituitarism postoperatively, requiring replacement with desmopressin, hydrocortisone, and levothyroxine. Subsequent imaging revealed some residual enhancement along the pituitary stalk (Fig. 1C and D). He was followed closely with serial imaging, and an increase in the size of solid tumoral suprasellar enhancement was noted in 2012 (Fig. 1E and F). The patient was clinically asymptomatic from this radiographic recurrence. Complicating his history in the prior year was a diagnosis of stage III colon cancer, treated with partial colectomy and chemotherapy with folinic acid, fluorouracil, and oxaliplatin beginning in January 2012 for 4 cycles. He presented to our institution at this time for a second opinion regarding management of his recurrent craniopharyngioma. Given that his vision was intact despite his disease progression, and due to concern for adhesion between the lesion and the optic chiasm, especially given his prior surgery, the patient underwent radiotherapy in March 2012 consisting of a total dose of 36 Gy in 12 fractions (plan shown in Fig. 2). PET/MRI performed in March demonstrated a metastatic liver lesion and increased uptake in mediastinal lymph nodes, so to facilitate the delivery of adjuvant chemotherapy for his colon cancer he was transitioned to folinic acid, fluorouracil, irinotecan, and bevacizumab; this regimen was later simplified to bevacizumab and capecitabine in late 2012, with continuation of capecitabine alone in December 2012.

Dabarfenib Therapy and Follow-Up

The patient tolerated radiation therapy well and was once again followed with serial imaging. He initially responded well to radiation therapy, with a reduction in the size of the lesion to a 4–5-mm remaining enhancing suprasellar nodule that remained stable for more than 2 years (Fig. 1G and H). He did experience progression of his colon cancer; hypermetabolic left supraclavicular lymph nodes were treated with radiation in late 2013. He had no further evidence of disease progression, and ongoing therapy with capecitabine was halted in December 2014. However, in early 2015 enlargement of the craniopharyngioma tumor was again noted (Fig. 3A and B). This patient’s case was discussed in a neurooncology multidisciplinary board meeting and both surgery and re-irradiation options were not recommended due to the high risk of treatment-related morbidity. He once again remained clinically asymptomatic beyond his hypopituitarism. The fixed tumor specimens from his original resection were obtained to assess for the BRAF V600E mutation. Presence of the mutation was confirmed in his original lesion, and treatment with
dabrafenib was initiated at 150 mg twice daily. Shortly after the start of dabrafenib therapy, the patient reported joint pain, and the decision was made to reduce the dosage of dabrafenib to 150 mg daily. He tolerated this reduced dose well, and after several weeks the dose was increased to 225 mg daily, which he continued to tolerate well. Imaging obtained approximately 2 months following the initiation of dabrafenib demonstrated enlargement of the cystic component of the tumor, but the volume of the solid enhancing portion had decreased (Fig. 3C and D). Given that the patient’s visual fields remained preserved at this time, the decision was made to continue therapy and close observation. Subsequent imaging demonstrated no further enlargement of the lesion and after 6 months of therapy began to demonstrate significant reduction in the size of both the cystic and solid enhancing components of the lesion. After 9 months of therapy, minimal residual tumor remained, and this remained stable on serial scans until 1 year after the initiation of dabrafenib therapy (Fig. 3E and F). At that time, given the patient’s stable disease on multiple imaging studies, the decision was made to transition him off of dabrafenib therapy and to a period of close observation. On subsequent imaging studies, his burden of disease remained stable, with the recent study completed just over 1 year following cessation of dabrafenib therapy (Fig. 3G and H).

Discussion

Given that craniopharyngiomas are locally aggressive suprasellar tumors, surgical intervention and radiotherapy can result in morbidity secondary to collateral injury to adjacent structures if the tumor is adherent and therefore unable to be removed. Hence, despite aggressive multimodal treatments that comprise the current standard of care, these tumors often recur and are recalcitrant to further treatment. Thus, craniopharyngiomas are an ideal tumor for which to use targeted therapy, as either an adjuvant or potentially up-front treatment.6

There are two main histological subtypes of craniopharyngioma with similar clinical presentation and behavior, i.e., adamantinomatous and papillary.6 The papillary subtype is more frequent in adults.6 BRAF V600E is a targetable mutation, which has recently been described in the majority of papillary craniopharyngiomas.2 BRAF is a protooncogene that encodes a serine/threonine kinase involved in growth factor signaling and regulation. Mutations in BRAF that transform the B Raf kinase into a constitutively active form result in cell proliferation and tumor growth. The BRAF V600E mutation has been described in 7% of human cancers.7 It is targeted in malignant melanoma and non–small cell lung cancer using inhibitors such as vemurafenib and dabrafenib, but these agents have also been used as targeted therapy for other tumor types with BRAF V600E mutations, including pleomorphic xanthoastrocytoma, ganglioglioma, and a BRAF V600E–mutant glioblastoma with systemic metastases.4,9,10

Recently, a patient with a multiply recurrent BRAF V600E–mutant papillary craniopharyngioma was reported as having been treated with dabrafenib and the MEK inhibitor trametinib with an excellent result, remaining symptom-free 7 months into treatment.1 We report the longest known follow-up with a patient with BRAF V600E–mutant craniopharyngioma treated with a BRAF V600E inhibitor. In contrast to the prior report, we used dabrafenib monotherapy at a dose of 225 mg daily for 1 year, and report 1 year of follow-up after treatment discontinuation. Of note, initial cystic enlargement observed on the first follow-up MRI performed 2 months following the beginning of dabrafenib treatment in our patient may have been attributable to “pseudoprogression” in which the initial radiographic progression noted early in treatment is then followed by lesion shrinkage, as was found in our patient. While pseudoprogression is a well-defined phenomenon early after radiation/chemotherapy treatment of patients with glioma, pseudoprogression in the context of BRAF-targeted treatment of papillary craniopharyngioma.
Gioma has not previously been described and therefore may need to be considered when assessing imaging studies for response versus recurrence in upcoming clinical trials evaluating BRAF inhibitors to treat papillary craniopharyngiomas. In this context, it is also important to consider the role of the patient’s prior radiation in this apparent recurrence. Given that no further tissue sampling was obtained prior to initiation of dabrafenib therapy, it is possible this recurrence represented a late radiation-related treatment effect. However, given the appearance of this recurrence nearly 3 years after completion of radiation, the likelihood of it representing radiation-related transient pseudoprogression is very low. Furthermore, were this lesion to represent true delayed radiation necrosis, we would not anticipate it to improve spontaneously over a relatively short interval.

This case lends support to the use of small-molecule inhibitors such as dabrafenib as an additional tool in the challenging treatment of papillary craniopharyngiomas. The case reported here, in conjunction with that recently reported by Brastianos et al. as discussed above, demonstrates that BRAF V600E inhibitors can have a potent effect on these uncommon tumors that harbor the BRAF V600E mutation. Further investigation is needed to determine the appropriate duration, dose, and combination of small-molecule therapeutics used. Regardless, based on our experience, the use of a targeted BRAF V600E inhibitor such as dabrafenib represents a promising therapeutic consideration in patients for whom repeat surgery presents significant risks, and who do not require an emergency decompressive procedure. If papillary craniopharyngiomas could be reliably identified preoperatively, these agents could be used as a neoadjuvant therapy to reduce the preoperative tumor volume and potentially reduce morbidity associated with surgical intervention. An ongoing cooperative group trial (Alliance A071601) is testing the combination of BRAF/MEK inhibition in patients with BRAF V600E–mutant craniopharyngioma.

### References


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