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LETTER TO THE EDITOR

BRAF V600E mutation: A treatable driver mutation in pleomorphic xanthoastrocytoma (PXA)

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To the Editor,

BRAF V600E mutations have therapeutic implications in a wider range of tumors than previously considered. Anaplastic pleomorphic xanthoastrocytoma (PXA), a rare tumor entity, accounts for less than 1% of all astrocytic tumors. Prognosis of these tumors is poor and similar to anaplastic astrocytomas and glioblastoma. Two-thirds of PXA, including classical (WHO grade II) and anaplastic WHO grade III tumors, harbor a specific *BRAF* point mutation V600E [1,2].

Case report

We report the case of a 29-year-old Caucasian female patient who presented with headaches, left-sided visual impairment and paresthesias in her left upper arm. Cranial magnetic resonance imaging (MRI) revealed a contrast enhancing and cystic mass in the right temporo- occipital lobe that extended into the parietal lobe (Figure 1). Subtotal resection was performed and histopathological examination rendered an astrocytic neoplasm with a compact fascicular architecture that partially infiltrated the dura. The tumor cells, including pleomorphic and lipid-laden forms were embedded in a reticulin-rich stroma. In addition, perivascular collections of lymphocytes and occasional eosinophilic granular bodies were seen. Although the tumor lacked necrosis or microvascular proliferation, up to five mitotic figures/10hpf were found. The MIB1 proliferation index approached 20% and glial fibrillary acidic protein (GFAP) showed strong expression in the tumor cells. Additionally, CD34 immunopositivity was detected in some of the neoplastic cells. The findings were in accordance with an anaplastic PXA (aPXA). Postoperative radiation therapy with 54 Gy was applied. One year later the patient presented with symptoms similar to her initial presentation. MRI demonstrated local recurrence, which prompted a second surgical intervention to completely remove the tumor. Histologic review confirmed the diagnosis of aPXA; the tumor tissue was tested for molecular abnormalities using PCR and was found to harbor a point mutation in the *BRAF* V600E and lacked mutations in *IDH1/2* genes. Additional treatment was refused by the patient. Two months later tumor progression with increased perfusion was noted on MRI, while the performance status of the patient remained unchanged. Chemotherapy with temozolomide (TMZ) 150 mg/m^2 5/28 days was started with a delay of three months after the last surgery. Despite this treatment the patient gradually worsened with the recurrence of headaches, visual disturbances and a drop of the Karnofsky Performance Status (KPS) from 90% to 70%. After two cycles of TMZ, cranial MRI demonstrated increased size of the contrast enhancing lesion and surrounding T2/FLAIR hyperintensities consistent with progressive disease.

The patient underwent a third resection and the diagnosis of aPXA was again confirmed. Within three weeks, the patient presented with clinical symptoms of tumor progression on MRI.

Following the experience of recently published case reports [3–6] and the lack of standard treatment

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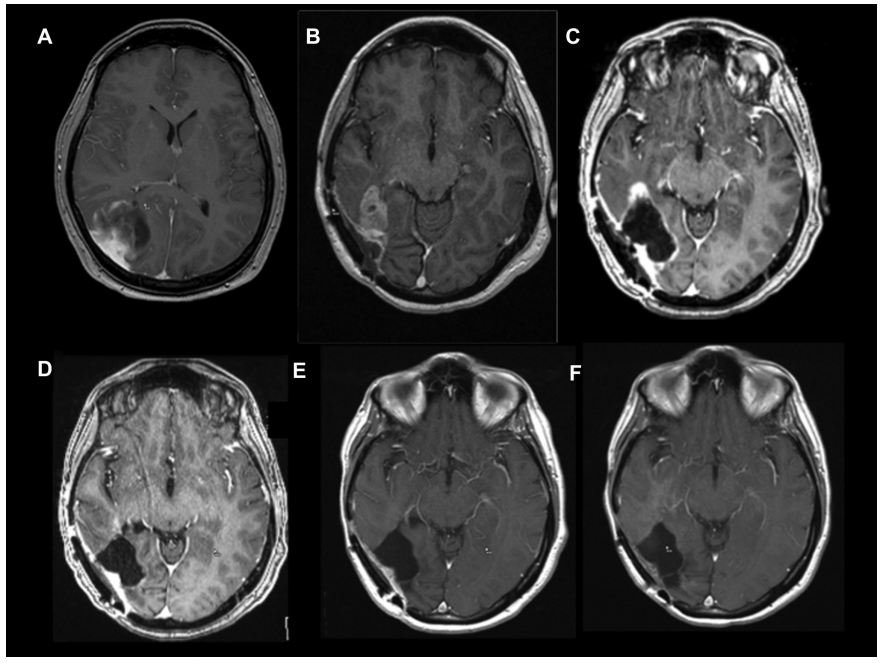

Figure 1. T1, contrast enhanced, axial MRI. A: anaplastic pleomorphic xanthoastrocytoma at diagnosis (17.1.2012), contrast enhanced tumorwith cystic component, B: prior to 3th surgery (26.11.2013), C: one month after 3th surgery (27.12.2013), D: five weeks on vemurafenib (31.1.2014), E: five months on vemurafenib (14.5.2014), F: one year on vemurafenib (22.1.2015).

options, the patient consented to treatment with the BRAF-inhibitor vemurafenib (Zelboraf®, 960 mg twice daily) and abstained from steroids.

Within two weeks of treatment the patient's headaches and visual disturbances subsided. At her next radiological follow-up, five weeks after the first dose of vermuarfenib, the MRI showed tumor remission in the contrast-enhanced T1 and FLAIR-weighted images. The patient, who has been on continuous treatment with vemurafenib for 12 months at the time of this report, maintains a good performance status (KPS 70-80). Only minor adverse effects, consisting of a transient skin rash, could be attributed to vemurafenib therapy. The most recent MRI (January 2015) reveals subtle and diffuse contrast enhancement in the temporal lobe, indicating tumor progression (Figure 1); however, the patient remains asymptomatic, three years after diagnosis of aPXA.

Conclusion

Recent clinical studies have established that genetically defined subgroups of solid cancers may respond to therapeutic interventions that target tumor driver mutations. Our case and others [3–5] demonstrate that even rapidly progressive and treatment resistant aPXA with a *BRAF*V600E mutation can be successfully treated with vemurafenib monotherapy for a sustained and clinically meaningful period of time. Resistance mechanisms and possible rescue treatments for patients with *BRAF*V600E mutated PXA, need to be addressed in clinical trials complemented by translational research.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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