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Case Report

Successful Treatment with Dabrafenib/Trametinib of a Malignantly Transformed and Metastasized BRAF V600E Mutant Pleiomorphic Xanthoastrocytoma: A Case Report and Review of the Literature

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Keywords

Pleiomorphic xanthoastrocytoma · Anaplastic pleiomorphic xanthoastrocytoma · Metastasic disease · BRAFV600E mutation · BRAF/MEK inhibitors · Targeted therapy

Abstract

Introduction: Pleiomorphic xanthoastrocytoma (PXA) is considered a low-grade glioma with a favorable prognosis following surgical resection. We present a case report of a *BRAF*^{V600E} mutant malignantly transformed and disseminated PXA that was successfully treated with BRAF-/MEK-targeted therapy (dabrafenib/trametinib). ***Case Presentation:*** At the age of 16 years, our patient underwent an initial subtotal resection of a right occipital PXA. Six months later, a reintervention for an asymptomatic tumor recurrence was performed and complete resection was achieved. The patient has been followed up by MRI for 14 years without arguments for recurrence but was lost to follow-up thereafter. At 38 years of age, he presented with a

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symptomatic local recurrence with extra-cerebral soft tissue extension, for which a third surgical resection was performed. Anatomopathological examination reported a grade 3 anaplastic PXA (aPXA); molecular analysis detected a *BRAF*^{V600E} mutation. Three months later, before the initiation of radiotherapy, a local tumor recurrence was diagnosed, for which he underwent a fourth surgical resection. Radiotherapy was performed following the surgical debulking. One month after completion of radiotherapy, disease progression was documented including multiple sites of extracranial metastases (skeletal, lung, cervical lymph node, and subcutaneous metastases). Systemic treatment with a combination of BRAF-/MEK-inhibitors (dabrafenib/trametinib) was initiated and resulted in a rapid and deep tumor response (partial response according to RECISTv1.1) and absence of *BRAF*^{V600E} mutant ctDNA in plasma at 6 weeks after treatment initiation. A near-complete metabolic remission was documented on [^{18}F]FDG-PET/CT 3 months after starting systemic therapy. ***Conclusion:*** We present a rare case of malignant transformation and systemic dissemination of a *BRAF*^{V600E} mutant PXA, occurring 20 years after the initial diagnosis. This case highlights the importance of long-term follow-up of patients diagnosed with these rare central nervous system tumors that initially are considered benign and also illustrates that BRAF/MEK inhibition can be an effective therapy for *BRAF*^{V600E} mutated PXA, underscoring the importance of performing molecular genetic profiling of these tumors.

Introduction

Pleiomorphic xanthoastrocytoma (PXA) is a rare glial tumor accounting for less than 1% of all astrocytomas. These tumors most commonly occur in children and young adults (<30 years) and are typically located superficially in the supratentorial space, mainly in the temporal lobe [1]. According to the WHO 2021 classification, they are considered grade II tumors [2]. Histologically, PXA are characterized by pleomorphic and multinucleated cells with spindle cells, lipid and granular bodies, although without mitosis and necrosis [3, 4]. The prognosis is favorable following complete surgical resection, despite histological pleiomorphism, with 5-year overall survival (OS) rates of 75–80% [4]. Malignant transformation to an anaplastic PXA (aPXA) occurs in 9–20% of cases [5, 6]. aPXA is characterized by the same histological features as a PXA but has more than 5 mitoses per 10 high power field and may feature necrosis [1]. It is considered a WHO grade 3 tumor and is known to follow a more aggressive clinical evolution and have a less favorable outcome (5-year OS of 50–60%) [4]. Sixty-five to seventy-five percent of the PXAs are known to carry a BRAFV600E mutation. We present a rare case of a secondary BRAFV600E mutant aPXA with extracranial metastases that was successfully treated with small-molecule BRAF-/MEK-inhibitors (dabrafenib/trametinib). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534731).

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At 16 years old, our patient presented with headaches and visual impairment. A partially cystic right occipital lesion with significant mass effect was discovered on imaging of the brain (shown in Fig. 1). He underwent a subtotal resection with complete recovery of his symptoms.

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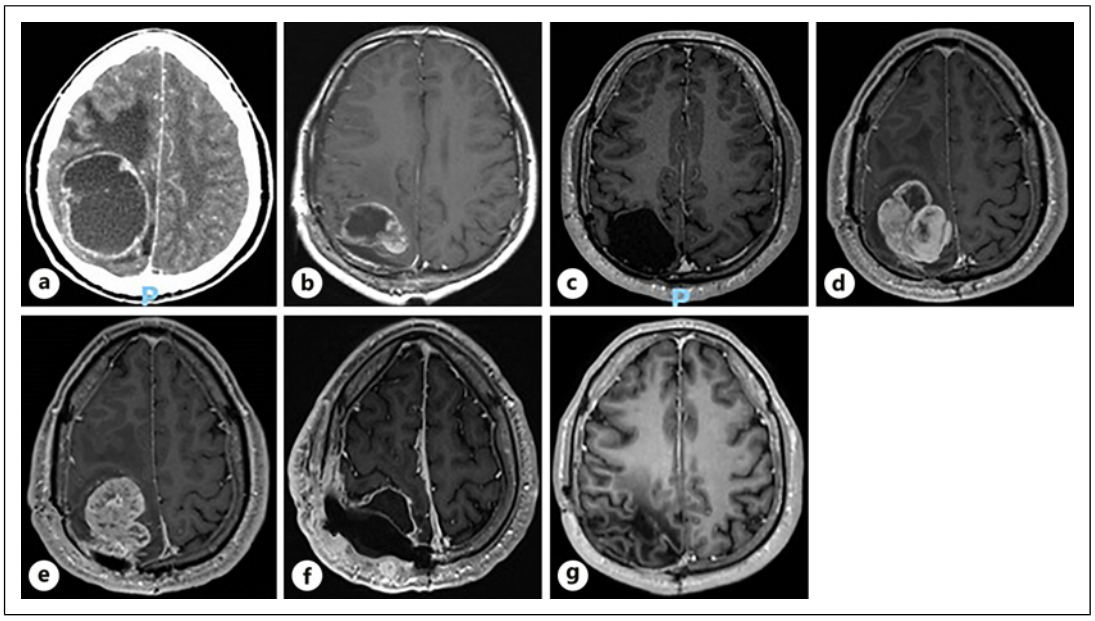

Fig. 1. Radiological intracranial evolution. **a** CT scan at first presentation showing a cystic PXA. **b** MRI of the brain showing first recurrence of the PXA 6 months after initial surgical resection. **c** The patient was followed by MRI which showed no evidence of disease during 14 years after gross total resection. **d** MRI of the brain revealing a second recurrence after 20 years of progression free survival. **e** MRI of the brain showing a third recurrence 3 months after third surgical resection. **f** MRI of the brain showing a fourth recurrence with subcutaneous after fourth surgical resection and radiotherapy (2 × 20 Gy), accompanied by multiple extracranial metastases (the latter not visible on the depicted image). **g** MRI of the brain showing a complete intracranial response 2 months after initiation of BRAF/MEK inhibition therapy.

A pleiomorphic xanthoastrocytoma (WHO grade 2) was confirmed pathologically, and follow-up was initiated. Only 6 months later, a reintervention for an asymptomatic recurrence took place, and a gross total resection (GTR) was achieved. The patient was followed up by MRI for 14 years with no arguments for recurrence, after which he was lost to follow-up. Eight years after the last follow-up visit, at 38 years of age, the patient presented at the emergency room with left hemiparesis and subcutaneous swelling near the scar area of his previous cranial surgeries. MRI revealed tumor recurrence with extra-cerebral soft tissue extension (shown in Fig. 1). A surgical resection (macroscopic complete resection) was performed which resulted in complete resolution of the hemiparesis. The anatomopathological report indicated transformation to a WHO grade 3 anaplastic PXA (microscopic findings are shown in Fig. 2). Next-generation sequencing (NGS) was performed, identifying a pathogenic $BRAF^{V600E}$ point mutation.

Adjuvant radiotherapy (RT) was proposed but not initiated since the patient did not show up for his planned appointments. Eventually, he presented 3 months after surgery with complaints of headache and recurrence of left hemiparesis. Tumor recurrence (shown in Fig. 1) was confirmed on MRI, and a fourth surgical resection was performed. On this occasion, radiotherapy was initiated in the early postoperative phase. Thirty fractions of 2 Gy were planned, but the patient only completed 20 fractions. One month after his last radiotherapy session, he was admitted to the emergency department with subacute pain in the shoulders, neck, and chest. At clinical examination, significant subcutaneous swelling at the operation site was noticed. Since disease recurrence was suspected, an [^{18}F]FDG-PET/CT was performed, confirming multiple extracranial metastases with bone metastases of the skull and vertebrae (C3 to Th1), lung, lymph node, and subcutaneous metastases. The diagnosis of a

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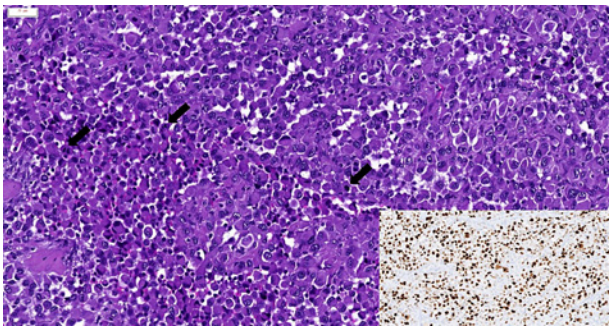

Fig. 2. Microscopic findings. Microscopic features of the resection specimen shows a highly cellular pleomorphic proliferation with several multinucleated astrocytes (H&E, ×20). There are several mitoses (arrows) and the proliferation index is above 60% (inset, Ki67, ×20).

metastatic *BRAF*^{V600E} mutated anaplastic pleiomorphic xanthoastrocytoma was thus established, and systemic treatment with BRAF/MEK inhibitors (dabrafenib 150 mg BID and trametinib 2 mg OD) was initiated, in analogy with BRAFV600E mutant melanoma. As early as 10 days after treatment initiation, there was a favorable clinical response with reduction of the subcutaneous metastases. *BRAF*^{V600E} mutant circulating cell-free tumor DNA (*BRAF*^{V600E} ctDNA) was undetectable after 6 weeks of treatment. Thoracic and abdominal CT at 6 weeks showed a partial response according to the RECIST v1.1 criteria [7]. MRI of the brain performed 2 months after treatment initiation confirmed a decrease of contrast enhancement (shown in Fig. 1). [^{18F}]FDG-PET/CT at 3 months showed an extracranial near-complete remission with disappearance of all metabolically active subcutaneous, bone, lung metastases as well as cervical and hilar adenopathies (shown in Fig. 3). Only one moderately PET-positive 7-mm left cervical lymph node remained. At 8-month follow-up after initiation of the BRAF/MEK inhibition, the patient remains free of symptoms and tolerates the treatment without any side effects.

Discussion

Systemic dissemination at the time of malignant transformation of aPXA is infrequent, often occurring by spreading through the CSF and resulting in spinal metastases over the neuraxis [4]. Metastases from PXA outside of the central nervous system are very rare, with only a few reported cases, mostly in the pediatric patient population [8]. Only one case report of metastasis affecting the scalp has been described [9]. In our case, the multiple organ metastases suggest hematogenous dissemination, making it unique in the literature to the best of our knowledge.

Given the rare occurrence of aPXA, no formal treatment guidelines based on prospective randomized clinical trials have been established to date. However, based on consensus, gross total resection should always be pursued to improve outcome. There is no evidence that adjuvant radiotherapy improves outcome in grade 2 tumors, but, given the worse prognosis of anaplastic aPXA or subtotally resected PXA, salvage treatment with radiotherapy or cytotoxic chemotherapy is often considered [3–6, 10]. In general, chemotherapy is considered the least effective [4–6].

In terms of differential diagnosis for anaplastic PXA, glioblastoma should be considered because of the histopathologically similar pattern. Contrary to glioblastoma, where BRAF mutation is very rare, 50–78% of patients with PXA have a *BRAF* mutation, mostly *BRAF*^{V600E} and, to a lesser extent, *BRAF* ^{M600} [3, 4]. *BRAF* mutation is less likely in aPXA with a reported incidence varying between 17 and 65% [4]. The BRAF mutation has prognostic value for better survival compared to BRAF-wild type tumors but also predictive value for response to targeted therapy [4].

BRAF and BRAF/MEK inhibitors (BRAF/MEKi) can lead to radiographic and clinical responses in *BRAF*^{V600mut} adult and pediatric glial tumors [3, 4, 11–13]. In a retrospective cohort of 28 adult patients with recurrent or disseminated *BRAF*^{V600E} ganglioglioma (n = 9), pleomorphic

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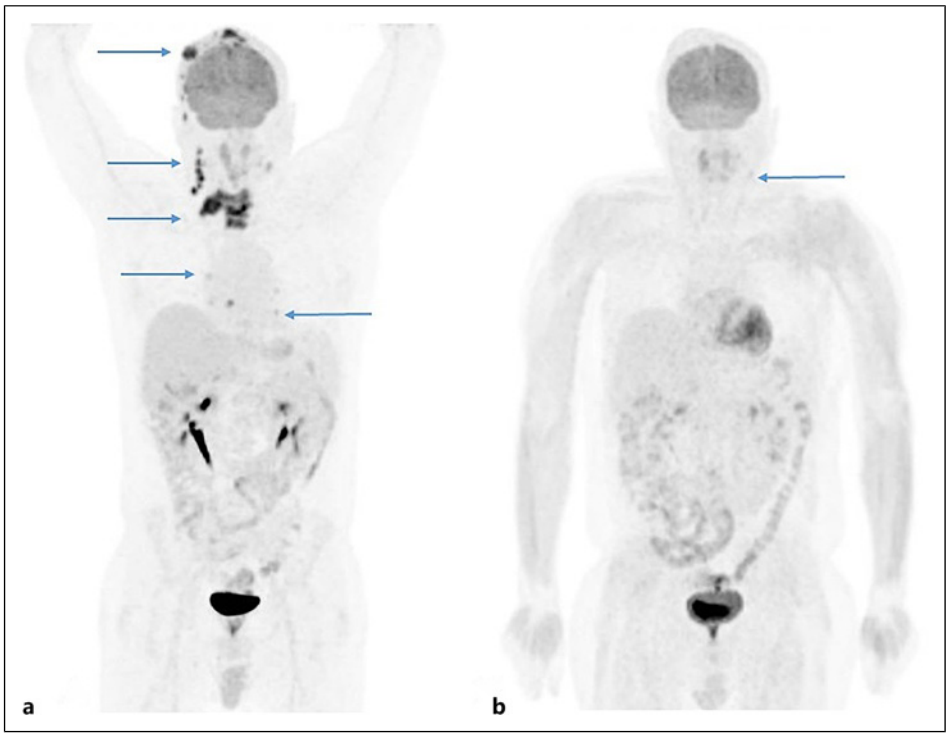

Fig. 3. Extracranial evolution assessed by [^{18}F]FDG-PET/CT. **a** Baseline [^{18}F] FDG-PET/CT showing metabolically active bone metastases left parietal, cervical C3, C4, C6 (with paravertebral extension), C7, and Th1; subcutaneous metastases from right parietal to retro-auricular right; left and right cervical adenopathies; bilateral lung metastases; and bilateral hilar adenopathies (arrows). **b** [^{18}F] FDG-PET/CT 3 months after initiating therapy with BRAF/MEK inhibitors: near complete remission with residual weak metabolic activity in one cervical adenopathy at the left side (arrow).

xanthoastrocytoma (n = 9), and diffuse glioma (n = 10) treated with BRAF/MEK inhibitors, a partial or complete response was seen in almost 40% of cases [12]. Response to BRAF/MEKi (CR/PR) was associated with a significantly longer median progression-free survival (PFS) and OS compared to patients who achieved stable disease (SD) or progressive disease (PD) (PFS: 18 months in responders vs. 9 months and 2 months when SD resp. PD; $p < 0.0001$). On univariate and multivariate analyses, only response to BRAF/MEKi proved to be an independent predictor of OS (hazard ratio 0.15, 95% CI 0.03–0.67, p = 0.013). An overview of the outcomes of trials using BRAF/MEKi in glial tumors, including PXA can be found in Table 1 [3, 11–13].

As illustrated by our case, treatment with BRAF/MEK inhibitors can lead to a fast and significant clinical and radiographic response in patients with metastatic $BRAF^{V600E}$ mutated aPXA. Response to BRAF/MEKi was assessed using $BRAF^{V600E}$ detection on ctDNA (circulating tumor DNA). Plasma ctDNA is an increasingly used technique in precision oncology, providing non-invasive comprehensive genomic profiling of solid malignancies, with diagnostic, therapeutic, and prognostic implications, as well as promising applications in screening and follow-up [14]. Plasma ctDNA analysis can be used as an alternative diagnostic tool, avoiding the potential risks associated with tumor biopsy. Rapid changes in ctDNA could act as a strong prognostic biomarker for outcome prediction on or after treatment. In metastatic melanoma patients, a significant decrease or disappearance of $BRAF^{V600E}$ ctDNA within 12 weeks of BRAF/MEK inhibitor treatment initiation was observed to be directly related to treatment response and to be predictive of longer progression-free survival [15]. Conversely, an appearance or increase in cancer-specific mutant ctDNA appears to be an early predictor of disease progression. We

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Table 1. Overview of trials using BRAF/MEKi in glial tumors

		[3]	[12]	[13]	
Cohort	Total	24	28	Grade II 13	Grade III 13
	(a)PXA	7	9	2	5
	Ganglioglioma	6	9	4	1
	Diffuse glioma	11	10	7	7
CR or PR	Cohort	25%	40%	69%	38%
	(a)PXA	42.9%	No significant subgroup variation	Not known	Not known
PFS	Cohort	5.5 months	Response group: 18 months SD group: 9 months PD group: 2 months	14 months	3.8 months
	(a)PXA	5.7 months	No significant subgroup variation	Not known	Not known

personally believe that given the impressive activity of BRAF/MEK inhibition in this unique case, treatment with BRAF/MEK inhibitors should be considered in patients with BRAF-mutated PXA and even in the neo-adjuvant stage before surgery, radiation therapy, and/or chemotherapy.

Conclusion

WHO-grade 2 PXA are considered low-grade gliomas with relatively good prognosis after gross total resection. Nonetheless, it is important to recognize their malignant potential since anaplastic transformation occurs in up to 20% of cases. Since recurrence can occur after many years long-term follow-up is imperative.

If anaplastic features are present, complete resection followed by adjuvant therapy such as radiotherapy or targeted therapy is preferred. Moreover, BRAF mutations are very frequent in PXA (even up to 75%) and treatment with BRAF/MEK inhibitors has high objective response rates, underscoring the importance of performing genomic profiling of these tumors. Similar to other cancer types, monitoring of tumor associated mutations on ctDNA at baseline and during treatment holds promise as a non-invasive assessment of tumor response.

Statement of Ethics

This case study was conducted ethically, in accordance with the World Medical Association Declaration of Helsinki. Ethical approval is not required for this case study in accordance with local or national guidelines. Written informed consent for publication of the details of his medical case and any accompanying images was obtained from the patient in 2022.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Writing: E. Vermeulen, A.-S. Vander Mijnsbrugge, and J. Duerinck. Review and editing: E. Vermeulen, A.-S. Vander Mijnsbrugge, S. Brock, F. Vaeyens, I. Dirven, A. Ciçek, W. Marcelis, S. Klein, M. Bruneau, B. Neyns, and J. Duerinck.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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