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Case Report
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Durable Remission in a Patient with Erdheim-Chester Disease Carrying a BRAF V600E Mutation Under Dabrafenib Treatment

Ulrich Schneeberger[1], Christoph Woernle[2], Kiriaki Kollia[3], Katrin D Stumpe[3], Elisabeth J Rushing[4], Rene Bernays[2] and Christoph Renner[1]*

[1]Department of Oncology, Onkozentrum Hirslanden, Switzerland

[2]Department of Neurosurgery, Onkozentrum Hirslanden, Switzerland

[3]Departement of Radiology, Onkozentrum Hirslanden, Switzerland

[4]Department of Neuropathology, University Hospital Zurich, Switzerland

Abstract

We report on a patient with Erdheim-Chester Disease (ECD) carrying a BRAF V600E mutation with a complete regression of a dural tumor as well as brainstem signal alterations following therapy with dabrafenib for more than 2 years. Initial neuroimaging studies including CT and MRI showed dural masses bifrontoparietal and a right-sided tentorial mass in the cerebellopontine angle. Biopsy revealed ECD with a BRAF V600E mutation. The patient underwent initial therapy with vemurafenib. However, treatment was terminated due to adverse effects. Accordingly, dabrafenib therapy at a dose of 75 mg twice daily was started, which was well tolerated. Following more than two years of dabrafenib treatment, the patient remains in complete remission regarding the CNS lesions with stable skeletal lesions.

Introduction

Current consensus guidelines for managing patients with Erdheim-Chester (ECD) are based on pathogenesis, epidemiological data, laboratory and radiographic analysis as well as mutation analysis, which impacts therapy with BRAF inhibition. Therapies are based on the recommendation, although therapy with dabrafenib has not yet been considered as a therapeutic option [1].

Case Presentation

In the summer of 2016, a 73-year-old female patient presented with fever, weight loss and lymph node swelling. Laboratory studies revealed leukocytosis and mildly increased C-Reactive Protein (CRP). Neuroimaging studies including CT and MRI showed dural masses bifrontoparietal and a tentorial mass in the right cerebellopontine angle (Figure 1A, 1B). Pathological examination of the biopsy revealed ECD with a BRAF V600E mutation as previously reported [2]. After the pathological diagnosis was rendered, additional systemic lesions were detected by 18 F-FDG Positron Emission Tomography/Computed Tomography (PET/CT) in the humerus, femur, piriform sinus, ilium, clavicles and mandible (Figure 2). Based on the BRAF V600E mutation, the patient underwent treatment with the BRAF inhibitor vemurafenib at the dose of 960 milligrams per day. The patient showed clinical improvement of her neurological symptoms as well as general condition within eight weeks with mild to moderate side-effects.

During ongoing treatment, symmetric polyarthritis of the shoulder joint, wrist and ankle developed accompanied by joint effusions. The patient also noted generalized malaise, loss of appetite, mood alterations, which triggered poor compliance. At the request of the patient, therapy was discontinued. Subsequently, the patient's arthritic symptoms completely resolved. Almost two months after the treatment was discontinued, the patient presented with increasing tiredness, fatigue and increasing respiratory distress. The patient's symptoms correlated with radiographic evidence of progression of the underlying disease. The condition of the patient continued to deteriorate, leading to hospital re-admission. Consequently, Dabrafenib, 75 mg twice daily was started. The therapy was tolerated without further side effects under inpatient supervision. After three months of therapy at a single dose of 75 mg/day, the patient returned for follow-up evaluation. Although the patient complained of limited physical strength, the cranial MRI showed a significant regression of the

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Correspondence:
Ulrich Schneeberger, Department of Oncology, Onkozentrum Hirslanden, Witellerikerstr 40, 8032 Zürich, Switzerland,
E-mail: ulrich.schneeberger@gmx.at

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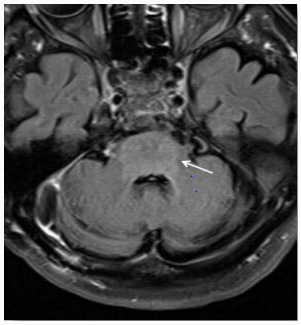

Figure 1A: Hyper intense diffuse tumor in the pons in FLAIR images (white arrow) without evidence of contrast enhancement.

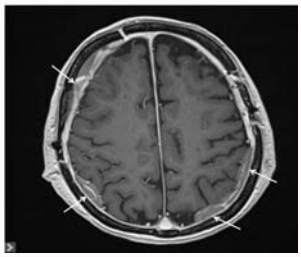

Figure 1B: Enhancing dural masses at the convexity in T1 images after contrast administration (white arrows) with moderate contrast enhancement after partial resection.

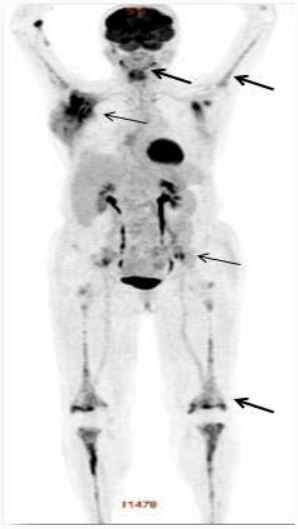

Figure 2: 18 F-FDG (Fluoro Deoxy Glucose) PET/CT: Maximum Intensity Projection (MIP) PET/CT scan shows diffusely increased FDG uptake in osteosclerotic bone changes in the mandible and in the diaphysis of both humeri, femora and tibiae as well as in the periarticular region of the knee joints (thick black arrows). In addition diffusely increased FDG activity is found in axillary and iliac lymph nodes on both sides (thin black arrows).

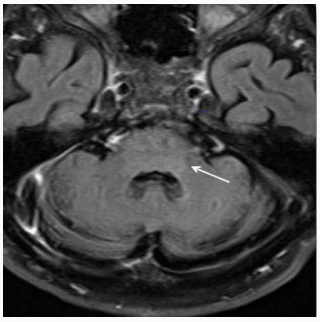

Figure 3A: Partial regression of the hyper intense, non-enhancing tumor in the pons in FLAIR images (white arrow).

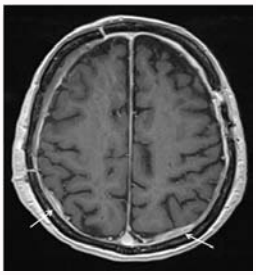

Figure 3B: Partial regression of the enhancing dural masses at the convexity in T1 images after contrast administration (white arrows).

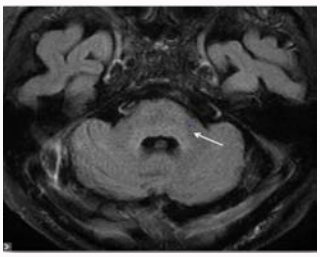

Figure 4A: Subtotal regression of the hyper intense, non-enhancing tumor in the pons with regression of the mass effect and beginning atrophy in FLAIR images (white arrow).

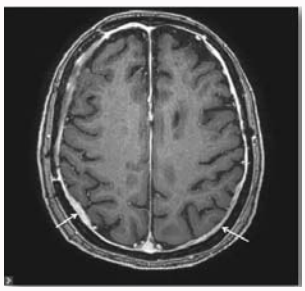

Figure 4B: Subtotal regression of the enhancing dural masses at the convexity in T1 images after contrast administration (white arrows).

supratentorial dural tumor, a reduction in brainstem signal alteration and regression of the manifestation in the clivus (Figure 3A, 3B). After eight months of continuous therapy with dabrafenib doses of 75 mg to 150 mg daily, another cranial MRI follow-up imaging was performed, whereupon a further regression of the tumor manifestation in terms of a further size reduction of the dural mass and reduced signal enhancement in the brainstem area were confirmed (Figure 4A, 4B). In the last follow-up, two years after initial diagnosis, cranial MRI showed complete regression of the residual dural tumor mass as well as complete regression of the signal alterations in the brainstem. In addition, the patient's systemic symptoms had resolved (Figure 5A, 5B).

Discussion

Contemporary therapeutic strategies for ECD vary according to the anatomic location of lesions and degree of involvement. In the past, corticosteroids and cytotoxic drugs were the mainstay of

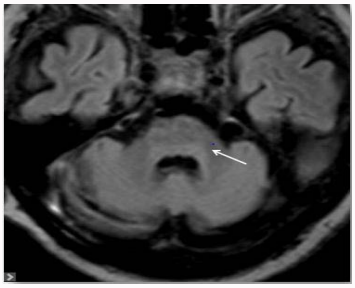

Figure 5A: Total regression of the tumor in the pons with residual gliosis and severe atrophy in FLAIR images (white arrow).

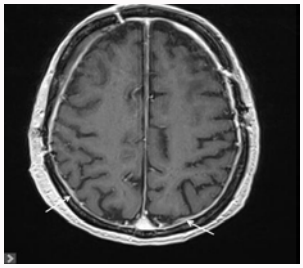

Figure 5B: Complete regression of the enhancing dural masses at the convexity in T1 images after contrast administration (white arrows).

therapy. Currently, most guidelines favor interferon-alpha as first line therapy. TNFα blockers (infliximab), tyrosine kinase inhibitors (E.g. imatinib) and recombinant inhibitors of interleukin-1 receptor (Anakinra) have been used successfully in selected cases [3]. More recently, BRAF V600E mutations were detected in approximately 50% of all ECD patients. Some patients have responded dramatically to therapy with the BRAF inhibitor vemurafenib [4]. To date, there are no reports on other BRAF inhibitors such as dabrafenib. The current case describes the favorable toxicity profile and long-term efficacy of dabrafenib therapy in a patient with ECD, exceeding two years. As is the case with vemurafenib, the optimal dose of BRAF inhibitors in ECD is unknown, but might be lower than doses used in melanoma treatment. Our case underscores the efficacy of lower BRAF inhibitor doses and provides evidence of a durable effect with a daily dose of 75 mg to 150 mg dabrafenib.

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