

Combined Treatment with Vemurafenib and Cobimetinib in Langerhans Cell Histiocytosis and Erdheim-Chester Disease Overlap Syndrome: A Case Report

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Abstract

Histiocytoses are clonal disorders diseases derived from the monocyte-macrophage lineage. The Erdheim–Chester disease (ECD) and Langerhans cell histiocytosis (LCH) may occur in association with overlapping clinical, histopathological and molecular features, harboring somatic MAP2K1 mutations in more than 50% of patients. BRAF and MEK inhibitors have shown to be efficacious in ECD and LCH, including responses in patients with CNS involvement.

This case report describes a 59-year-old woman who presented with vemurafenib-refractory ECD/LCH overlap syndrome treated with vemurafenib/cobimetinib dual therapy, with rapidly progressing neurological involvement after its initiation.

Although targeted therapy plays a crucial role in treatment of histiocytosis, only anecdotal clinical cases treated with dual therapy have been reported in ECD or LCH and collaborative trials are needed to improve outcomes.

Keywords: Mixed histiocytosis; Erdheim–Chester disease; Langerhans cell histiocytosis; Cobimetinib; Vemurafenib

Introduction

Histiocytic disorders are a heterogenous group of rare progressive and multisystemic diseases, which can be classified as either Langerhans cell histiocytosis (LCH) or non-LCHs according to clinical, anatomical and mutational findings.

Erdheim–Chester disease (ECD) is a non-LCH that belongs to the Langerhans 'L' group together with LCH. Both derive from the monocyte-macrophage lineage with recurrent clonal mutations, such as BRAF^{V600E} in early, multipotent progenitor cells [1,2]. ECD is characterized by xanthogranulomatous infiltration produced by Touton-like giant cells, lymphocytic aggregates and CD68/CD163 positive-CD1a/S100 negative foamy histiocytes [3,4]. Conversely, LCH expresses the histiocyte markers CD1a, S100, CD207 (langerin) and CD68low [1].

The existence of a possible common progenitor for ECD and LCD may explain the fact that almost 20% of ECD cases were previously diagnosed as LCH [2,3]. ECD/LCH overlap has been recognized, however its prevalence is unknown. Hervier et al emphasized the high frequency of mixed histiocytosis (MH) in a series of 23 cases [5].

The identification of the BRAF^{V600E} mutation in ECD/ LCH (2010) has been reported in 69% of patients with MH compared to 57% and 54% in isolated LCH and ECD, respectively [2,3-6]. In 2012, 3 patients with refractory ECD (2 of them had LCH involvement) were treated with vemurafenib, with clinical and radiological improvement after one month of treatment [7]. Five years later, vemurafenib achieved FDA approval for the treatment of ECD based on the results of the VE-BASKET [8] and the LOVE trial [9].

In addition, the improved knowledge about the RAS-RAF-MEK-ERK pathway has been gained by the characterization of additional, activating mutations, such as ARAF, RAF1, NRAS, KRAS, and MEK1/2. Interestingly, MEK inhibitors have shown clinical efficacy regardless of genotype [10, 11]. Recently, promising outcomes have been reported in 3 ECD patients with BRAFV600E mutation and central nervous system (CNS) involvement with vemurafenib/cobimetinib combined therapy after progression on single agent vemurafenib. Two of them achieved complete metabolic remissions evaluated by imaging techniques and all of them showed neurological improvement [12].

Herein, we report on vemurafenib/cobimetinib combination regimen in a BRAF-mutant vemurafenib-refractory MH patient with multisystemic involvement and progressive neurodegenerative symptoms.

Case Report

A 59 years-old woman with a 1-year history of bone pain (especially back pain, lower limbs and shoulder), paresthesia of lower limbs, constitutional symptoms, hepatosplenomegaly, bilateral exophthalmos and xanthelasma palpebrarum. Technetium-99m (^{99m}Tc) bone scan showed increased uptake in the diaphyses and metaphyses sparing the epiphyses of the femur and tibia, while computed tomography scan revealed perinephric soft tissue infiltrate and sheathing of the whole thoraco-abdominal aorta. (¹⁸F)-fluorodeoxyglucose (FDG)-PET (FDG-PET)-imaging revealed moderate uptake in visceral and bone lesions... Also, right atrial and ventricle pseudotumor was observed by magnetic resonance imaging (MRI) (Figure 1).

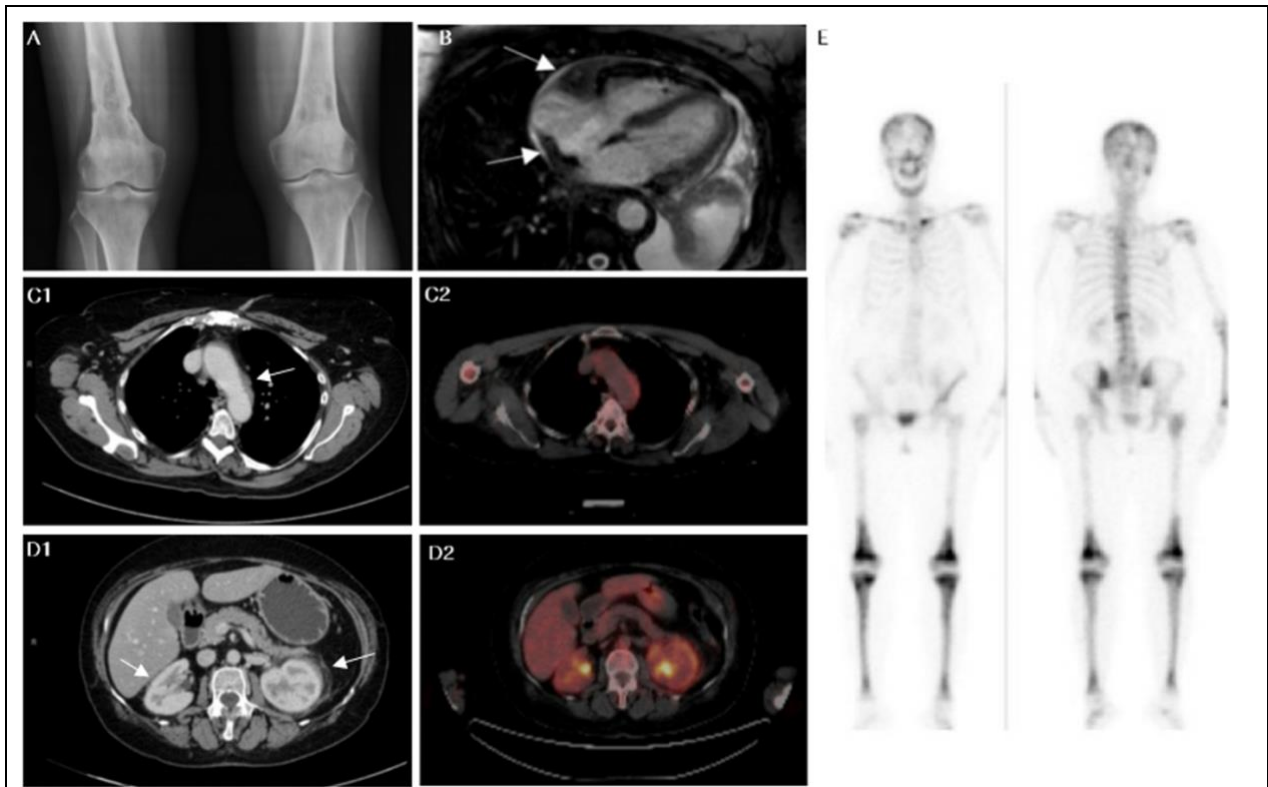


Figure 1: (A):Radiographic findings of ECD/ LCH. Bone x-ray shows lytic lesions and bone erosions in the distal extremity of both femurs; (B): Right atrial and ventricle mass is demonstrated in MRI; (C1): Axial CT scan shows the sheathing of the whole thoracic aorta called “coated aorta”. (C2): FDG-avid peri-aortic soft tissue in PET scan (SUVmax 4,32); (D1): Perirenal fat infiltration referred to as a “hairy kidney”. (D2): Increased FDG-glucose uptake in perirenal soft tissue (SUVmax 6,49 in left side; 4,86 in right side); (E): ^{99m}Tc imaging demonstrating increased uptake in the distal ends of the lower limbs.

Bone biopsies on target lesions revealed the existence of the ECD/LCH overlap syndrome, showing an infiltrate by CD68-CD1a- foamy histiocytes and histological lesions where CD1a, Langerin and S100-positive Langerhans cells were found (Figure 2).

Initially, the BRAF^{V600E} mutation was not detected, probably due to low tumor load of the first sample, so an additional bone biopsy was performed in which the BRAF^{V600E} activating mutation was detected. Whole-exome sequencing also identified mutations in CSDE1 (c.35G>A; p.Gly12As; Variant allele frequency [VAF]: 8.42%) and KRAS (c.436G>A; p.Ala146Th; VAF: 4.56%).

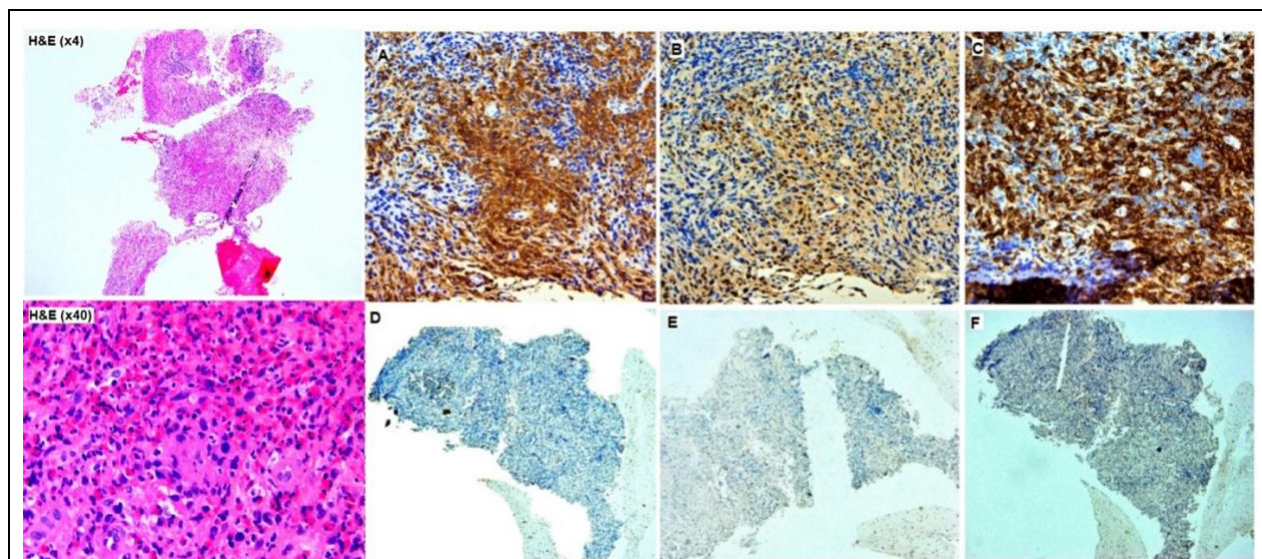


Figure 2: Pathologic and immunohistochemical findings of mixed histiocytosis in bone biopsy. Haematoxylin-eosin stain (H&E, x4 and x40) images show fibroconnective tissue and fragments of bone material infiltrated by mixed inflammatory cellularity: histiocytes, abundant eosinophils, and polymorphonuclear cells. Top: Histological features of Langerhans cell histiocytosis; (A): Immunoreactivity of CD1a expression by Langerhans cells (x20); (B): Expression of the histiocyte marker S100 (x20); (C): CD207 (langerin)-positive cells (x20). Bottom: Tissue biopsy showing histiocytes with non-Langerhans features. Immunohistochemical analysis shows CD1a-negative (D, x4), S100-negative (E, x4) and CD207-negative (F, x4) foamy histiocytes.

Induction chemotherapy with weekly vinblastine (6 mg/m²) and prednisolone 40 mg/m² for 6 weeks was started on October 2019. Subsequently, in maintenance treatment, daily oral mercaptopurine (6-MP) 40 mg/m² was associated with vinblastine every 3 weeks. Prednisolone was tapered weekly. MRI and FDG-PET were performed to assess tumor burden.

After 10 cycles of treatment, a partial response was observed by FDG-PET. However, after 1-year of treatment, new-onset neurological symptoms characterized primarily by cerebellar dysfunction and radiographic lung involvement were detected. Brain MRI at this time demonstrated periventricular white matter lesions that were hyperintense on T2/FLAIR images and global brain atrophy. Cerebrospinal fluid (CSF) protein was slightly elevated (1.31 g/l) and polymerase chain reaction (PCR) for JC-virus deoxyribonucleic acid (DNA) was negative.

Due to disease progression, vemurafenib 960 mg PO twice daily was started as single agent. Photosensitivity was a bothersome complication of the treatment; therefore, vemurafenib dose had to be lowered to 480 mg PO twice daily. After one month of treatment, a partial response with generalized decrease in the uptake of thoracic and perirenal soft tissue lesions was achieved. The patient experienced a progressive worsening of neurological symptoms. This fact was determinant to initiate third-line therapy based on dual BRAF/MEK inhibition in order to achieve a greater depth of response including the CNS.

Cobimetinib was associated at a starting dose of 60 mg daily for 21 days of each 28-day cycle. However, after 2 cycles of combined therapy, the patient was admitted to our hospital with rapidly progressive neurological deterioration presenting delirium, dysarthria, headache and worsening ataxia, rendering her bed-bound.

Intriguingly, the MRI at this time showed improvement of white matter lesions (Figure 3) and stable disease was seen on FDG-PET scan with a slight decrease in the inflammatory activity of visceral lesions and soft tissue tissues, although an increase in bone uptake was observed at multiple levels.

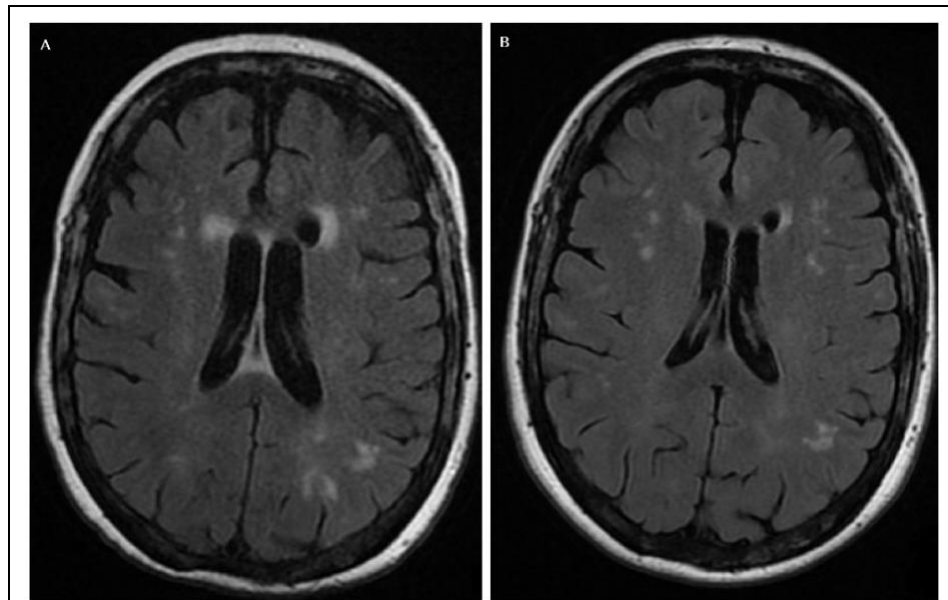


Figure 3: Brain magnetic resonance imaging; (A): Before vemurafenib/Cobimetinib dual therapy. MRI shows periventricular white matter hyperintensities and global brain atrophy on T2/FLAIR images; (B): After vemurafenib/Cobimetinib dual therapy, MRI shows radiological improvement of the bihemispheric white matter lesions.

Vemurafenib and cobimetinib therapy was discontinued and corticosteroid therapy was started (initial dose of 8 mg of dexamethasone IV followed by 4 mg IV daily), leading to a transient improvement in speech fluency, swallowing and fine motor skills. In agreement with the family, treatment was not resumed and palliative care was started.

Discussion

Mixed histiocytosis or ECD/ LCH overlap syndrome is believed to derive from activating mutations targeting the BRAF/MPAK pathway of early ancestor cells of the monocyte-macrophage system. While recognized as an entity in the revised WHO class (2016), its diagnosis is challenging and less than 100 adult patients have been reported.

Our patient with MH displayed characteristics very similar to those of cases with isolated ECD. In this disease, skeletal involvement is practically invariably present (95%), being the most affected bones femur and tibia, with symmetric diaphyseal osteosclerosis with avid FDG uptake at bone scan [3,6,13,14]. About 50% of patients may feature extra-skeletal manifestations, such as constitutional symptoms, retroperitoneal involvement leading to with obstructive acute kidney injury, skin manifestations, neurological alterations, diabetes insipidus and pulmonary or cardiac manifestations secondary to tumor infiltration [3,4,14,15].

Determination of mutations which produce constitutive activation of the mitogen-activated protein kinase (MAPK) pathway is a standard of care. The high prevalence of BRAF^{V600E} variant confirms the clonal nature of the disease [1,5,16]. This mutation was shown to occur with a similar frequency (>50% of patients) in non-Langerhans cell histiocytosis and histiocytosis X [1,6,10] correlating with a more severe disease development involving the atrium or the CNS [2,3,13].

This finding was key for assessing the effectiveness of targeted therapies against BRAF in 2012 in ECD, with excellent results being reported in small case series [7].

Similar response was obtained in patients from the LOVE trial (cohort of 54 patients with ECD including 20 MH patients) [9]. The results of this study show a high response rate of 91% in BRAF^{V600E}-mutated ECD. Later, excellent outcomes were obtained in 26 patients from the VE-BASKET trial (no MH patients were included). All patients evaluated by FDG-PET/CT achieved metabolic response with 2-year progression-free survival (PFS) of 86% at 2-year of follow-up (95% CI, 72% -100%) and 2-year overall survival (OS) of 96% (95% CI, 87% -100%) [8].

On the other hand, synergy is expected between MEK 1/2 and BRAF-inhibitors, as they interfere in the same pathway at different levels. However, only anecdotal clinical cases treated with dual therapy have been reported with favourable responses [12,17,18].

Here, we present to the best of our knowledge the first report on the combination of vemurafenib and cobimetinib in a MH patient harboring the BRAF^{V600E} mutation with rapidly progressing neurological symptoms after initiation of dual therapy. Though, MRI showed partial response of T2/FLAIR-hyperintense lesions without restricted diffusion. This clinical deterioration led to treatment discontinuation, with a temporarily neurological improvement. Previously, adverse events with BRAF/MEK inhibitors such as acute encephalopathy, have been reported in melanoma cases. Engel et al. reported a suspected case of reversible posterior encephalopathy after vemurafenib and cobimetinib initiation in metastatic melanoma, identifying three more cases of acute-onset encephalopathy after combined treatment with BRAF and MEK inhibitors [19]. In ECD patients, Saunders et al. reported more serious adverse effects in those ECD patients who received dual therapies [20].

In conclusion, the ECD/LCH overlap syndrome shares the same pathogenetic link between ECD and LCH, being ECD the major component of the disease. The discovery of activating mutations in the MAPK/ERK pathway, has led researchers to investigate targeted immune-modulatory therapies. However, questions remain regarding efficacy, optimal combination and duration of treatment. Multinational efforts are needed in this rare entity to address these questions within clinical trials.

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