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Histiocytosis and Erdheim-Chester Disease Overlap Syndrome

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Description

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. 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-LHC that belongs to the Langerhans 'L' group together with LCH. Both derive from the monocyte-macrophage lineage with recurrent clonal mutations, such as BRAFV600E in early, multipotent progenitor cells. ECD is characterized by xanthogranulomatous infiltration produced by Touton-like giant cells, lymphocytic aggregates and negative foamy histiocytes.

Therapy after Progression

Interestingly, MEK inhibitors have shown clinical efficacy regardless of genotype. 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. Lower limbs and shoulder), paresthesia of lower limbs, constitutional symptoms, hepatosplenomegaly, bilateral exophthalmos and xanthelasma palpebrarum. Technetium-99m 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 imaging revealed moderate uptake in visceral and bone lesions. Also, right atrial and ventricle pseudotumor was observed by magnetic resonance imaging.

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 JCvirus desoxyribonucleic 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.

Neurological Deterioration

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 and headache and worsening ataxia, rendering her bed-bound. Intriguingly, the MRI at this time showed improvement of white matter lesions and stable disease was seen on FDGPET 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. 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. 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. 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.

Determination of mutations which produce constitutive activation of the mitogen-activated protein kinase (MAPK) pathway is a standard of care. The high prevalence of BRAFV600E variant confirms the clonal nature of the disease. This mutation was shown to occur with a similar frequency (>50% of patients) in non-Langerhans cell histiocytosis and histiocytosis X correlating with a more severe disease development involving the atrium or the CNS. 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. 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. 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 BRAFV600E mutation with rapidly progressing neurological symptoms after initiation of dual therapy. Though, MRI showed partial response of T2/FLAIR-hyperintese 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 metastasic melanoma, identifying three more cases of acute-onset encephalopathy after combined treatment with BRAF and MEK inhibitors. In ECD patients, Saunders et al. reported more serious adverse effects in those ECD patients who received dual therapies. 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.