Complete remission of critical neurohistiocytosis by vemurafenib

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ABSTRACT

Objective: To describe a patient with life-threatening brainstem neurohistiocytosis who recovered completely upon targeted treatment with the V600E mutation-specific BRAF inhibitor vemurafenib.

Methods: We report clinical, histologic, genetic, and sequential imaging findings, including fluo-rodeoxyglucose (FDG)-PET, over a follow-up period of 11 months.

Results: The patient presented with central hyperventilation, skeletal and perirenal Erdheim-Chester disease, and cutaneous Langerhans cell histiocytosis. A BRAF V600E hotspot mutation was detected in all afflicted tissues. Therapy with vemurafenib led to complete and stable clinical remission of CNS lesions and systemic disease that could be demonstrated by brain MRI and whole-body FDG-PET.

Conclusions: Neurologic involvement in Erdheim-Chester disease usually confers a poor prognosis. In this patient, vemurafenib was well-tolerated and highly efficacious for severe brainstem involvement in Erdheim-Chester disease with overlapping Langerhans cell histiocytosis. This case illustrates the heterogeneous phenotypic spectrum of neurohistiocytosis and underscores the importance of genetic testing.

Classification of evidence: This article provides Class IV evidence. This is a single observational study without controls. *Neurol Neuroimmunol Neuroinflamm* 2015;2:e78; doi: 10.1212/NXI.0000000000000078

GLOSSARY

CIP = critical illness polyneuropathy; **ECD** = Erdheim-Chester disease; **FDG** = fluorodeoxyglucose; **LCH** = Langerhans cell histiocytosis.

Histiocytosis encompasses a group of rare systemic disorders of largely unknown origin, although some forms are likely to arise from neoplastic transformation leading to proliferation of histiocytes in affected tissues. Among them, Erdheim-Chester disease (ECD), which predominantly affects adult patients, is characterized by typical symmetric infiltration of long bones as well as aortal and perirenal involvement. Here we report a case of ECD and cutaneous Langerhans cell histiocytosis (LCH) overlap syndrome with life-threatening CNS involvement due to neurogenic hyperventilation responding dramatically to targeted therapy.

CASE REPORT A 59-year-old Caucasian woman was admitted to our neurointensive care unit with altered level of consciousness after a suspected syncope. Her medical history included submammary cutaneous lesions, which were diagnosed as LCH 15 months before and treated successfully with thalidomide. In addition, after seeking medical advice for knee pain, a nontraumatic tibial fracture was diagnosed. A bone biopsy was performed and did not demonstrate a malignancy but at the time was considered otherwise nondiagnostic.

At presentation, the patient was somnolent with intact motor function and sensation. She was hyperventilating with pronounced hypocapnia (P_{CO_2} 12 mm Hg) and respiratory alkalosis (pH 7.6). Retrospectively, fast

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breathing had been observed for weeks, as well as dysphagia, fatigue, and lethargy. MRI scans showed T2 hyperintense and partly contrast-enhancing pontine, cerebellar, cerebellar peduncle, and occipital lesions (figure 1, A and C). A chest and abdominal CT showed perirenal and periaortal fibrosis with "hairy kidney" and "coated aorta" appearance, which raised the differential diagnosis of ECD. Supporting evidence was provided by Tc^{99} scintigraphy, which had been performed 2 years earlier because of the abovementioned nontraumatic tibia fracture and showed symmetric bilateral Tc^{99} uptake in the long bones of the lower extremities (figure 2A). CSF analysis at the current presentation showed elevated lactate and protein levels but normal cell counts and glucose. The diagnosis of ECD was finally proven by a perirenal biopsy revealing diffuse infiltration of CD1a-negative histiocytes. Reevaluation of skin biopsies, however, confirmed the presence of CD1a-positive histiocytes, whereas the tibia samples showed a histiocytic infiltrate with both CD1a-negative and CD1a-positive phenotypes. Due to recent reports of frequent mutations in the B-Raf proto-oncogene, serine/threonine kinase (BRAF) gene in both Langerhans cell and Erdheim-Chester histiocytosis,[1–3] sequencing of BRAF exon 15 was performed. A heterozygous V600E point mutation was found in all lesions (perirenal, bone, and skin).

Due to respiratory failure from hyperventilation and pneumonia with subsequent sepsis, mechanical ventilation was needed. Neurogenic hyperventilation was treated by morphine application. After a course of 5×1 g IV methylprednisolone without clinical benefit, targeted therapy with the oral V600E mutation-specific BRAF inhibitor vemurafenib was started (960 mg twice daily). Rapid improvement in consciousness and hyperventilation was observed within weeks of treatment. Recovery was delayed due to a flaccid tetraparesis caused by critical illness polyneuropathy (CIP).

After 6 months of vemurafenib treatment, the patient had recovered completely from hyperventilation and dysphagia, mental status was normal, and CIP-related motor symptoms had resolved. Brain MRI showed remission of both T2 hyperintensities and contrast enhancement in all infratentorial lesions (figure 1, B and D). Whole-body fluorodeoxyglucose (FDG)-PET (figure 2, B and C) also showed regression of glucose uptake in bone manifestations (maximum standardized uptake values in left humerus lesions at the beginning and after 6 months of treatment: 4.0 vs 1.5). Unfortunately, lower extremities were not imaged in the baseline FDG-PET scan. Cutaneous lesions had regressed under BRAF therapy with residual erythema. C-reactive protein levels stably returned to nearly normal levels (figure 2D). To evaluate whether continuous treatment of stable disease is necessary, vemurafenib has been tapered to a maintenance dosage of 480 mg/day under careful clinical monitoring. No relapse has been observed over the clinical follow-up period of 11 months.

DISCUSSION ECD is a non-LCH with variable clinical presentation that affects multiple organs. Skeletal involvement with bilateral symmetric histiocytic infiltration of long bones, especially tibiae, as well as perirenal and periaortic infiltrations are most characteristic for the disease. Regarding CNS manifestation, which is a negative prognostic factor,[4] hypophysitis, brainstem and cerebellar lesions, and, less commonly, supratentorial lesions have been described.[5–7] Thus, presentation with diabetes insipidus and ataxia is common.[8–10] In our case, typical infratentorial lesions were seen, even though presentation with central hyperventilation has not been described before to our knowledge. Neurogenic hyperventilation itself is a rare condition and is usually found in diffuse lesions of the pons and medulla oblongata, although association with cerebellar peduncle lesions has been described.[11,12]

ECD is differentiated from other forms of histiocytosis by the immunohistochemical phenotype of histiocytic lesions. Typically, lipid-laden $CD68^+$ $CD1a^-$ histiocytes surrounded by fibrosis are seen.[13]

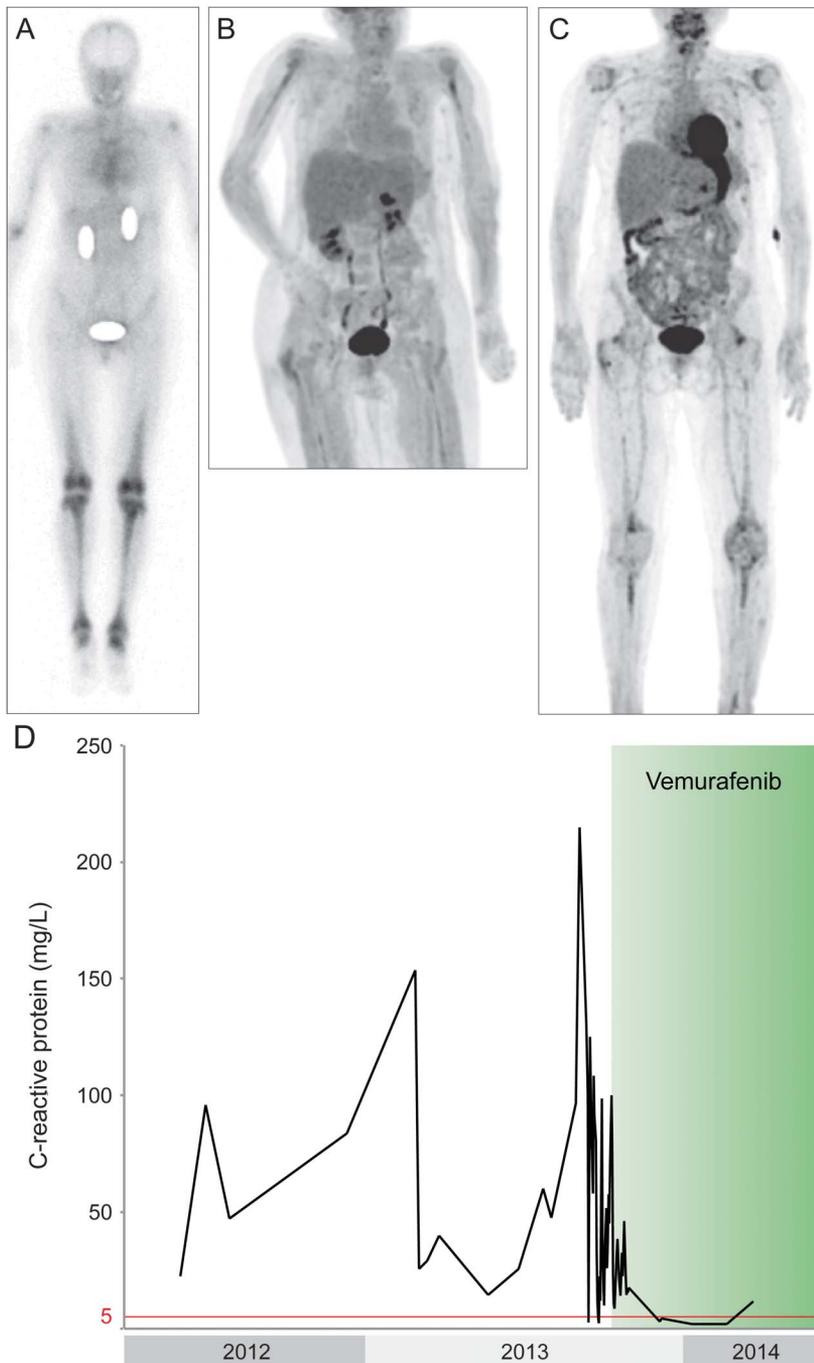**Figure 1   MRI of brainstem manifestation**
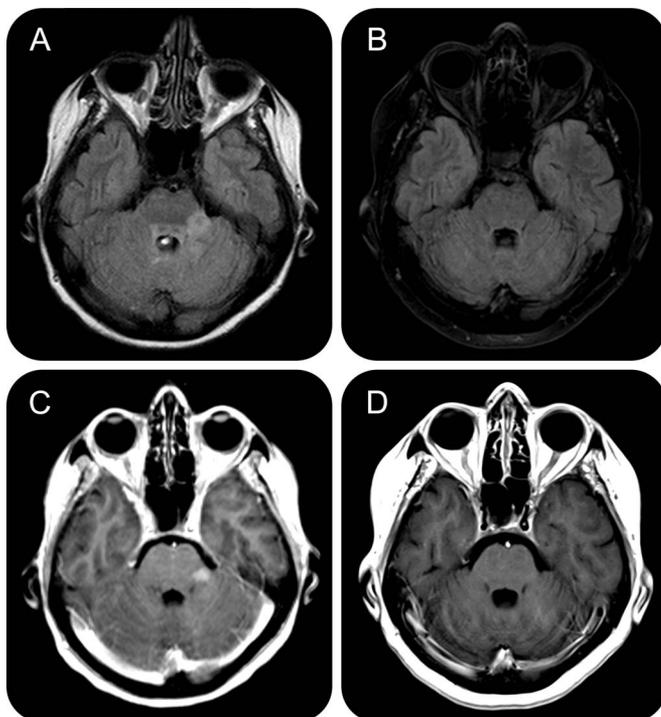
MRIs at presentation (A, C) and at 6-month follow-up (B, D) show regression of T2 hyperintensities (A, C) and contrast enhancement (B, D) under vemurafenib treatment.

Figure 2 Assessment of systemic disease activity

Tc[99] scintigraphy (A) and fluorodeoxyglucose PET imaging (B, C) at disease onset 2 years before acute deterioration (A), at current presentation (B), and at 6-month follow-up (C) show regression of glucose uptake in bone lesions under vemurafenib treatment (B, C). PET images were normalized to standardized uptake values. (D) C-reactive protein levels (mg/L) decreased upon targeted therapy. The course of disease is shown from first presentation to the Department of Dermatology to 6-month follow-up.

BRAF mutations have recently been described in both LCH and ECD.[1–3] Here we describe an overlap of both diseases and could verify the key mutation in 3 afflicted organs. Since a brain biopsy was not performed due to the delicate localization of the lesions, it remains unclear whether the CNS infiltration would show CD1a-negative or -positive histiocytes

and allow a classification of either ECD or LCH. However, the occasional finding of *BRAF* mutations in ECD and LCH lesions within the same patient[14–16] lends further support to the hypothesis that both diseases are of common origin.

For treatment of ECD, use of interferon α, imatinib, cladribine, and recombinant interleukin-1 receptor have been reported, while earlier treatment regimens included steroids and cytotoxic agents. Targeted therapy with vemurafenib has initially been reported in 3 cases,[17] and CNS efficacy was recently demonstrated in a patient with suprasellar ECD[18] and a case of temporal histiocytic sarcoma.[19] Despite severe brainstem involvement, our patient recovered completely upon continuing treatment with vemurafenib. Targeted treatment thus provides an option even when the parenchymal CNS is affected and underscores the importance of *BRAF* mutation screening in histiocytosis. We continued vemurafenib administration to achieve permanent remission, but prospective studies are needed to investigate maintenance treatment regimens and tolerance.

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