Complete remission of critical neurohistiocytosis by vemurafenib

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 fluorodeoxyglucose (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 (PCO2 12 mm Hg) and respiratory alkalosis (pH 7.6). Retrospectively, fast
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 occip-
tal lesions (figure 1, A and C). A chest and abdom-
inal CT showed perirenal and periaortal fibrosis
with “hairy kidney” and “coated aorta” appearance,
which raised the differential diagnosis of ECD. Sup-
porting evidence was provided by Tc99 scintigraphy,
which had been performed 2 years earlier because of
the abovementioned nontraumatic tibia fracture
and showed symmetric bilateral Tc99 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 sam-
ple 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 (per-
irenal, 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 ben-
efit, targeted therapy with the oral V600E muta-
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 tet-
raparesis caused by critical illness polyneuropathy
(CIP).

After 6 months of vemurafenib treatment, the
patient had recovered completely from hyperventila-
tion 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 regres-
sion of glucose uptake in bone manifestations (max-
imum standardized uptake values in left humerus
lesions at the beginning and after 6 months of treat-
ment: 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 sta-
bly returned to nearly normal levels (figure 2D). To
evaluate whether continuous treatment of stable dis-
edase 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 histio-
cytosis 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 hyperin-
tensities (A, C) and contrast enhancement (B, D) under vemurafenib treatment.
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 patient14–16 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 ECD18 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.

AUTHOR CONTRIBUTIONS

Dr. Euskirchen: study concept and design, drafting and revising the manuscript. Dr. Haroche: analysis and interpretation of clinical and imaging data. Dr. Emile: acquisition, analysis, and interpretation of histologic data. Dr. Buchert: acquisition, analysis, and interpretation of PET imaging data. Dr. Vandersee: analysis and interpretation of clinical data. Dr. Meisel: study supervision, interpretation of clinical data, drafting and revising the manuscript. All authors approved submission of the manuscript.

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REFERENCES


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