Dramatic Efficacy of Interferon and Vemurafenib on Psychiatric Symptoms Revealing BRAF^{V600E} Mutated Erdheim-Chester Disease

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Case Report

Keywords: histiocytosis, Erdheim-Chester disease, delirium, neopterin, interferon, targeted therapy

Posted Date: March 2nd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1391592/v1>

Abstract

Erdheim-Chester disease (ECD) is a rare histiocytosis with underestimated neurological involvement. Neurological manifestations are heterogeneous depending on disease location and mechanisms, but psychiatric symptoms have not been described to date in the clinical spectrum of neuro-ECD.

An 81-year-old woman was referred to the hospital because of delirium with auditive and visual hallucinations, severe cognitive impairment and cerebellar syndrome. Brain magnetic resonance imaging showed FLAIR hyperintensity lesions in the pons, upper cerebellum peduncles. Blood and cerebrospinal fluid (CSF) analysis were normal except for an elevated neopterin level in the CSF. Whole-body CT scan (^{18}F FDG-PET) showed peri-nephric fat infiltration and aorta adventitia sheathing with radiotracer uptake in the pons, vessels, peri-nephric fat, and bone lesions, which were characteristic of ECD. The diagnosis was confirmed on perirenal tissue biopsy, which also showed a *BRAF*^{V600E} mutation.

Treatment with interferon resulted in resolution of delirium, and BRAF inhibitor subsequently resulted in partial remission of all active sites.

This case highlights that delirium can be the first manifestation of neurodegenerative ECD. Interferon and targeted therapy appear to be effective in this situation.

Introduction

Erdheim-Chester disease (ECD) is a rare clonal histiocytosis characterized by clinical and radiological features (long bone and sinus osteosclerosis, peri-nephric fat infiltration, cardiovascular involvement) associated with compatible histology¹ (CD68+, CD1a- tissue infiltrate with frequent mutation of the mitogen-activating protein kinase pathway gene). Neurological involvement is underestimated and mainly represented by isolated or combined pseudo-tumor, neurodegenerative or vascular lesions. The diagnosis of neuro-ECD is based on magnetic resonance imaging showing most often T1 contrast enhanced and hyperintense T2 FLAIR lesions in meninges, brain parenchyma of hypothalamic-pituitary axis². Patients may also suffer from a neurodegenerative form³. The neurological signs are protean, and consist mainly of a cerebellar disability, cognitive impairment and/or pyramidal tracts symptoms depending on the location and mechanism of the lesions. However, psychiatric manifestations (i.e., delirium, hallucinations) have not been reported in the spectrum of neuro-ECD^{4,5}. Despite emerging targeted therapies, neuro-ECD's prognosis remains poor⁶, particularly in neurodegenerative forms. We describe the first case of neuro-ECD with delirium as initial symptom regressing with ECD-specific therapies.

Methods

This case report did not require an institutional review board according to the French legislation and was conducted in accordance with the declaration of Helsinki.

Histology was performed on 4-micrometer thick tissue sections after staining with Hematoxylin & Eosin and immunohistochemistry, including at least CD1a, S100, and CD68 primary antibodies. Detection of mutations was performed on tissue biopsies infiltrated by histiocytosis. Tumor DNA was extracted from formalin-fixed and paraffin-embedded tissues. Detection of *BRAF*^{V600E} mutation was performed using picodroplet digital PCR⁷.

Clinical case:

An 81-year-old woman was referred to the hospital for delirium, severe cognitive impairment, and cerebellar syndrome. She had a medical history of central retina vein occlusion and Grave's disease. The neuropsychiatric problem began 8 months earlier with delirium combining auditory and visual hallucinations requiring hospitalization. At that time, the neurological examination showed a static and dynamic cerebellar syndrome. Cerebral computed tomography (CT) scan and repeated electroencephalograms were unremarkable. Analysis of blood samples was normal. The patient was considered having an age-related cognitive decline and was discharged with antipsychotic treatments (olanzapine). Delirium and neurological disability remained stable.

The appearance of delirium characterized by delusional persecution syndrome with persistent auditive and visual hallucinations with total adherence prompted a new hospitalization. She also had complete anosognosia with associated cognitive decline. Neurological examination showed a cerebellar syndrome, with Scale for Assessment and Rating of Ataxia (SARA) score at 14 associated with cognitive impairment (Mini-Mental State Examination: 22/30). She also had delusional persecution syndrome with auditive and visual hallucinations. Extra-neurological features included dyspnea secondary to pericardial effusion.

Because of the persistent cerebellar syndrome, brain magnetic resonance imaging (MRI) was performed. It showed FLAIR hyperintensity lesions in the pons and upper cerebellum peduncles and a left orbital pseudotumor (Figure 1-2). Blood tests for infections, immune-mediated inflammatory diseases, vitamin deficiencies or drug or toxic intake were unremarkable. CSF analysis was normal, especially for oligoclonal bands and antibodies associated with paraneoplastic syndrome. Tau protein level was 274 ng/L (N<400), and phosphorylated isoform was 33 ng/L (N<60). Neopterin level was 9.4 nmol/L (N<5).

A whole-body CT scan was performed to rule out cancer and showed bilateral peri-nephric fat infiltration and aortic vascular sheathing (Figure 1). The ¹⁸FDG-PET scan revealed radiotracer uptake in the pons, right atrium, aorta adventitia and peri-nephric fat. It also showed bilateral symmetric osteosclerosis of long bones, highly suggestive of ECD. Perinephric fat biopsy confirmed the diagnosis of ECD with tissue infiltration by fibrosis and foamy CD68⁺ CD1a⁻S100⁻ histiocytes. Pyrosequencing revealed a *BRAF*^{V600E} mutation.

The patient first received interferon-alpha (180 micrograms/weekly for 2 weeks) allowing a rapid regression of the hallucinations and the malignant state after 10 days. After molecular status establishment, the patient received a *BRAF* inhibitor for aggressive multisystemic ECD.

At eight weeks of follow-up, neurological examination showed complete regression of delirium with a slight improvement in cerebellar syndrome (SARA score:12) and cognitive status (MMSE:26/30). Brain MRI showed partial regression of lesions in the pons. The ¹⁸FDG-PET showed a decrease in radiotracer uptake in all ECD sites consistent with a partial metabolic response according to PERCIST criteria (Figure 3).

Discussion

To our knowledge, we report the first presentation of neuro-ECD with delirium including visual and auditive hallucinations as the main initial symptom.

The neurological spectrum of ECD mainly involves the hypothalamic-pituitary axis, the meninges or the brain parenchyma, leading to endocrinopathies and/or neurological focal deficit². Manifestations are heterogeneous, ranging from fatigue to stroke, mainly depending on ECD locations and presentation.

Pachymeningeal thickening may cause diffuse plaque extension in dural structure, mimic meningioma, or involve spinal cord⁸. Tumor lesions mainly affect all structures of CNS. Degenerative lesions may be responsible for hyperintense T2 abnormalities within the posterior fossa (i.e. corpus medullare, dentate nuclei) and atrophic changes in the cerebellum or the brain stem^{2,4,5}. Notably, intermittent neurologic manifestations such as uncontrolled crying, laughing or more generally inappropriate behavior related to pseudobulbar palsy have been reported in a cohort of ECD patients, but none of them had pure psychiatric symptoms related to ECD⁹. Mood swings have also been previously described and may be secondary to interferon therapy or ECD-related fatigue⁹.

In our clinical case, the onset of psychiatric disorders was suggestive of an organic disease because of age, cerebellar involvement, and resistance to antipsychotic treatment. In our patient, the cerebellar disability was crucial for the diagnosis, since the acquired conditions affecting the cerebellum at that age are restricted¹⁰, including drugs and toxics, inflammatory, vascular and metabolic diseases, infections, and neoplastic diseases, among which histiocytosis.

The diagnosis of neuro-ECD is based on the MRI presentation, the exclusion of differential diagnoses (i.e. paraneoplastic syndrome, infections, vasculitis), and normal CSF analysis². Meanwhile, the neopterin level was elevated in our presentation. The elevation of neopterin in the CSF has been reported in several disorders, including acute viral and bacterial infections and chronic neuroinflammatory diseases^{11,12} but not dementia¹³. Neopterin is a neurological biomarker of brain inflammation mainly produced by activated macrophages and microglia after interferon-gamma exposure¹⁴. CSF neopterin is also elevated in patients with hemophagocytic lymphohistiocytosis¹⁵. In this case, the elevation of neopterin in CSF could directly reflect histiocytic activation during histiocytosis since the cultures were sterile and other neurologic conditions were ruled out.

Interestingly, ECD patients may have a diffuse reduction of cortical thickness and gray matter¹⁶ as described in patients with a high risk of psychosis¹⁷. In this case, we hypothesize that psychotic presentation might be related to a progressive diffuse reduction of cortical thickness related to ECD.

Treatment of ECD, which depends on staging and molecular status¹ is based on conventional agents (pegylated interferon, mammalian target of rapamycin inhibitors), biological agents (interleukin-1 or tumor necrosis factor alpha inhibitors), or targeted therapies (BRAF/MEK inhibitors) in life-threatening situations¹.

In our case, the initial efficacy of interferon on delirium reinforces the causality of histiocytosis in psychiatric symptoms. Targeted therapies (BRAF or MEK inhibitors) are recommended for neurological forms of histiocytosis, although drug delivery to the CNS is incomplete, making therapeutic response unpredictable and heterogeneous. Furthermore, imaging improvement does not always correlate with clinical response, especially in neurodegenerative forms. However, this case report highlights that interferon followed by BRAF inhibitor may induce partial remission in neurodegenerative ECD and improve psychiatric symptoms.

Conclusion

This report highlights the first case of delirium as initial manifestation of neurodegenerative ECD resolute with ECD-specific therapies.

List Of Abbreviations

CSF
Cerebral Spinal Fluid
CT
Computed Tomography
ECD
Erdheim-Chester disease
¹⁸FDG-PET
(¹⁸F) FluoroDeoxyGlucose Positron Emission Tomography
FLAIR
Fluid-Attenuated Inversion Recovery
MMSE
Mini-Mental State Examination
PCR
Polymerase Chain Reaction
PERCIST
Positron Emission Tomography Response
SARA

Declarations

This case report did not require an institutional review board according to the French legislation and was conducted in accordance with the declaration of Helsinki.

Written informed consent was obtained from the individual for the publication of any potential identifiable images or data included in this article.

The raw data supporting the conclusion of this article will be made available by the authors without undue reservation.

The authors declare no competing financial interest related to this work.

The authors did not received any funding related to this work.

JR and AM wrote the initial draft. CPO performed the brain MRI analysis and FC performed the metabolic evaluation. GT confirmed the ECD diagnosis on histological sample and determined the BRAF mutational status.

All authors provided primary care for the patient, critically reviewed the manuscript for the scientific content and approved the final version of the manuscript.

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Figures

Figure 1

Radiological and histological features of the patient suffering from Erdheim-Chester disease (ECD) at diagnosis.

- A) Axial Brain MRI showing hyperintense signal in the pons on T2-Flair sequence
- B) Axial CT scan showing sheathing of aorta adventitia
- C) Axial CT scan showing bilateral perinephric fat infiltration defined as “hairy-kidney”
- D) Axial heart MRI showing a right atrium mass suggestive of a pseudo-tumor.
- E) Sagittal ^{18}F fluorodeoxyglucose positron emission tomography demonstrating radiotracer uptake in meta-diaphysis
- F) Histopathological analysis of a CT-scan guided peri-renal adipose tissue biopsy showing massive infiltration by numerous foamy histiocytes and small lymphocytes, with features of cytosteatonecrosis (HES, magnification x300)
- G) Same biopsy sample with immunostaining showing CD163 positive histiocytes (brown staining, magnification x300)
- H) Sample biopsy showing the absence CD1a positive cells (brown staining, magnification x300)

Figure 2

Radiological brain imaging of the ECD patient at diagnosis.

- A) Axial Brain MRI showing hyperintense signal in the pons on T2-Flair sequence
- B) Axial Brain MRI showing left orbital pseudo-tumor in Fat-saturated post gadolinium T1 imaging
- C) Axial Brain MRI showing no abnormality in T1 sequence before gadolinium enhancement
- D) Axial Brain MRI showing no abnormality in T1 sequence after gadolinium enhancement

Figure 3

Radiological and metabolic evolution of the ECD patient before and after vemurafenib.

Axial ^{18}F fluorodeoxyglucose positron emission tomography before (A) and (B) after 8 weeks of vemurafenib therapy showing a decrease in radiotracer uptake in pons, concordant with a decrease in radiotracer uptake in the femurs (C-D) compatible with partial metabolic disease.

Metabolic changes correlate with a decrease of the intensity of FLAIR signal in the pons as assessed by axial Brain Magnetic Resonance Imaging before (E) and after 8 weeks (F) of treatment.