Langerhans cell histiocytosis with initial central nervous system presentation as a mimic of neurosarcoidosis

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Abstract

We report the case of a 58-year-old Caucasian woman who presented with a subacute cerebellar syndrome accompanied by disturbance of the hypothalamic–pituitary axis and was diagnosed with isolated neurosarcoidosis based on radiological findings including typically located cerebral lesions (infratentorial and pituitary stalk). Due to persistent clinical and radiological disease activity during several years despite escalation of immunosuppressive treatment, the diagnosis was reevaluated, and a transsphenoidal biopsy of a lesion at the pituitary stalk was performed revealing Langerhans cell histiocytosis. In this case, we discuss the different steps leading to the diagnostic error, as well as the presence of red flags, which should have led to an earlier diagnostic reevaluation.

Keywords

Langerhans cell histiocytosis, neurosarcoidosis, MRI, central nervous system, diagnostic

Case description

A 58-year-old Caucasian woman was referred in August 2014 because of a slowly progressive cerebellar syndrome (dizziness, ataxia, dysmetria, and dysarthria) with initial manifestation in April 2014 accompanied by executive deficits and hypersomnia with additional disturbance of the hypothalamic–pituitary axis (HPA). Cranial magnetic resonance imaging showed patchy hyperintense to Fluid-attenuated inversion recovery (FLAIR)-hyperintense lesions with gadolinium uptake bilaterally along the middle cerebellar peduncle and faint pial enhancement along the midbrain (Figure 1(a)) and the hypothalamus as well as thickening of the pituitary stalk (Figure 1(b) and (c)). Thoracoabdominal computer tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET) did not provide any evidence for any extra-cerebral lesions. Repeated examination of cerebrospinal fluid (CSF) showed slightly increased protein (0.48 g/l) and non-CSF-specific oligoclonal bands (1 cell/ul; glucose, lactate levels unremarkable). Due to the infratentorial distribution of the parenchymal white matter lesions, as well as the involvement of the HPA, isolated neurosarcoidosis was suspected. However,

lysozyme, angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL-2R) were not elevated in the serum, and C-reactive protein levels were within normal range. Because of low cellularity in CSF, flow cytometry with T-lymphocyte ratio was not conclusive.

After an initially positive response to intravenous steroids (size reduction of the lesions, clinical improvement), the patient developed severe cushingoid glucocorticosteroid side effects under long-term prednisolone therapy,

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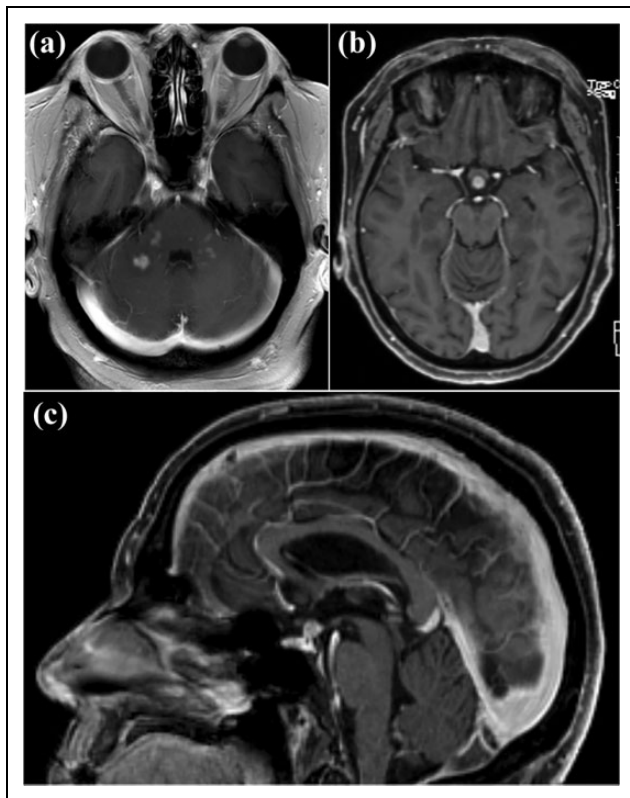Email: cecilia.friedrichs-maeder@insel.ch

Figure 1. T1-weighted Gd-enhanced magnetization-prepared rapid gradient echo sequences (TR 2530 ms, TE 2.96 ms, FoV r250 mm, voxel size $1.0 \times 1.0 \times 1.0$ mm^3, acquisition time 4:30 min 160 slices) revealed multifocal patchy enhancement along the mid-cerebellar peduncles (a), faint pial enhancement along the mesencephalon (c), and thickening of the pituitary stalk with expansion of the optic chiasm ((b) and (c)).

Figure 2. Histologically, the biopsy showed a dense lymphohistiocytic infiltrate (a). Morphological interpretation was limited by extensive crush artifacts, but there was extensive CD1a immunostaining (b), consistent with the presence of abundant Langerhans cells.

requiring steroid-sparing immunosuppressive treatment with methotrexate from February 2015 and infliximab from March 2016. Despite therapeutic escalation (up to 1000 mg infliximab intravenous every 4 weeks), she continued to show clinical and radiological signs of significant disease activity and prednisolone could not be tapered off (due to disease activity, secondary adrenal gland insufficiency, and a disease-mediated hypopituitarism). Notably, radiological evaluation of chest pain in January 2016 led to the identification of an osteolytic rib lesion of unknown origin and dignity. Unfortunately, despite two consultations in which the benefit and importance of a diagnostic workup were emphasized, the patient refused to undergo a diagnostic biopsy after the informed consent discussion at the radiology department. However, follow-up of the lesion did show neither metabolic activity nor a local progression or evidence for new lesions. In July 2016, methotrexate had to be stopped due to elevated liver enzymes and was shortly replaced by leflunomide (stopped in October 2016 because of stomatitis). However, due to clinical and radiological deterioration with the appearance of new cerebellar lesions, methotrexate was restarted in July 2017. Despite combined immunosuppressive treatment with
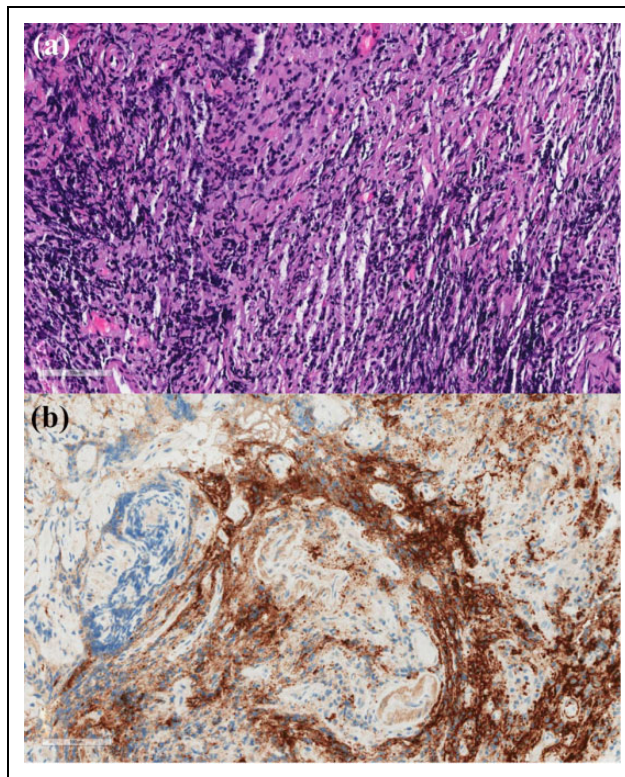
infliximab, methotrexate, and prednisolone, the patient showed only temporary amelioration and repeated radiological progress, while she developed numerous infections and endocrine side effects of these medications (corticotropic insufficiency, Cushing syndrome, and recurrent bilateral pyelonephritis). Additionally, as the course of the disease evolved, clinical evaluation became increasingly difficult due to a functional neurological component. Finally, in March 2018, considering the persistent significant disease activity and side effects of the inefficient therapy, as well as the most likely irreversible panhypopituitarism, a transsphenoidal biopsy of the lesion at the pituitary stalk was performed.

Histologically, the biopsy showed fibrotic tissue with a lymphohistiocytic infiltrate (Figure 2(a)), but no granulomas. Morphological evaluation was limited due to extensive crush artifacts. With this limitation, no histiocytic cells with nuclear grooves or eosinophils were identified, but immunohistochemistry for CD1a (Figure 2(b)) and Langerin (not shown) showed extensive staining in a pattern consistent with Langerhans cells. Next-generation sequencing (Ion AmpliSeq Oncomine Focus Fusion Panel) revealed a specific mutation in the serine/threonine-protein kinase B-Raf (BRAF V600E) as sole molecular alteration, corroborating a diagnosis of Langerhans cell histiocytosis (LCH).

Based on an interdisciplinary discussion and the presence of the BRAF V600E mutation treatment with cladribine was intended. However, the patient unexpectedly died in May 2018 at home without the presence of any witnesses and before the treatment was initiated. Unfortunately, the cause of death remains unknown because no consent for an autopsy was obtained from the next of kin.

LCH features

Langerhans cells derive from myeloic progenitor cells of the bone marrow.[1] LCH is a rare clonal proliferative disorder of the dendritic cell system, characterized by abnormal interaction of pathologic Langerhans cells with T-cells and chronic inflammation.[2] Despite the predilection for bone structures leading to osteolytic lesions, proliferating cells may infiltrate almost any organ (with the exception of kidneys and heart) and can present as isolated lesion, single organ, or multisystem disease. Involvement of the central nervous system (CNS) is rare (6% at diagnosis), is most often found in patients with multisystem disease, and may result from an extension or propagation of osteolytic lesions of the neuro- or viscerocranium (sphenoid, orbital, and ethmoid, temporal).[3] The most common clinical manifestation is hypopituitarism following infiltration of the pituitary gland, which can be the initial clinical presentation.[4] Involvement of other CNS structures mostly occurs later during the course of the disease.[5]

There are no universally accepted international guidelines available for the treatment of adult LCH patients; however, there are experts' recommendations that serve as a guide in the treatment.[6] Treatment in LCH patients should be based on the site and extension of the disease. The specific management of CNS-LCH includes chemotherapy that crosses the blood–brain barrier, radiation, or a combination of both. It has been reported that several agents are efficient in neurological forms of LCH such as cladribine, vinblastine, prednisone, methotrexate, and cytarabine with or without vincristine.[1,7–9] In addition, retinoic acid and intravenous immunoglobulin associated to chemotherapy may stabilize neurodegenerative lesions.[10,11] Starting therapy with cladribine or cytarabine seems nowadays the most adequate approach for CNS-LCH. Several retrospective cases and one prospective trial have demonstrated that patients harboring BRAF V600E mutations can be effectively treated with vemurafenib or dabrafenib.[12] Furthermore, unlike pediatric recommendations, radiotherapy is an effective treatment option with acceptable side effects for adult patients in selected situations. Proper replacement of hormonal deficiencies should always be considered.

Diagnostic error and red flags

Here we present a case of atypical clinical and radiological presentation of LCH, which was diagnosed and treated as an isolated neurosarcoidosis for several years. This case underlines the need for a repetitive reevaluation of a suspected diagnosis, as long as the diagnosis is not histologically proven and especially in the case of rare diseases and an incomplete therapeutic response. In our case, the presence of an unexplained lytic lesion in the rib should have caused an earlier thorough reevaluation of the underlying disease. Elements leading to the initial misdiagnosis of neurosarcoidosis were mainly the atypical clinical and radiological presentation with early isolated CNS manifestation including primarily extensive infratentorial parenchymal lesions. Neurologic symptoms represent the first defining manifestation of sarcoidosis in 50–70% of cases,[13,14] while involvement of CNS structures in LCH mostly occurs later during the course of the disease.[15] However, recent evidence suggests that CNS involvement in LCH could be underestimated due to discrete neurological symptoms.[5] As in our case, radiologically, neurosarcoidosis typically presents with multiple or solitary, mainly infratentorial lesions with T2 prolongation and post-contrast enhancement, as well as leptomeningeal involvement.[16,17] This lesion pattern is thought to be secondary to spread of inflammation from the leptomeninges along Virchow-Robin spaces[18,19] and can lead to involvement of skull base structures, in particular the HPA.[20] Intraaxial manifestations of LCH involve multiple white matter lesions with radiological characteristics resembling those of neurosarcoidosis but mostly supratentorial, as well as bilateral symmetric infratentorial gray matter lesions of the dentate nucleus of the cerebellum or basal ganglia leading to cerebellar symptoms and cognitive deficits.[5] Our patient presented supra- and infratentorial white matter lesions compatible with neurosarcoidosis, however lacking the classical leptomeningeal involvement. The HPA was involved with several lesions of the hypothalamus and pituitary stalk, which has been described in up to 50% of patients with LCH[15,19] and 18% of patients with neurosarcoidosis.[20]

Finally, isolated CNS manifestation with disseminated predominantly infratentorial parenchymal white matter lesions together with the higher prevalence of sarcoidosis (100–200 per 1,000,000 population vs. 1–2 per 1,000,000 population for LCH[21,22]) pointed to neurosarcoidosis as the most likely diagnosis. To our knowledge, only one case of late-onset LCH presenting with cerebellar ataxia as an initial symptom has previously been described.[23] Alternative radiological diagnosis of multiple (mainly) infratentorial lesions includes demyelinating disorders, cerebral angiitis of the CNS, lymphoma, and rare differential diagnoses such as Erdheim–Chester disease (histiocytic disease with non-Langerhans cells) and chronic lymphocytic inflammation with steroids to pontine perivascular enhancement response to steroids (CLIPPERS).

Retrospectively, several red flags characterize this case. Even under intensified immunotherapy, the patient only showed temporary amelioration however persistent

radiological disease activity. Because many inflammatory and even infectious or neoplastic disorders may transiently respond to immunosuppressive treatment, a recent consensus on diagnostic criteria for neurosarcoidosis[24] chose not to include treatment response. Potential biomarkers of neurosarcoidosis were unremarkable (ACE activity, sIL-2R), however varying sensitivity and specificity due to extent of organ involvement argues for use of these markers for assessing disease activity, but not for diagnostic purposes.[25] Osteolytic bone lesions are typical for LCH, as proliferating cells derive from myeloic progenitor cells of the bone marrow.[1] However, although less common, bone involvement also occurs in up to 13% of sarcoidosis patients.[26] Unfortunately, by the time the rib lesion was diagnosed, the patient refused to perform a (minimally invasive) axillary biopsy, which retrospectively could have provided precious diagnostic information. Furthermore, along with progression of the disease, adherence to treatment decreased, and additional functional neurological components made clinical evaluation increasingly difficult, which can also be considered as a red flag for the need of diagnostic reevaluation.

The natural history of adults with CNS-LCH is very variable and unpredictable. As in the case presented here, location of the lesions and their inaccessibility to the diagnosis without invasive interventions might cause delays in the diagnosis and consequently in the beginning of treatment. However, despite the delay, this patient survived 39 months after the first diagnosis of intracerebral lesions in August 2014. The treatment received to treat neurosarcoidosis may have played indeed a role, since many of the received drugs are also recommended to treat CNS-LCH. Particularly interesting is the fact that she received treatment with infliximab for a total of 19 months.[27] There are at least eight cases reported in the literature describing an evolution benefit of CNS-LCH under infliximab. Tumor necrosis factor (TNF) inhibitor infliximab does not normally penetrate the CNS, disruption of the blood–brain barrier can hypothetically occur in CNS-LCH patients providing a portal of access to these antibodies. In our case, none of these agents led to full control of the disease, whether they acted by slowing disease progression remains unclear.

Altogether this case underscores the need to obtain definitive pathological diagnosis of uncommon pathologies before initiating or at least after failure of long-term immunosuppressive treatment. In our case, the location of lesions at sites difficult to biopsy and biopsy refusal for the osteolytic lesion in the rib led to an extensive diagnostic delay.

Author contributions

CFM and CF contributed equally to this work.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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