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Langerhans Cell Histiocytosis in an Adult with Involvement of the Calvarium, Cerebral Cortex and Brainstem: Discussion of Pathophysiology and Rationale for the Use of Intravenous Immune Globulin

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Key Words

Langerhans cell histiocytosis · Extrapulmonary manifestation · Neurodegeneration · Paraneoplastic inflammation

Abstract

We report a case of Langerhans cell histiocytosis in a 64-year-old male who presented with symptoms and signs of brain involvement, including seizures and hypopituitarism. The diagnosis was confirmed with a biopsy of a lytic skull lesion. The disease affecting the bone showed no sign of progression following a short course of cladribine. Signs of temporal lobe involvement led to an additional biopsy, which showed signs of nonspecific neurodegeneration and which triggered status epilepticus. Lesions noted in the brainstem were typical for the paraneoplastic inflammation reported in this condition. These lesions improved after treatment with cladribine. They remained stable while on treatment with intravenous immune globulin.

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Introduction

Langerhans cell histiocytosis (LCH) refers to a clonal, neoplastic expansion of Langerhans cells. Stimulation by tumor necrosis factor α and granulocyte-monocyte colony-stimulating factor has been implicated in the pathogenesis (as has human herpesvirus 6). It most commonly affects children between the age of 1 and 4, although cases have been described in all age groups; the incidence in pediatrics has been estimated at 2–5 per million/year [1].

It is exceptional for LCH to present with brain involvement as the sole presenting symptom. This complication is reported as occurring in 1–4% of patients with multisystem disease, typically 5–20 years from the initial diagnosis. It is thought to be more common in men (2:1) [2]. Brain involvement has been noted to be more common in those with skull lesions [1].

Case Report

Our patient was a 64-year-old, right-handed man. The time course of his illness is summarized in [table 1](#). His symptoms began 2 years before his presentation to our service. He developed depression, anxiety and agitation, which led to his retirement from construction work. Shortly thereafter, he developed episodes described as hyperventilation, lasting from seconds to minutes, mostly in the morning, which were followed by confusion and a severe ‘pounding’ headache affecting the whole head, both of which lasted for hours.

One year prior to presentation, his family described personality changes (it was hard for them to characterize this further) and worsening confusion, particularly over the preceding 3 months. When these changes began, he was diagnosed with hypothyroidism and diabetes insipidus.

Three months before presentation, he developed weakness of the right leg, which had been slowly progressing since. Two weeks prior, it became so bad that he needed help walking. At this time, he also noticed weakness of the right arm and slurring of speech, which led him to seek medical help.

He had been diagnosed with peripheral arterial disease (claudication in his left leg) 4 months prior to presentation, and paroxysmal atrial fibrillation 1 month prior, for which he was taking warfarin. He continued to smoke 2–3 cigarettes a week. His initial review of systems revealed that he was anorexic and had lost 30 lb over the last 2 years. He also complained of a loss of libido and an occasional shortness of breath when walking.

On initial exam, he was unable to sustain upward gaze; vertical saccades were followed by a slow downward drift, then a compensatory saccade. He had a weakness of the right side of his face, sparing the forehead. He was weak throughout, with strength of 4–/5 on his right side in an upper motor neuron pattern with signs of spasticity; Babinski’s reflex was present on this side. The left side was 4+/5, with a similar pattern. Cerebellar function and sensation were unimpaired.

His initial complete blood count, comprehensive metabolic panel, serum protein electrophoresis and folate were normal apart from a white cell count of $13 \times 10^9/l$ (95% neutrophils) and platelets of $570 \times 10^9/l$. His sodium was initially normal, but, during his admission, it was generally in the range of 145–160 mmol/l.

His international normalized ratio was 2.9; the C-reactive protein was 30 mg/l (<10), and the erythrocyte sedimentation rate 60 mm/h (<20). His B₁₂ level was low at 375 pg/ml (>400). He was hypothyroid with a thyroid-stimulating hormone (TSH) level of 5.6 μ IU/ml

(<4.9) and a free T4 of 0.6 ng/dl (>0.7). He had hypogonadism (presumably secondary) with total testosterone of <20 ng/dl (>200). His morning cortisol and ACTH levels were normal. Additional pituitary tests were deferred.

A lumbar puncture was done shortly after admission, showing 4 red cells, 9 white cells (56% lymphocytes, 43% macrophages), and a protein level of 45 mg/dl (<35). His glucose was normal as was his IgG synthesis rate. Oligoclonal bands were absent and cytology showed no signs of malignancy.

Shortly after admission, a complete serum paraneoplastic panel was sent; this was negative. The antibodies reported were: anti-neuronal nuclear types 1–3, anti-glial nuclear type 1, Purkinje cell types 1–2 and type Tr, amphiphysin, CRMP-5-IgG, striatal, T/Q and N-type calcium channels, ACh receptor-binding, ACh receptor ganglionic and neuronal voltage-gated K⁺ channels.

Brain images on presentation are shown on the left in [fig. 1a–f](#). A CT showed lytic bone skull lesions. MRI is notable for the presence of T2-hyperintense lesions in the left frontal lobe, the right mesial temporal lobe and the brainstem, which were minimally enhanced. An MR perfusion scan of the brain showed no significant increase in relative blood volume or relative blood flow in these lesions. A CT of the thorax, abdomen and pelvis showed 5 small lung nodules (maximum diameter 6 mm) and a pneumatocele in the left lower lobe. As there was nothing further on history, exam or initial investigations to suggest cancer anywhere else, a PET/CT was not performed.

A biopsy of the left frontal bone lesion was performed. This is shown in [figure 2](#). Immunohistochemistry shows the lesion to be CD1a- and S100-positive, which is characteristic for histiocytosis.

Initially, we were unsure of the cause of his right temporal lesion. Given the rarity of LCH with onset in the central nervous system (CNS) in adults, the possibility of another tumor was raised, and so a second biopsy was performed. In retrospect, it would have been better to avoid performing this, as the diagnosis was already clear and his other lesions were attributable to LCH. Furthermore, the procedure precipitated status epilepticus and led to preventable complications which ultimately contributed to his death. The biopsy is shown in [figure 3](#). This illustrates mild edema, hypercellularity and reactive changes, all of which are consistent with the edge of an inflammatory process. No Langerhans or neoplastic cells are seen.

Following the biopsy, it was necessary to induce coma to control his seizures. He was also re-intubated. Septic shock (likely due to ventilator-associated pneumonia) and a pulmonary embolism complicated his course thereafter. He remained intubated for 3 weeks. At the end of this period, he was given methylprednisone 1,000 mg i.v. for 3 days, with no sign of improvement. Thereafter, he started cladribine 1.4 mg/m²/day for 5 days. Cycles were planned every 3 weeks, but delayed due to pancytopenia and infection. He remained clinically stable after 4 cycles of this regimen. Histiocytosis affecting his skull was thought to be in remission as a result of the treatment, as there was no sign of new or enlarging lytic lesions.

After discharge from the ICU, he showed signs of critical illness myopathy/neuropathy. There was widespread muscle atrophy and generalized weakness. He was unable to stand without support and his tracheostomy remained in place.

Given the suspicion of paraneoplastic brainstem inflammation, he was started on intravenous immune globulin (IVIG) 400 mg/kg × 5 days. Two weeks after the initial treatment, the brainstem showed some improvement in the degree of FLAIR hyperintensity ([fig. 1i, j](#)). An MRI 1 month after a second course of IVIG showed these changes to be stable overall, with some increase in pontine enhancement ([fig. 1k, l](#)).

He then developed recurrent pneumonia and septic shock, again requiring an ICU admission. Following this, his family elected a palliative approach to care and he died 6 months after his initial presentation.

Discussion

Our patient's episodes of hyperventilation followed by confusion are typical for seizures involving the right mesial temporal lobe; the similarity to panic attacks has previously been identified in a case series [3]. The development of status epilepticus following biopsy of this region lends support to this being an epileptogenic focus.

In his cerebrospinal fluid (CSF), the finding of a high proportion of macrophages is striking. We were unable to find literature specifically addressing the significance of this finding; classically it is said to be associated with meningitis due to fungi or tuberculosis [4]. None of the other case reports we studied, including one with Langerhans cells in the CSF, reported this finding [5]. One series has shown elevations of neurofilament protein light chain, glial fibrillary acid protein and total tau protein in the CSF of patients with LCH affecting the brain [6].

Treatment of adults with LCH has recently been the subject of expert panel recommendations [7]. These advise the use of cladribine for patients such as ours with multisystem and CNS involvement (cytarabine is thought to be a reasonable alternative). Typically, 6–12 monthly cycles are recommended with an assessment after 2–3 cycles. Myelosuppression is the main dose-limiting toxicity; this has best been studied in the setting of hairy cell leukemia where neutropenia was reported in 70%, anemia (Hb <8 g/dl) in 35% and thrombocytopenia in 10% of patients [8].

The most recent and thorough description of the neuropathology of LCH comes from a series of 12 cases from Grois et al. [9] in 2005 (of note, 2 of these 12 presented with CNS involvement). The authors divide the pathology into 3 categories: (1) the typical circumscribed granulomas found in other organs; (2) infiltrating granulomas with profound T-cell dominated inflammation and severe neurodegeneration; (3) neurodegenerative lesions lacking Langerhans cells, typically affecting the brainstem and cerebellum and resembling paraneoplastic encephalitis. It appears that the temporal and frontal lesions in our patient were of the second type; it is probable that the biopsy came from the neurodegenerative part of the lesion rather than that containing Langerhans cells. The MRI appearances of the brainstem in our patient are typical of the third type.

The presence of inflammation without Langerhans cells has led to the view that these lesions are paraneoplastic in origin and that the neurodegeneration seen is thus autoimmune. The neoplasm in question here is LCH itself. The Langerhans cells are thought to take up normal neuronal antigens, provoking an immune response to these; alternatively, the immune system may target antigens shared by Langerhans cells and microglia. If an antigen is involved, the pathology reported by Grois et al. [9] suggests that the inflammation is primarily T-cell mediated rather than humoral. This would suggest a cytoplasmic origin for the antigen. The antigens responsible for this phenomenon have not been identified and thus it was to be expected that our patient's paraneoplastic panel was negative [10].

Using multiple immunosuppressants sequentially means that a correlation with the patient's response is challenging. Langerhans cells in their normal form are thought to have a lifespan of months, and LCH is characteristically a slowly progressive disorder. By contrast, cytotoxic T-cells typically have a half-life of 24–48 h when activated. Cladribine leads to DNA breakage and a depletion of ATP. When used in the treatment of leukemia and lymphoma, it

is typically given every 4 weeks. Thus, the initial doses of cladribine would have been expected to lead to the death of a majority of neoplastic histiocytes while the T-cell-mediated inflammation would have been expected to resume within 3–4 weeks. This is borne out on serial MRIs (fig. 1).

IVIg would not have been expected to affect the viability of Langerhans cells, but should have reduced T-cell activity for 3–4 weeks. It leads to a selective decrease in T-cells overall and an increase in regulatory T-cells. In children with LCH, IVIg has been reported to contribute to a stabilization of inflammation in 4/5 patients treated and to enable long-term remission in 1 case [11, 12]. It has been suggested that IVIg be given prophylactically to prevent the development of CNS complications of LCH, particularly diabetes insipidus, which tends to be irreversible [13]. Alternative agents reported to treat the paraneoplastic inflammation in LCH include vincristine/cytarabine and all-trans-retinoic acid. The use of steroids in our patient would not have been expected to have had long-lasting effects.

Bearing the above in mind, as well as the results of treatment in other T-cell-mediated paraneoplastic conditions, strong consideration should be given to agents that primarily target T-cells: steroids, IVIg, plasma exchange and mycophenolate mofetil or cyclophosphamide [14].

Other paraneoplastic disorders recognized in patients with LCH include cancer-associated retinopathy and spinocerebellar degeneration. This latter is distinct from that affecting the brainstem in our patient.

Conclusions

Brain imaging should always be undertaken in an older patient with episodes suggestive of seizures, diabetes insipidus of central origin or symptoms suggestive of pituitary dysfunction. Close attention to bone may be necessary to identify lesions typical of LCH. Once a diagnosis of LCH is made, a brain biopsy is not essential if the MRI appearances are typical for the inflammatory processes that accompany this condition.

Paraneoplastic inflammation requires treatment concurrently with LCH. Once LCH appears stable, prolonged treatment may be needed to prevent recurrence of inflammation. IVIg appears to be a reasonable adjunct to cladribine, particularly in a case such as this where cytopenias or infections limit the use of conventional chemotherapy.

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Table 1. Time course of the disease

Time (approximate)	Time, days	Event	MRI (fig. 1)
-2 years		Depression, seizures	
-1 year		Personality changes	
		Diabetes insipidus, hypothyroidism	
-3 months		Worsening confusion	
		Weakness of right leg	
-2 weeks		Weakness of right arm, slurred speech	
0		Presentation to our institution	a–f
Day 2	2	Bone biopsy	
Week 2	13	Resection of right temporal lesion; status epilepticus	
Week 4	22	Extubated	
		Methylprednisone 1,000 mg i.v. ×3 days	
Week 5	34	Cladribine 1.4 mg/kg i.v. ×5 days, cycle 1	
Week 11	76	Cladribine, cycle 2	
3.5 months	108	Cladribine, cycle 3	g, h
4 months	123	IVIg 400 mg/kg i.v. ×5 days, cycle 1	
4 months	135	IVIg 400 mg/kg i.v., cycle 2	i, j
	140	Cladribine, cycle 4	
	170		k, l
6 months	190	Died following respiratory infection	

Time (days) denotes the day when the treatment ended. All cycles of cladribine and IVIg were 5 days.

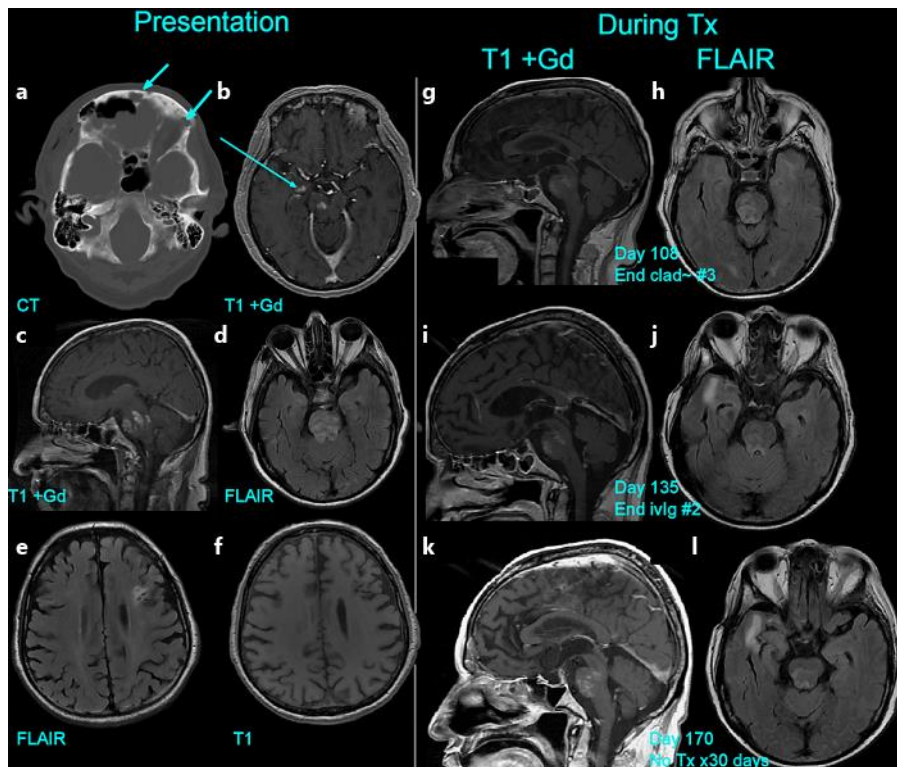


Fig. 1. Imaging at the time of diagnosis and throughout the course of treatment. See table 1 for timing of MRIs relative to disease course and treatment. MRIs are 1.5 T. Left-hand side: imaging on presentation. **a** Axial CT (bone windows) shows lytic lesions affecting the calvarium bilaterally (blue arrows). **b** Enhancement of the right mesial temporal lobe. This is the lesion that was biopsied (blue arrow). **c, d** Pontine inflammation. Post-contrast image (**c**) shows diffuse, patchy enhancement. FLAIR hyperintensity (**d**) is evident in the pons and the pituitary gland. **e, f** Left frontal inflammation. FLAIR image (**e**) shows hyperintensity with associated cystic degeneration. The latter is best seen on T1-weighted imaging (**f**). Right-hand side: imaging during treatment. **g, h** Response to cladribine (same day as completed cycle No. 3). Improvement in enhancement (**g**) and FLAIR hyperintensity (**h**) versus images **c** and **d**. **i, j** Response to IVIG (same day as completed cycle No. 2). Enhancement remains stable. Brainstem FLAIR hyperintensity improved (**j** vs. **h**). One month after the most recent cycle of cladribine. **k, l** Disease stable (no treatment for 30 days). Some worsening of pontine enhancement, although not as marked as when the patient first presented (**k** vs. **c**).

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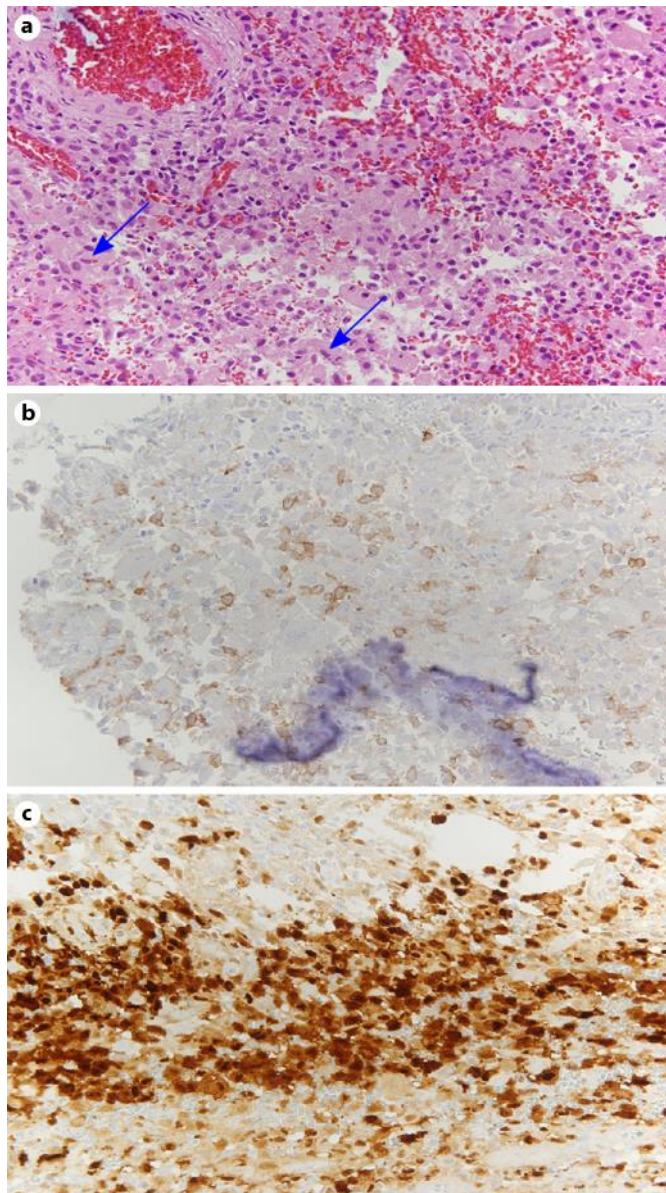


Fig. 2. Left frontal bone biopsy. Images labeled top to bottom. **a** Magnification is $\times 40$. HE staining. Langerhans cells are visible as large, oval, mononuclear cells with coffee-bean-shaped nuclei and moderately abundant, slightly eosinophilic cytoplasm. The nucleus is prominent with fine chromatin and thin nuclear membranes with grooved, folded, or indented nuclear contours, imparting a ‘twisted towel’ or ‘coffee bean’ appearance. There are few cytoplasmic vacuoles, little or no phagocytic material and no dendritic processes. Many such cells are seen and 2 good examples are highlighted (blue arrows). **b** CD1a staining shows a diffuse uptake by Langerhans cells. **c** S-100 staining for Langerhans cells is strongly positive.

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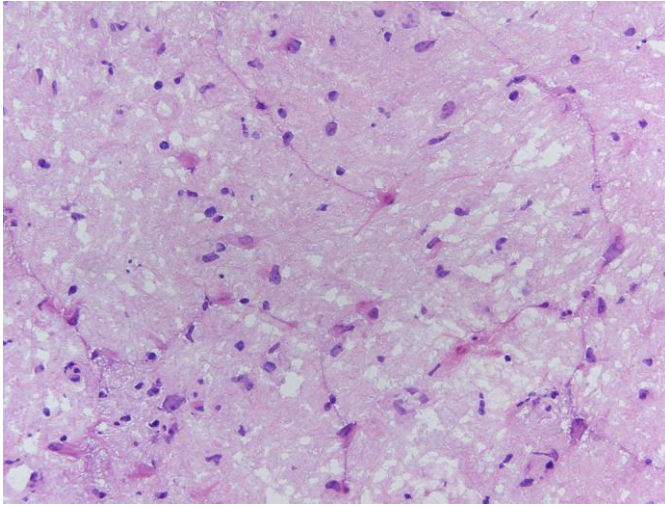


Fig. 3. Right temporal lobe biopsy. HE staining. Magnification is $\times 40$. Mildly hypercellular and gliotic gray matter with focal reactive changes. No neoplasia is seen.