

## Case Report

# Enlargement of Langerhans cell histiocytosis of the hypothalamus with progression into the basal ganglia and white matter

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## Abstract

**Background:** Langerhans cell histiocytosis (LCH) is a rare disease that may affect the central nervous system; it is caused by dendritic cell proliferation, and typically occurs in children. LCH frequently appears in the pituitary stalk and rarely results in multiple enhanced lesions in the brain parenchyma.

**Case Description:** We present a case of a 40-year-old woman who developed panhypopituitarism and central diabetes insipidus in the postpartum period requiring hormone replacement therapy. At first, magnetic resonance imaging only revealed thickening of the pituitary stalk; while 6 months later, a single enhanced mass lesion was detected in the hypothalamus. Another 5 months later, the lesion had enlarged with appearance of multiple, enhanced satellite lesions in the basal ganglia and white matter. The patient underwent successful craniotomy to obtain a biopsy sample; LCH of the hypothalamus was definitively diagnosis by histopathological examination. Steroids were administrated and resulted in significant reduction of all lesions.

**Conclusions:** Definitive histopathological diagnosis and subsequent appropriate therapy, such as steroid administration, are required when LCH lesions in the hypothalamus become progressively enlarged and new lesions appear in the brain parenchyma.

**Key Words:** Brain parenchyma, hypothalamus, Langerhans cell histiocytosis, multiple enhanced lesions, steroid

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## INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease that may affect the central nervous system (CNS); it is caused by dendritic cell proliferation, and typically occurs in children.<sup>[5]</sup> The clinical presentation of LCH varies from single to multiple lesions, and the clinical outcome depends on the affected systemic organs. Some patients with LCH only require radiological observation, while others have a poor prognosis despite aggressive

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multimodal treatment.<sup>[5]</sup> Although LCH in the CNS frequently occurs in the hypothalamus, intraparenchymal satellite lesions have been reported in previous case reports.<sup>[6,9]</sup> However, the clinical features of LCH with satellite parenchymal lesions remain unknown. We experienced a rare case of LCH of the hypothalamus resulting in multiple satellite lesions in the basal ganglia and white matter. The patient was successfully treated with steroids after histological confirmation.

## CASE DESCRIPTION

A 40-year-old Japanese woman visited our hospital with complaints of thirst, polydipsia, and polyuria. She had delivered her first baby without any perinatal difficulties 6 months earlier. From her symptoms, she was diagnosed with central diabetes insipidus (DI) by an endocrinologist, and the DI was controlled by desmopressin. Subsequently, the patient developed symptoms of fatigue, galactorrhoea, and amenorrhea, leading to the diagnosis of panhypopituitarism. T1-weighted magnetic resonance imaging (MRI) showed thickening of the pituitary stalk and disappearance of hyperintensity in the posterior lobe of the pituitary gland [Figure 1a]. Whole-body computed tomography revealed no other abnormalities. After 6 months, the mass lesion in the hypothalamus had clearly enlarged; she was referred to our department for biopsy of the lesion for definitive diagnosis [Figure 1b]. No procedure for cerebrospinal fluid sampling, such as lumbar puncture, was performed before the biopsy.

She was alert, and no neurological abnormalities were found. After another 5 months, follow-up MRI revealed that the lesion in the hypothalamus had further enlarged and new, multiple enhanced lesions were detected in the basal ganglia and white matter [Figure 2a and b]. Biopsy of the hypothalamic lesion was performed using bifrontal craniotomy. Using the interhemispheric approach with opening of the lamina terminalis, we detected a white,



**Figure 1:** T1-weighted sagittal magnetic resonance imaging images with contrast enhancement. (a) The image was obtained at the time of diagnosis of panhypopituitarism, showing the pituitary stalk thickening (white arrowhead). (b) Image after 6 months showed that the lesion at the hypothalamus was enlarged (white arrowhead)

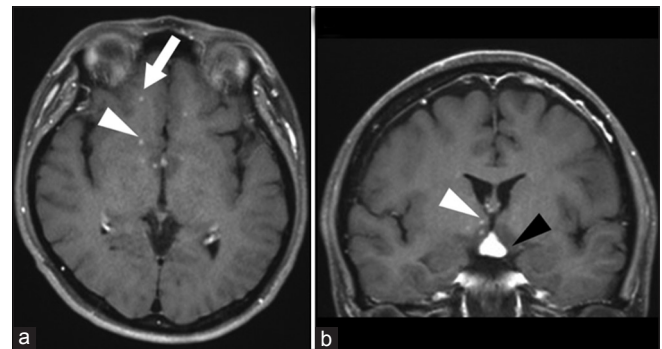
solid lesion in the hypothalamus. Although the lesion was solid and bled easily, sufficient samples were obtained for histological examination. Her postoperative course was uneventful.

Histopathological examination of the surgical specimens showed remarkable invasion of several types of inflammatory cells with fibrosis [Figure 3a]. Some of the inflammatory cells were immunoreactive for CD1a, which is a definitive marker of dendritic cells [Figure 3b], and others were immunoreactive for CD68, CD8, and CD20, which are markers for macrophages, T lymphocytes, and B lymphocytes, respectively [Figure 3c-e]. There was also immunoreactivity for glial fibrillary acidic protein, which marks a response for reactive astrocytes [Figure 3f].

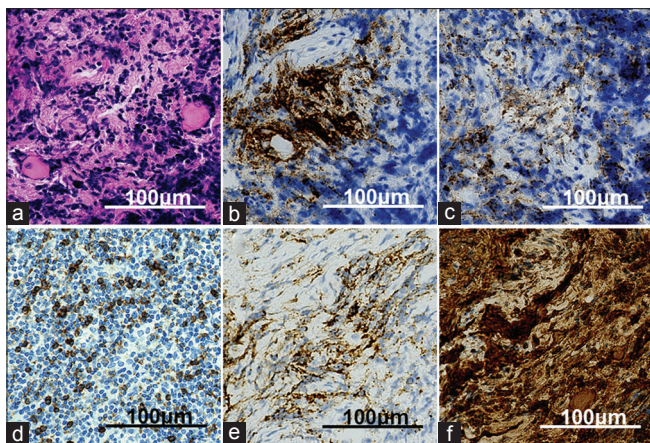
Finally, we diagnosed the lesion as LCH in the CNS. After steroids were started (60 mg/day of prednisone) for 1 month, all lesions in the hypothalamus, basal ganglia, and white matter were clearly reduced in size, as detected on MRI. Steroid treatment was gradually decreased, and no recurrence has been observed 18 months postoperatively [Figure 4a and b].

## DISCUSSION

In this present report, we described the case of a woman who developed LCH manifesting as panhypopituitarism and DI in the postpartum period. At first, the lesion only involved the pituitary stalk and spread to the hypothalamus 6 months later. In addition, the lesion became further enlarged and, after another 5 months, multiple new lesions emerged in the basal ganglia and white matter. Therefore, biopsy was performed to determine the therapeutic strategy. Finally, LCH was diagnosed by histology. This is an extremely rare case, which revealed sequential changes of hypothalamic LCH with multiple satellite lesions in the basal ganglia and white matter, and these lesions were reduced in size directly after steroid administration.



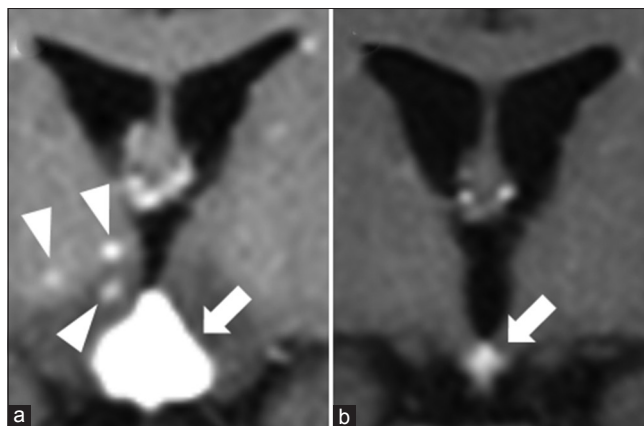
**Figure 2:** T1-weighted magnetic resonance imaging images with contrast enhancement. (a) Axial image showed that new multiple enhanced lesions were present at the basal ganglia (white arrowhead) and deep white matter in the frontal lobe (white arrow). (b) Coronal image showed that the lesion at the hypothalamus had progressed (black arrowhead), and there were some enhanced lesions surrounding the hypothalamus (white arrowhead)



**Figure 3: Histopathological findings of surgical specimen. (a)** Hematoxylin and eosin staining showed highly present fibrosis and inflammatory cells invasion. **(b)** Immunoreactivity for CD1a, which is definitive marker of dendritic cell, was found. Positivity for CD68 **(c)**, CD8 **(d)**, and CD20 **(e)** was indicative of the presence of macrophages, T lymphocytes and B lymphocytes, respectively. **(f)** Immunoreactivity for glial fibrillary acidic protein, a marker for nerve fibers was strongly positive

Although monoclonal proliferation of dendritic cells has been considered the cause of LCH, the exact mechanisms remain unknown. Definitive diagnosis of LCH was obtained by immunohistological examination of surgical specimens. The specimens showed invasion of aggressive inflammatory cells that immunoreacted with CD1a. It is reported that the annual incidence of LCH is 0.5 cases per 100,000 children younger than 15 years, but the incidence in adults remains unknown.<sup>[9]</sup> There is organic predominance in the lung among adult patients with LCH and an etiological relationship between smoking and LCH in the lungs.<sup>[4,11]</sup> The clinical presentations and outcomes of LCH vary, and treatment depends on whether there are single or multiple lesions and on whether high-risk organs, such as the bone marrow, liver, spleen, and lungs, are involved.<sup>[5]</sup> Most isolated skin lesions are self-limited and disappear without treatment, and single bone lesions treated with surgical resection or radiation therapy have excellent prognoses.<sup>[5]</sup> Previous reports have described that some patients with LCH had good outcomes with steroid administration.<sup>[1]</sup> However, LCH occasionally has a poor prognosis when it affects multiple systemic organs, even if aggressive chemotherapy is administered.<sup>[8]</sup> In some cases, malignancy or immune reactivation might appear during the clinical course.<sup>[2,5]</sup> Although no genetic examination was performed in our case, genetic examinations, such as BRAF V600E and MAP2K1 mutations, are recommended to make a prognosis.<sup>[5]</sup>

The hypothalamus, one of the most common regions where LCH appears, is involved in approximately 40% of LCH cases in the CNS and is well-known as a clinical landmark of DL.<sup>[10]</sup> In contrast, diverse forms of LCH originating from other CNS lesions exist, but they are rare.<sup>[9]</sup> Few reports have found LCH in the CNS associated



**Figure 4: T1-weighted coronal magnetic resonance imaging images with contrast enhancement. (a)** Before steroid administration, there were enhanced lesions at the hypothalamus (white arrow) and the cerebral parenchyma (white arrowheads). **(b)** Eighteen months after administration of steroid, the enhanced lesion at the hypothalamus was reduced (white arrow), and the lesions at the brain parenchyma were completely diminished

with multiple enhanced lesions in the brain parenchyma, similar to our present case.<sup>[6,7,9]</sup> However, an adult LCH case with progressively enhanced CNS lesions affecting the hypothalamus and brain parenchyma is extremely rare. In one of the reported cases, whole-brain autopsy was performed and revealed particular histopathological features, including diffuse inflammation, mainly composed of CD8+ T lymphocytes present in the whole brain and CD20+ B lymphocytes only at the perivascular lesions. These autopsy findings led to the notion that the multiple enhanced lesions in the brain parenchyma detected on MRI might have been inflammatory active perivascular lesions, composed of lymphocytes as determined by histopathological examination.<sup>[7]</sup> LCH lesions consist of different types of inflammatory cells; the level of invasion and percentage of these cells differ for each organ.<sup>[3]</sup> Notably, the cerebral LCH parenchymal lesions in the CNS in our case mainly consisted of lymphocytes.

Because of its low incidence, the treatment of LCH in the CNS has not been established. Previous reports have described some treatment strategies, such as surgery, radiation, anti-inflammatory medications, anti-angiogenic medications, and chemotherapy. These treatments are administered depending on the clinical presentation in the CNS.<sup>[6]</sup> In the present case, steroid administration induced remarkable size reduction of the enhanced LCH lesions in the hypothalamus and brain parenchyma. In addition, no recurrence or neurological deterioration has been noticed. This clinical course confirmed that the enhanced lesions in both the hypothalamus and brain parenchyma were mainly provoked by local aggressive inflammatory responses. In our case, steroid administration effectively induced anti-inflammatory actions that affected all lesions. It can, therefore, be speculated that decreased enhancement of cerebral

parenchymal lesions is caused by inflammatory active responses by lymphocytes and dendritic cells.

We experienced an extremely rare case of LCH of the hypothalamus leading to multiple enhanced lesions in the basal ganglia and white matter. Definitive diagnosis was made by biopsy, and steroid administration reduced these lesions without recurrence over 1 year. When a patient has a lesion in the hypothalamus and multiple other lesions in the brain parenchyma suggestive of LCH, early biopsy for definitive diagnosis and steroid administration are strongly recommended. The present case suggests that the enhanced lesions of LCH in the CNS, mainly composed of lymphocytes, can spread to the brain parenchyma but can be promptly reduced after steroid administration.

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### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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