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Langerhans Cell Histiocytosis of the CNS Presenting With Diabetes Insipidus and Fever of Unknown Origin: A Case Report

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Abstract

Langerhans cell histiocytosis (LCH) is a rare neoplastic disorder caused by clonal proliferation of Langerhans cells. LCH of the CNS can involve the suprasellar region and typically presents with headache, fever of unknown origin, and diabetes insipidus. A high index of suspicion is therefore needed when encountering such a presentation. We present the case of a 32-year-old woman who presented mainly with fever of unknown origin, frontal pressure headache, episodes of vomiting, and intermittent right-sided paresthesia. Her clinical course began with a diagnosis of fever of unknown origin approximately two years earlier. Initial evaluation revealed hypernatremia, prompting an endocrine referral. Subsequent investigation at the referring institution established a diagnosis of diabetes insipidus, with brain MRI demonstrating a suprasellar lesion. Due to prolonged hospitalization, the patient was subsequently referred to a tertiary care center, where MRI demonstrated a well-defined, enhancing, T2-isointense lesion centered in the hypothalamic-chiasmatic region, measuring approximately 16 × 17 × 12 mm (anteroposterior, transverse, and superoinferior dimensions), with adjacent edema in the hypothalamic region and optic tracts. At that point, she had diagnoses of diabetes insipidus, primary hypothyroidism, and diabetes mellitus, the latter noted in the context of obesity. Her medications included desmopressin, insulin aspart, insulin degludec, and levothyroxine. Biopsy confirmed CNS LCH, with immunohistochemistry revealing a BRAF V600E mutation. The patient underwent surgical debulking via right frontal craniotomy, leaving a residual mass measuring 9 × 9 × 7 mm. She was subsequently started on vemurafenib, a targeted BRAF inhibitor. No radiation therapy was administered, and she remains on an intermittent dosing schedule (one week on, one week off) under continued neurosurgical follow-up nearly two years after treatment initiation. This case shows that LCH may present with unexpected clinical features. Because the differential diagnosis can be complex, recognizing the typical and atypical clinical presentations of CNS LCH is crucial for early diagnosis, as CNS involvement can be easily missed.

Categories: Neurosurgery
Keywords: adult, central nervous system, diabetes insipidus, diabetes mellitus, fever of unknown origin, langerhans cell histiocytosis, suprasellar mass

Introduction

Langerhans cell histiocytosis (LCH) is now recognized as a clonal neoplastic disorder driven by activating mutations in the mitogen-activated protein kinase (MAPK) pathway, most commonly BRAF V600E, with MAP2K1 mutations identified in a subset of BRAF wild-type cases [1,2]. LCH mainly affects children but can occur in any age group [1]. LCH of the CNS is classified among the hematolymphoid tumors [3].

CNS LCH presents in two major clinicopathologic forms: granulomatous/tumoral mass lesions, most frequently involving the hypothalamic-pituitary axis, infundibulum, or choroid plexus; and neurodegenerative LCH, a progressive process affecting the cerebellar dentate nuclei, basal ganglia, and pons [1]. LCH can present with a wide range of symptoms and may involve any system in the body. Clinically relevant manifestations of CNS LCH include those reflecting increased intracranial pressure and mass effect (e.g., headache, nausea and/or vomiting, ataxia, and seizures) and hypothalamic-pituitary endocrinopathy (e.g., polyuria and polydipsia) [4,5].

Definitive diagnosis of LCH requires histopathological examination and immunohistochemical staining of biopsied tissue, with positive staining for CD1a, CD207/Langerin, and S100 [6]. Treatment options for LCH include chemotherapy, radiation therapy, surgery, immunotherapy, targeted therapy, stem cell transplantation, other drug therapies, and observation [7]. Moreover, the prognosis of CNS LCH depends on the patient's age, chemotherapy resistance, and the presence of cell-free BRAF V600E in plasma [8].

In adults, cases of CNS LCH with atypical presentations are frequently underrecognized. In this report, fever

of unknown origin was the dominant initial presenting feature, preceding the eventual recognition of hypothalamic-pituitary involvement, an atypical diagnostic sequence that underscores the importance of considering LCH in the differential diagnosis of prolonged, unexplained fever. We report this case to highlight this atypical presentation of CNS LCH.

Case Presentation

A 32-year-old woman presented to a local hospital with fever of unknown origin two years earlier. The fever was intermittent and persisted over a two-year period, with recorded temperatures above 37.5°C that did not respond effectively to antipyretic therapy. Other complaints included frontal pressure headache, episodes of vomiting, and intermittent right-sided paresthesia. She had a known history of diabetes insipidus, hypothyroidism, and diabetes mellitus.

Her symptoms began two years earlier, when physicians diagnosed her with fever of unknown origin and subsequently with diabetes insipidus due to elevated sodium levels. During this time, the patient was followed by an endocrinologist and underwent multiple MRI examinations. Although these examinations showed no skull lesions, they revealed a well-defined, enhancing, T2-isointense lesion centered in the hypothalamic-chiasmatic region.

According to radiology reports from the referring institution, the lesion was first identified in April 2024, measuring approximately 0.6 cm. Follow-up MRI performed at our institution in November 2024, approximately seven months later, demonstrated interval growth of the lesion to 16 × 17 × 12 mm (1.6 cm) (Figure *1*).

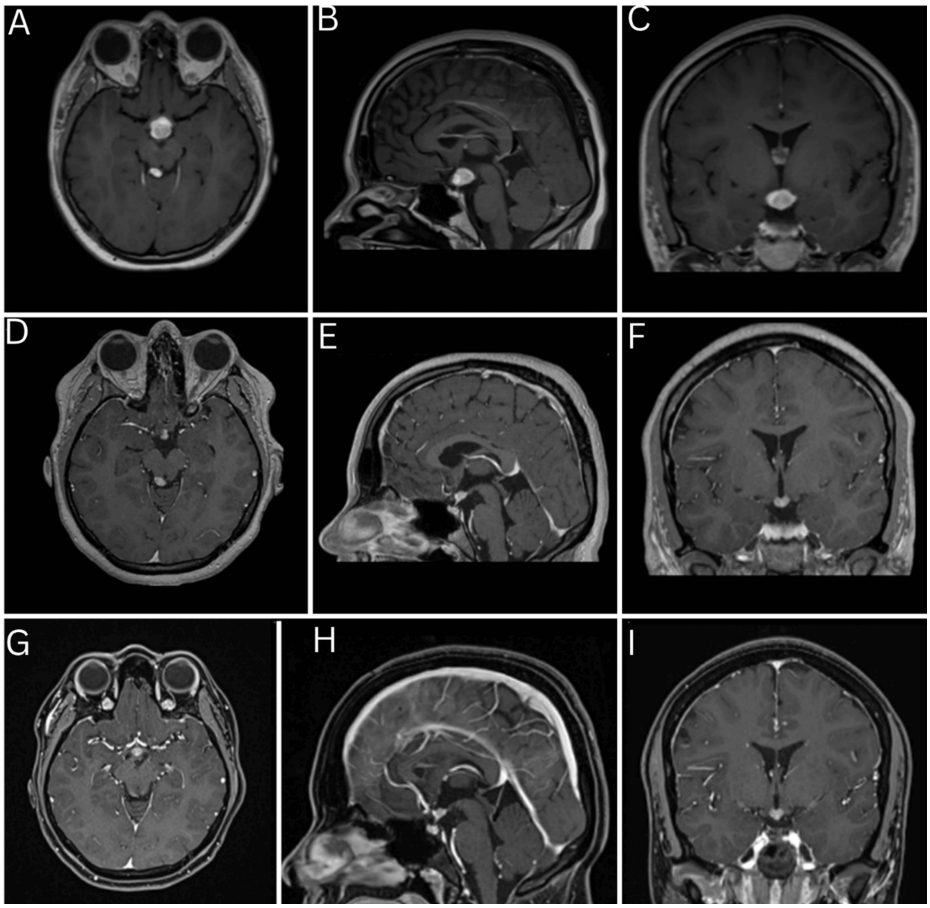


FIGURE 1: Pre- and postoperative brain MRI (arrows indicate the lesion/area of interest in each panel).

Preoperative axial (A), sagittal (B), and coronal (C) T1 contrast-enhanced images show a well-defined, enhancing suprasellar lesion centered in the hypothalamic-chiasmatic region, measuring 16 × 17 × 12 mm, with an incidental quadrigeminal cistern lipoma. Postoperative axial (D), sagittal (E), and coronal (F) T1 contrast-enhanced images demonstrate regression of the lesion, with a reduction in size to 9 × 9 × 7 mm, consistent with surgical debulking. One-year postoperative axial (G), sagittal (H), and coronal (I) images show stable, small nodular enhancement within the hypothalamic-suprasellar region.

On presentation, the patient denied seizures, loss of consciousness, focal neurologic deficits, or symptoms suggestive of an upper respiratory tract infection or other systemic infection. She was stable and alert, with a Glasgow Coma Scale score of 15/15.

Cranial nerve examination revealed pupils measuring 3 mm and reactive bilaterally, with normal visual fields and intact light and accommodation reflexes (CN II); normal extraocular movements (CN III, IV, and VI); normal facial sensation across all three divisions (CN V); normal facial muscle movement (CN VII); decreased hearing of high-frequency tones (CN VIII); normal shoulder shrug and head turning with full power (5/5) (CN XI); and normal tongue movement (CN XII).

Motor examination of the upper extremities showed normal tone without tremor or fasciculation, full power (5/5), and a negative pronator drift, with intact sensation. Examination of the lower extremities showed normal tone without tremor or fasciculation, full power (5/5), and intact sensation. Gait was normal, with good speed and arm swing, and no truncal ataxia was noted while standing.

Diabetes insipidus had already been diagnosed and managed with desmopressin at the referring institution before transfer to our hospital; detailed urine output and osmolality data from that workup were not available at our center. At the time of transfer, the patient's diabetes insipidus was clinically controlled. Preoperative laboratory evaluation at our institution revealed a serum sodium level of 139 mEq/L. An anterior pituitary hormone panel showed an elevated thyroid-stimulating hormone level of 6.140 mIU/L, consistent with primary hypothyroidism, with adrenocorticotropic hormone, follicle-stimulating hormone, and luteinizing hormone levels within normal limits (13.8 ng/L, 1.6 IU/L, and 3.1 IU/L, respectively); growth hormone and prolactin were not assessed. Glycemic evaluation revealed a hemoglobin A1c level of 9.7%.

The patient underwent surgical debulking via frontal craniotomy and a subfrontal approach, leaving a residual mass measuring 9 × 9 × 7 mm. The frontal craniotomy approach was selected at the surgeon's discretion. Pathology showed LCH with marked chronic inflammatory infiltrate and reactive gliosis (Figure *2*).

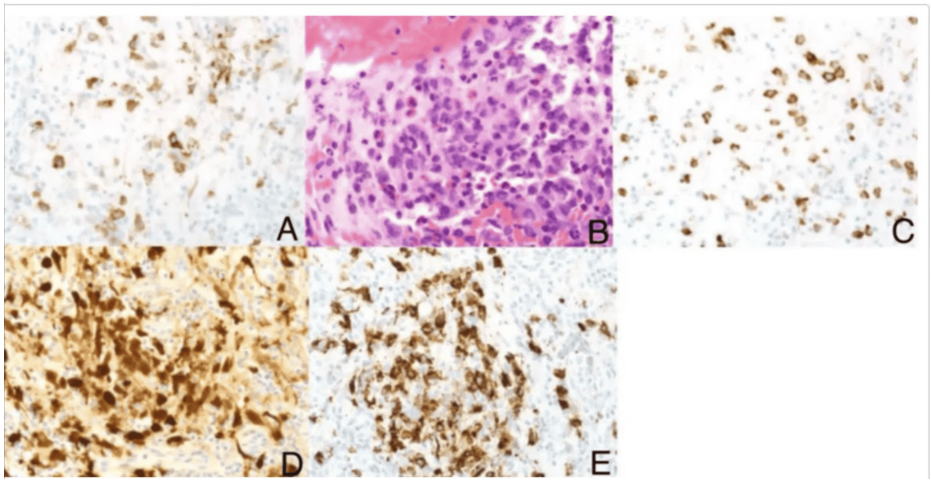


FIGURE 2: LCH: histopathological and immunohistochemical findings.

Histopathological and immunohistochemical findings of the biopsy specimen (original magnification, ×400). (A) CD1a immunostain (clone EP3622, Cell Marque) showing positive cytoplasmic staining in Langerhans cells. (B) Hematoxylin and eosin stain showing a group of Langerhans cell histiocytes with reniform nuclei and nuclear grooves within a background inflammatory infiltrate containing numerous eosinophils. (C) BRAF immunostain (clone VE1, Ventana) showing positive staining in Langerhans cells, indicating a V600E mutation. (D) S100 immunostain (polyclonal, Ventana) showing strong nuclear and cytoplasmic staining. (E) Langerin (CD207) immunostain (clone 12D6, Cell Marque) showing positive staining in Langerhans cells.

LCH, Langerhans cell histiocytosis

Postoperatively, the patient recovered with an intact baseline neurologic examination and a decrease in tumor size (Figure *1*). Postoperative MRI in May 2025 demonstrated a residual mass measuring 9 × 9 × 7 mm. Postoperatively, the patient's serum sodium ranged from 145 to 146 mEq/L, and she remained on an unchanged desmopressin dose of 60 mcg. She continues to receive follow-up care from endocrinology at her local hospital.

One month later, the hematology department started the patient on vemurafenib at a dose of 480 mg (two tablets) orally every 12 hours; no radiation therapy was administered. After one year of therapy, the dosing

regimen was changed to an intermittent schedule of one week on and one week off, which the patient continues at the time of this report. Given the known risk of QT prolongation with BRAF inhibitors, the patient underwent regular cardiac monitoring. During treatment, the patient developed acute kidney injury and multiple new moles on her face, arms, and right foot; however, a definitive causal relationship with vemurafenib could not be established. Follow-up MRI at one year (November 2025) demonstrated stable nodular enhancement in the hypothalamic-chiasmatic region, consistent with residual disease rather than recurrence. The patient has remained under neurosurgical follow-up for nearly two years and continues to be monitored.

Discussion

LCH is a rare myeloid neoplastic disorder caused by clonal expansion of myeloid precursors, leading to a spectrum of disease that can affect many organs [1,2,9-11]. The incidence of LCH reaches up to 8.9 cases per million children younger than 15 years per year, with a median age of three years. LCH is rare in adults, with an estimated incidence of one to two cases per million [11,12].

Several theories have been proposed regarding the cause of LCH. One involves the clonal expansion of CD1a+/CD207+ myeloid hematopoietic progenitors in the bone marrow, followed by differentiation into monocytes and their circulation as Langerhans cells. LCH mainly affects the MAPK signaling pathway [2]. BRAF mutations such as V600E are found in approximately 40-70% of cases, whereas MAP2K1 mutations occur in BRAF-negative cases [13].

The presentation of LCH varies widely, as it may affect various organs, including osseous structures, skin, lymph nodes, and visceral organs such as the lungs, liver, and spleen [11]. Endocrine involvement commonly presents as diabetes insipidus [9]. CNS manifestations of LCH include polyuria, polydipsia, headache, gait disturbance or ataxia, visual impairment, nausea and/or vomiting, and seizures [4,5]. Fever can occasionally occur in patients with LCH; however, its significance is unclear [14].

The diagnosis of LCH is challenging because the disease can affect any organ, and specific tests are selected according to the organ involved. Therefore, a high index of suspicion is required when such clinical features are present. The diagnostic evaluation of LCH includes laboratory studies, imaging, and other tests [6]. Despite clinical investigations, laboratory studies, and imaging, LCH is confirmed primarily through tissue biopsy, based on histological and immunophenotypic examination of lesional tissue obtained from the most accessible and representative lesion [6]. MRI is the most useful diagnostic tool for LCH with CNS involvement [7,8,15-17].

Treatment of LCH initially depends on whether the disease is single-system or multisystem and whether it involves low-risk or high-risk organs (e.g., bone marrow, liver, and spleen) [18]. Management of CNS LCH varies among patients, and there is no consensus on treatment; new treatments are being evaluated in clinical trials. Current treatment options include surgical resection, radiation therapy, and chemotherapy [18]. The prognosis of LCH is poor when diagnosis occurs after 60 years of age, in patients with chemotherapy resistance, and in the presence of cell-free BRAF V600E in plasma [19].

Conclusions

The clinical presentation of CNS LCH can include unexpected features, such as fever of unknown origin and diabetes insipidus. Fever of unknown origin, in particular, is a deceptive presentation that may be overlooked, delay diagnosis, or lead to an incorrect diagnosis and treatment. Therefore, a high index of suspicion is required to prevent further complications.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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