

Adult-Onset Langerhans Cell Histiocytosis With Calvarial and Hypothalamic Involvement: Two Cases

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Langerhans cell histiocytosis (LCH) is a rare clonal proliferative disorder of bone marrow-derived dendritic cells that is uncommon in adults. Its clinical presentation varies depending on the organ involved. Central nervous system (CNS) involvement poses a critical therapeutic challenge because of permanent neurological dysfunction. Here, we report two contrasting cases of adult-onset LCH with distinct clinical outcomes.

Case 1 involved a 36-year-old woman presenting with a persistent headache. Neuroimaging revealed a solitary osteolytic lesion in the left parietal bone with dural thickening. Surgical resection was performed, and histopathological examination revealed characteristic Langerhans cells with positive S-100 immunostaining, confirming the diagnosis of LCH limited to the calvarium. The patient was treated with bisphosphonates and remained stable without systemic involvement.

Case 2 involved a 26-year-old man presenting with cognitive impairment, somnolence, polyuria, and endocrine dysfunction. Magnetic resonance imaging revealed an enhancing hypothalamic lesion. Histopathological and immunohistochemical analyses confirmed LCH with CD1a and S-100 positivity. BRAF V600E mutation was not detected via pyrosequencing. Systemic chemotherapy with cladribine resulted in partial tumor regression; however, the cognitive dysfunction persisted.

These contrasting cases highlight that disease distribution, particularly CNS involvement, influences therapeutic strategies and neurological outcomes in adult LCH. Our findings emphasize that early diagnosis and proactive systemic evaluation are essential as functional recovery remains limited once neurological damage occurs, even with successful cytoreductive therapy.

Key words: Langerhans cell histiocytosis, Central nervous system, Hypothalamus

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disorder characterized by clonal proliferation of bone marrow-derived dendritic cells. Adult-onset LCH is uncommon with heterogeneous clinical manifestations depending on the organs involved. Central nervous system (CNS) involvement is important as it may cause cognitive impairment and endocrine dysfunction, leading to irreversible neurological sequelae if the diagnosis is delayed. Here, we report two adult cases of LCH with contrasting clinical presentations to highlight the importance of the early recognition of CNS involvement and comprehensive systemic evaluation.

CASE PRESENTATION

[Case 1] A 36-year-old woman

[Chief Complaint] Headache

[Present Illness] The patient initially visited a local clinic complaining of headache, and was diagnosed with tension-type headache and migraine. Despite treatment with oral medication, symptoms did not improve. Brain magnetic resonance imaging (MRI) revealed dural thickening and an intraosseous lesion

in the left parietal region. Based on these findings, LCH was suspected and the patient was referred to our department for further evaluation.

[Past Medical History] Wolff–Parkinson–White syndrome

[Medication and Social History] The patient did not take any regular medication and reported no smoking or alcohol consumption.

[Clinical Findings on Admission] The patient was fully alert with a Japan Coma Scale score of 0. Physical examination revealed mild tenderness in the left parietal region. The patient reported no headache or nausea at the time of evaluation. Neurological examinations revealed no focal deficits. Functional assessment revealed a modified Rankin Scale (mRS) score of 0 and Karnofsky Performance Status (KPS) score of 100.

[Laboratory Findings] Laboratory tests revealed mild inflammatory changes, anemia, and elevated serum immunoglobulin G (IgG) levels. Other routine biochemical parameters were normal.

[Imaging Findings] Non-contrast head computed tomography (CT) demonstrated an osteolytic lesion in the left parietal bone. Contrast-enhanced MRI revealed

enhancement corresponding to the bone lesion, with dural thickening. In addition, FDG-PET/CT showed no abnormal uptake in the trunk but demonstrated focal uptake corresponding to the osteolytic lesion in the skull (Fig. 1).

[Intraoperative Findings] Surgery revealed a reddish, hypervascular lesion in the left parietal bone (Fig. 1). The lesions comprised soft tissues and osseous components. The dura mater showed increased vascularity without direct tumor invasion.

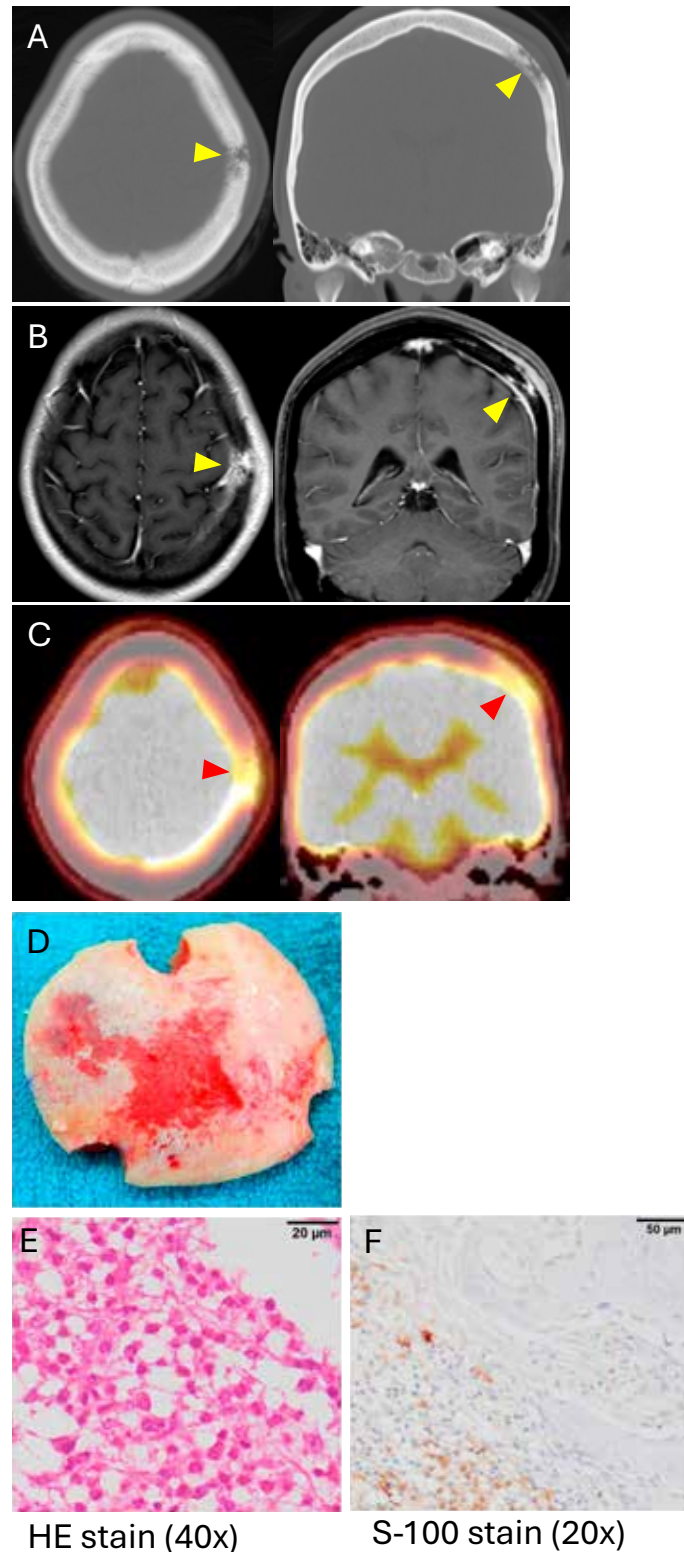


Fig. 1 Case 1 (36-year-old female)

A. Head CT revealed osteolytic changes in the left parietal bone (arrow head). B. Head MRI showed contrast enhancement and dural thickening corresponding to the osteolytic lesions seen on CT (arrow head). C. PET-CT showed no uptake in the trunk but demonstrated uptake corresponding to the osteolytic lesion (arrow head). D. The bone lesion appeared reddish and hypervascular, with mixed soft and osseous components. E. H&E sections revealed cells with horseshoe-shaped nuclei. F. The tumor cells were immunoreactive for S-100, but CD1a staining was uninterpretable.

[Pathological Findings] Histopathological examination with hematoxylin and eosin (H&E) staining revealed characteristic Langerhans cells with grooved coffee bean-shaped nuclei. Immunohistochemical analysis showed positive staining for the S-100 protein. In this case, CD1a expression was not evaluated (Fig. 1).

[Additional Examinations] Bone marrow biopsy revealed no abnormalities.

[Diagnosis] Based on clinical, radiological, and pathological findings, the patient was diagnosed with cranial LCH, which was classified as single-system LCH (SS-LCH) according to the WHO classification.

[Treatment and Clinical Course] The patient received bisphosphonate therapy for pain and oral iron supplementation for anemia. Her clinical symptoms improved with no evidence of systemic disease progression during follow-up.

[Case 2] A 26-year-old man presented with cognitive impairment and systemic symptoms.

[Chief Complaint] Cognitive impairment and nausea

[History of Present Illness] The patient presented to a local internal medicine clinic complaining of memory disturbance, general fatigue, and nausea. The patient was treated with oral iron supplementation for anemia, but symptoms did not improve. Subsequently, brain MRI revealed an intracranial lesion in the hypothalamic region, and the patient was referred to our department for further evaluation.

[Past Medical History and Social History] The patient had infectious mononucleosis, mumps, and a right ankle fracture. Oral iron and folic acid were administered. He smoked 4–6 cigarettes per day and occasionally consumed alcohol.

[Clinical Findings on Admission] The patient was drowsy with a Japan Coma Scale score of 2. His body temperature was 37°C, indicating low-grade fever. The patient had nausea and fatigue without headaches. Polyuria and pica were observed. Physical examination revealed sparse body hair, with loss of pubic and axillary hair.

Neurological examination revealed disorientation and somnolence, without focal motor deficits. Cognitive assessment using the Mini-Mental State Examination revealed a score of 23/30, with impaired orientation to time and place and delayed recall. The Trail Making Test–Japanese version (TMT-J) result was borderline. Functional assessment showed an mRS score of 2 and KPS score of 70.

[Laboratory Findings] Laboratory and endocrinological findings on admission are summarized in Table 1. The results indicated anemia, hypernatremia, mild renal dysfunction, pan-hypopituitarism, and central diabetes insipidus (Table 1).

[Imaging Findings] Contrast-enhanced MRI revealed a 20-mm enhancing lesion extending from the hypothalamus to interpeduncular cistern. Whole-body CT showed hepatosplenomegaly (Fig. 2). Bone scintigraphy showed no abnormal uptake.

[Intraoperative Findings] Under general anesthesia, the head was secured using a four-pin fixation system. A Leksell frame-based stereotactic biopsy targeted the lesion to avoid vascular injury. Multiple tissue samples were collected. Intraoperative frozen section analysis confirmed the presence of tumor tissue. No complica-

Table 1 Laboratory findings of Case 2 on admission
Laboratory data demonstrated pancytopenia, mild renal dysfunction, electrolyte imbalance, and panhypopituitarism.

Hematology		
WBC	3,600	/ μ L
RBC	3.47×10^6	/ μ L
Hemoglobin	8.1	g/dL
Hematocrit	27.7	%
PC	10.8×10^4	/ μ L
Biochemistry		
Total protein	7.2	g/dL
Albumin	3.8	g/dL
AST	46	U/L
ALT	25	U/L
γ -GTP	60	U/L
LDH	189	U/L
ALP	74	U/L
BUN	8	mg/dL
Creatinine	1.35	mg/dL
Uric acid	5.0	mg/dL
Glucose	89	mg/dL
Sodium	146	mEq/L
Potassium	3.1	mEq/L
Chloride	110	mEq/L
Calcium	8.9	mg/dL
Total bilirubin	1.1	mg/dL
CRP	0.29	mg/dL
Serum iron	36	μ g/dL
Serum ferritin	127	ng/ml
Endocrinological findings		
GH	0.08	ng/mL
PRL	39.5	ng/mL
ACTH	11	pg/mL
LH	< 2.0	mIU/mL
FSH	1.0	mIU/mL
AVP	0.5	pg/mL
TSH	5.11	μ IU/mL
Free T3	2.16	pg/mL
Free T4	0.53	ng/mL
Cortisol	2.18	μ g/dL
Testosterone	< 0.03	ng/mL

WBC, white blood cell; RBC, red blood cell; PC, Platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CRP, C-reactive protein; GH, growth hormone; PRL, prolactin; AVP, arginine vasopressin.

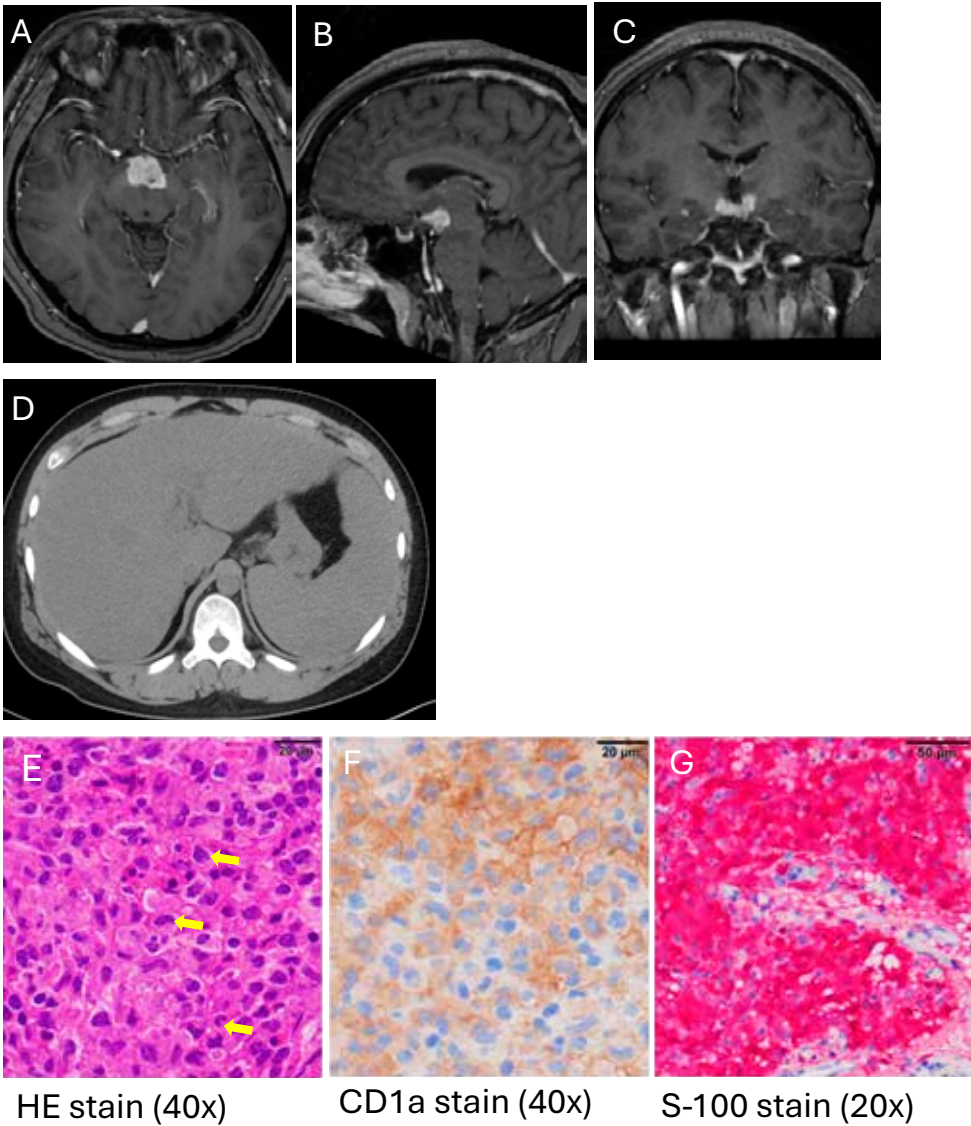


Fig. 2 Case 2 (26-year-old male)
A. (axial) B. (sagittal) C. (coronal) Contrast-enhanced MRI showed a 20-mm contrast-enhancing lesion involving the hypothalamus and extending into the interpeduncular cistern. D. Chest and abdominal CT demonstrated enlargement of the liver and spleen. E. Hematoxylin and eosin staining revealed cells with characteristic horseshoe-shaped nuclei (arrow). F. G. Immunohistochemistry demonstrated positive staining for CD1a(F) and S-100(G).

Table 2 Summary of clinical characteristics of two patients with Langerhans cell histiocytosis

	Case 1 (36-year-old female)	Case 2 (26-year-old male)
Symptoms	Headache	Disorientation to time and place, progressive cognitive decline, low-grade fever, nausea, pica
Laboratory findings	Anemia	Leukopenia, anemia, hypopituitarism
Imaging findings	Osteolytic lesion of the skull; increased FDG uptake at the same site on FDG-PET	Contrast-enhancing lesion in the suprasellar region
Surgical/pathological findings	Elastic soft tumor of the skull; presence of Langerhans cells; immunohistochemistry: S-100 positive	Presence of Langerhans cells; immunohistochemistry: S-100 positive, CD1a positive, BRAF V600E negative
Diagnosis	LCH with bone involvement	LCH with central nervous system involvement
Classification	SS-LCH	Suspected MS-LCH*
Treatment	Bisphosphonate therapy for bone pain	Chemotherapy

* This case showed radiological hepatosplenomegaly, which indicated multisystem organ involvement. However, biopsy of liver could not reveal the evidence of LCH. Therefore, we concluded that this case as “suspected MS-LCH”.
LCH, Langerhans cell histiocytosis; FDG-PET, fluorodeoxyglucose positron emission tomography; SS-LCH, single-system LCH; MS-LCH, multi-system LCH.

tions or new neurological deficits occurred post-operatively.

[Pathological Findings] Histopathological examination revealed characteristic Langerhans cells with grooved nuclei on H&E staining. Immunohistochemical analysis revealed positivity for S-100 protein and CD1a (Fig. 2). Langerin (CD207) immunostaining was not performed because it was not available at our institution. Molecular analysis via pyrosequencing revealed wild-type BRAF.

[Additional Examinations] Bone marrow biopsy revealed no abnormalities. A liver biopsy showed no infiltration of Langerhans cells.

[Diagnosis] Anemia and hepatosplenomegaly suggested systemic distribution of Langerhans cells; however, biopsy of the liver and bone marrow showed no evidence of tumor cells, and the patient was diagnosed with LCH involving the CNS with endocrine dysfunction. Although clinical and radiological findings including hepatosplenomegaly and endocrine abnormalities, suggested possible multisystem involvement, histopathological evaluation of the liver and bone marrow did not demonstrate Langerhans cell infiltration. Therefore, a definitive diagnosis of multisystem-LCH could not be established and we classified this case as “suspected MS-LCH” clinically.

[Treatment and Clinical Course] The patient was referred to a specialized hospital and treated with systemic cladribine chemotherapy. After two cycles, a partial response was observed in the hypothalamic lesion on follow-up MRI, and anemia improved. Based on the anemia improvement, systemic LCH involvement was strongly suspected, although a previous biopsy showed no evidence of systemic involvement. Although follow-up MRI scan showed an obvious reduction in the hypothalamic mass lesion, cognitive dysfunction persisted. Supportive hormonal replacement therapy with desmopressin for central diabetes insipidus and levothyroxine and corticosteroids for anterior pituitary insufficiency was initiated. Iron supplementation was continued to manage anemia.

DISCUSSION

These cases demonstrate the broad clinical spectrum of adult-onset LCH, from isolated bone involvement to aggressive CNS disease. LCH is a rare clonal disorder of the dendritic cell lineage in adults, with varying clinical course depending on disease distribution [1, 2]. This report describes two adult patients with contrasting patterns of organ involvement and clinical outcomes, highlighting the importance of accurate disease stratification and early recognition of CNS involvement (Table 2). According to the WHO classification, Case 1 was categorized as single-system LCH, whereas Case 2 was categorized as multisystem LCH, which may explain the marked differences in clinical presentation and outcome.

In Case 1, the disease was confined to a solitary cranial lesion without systemic involvement. Consistent with previous reports, localized bone lesions can often be managed effectively with surgical resection and supportive therapy, including bisphosphonates for pain in the bone and stabilization of osteolytic activity [3–5]. This patient achieved favorable local control without recurrence, supporting surgical intervention in selected

cases of resectable skull lesions.

In contrast, Case 2 presented with a hypothalamic lesion with endocrine dysfunction and cognitive impairment. CNS involvement in LCH occurs in 15–20% of patients and carries risk of irreversible neurological dysfunction, such as diabetes insipidus, panhypopituitarism, and progressive neurodegeneration [1, 2, 6]. In this case, although systemic chemotherapy achieved radiological and systemic disease control, residual brain dysfunction persisted, emphasizing the limited reversibility of CNS damage [7, 8].

These contrasting clinical courses underscore that treatment strategies for adult LCH should be individualized based on the disease extent and organ involvement. Comprehensive systemic evaluation, including whole-body imaging and endocrine assessment, is essential when LCH is suspected, even in patients with isolated cranial lesions. Early diagnosis and prompt initiation of systemic therapy may be critical for preventing permanent neurological impairment in CNS-involved LCH.

CONCLUSION

Here, we report two adult cases of Langerhans cell histiocytosis with distinct clinical presentations and outcomes. Localized cranial disease shows a favorable course after surgery, whereas CNS-involved multisystem disease results in persistent neurological dysfunction despite systemic therapy. These cases highlight that the clinical phenotype of adult LCH strongly influences the therapeutic strategy and prognosis. When cranial or intracranial lesions suggestive of LCH are identified, a comprehensive systemic evaluation should precede definitive treatment. Early recognition of CNS involvement and timely therapeutic intervention are essential for minimizing irreversible neurological damage.

ETHICS STATEMENT

All patients in this manuscript provided informed consent for the publication of their clinical details.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest associated with this manuscript.

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