

Adult-onset Langerhans cell histiocytosis changing CNS lesion from pituitary to suprasellar extension

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Summary

Langerhans cell histiocytosis (LCH) is a rare disease characterized by the proliferation of abnormal Langerhans cells in various tissues and organs, including bone, skin, the lungs, and the pituitary gland. Hypothalamic–pituitary lesions in LCH often cause central diabetes insipidus (CDI), but the natural course of LCH in the CNS remains to be elucidated. In this study, we report an interesting case of altered LCH lesions in the CNS from the pituitary to the hypothalamus in a 45-year-old woman. She developed symptoms of polyuria and was diagnosed with CDI with lymphocytic hypophysitis due to an enlarged pituitary gland with stalk thickening shown on MRI. Short-term glucocorticoid therapy cured pituitary enlargement, but serum prolactin levels gradually increased. Six years later, the immunohistological findings of a skin biopsy revealed positive for leukocyte common antigen, S-100, and CD1a expression, indicating a diagnosis of LCH. MRI revealed a new lesion in the hypothalamus without pituitary involvement, likely due to LCH. Chemotherapy improved LCH lesions both in the skin and hypothalamus, but therapy was stopped on the patient's request. Although adult-onset LCH is rare, it should be considered as a differential diagnosis in cases of CDI as the primary disease. The clinical course in the present case indicated that LCH lesion was altered from pituitary to suprasellar extension; where such changes were observed, the possibility of LCH should be considered.

Learning points:

- Diagnosing the primary disease of CDI is challenging; therefore, careful observation is necessary in pathologically unknown cases.
- Enhanced MRI should be performed in cases with suspected hypothalamic lesions, such as elevated serum prolactin.
- Although adult-onset LCH is rare, it should be considered a differential diagnosis in cases of CDI as the primary disease.
- The direction of changing CNS lesion from pituitary to suprasellar extension might be a unique MRI finding in LCH.

Background

Central diabetes insipidus (CDI) is caused by various pathological conditions, such as tumorous, inflammatory, or infectious diseases (1). A pituitary biopsy is not always required if the diagnosis is unclear. This procedure is

useful in certain situations, in the hands of experienced neurosurgeons. However, patients prefer to avoid invasive tests; therefore, the examination may not be approved. Careful follow-up is necessary in pathologically



unknown cases, and a biopsy should be performed when symptomatic pituitary enlargement is observed during the clinical course (1).

Langerhans cell histiocytosis (LCH) is a rare disease characterized by the proliferation of abnormal Langerhans cells in multiple systems (2, 3). Because of its various clinical features, LCH can easily be misdiagnosed. The prevalence of LCH in the CNS ranges from 3.4 to 57% (2), and hypothalamic–pituitary lesions of LCH often cause CDI. MRI findings of LCH are not specific for differentiating it from other diseases of the CNS (4, 5, 6), and histological examinations are necessary to diagnose LCH in the CNS. Even if a biopsy is performed, it is sometimes difficult to correctly diagnose LCH because of the deep location of the pituitary gland, small biopsy specimen size, and modification of steroid treatment (7). Therefore, it is important to accumulate information on the various clinical courses of LCH in the CNS.

Here, we report an interesting case of a relapsing, remitting course of LCH. MRI showed pituitary enlargement at the onset, but a hypothalamic lesion without pituitary abnormality at the time of diagnosis, which indicated that the LCH lesion was altered from the pituitary to the hypothalamus.

Case presentation

A 45-year-old woman with no medical history presented with thirst and polyuria. At the medical clinic, her urine analysis revealed a low specific gravity, and her symptoms persisted. The patient was suspected of having diabetes insipidus and was admitted to our hospital.

Her body weight and BMI were 57.2 kg and 23.4 kg/m², respectively. Her systolic and diastolic blood pressures were 108 and 64 mmHg, respectively. She had regular menstrual cycles. The patient's urine volume was approximately 8.5 L/day. Complete blood count, liver function, renal function, and electrolyte levels were within the normal ranges. Laboratory findings revealed a low urine osmolarity (75 mOsm/kg). The serum arginine vasopressin level was 2.0 pg/mL, which did not respond to high serum osmolarity in the hypertonic saline loading test. Serum prolactin (PRL) levels were mildly elevated (35 ng/mL), and other anterior pituitary hormone levels were within the normal range (Table 1). PRL showed a high response (peak 141.6 ng/mL at 30 min) in the thyrotropin-releasing hormone loading test. Follicle-stimulating hormone showed a low and prolonged response (peak 8.4 mIU/mL at 90 min) in the luteinizing hormone-releasing hormone loading test, while growth hormone showed a low response (peak 9.7 ng/

Table 1 Endocrine data during clinical course.

	At CDI onset (Fig. 1A1-3)	At LCH diagnosis* (Fig. 1C-3)	Reference range
ACTH (pg/mL)	26.6	13.6	7.4–55.7
Cortisol (µg/dL)	13.8	6.63	7.07–19.6
TSH (µIU/mL)	0.65	0.08	0.61–4.23
FT3 (pg/mL)	3.32	2.04	2.4–4.0
FT4 (ng/dL)	1.36	0.99	0.94–1.60
LH (mIU/mL)	4.9	<0.1	1.76–10.24**
FSH (mIU/mL)	3.8	0.59	3.01–14.72**
E2 (pg/mL)	133	<5.0	28.8–196.8**
GH (ng/mL)	0.53	0.42	0.13–9.88
IGF-I (ng/mL)	107	71	87–226
PRL (ng/mL)	35.0	139.4	6.1–30.5
ADH (pg/mL)	2.0	<0.4	<2.8

*Under prescription of desmopressin 120 µg and levothyroxine 50 µg; **At the follicular phase.

CDI, central diabetes insipidus; LCH, Langerhans cell histiocytosis.

mL at 15 min) in the growth hormone-releasing peptide 2 loading test. MRI revealed an enlarged pituitary gland with stalk thickening and the disappearance of the high-intensity signal in the posterior pituitary (Fig. 1A1, A2 and A3). Serum immunoglobulin G4 (IgG4) level was normal, rabphilin-3A antibody was negative, and no abnormalities were detected, indicating possible tumorous (human chorionic gonadotropin β, alpha-fetoprotein, and soluble interleukin 2 receptor), granulomatous (angiotensin-converting enzyme and lysozyme), autoimmune (perinuclear and cytoplasmic anti-neutrophil antibody), or infectious diseases (tuberculosis-specific interferon γ and β-D glucan). CT of the chest and abdomen revealed no abnormalities. Based on these findings, the patient was diagnosed with CDI, with lymphocytic hypophysitis as the likely cause. We recommended a pituitary biopsy for a definitive diagnosis; however, the patient refused it.

Investigation and treatment

Desmopressin treatment was initiated, followed by amelioration of polyuria. Short-term glucocorticoid therapy, starting with prednisolone (30 mg), tapered and stopped within a total of 3.5 months, was subsequently initiated for hypophysitis treatment. An improvement in the enlarged pituitary was observed (Fig. 1B1, B2 and B3), indicating that the primary disease could be a glucocorticoid-responsive lesion, such as lymphocytic hypophysitis. After glucocorticoid discontinuation, the pituitary appeared normal in size on plain MRI every 6 months; however, the serum PRL levels gradually increased

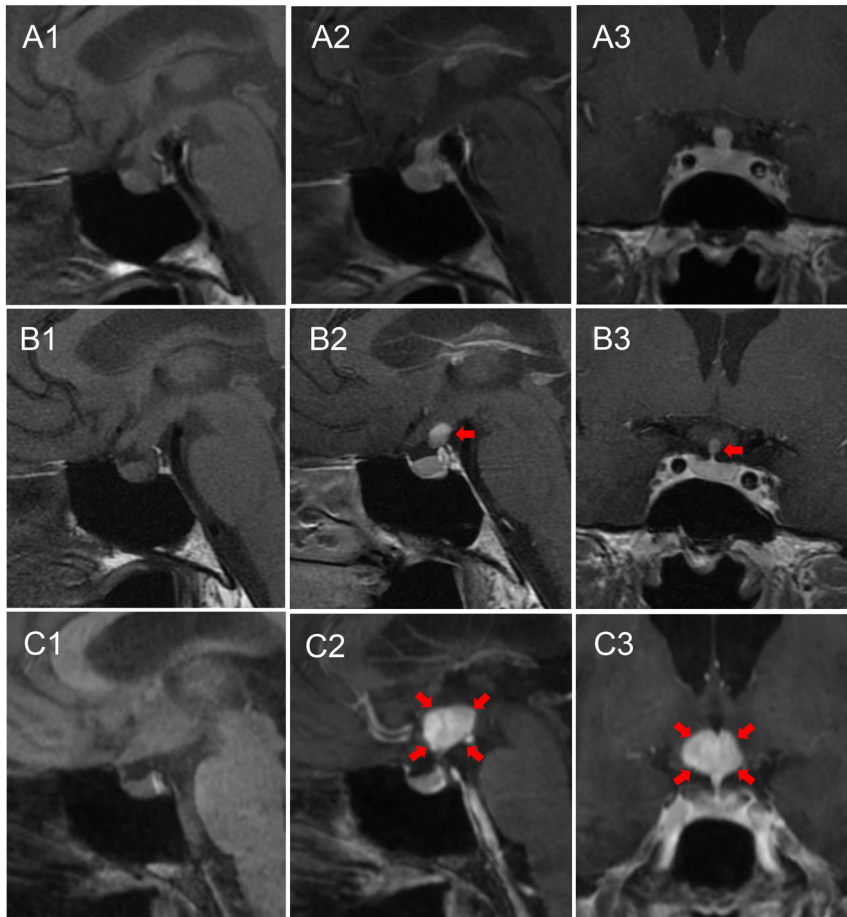


Figure 1

T₁-weighted MRI images in the sagittal (A1, B1, C1: plain, A2, B2, C2: gadolinium-enhanced) and coronal section (A3, B3, C3: gadolinium-enhanced). At the onset of central diabetes insipidus, an enlarged pituitary with stalk thickening is observed (A1, A2, and A3). Short-term glucocorticoid therapy ameliorated pituitary abnormality (B1, B2, and B3) with separated suprasellar enhanced lesion (arrow: B2 and B3). Six years later, the pituitary appears normal in size (C1, C2 and C3), and a new hypothalamic lesion has appeared (arrows: C2 and C3).

(Fig. 2). Secondary hypothyroidism and hypogonadism developed later, and thyroid hormone replacement therapy was initiated.

Six years later, the patient was admitted to our hospital with a fever. While the fever improved spontaneously, a skin biopsy was performed to examine the erythema of the vulva, and an immunohistochemical examination showed positive leukocyte common antigen, S-100, and CD1a expression (Fig. 3). Ki67 positive cells were 25–33% and *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) V600E mutation was negative. Therefore, the patient was diagnosed as having LCH. The serum PRL level was 139.4 ng/mL, and a panhypopituitarism tendency was observed (Table 1). Desmopressin and levothyroxine were prescribed continuously. Gadolinium-enhanced MRI revealed a new lesion in the hypothalamus (Fig. 1C1, C2, and C3). Lymphocytic hypophysitis rarely extends to the hypothalamus, and the skin biopsy which was positive for LCH implies this is the likely cause of the hypothalamic lesion. 18F-fluorodeoxyglucose (FDG)-PET revealed abnormal FDG accumulation restricted in the hypothalamus and inguinal skin lesions (Fig. 4).

^{99m}Tc-hydroxymethylenediphosphonate scintigraphy indicated no LCH lesions in the systemic bone. Chemotherapy using vinblastine, methotrexate, mercaptopurine, and prednisolone cured the erythema of the vulva and resulted in the shrinking of the hypothalamic lesion; however, the treatment was discontinued on the patient's request (Fig. 2).

Outcome and follow-up

The patient exhibited short-term memory deficits probably due to neuroendocrine hypothalamic dysfunction. As a result, it became difficult for the patient to attend our hospital, and her care was transferred to a closer practitioner.

Discussion

LCH is caused by the clonal expansion of myeloid precursors that differentiate into CD1a⁺/CD207⁺ cells and can involve various tissues and organs, including the bone, skin, lungs, and the pituitary gland (2, 3). The incidence

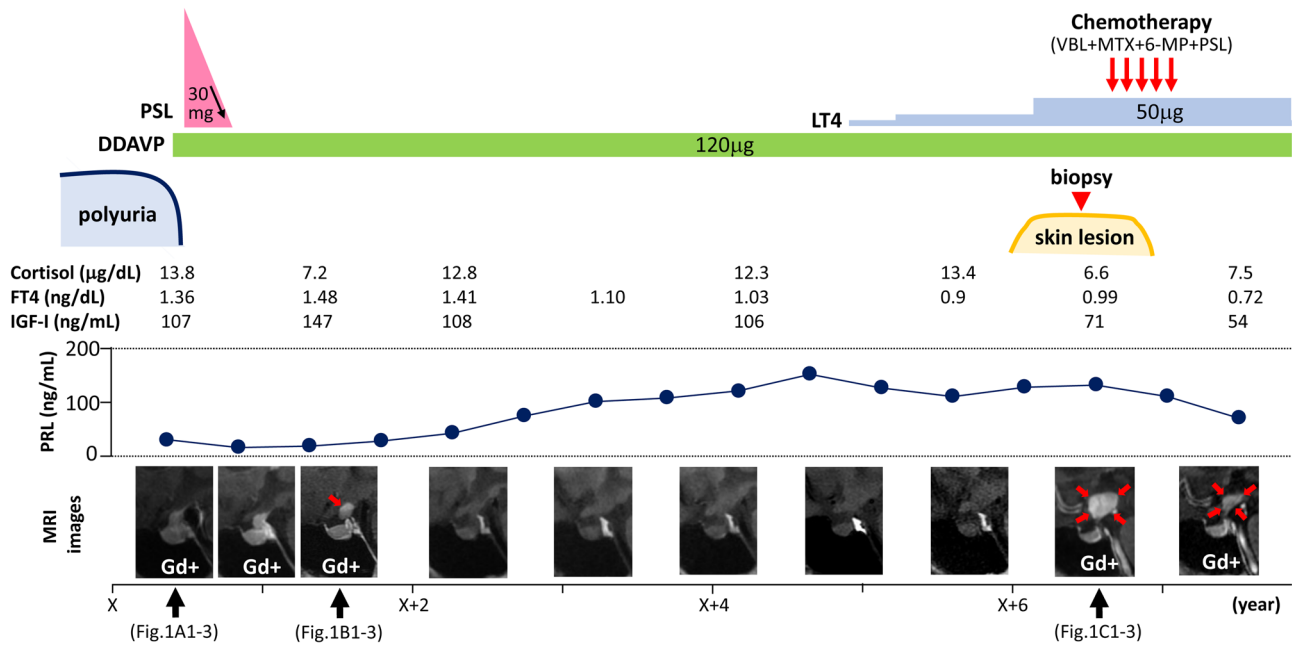


Figure 2

Clinical course of the present case with annually hypothalamic–pituitary imaging with gadolinium-enhanced (Gd+) or plain MRI in sagittal section. DDAVP cured polyuria and short-term PSL improved pituitary enlargement. Pituitary gland appeared normal from X+2 to X+6 years on plain MRI, but serum PRL levels elevated gradually. LT4 was started 4 years later due to secondary hypothyroidism. LCH was diagnosed by a skin biopsy 6 years later, and a new hypothalamic lesion appeared without pituitary involvement. Chemotherapy improved LCH lesions both in the skin and hypothalamus. PSL, prednisolone; DDAVP, desmopressin; LT4, levothyroxine; VBL, vinblastine; MTX, methotrexate; MP, mercaptopurine; PRL, prolactin.

of childhood LCH is 4.3 cases per million with a median age at diagnosis of 3.8 years old, and adult disseminated LCH is 0.07 cases per million (2); therefore, most clinical details of LCH are derived from studies in children. The clinical presentation of LCH varies from a single lesion to life-threatening dissemination. The classification is based on the site of lesions, the number of involved sites, and the involvement of at-risk organs (liver, spleen, or bone marrow) (2). In the present case, LCH involved a multisystem (CNS and skin) without at-risk organs. The immunohistochemical findings of the skin biopsy and

the entire clinical course indicated that LCH caused CNS lesions and pituitary dysfunction.

There are various differential diagnoses of primary diseases in CDI with pituitary enlargement, such as pituitary tumors (craniopharyngioma and germ cell tumor), inflammatory diseases (lymphocytic hypophysitis and IgG4 hypophysitis), granulomatous (sarcoidosis and granulomatosis with polyangitis), or infectious diseases (1). Recently, the rabphilin-3A antibody was found to be a useful marker for detecting lymphocytic infundibulo-neurohypophysitis (1), which was negative in the present

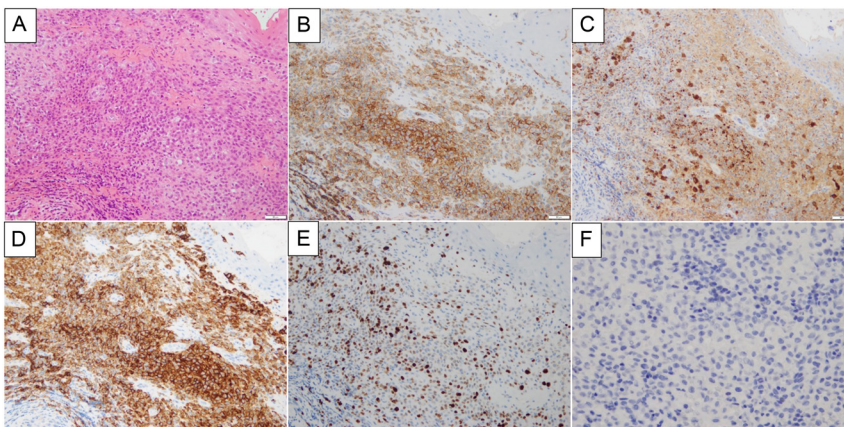


Figure 3

Pathological examinations of skin biopsy specimens for erythema of the vulva ((A): hematoxylin and eosin (HE) staining, (B, C, and D): immunohistochemical staining of leukocyte common antigen (B), S-100 (C), and CD1a (D)) are consistent with langerhans cell histiocytosis (LCH). Immunohistochemical findings show Ki67 positive cells are 25–33% (E) and *BRAF* V600E mutation is negative (F).

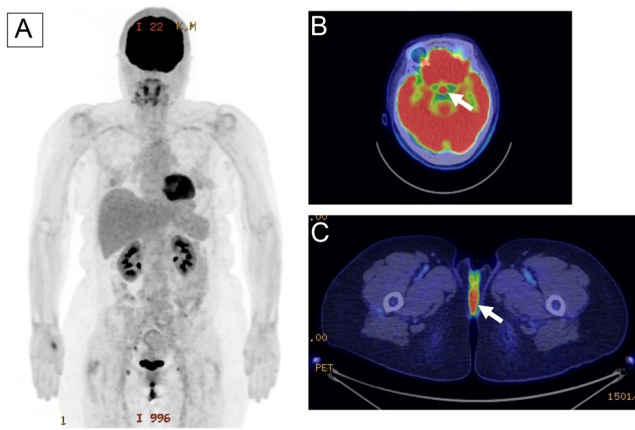


Figure 4
18F-fluorodeoxyglucose (FDG)-PET in the planner image (A) and axial section (B and C) indicate that LCH lesions are restricted in the hypothalamus and inguinal skin (arrow: B and C).

case. Although pituitary biopsy is useful for the diagnosis of these diseases, it can be avoided by patients because it is an invasive procedure. Although adult-onset LCH is rare, it should be considered as a differential diagnosis in cases of CDI as the primary disease, especially if there are other multisystem features.

CNS involvement in LCH can be divided into focal mass lesions and progressive neurodegenerative lesions (6). A focal mass was observed in the present case. The hypothalamic–pituitary axis is the most common LCH lesion in the CNS, frequently leading to CDI and anterior pituitary dysfunction, which require permanent hormone replacement therapy (4, 5, 6). In the present case, CDI appeared at the onset, and secondary hypogonadism and hypothyroidism occurred at later stages. Because pituitary enlargement was cured after short-term glucocorticoid therapy, the pituitary lesion was followed up with plain MRI in the present case; however, gadolinium-enhanced MRI should have been confirmed at an earlier phase. It is difficult

to detect hypothalamic lesions using plain MRI, and enhanced MRI should be performed in cases with suspected hypothalamic lesions, such as elevated serum PRL.

Although glucocorticoid administration reduced the initial pituitary lesion, the hypothalamic lesion gradually spread and was detected on gadolinium-enhanced MRI (Figs 1 and 2). LCH cases with spontaneous regression have been observed in some cases; however, relapse frequently occurs during long-term observation (8). Interestingly, the LCH lesion was altered from the pituitary to the hypothalamus in the present case. Similar cases have been previously reported, and the courses of MRI findings indicate that the LCH lesion was altered from pituitary or hypothalamus to suprasellar extension (Table 2) (5, 7, 9, 10). We could not find LCH lesions that extended in a reverse manner (from the hypothalamus to the pituitary) in the literature. Therefore, the direction from the pituitary to the suprasellar extension might be a unique MRI finding in LCH. Since hypothalamic–pituitary LCH prefers to form neurohypophyseal lesions and presents with CDI, it is tempting to speculate that these MRI findings might be caused by retrograde neurohypophyseal extension of LCH. It is also possible that pituitary lesions are more treatment-responsive than hypothalamic lesions. In the literature search, there are few cases that present serial MRI courses of LCH, and an accumulation of hypothalamic–pituitary LCH cases is necessary for the future to clarify this issue.

LCH patients with single-system disease restricted to a single site usually require only local therapy or observation, whereas those with more extensive disease require systemic therapy. Despite advances in the understanding of LCH pathogenesis, the current standard therapy for multifocal LCH remains empirically derived chemotherapy. In this case, standard chemotherapy improved LCH lesions in the skin and hypothalamus, but it was stopped according to the patient's request. Radiotherapy is considered an

Table 2 Summary of MRI findings in LCH similar to the present case.

No	Age	Sex	Endocrine dysfunction	Pre-treatment MRI findings	Treatment	Post-treatment MRI findings	Reference
1	N/A	N/A	N/A	Pituitary to hypothalamic lesion	Chemotherapy	Hypothalamic lesion	Grois <i>et al.</i> (5) case #12
2	50	F	CDI	Pituitary enlargement	Chemotherapy, radiosurgery	Hypothalamic lesion	Tan <i>et al.</i> (9)
3	44	F	CDI	Pituitary to hypothalamic lesion	Cabergoline	Hypothalamic lesion	Kono <i>et al.</i> (10)
4	28	F	CDI, Gnd, hPRL	Pituitary to hypothalamic lesion	Glucocorticoid	Hypothalamic lesion	Oda <i>et al.</i> (7) case #4
5	45	F	CDI, hPRL	Pituitary and stalk enlargement	Glucocorticoid	Hypothalamic lesion	Present case

CDI, central diabetes insipidus; F, female; Gnd, gonadotropin deficiency; hPRL, hyperprolactinemia; N/A, not applicable.



effective treatment option for LCH (3), although it was not selected in the present case. Mitogen-activated protein kinase pathway mutations and activated extracellular signal-regulated kinase have been identified in most LCH lesions (2), but the somatic *BRAF* V600E mutation was negative in the present immunohistochemical analysis. BRAF or mitogen-activated protein kinase inhibitors are used to treat relapsed and refractory LCH, but it remains uncertain whether these medications achieve a full cure (2).

In conclusion, although adult-onset LCH is rare, it should be considered a differential diagnosis in cases of central diabetes insipidus as the primary disease. The natural course of LCH in the CNS remains to be elucidated; therefore, the accumulation of various LCH cases is necessary. Altered CNS lesions from the pituitary to the hypothalamus were unique in the present case, where such changes were observed, the possibility of LCH should be considered.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

The patient has given written informed consent.

Author contribution statement

All authors were involved in patient care. Y Kadowaki and M Nakamura searched the literature. M Nishiyama was responsible for conceptualizing and drafting the manuscript. H Morisaka, S Fujimoto, Y Terada, and K Kojima reviewed and edited the manuscript.

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