Clinical Case Report

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Rapid exacerbation of lymphocytic infundibuloneurohypophysitis

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Abstract

Rationale: Lymphocytic hypophysitis is a relatively rare autoimmune disease defined by lymphocytic infiltration to the pituitary. Its rarity and wide spectrum of clinical manifestations make clarification of the pathology difficult. Here, we describe a case we examined from the primary diagnosis to final discharge, showing the serial progression of lymphocytic infundibuloneurohypophysitis (LINH) to panhypopituitarism with extrapituitary inflammatory invasion in a short period, and responding favorably to high-dose glucocorticoid treatment.

Patient concerns: Polyuria, General fatigue and Nausea/Vomiting.

Diagnoses: Central diabetes insipidus (CDI), Lymphocytic infundibuloneurohypophysitis (LINH).

Interventions: Desmopressin acetate, High-dose glucocorticoid (GC) treatment.

Outcomes: He was prescribed desmopressin acetate and subsequently discharged. A month later, he revisited our hospital with general fatigue and nausea/vomiting. A screening test disclosed hypopituitarism with adrenal insufficiency. MRI revealed expanded contrast enhancement to the peripheral extrapituitary lesion. He received high-dose GC treatment and the affected lesion exhibited marked improvement on MRI, along with the recovery of the anterior pituitary function.

Lessons: This case demonstrates the potential for classical LINH to develop into panhypopituitarsim. We consider this is the first documentation of approaching the cause of atypical LINH with progressive clinical course from the pathological viewpoint.

Abbreviations: GC = glucocorticoid, LINH = lymphocytic infundibuloneurohypophysitis.

Keywords: central diabetes insipidus, lymphocytic infundibuloneurohypophysitis, Rabphilin 3A

1. Introduction

Lymphocytic hypophysitis is classified into the subtypes of autoimmune hypophysitis that lymphocytes and plasma cells infiltrate into pituitary.[1] From involved lesions, they are classified to lymphocytic adenohypophysitis (LAH), lymphocytic infundibuloneurohypophysitis (LINH), and lymphocytic panhypophysitis (LPH). It has not been clarified whether these classified pathophysiologies are independent entities or overlapped each other. Classical manifestation of LINH is central diabetes inspidus and headache. The first-line therapy for LINH is not well established yet.

This time we experienced the unusual clinical course of LINH exhibited impairment of anterior pituitary function in short period. We considered this case to be significant in terms of sounding the alarm that close monitoring is recommended after the onset of LINH.

2. Case report

A 68-year-old Japanese male presented for the evaluation of polyuria and polydipsia lasting for 3 months. He had no significant medical history and was receiving no medication, including immunotherapy. He had no history of radiotherapy. His family and social histories were unremarkable. On physical examination, he showed mildly dehydrated skin. He did not complain of headache or visual field defect. Clinical laboratory data (Table 1) revealed sodium to be within the normal range (140 mEq/L), an undetectable serum AVP concentration, and unconcentrated urine osmolarity (199 mOsm/kg). T1-weighted MRI showed the absence of hyperintensity in the posterior lobe of the pituitary. Contrast-enhanced imaging revealed thickening of the infundibulum (4.88 mm) and delayed enhancement of the whole pituitary (Fig. 1A). Cystic components were not detected. As differential diagnosis, we considered IgG4-related disease, germinoma, malignant lymphoma, sarcoidosis, Wegener granulomatosis, Langerhans histiocytosis (LCH), fungal infection,

Editor: Suman Srinivasa.

Patient consent: Informed consent was obtained from the patient before the publication of this case report and accompanying images.

The authors report no conflicts of interest.

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Medicine (2017) 96:9(e6034)

Received: 17 September 2016 / Received in final form: 27 December 2016 / Accepted: 6 January 2017

http://dx.doi.org/10.1097/MD.0000000000006034

Table 1

Serial trends in blood counts and electrolytes at first-time admission, second-time admission, and 5 months after discharge.

	Normal range	First admission	Second admission	After GC treatment	Five mo after discharge
WBC, cells/μL	3200–9400	5140	7580	8680	7830
Eosinophil (%)	3.0–5.0	7	10	0.3	0.1
RBC, cell/μL	$3.34–5.29 \times 10^{12}$	4,810,000	4,720,000	4,470,000	5,460,000
Hb, g/dL	11.3–16.3	14.3	14.1	13.5	16.6
Hct (%)	32.7–48.7	42	40.1	38.8	48.3
Plt, cells/μL)	96–348	238,000	270,000	272,000	324,000
TP, g/dL	6.3–8.1	6.6	6.6	5.6	7
Alb, g/dL	3.9–5.1	4.1	4	3.5	4.2
T-bil, mg/dL	0.3–1.3	0.8	0.8	0.9	0.9
AST, IU/L	12.0–30.0	19	26	16	21
ALT, IU/L	10.0–42.0	22	34	27	17
γ-GTP, IU/L	9.0–54.0	30	46	32	27
Cre, mg/dL	0.65–1.06	0.74	0.69	0.69	0.77
BUN, mg/dL	8.0–22.0	10	15	15	17
Na, mEq/L	137–144	140	133	137	138
K, mEq/L	3.6–4.8	4	3.8	3.6	4.1
Cl, mEq/L	101–108	104	97	101	102

ALT = Aaanine transaminase, AST = aspartate transaminase, BUN = blood urea nitrogen, Cre = creatinin, γ-GTP = γ-glutamyltransferase, Plt = platelet, RBC = red blood cell, T-bil = total bilirubin, TP = total protein, WBC = white blood cell.

and tuberculosis. The following serum markers were measured, all of which were within their normal ranges: IgG/IgG4 (measured repeatedly), β human chorionic gonadotrophin, α-fetoprotein, soluble IL-2 receptor, glucose, C-peptide, and angiotensin-converting enzyme. Antipituitary antibody, antinuclear antibody, PR3-ANCA, antithyroid antibodies, anti-SS-A/B antibodies, and antiaquaporin 4 antibody were also measured, and all were found to be negative. Regarding infectious diseases, T-SPOT™ and β-D glucan were negative. Whole-trunk CT was performed to rule out the involvement of other endocrine organs,

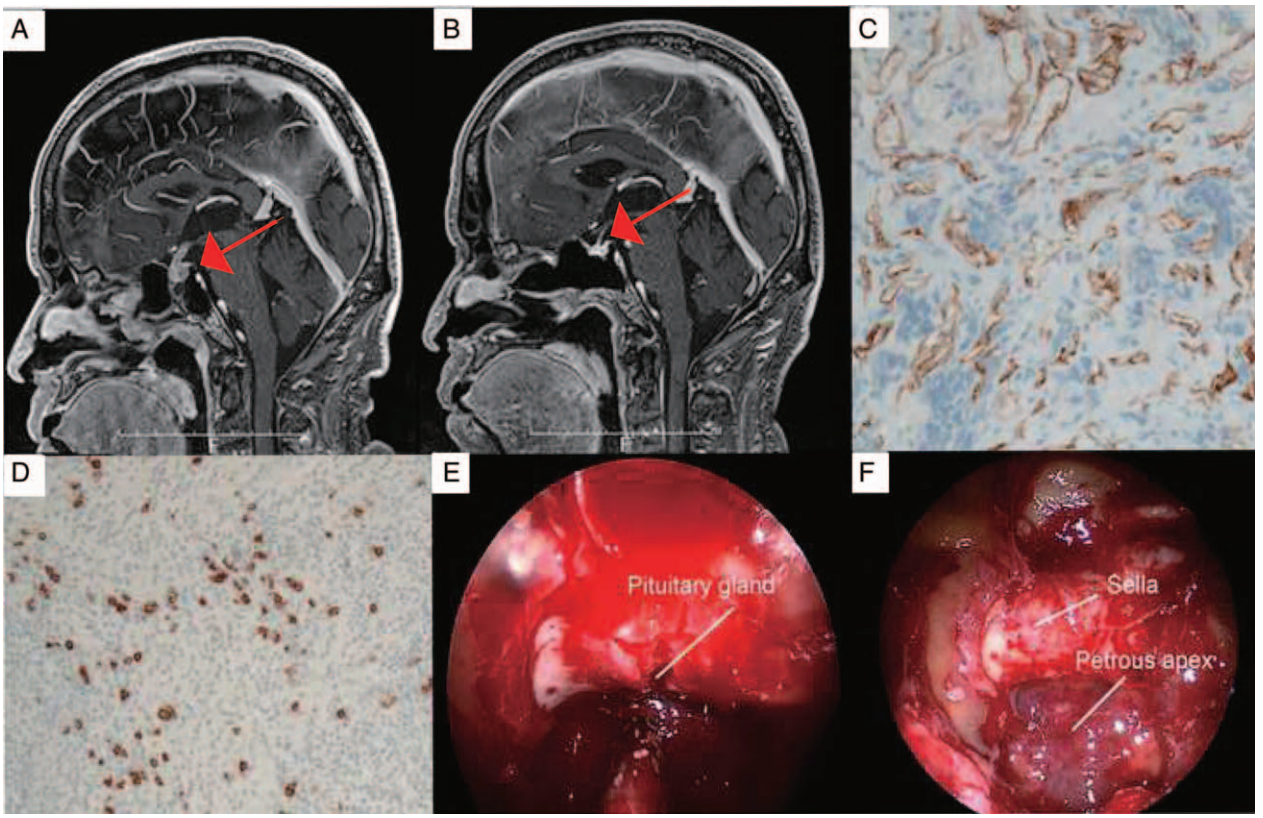

Figure 1. Representative images showing chronological changes in lymphocytic hypophysitis. Representative images of enhanced-contrast MRI. (A) At the time of the initial diagnosis. (B) After glucocorticoid treatment for 6 weeks. Arrowheads indicate pituitary lesion. (C–D) Pathological images of the petrous bone. (C) CD38 staining of tissue from the petrous bone. (D) IgG4 staining of tissue from the petrous bone. (E–F) Gross image of the affected lesion of the petrous bone during the operation.

Table 2

Test results of AVP tests (A) and 5% hypersaline loading test (B).

A

	0 min	30 min	60 min
Serum Osm, mOsm/kg H_2O	293	293	293
Urine Osm, mOsm/kg H_2O	366	432	470

B

	0 min	30 min	60 min	90 min	120 min	180 min
Serum Osm, mOsm/kg H_2O	291	297	302	305	311	316
Na, mEq/L	138	143	146	148	150	153
AVP, g/mL	1.3	1.3	1.3	1.3	1.6	0.9

AVP = arginine vasopressin.

and no morphological abnormality was detected. These findings established the possibility of clinical diagnosis of LINH. For additional confirmation, serum anti-Rabphilin 3A antibody, which was recently reported as a potential biomarker for the diagnosis of LINH,[1] was measured, and found to be positive.

For the definitive diagnosis, water deprivation test was considered at first. However, the patient exhibited the clinical manifestation of dehydration and strong thirsty on physical examination. Therefore, we concerned the progress of dehydration by water deprivation and decided to perform hypertonic (5%) saline administration test and AVH test instead for diagnosis of central DI. The principal purpose of administrating hypertonic saline is to observe AVP response by raising serum osmotic pressure, which is one of the major physiological stimulation in AVP secretion. An AVH test (IV 5U Pitressin) revealed an increase in urine osmolarity after administration (470 mOsm/kg) (Table 2A), whereas a low maximal AVP (1.6 pmol/L) with raised plasma osmolarity (311 mOsm/kg) was observed on 5% hypertonic saline infusion (0.05 mL/kg/min for 120 min) (Table 2B). These functional tests established the diagnosis of partial diabetes insipidus. To evaluate the effect on the anterior lobe function, stimulation tests were performed 2 days after taking MRI by administering corticotropin releasing hormone (CRH) (100 μg), gonadotropin releasing factor (GRF) (100 μg), thyroid stimulating hormone (TRH) (0.4 mg), and luteinizing hormone releasing hormone (LHRH) (0.1 mg) intravenously (Fig. 2). This stimulation tests are widely used in Japan for the evaluation of anterior pituitary function were performed by administering CRH (100 μg), GRF (100 μg), TRH (0.4 mg), and LHRH (0.1 mg) intravenously and serum growth hormone (GH), insulin-like growth factors 1, adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH), and cortisol were measured in 30, 60, 90, and 120 minutes. These tests detected no impairment in the response to the stimulation, as well as basic secretion. The patient was subsequently discharged with the prescription of oral desmopressin acetate (60 μg daily).

One month later, in the morning, he visited our outpatient clinic with the chief complaints of general fatigue, nausea/vomiting, and pain at the back of his left eye lasting for several days. On physical examination, he was normotensive (122/88 mmHg) with a sinus heart rate (71 bpm). He did not complain of a headache. No visual field defect was observed. Laboratory evaluation revealed elevated eosinophils, decreased cortisol (11:00 am: 0.5 μg/dL), combined with decreased basal values of pituitary hormones (decreased ACTH, TSH, FT4, testosterone, and LH), and elevated PRL. Acute adrenal insufficiency accompanied by panhypopituitarism was suspected, he was admitted to our hospital again, and we started fluid resuscitation and the administration of intravenous hydrocortisone (100 mg daily). Contrast-enhanced MRI demonstrated enlargement of the stalk and pituitary with homogenous contrast enhancement similarly to the previous MRI. Additionally, a suspicious new

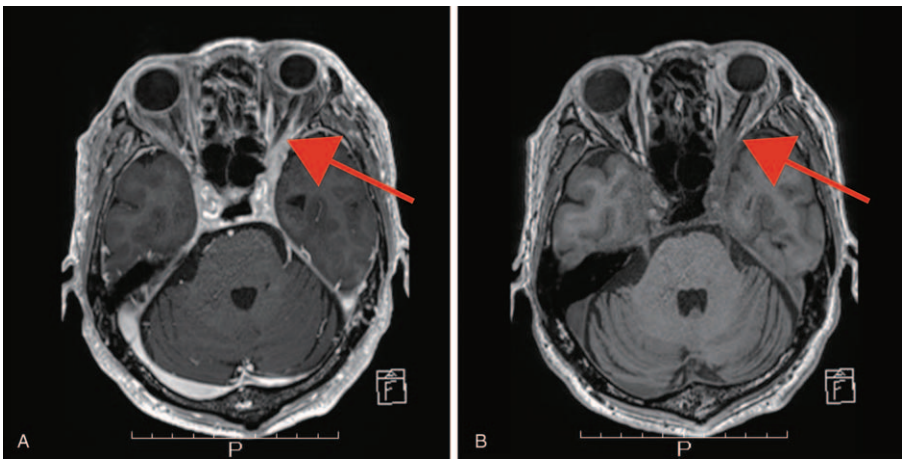

Figure 2. Transverse MRI images at second-time admission showing involved lesion in left optic canal (red arrowhead). (A) T1-weighted image. (B) T2-weighted image.

Table 3

Serial trends in baseline hormone values at baseline and 60 minutes after stimulation tests with CRH (100 μg), GRF (100 μg), TRH (0.4 mg), and LHRH (0.1 mg) at first- and second-time admission and baseline values of 5 months after discharge.

Baseline values	Normal range	First admission	Second admission	After GC treatment	Five mo after discharge
GH, ng/mL	<2.10	0.24	1.09	0.74	0.93
PRL, ng/mL	3.6–16.3	12.2	22.5	19.1	9
ACTH, pg/mL	7.2–63.3	27.2	6.4	10.8	14.5
LH, mIU/mL	1.7–8.6	6.1	1.3	6.4	3.5
FSH, mIU/mL	1.50–12.4	6.9	2	11.6	10.4
TSH, μIU/mL	0.5–5.0	1.04	0.267	3.16	1.15
Cortisol, μg/dL	5.0–15.0	9.8	0.5	4.1	15

60 min after stimulation	Normal range	First admission	Second admission	After GC treatment
GH, ng/mL	<2.10	3.65	9.76	3.58
PRL, ng/mL	3.6–16.3	24.8	29.3	28.6
ACTH, pg/mL	7.2–63.3	59.3	39.6	41
LH, mIU/mL	1.7–8.6	18.8	16.5	15.8
FSH, mIU/mL	1.50–12.4	12.1	5.6	15
TSH, μIU/mL	0.5–5.0	5.75	2.61	12.6
Cortisol, μg/dL	5.0–15.0	18.8	6	7.4

ACTH = adrenocorticotropic hormone, CRH = corticotropin releasing hormone, FSH = follicle stimulating hormone, GH = growth hormone, GRF = gonadotropin releasing factor, LH = luteinizing hormone, LHRH = luteinizing hormone releasing hormone, PRL = prolactin, TRH = thyroid stimulating hormone, TSH = thyroid stimulating hormone.

affected lesion appeared in the left optic canal, bilateral cavernous sinus, and right petrous bone (Fig. 2). Stimulation tests performed 1 day after MRI showed a preferential decrease in baseline values and reactions involving TSH, ACTH, and cortisol (Table 3).

To investigate the culprit lesion of hypopituitarism, we performed the insulin tolerance test (0.05 U/kg). There was an increase in ACTH and cortisol in response to hypoglycemia. Based on the results, a functional effect on the hypothalamus was deemed less likely. To verify the pathophysiological diagnosis, biopsy was performed with an endonasal endoscopic approach, and tissue was taken from the anterior lobe of the pituitary and right petrous bone with mucosa on its surface (Fig. 1E and F). The infiltration of lymphocyte-like cells was not observed in a sample from anterior pituitary (Fig. 1C). Immunohistochemistry showed CD38 negative in sample from anterior pituitary, except for perivascular physiologic accumulation. In sample from petrous bone, there was dense infiltration of $CD38^+$small lymphocytes. There were also small amount of infiltration of plasma cells (Fig. 1D). There was no increase in $IgG4^+$ cells (17%, 14/hpf) in the sample from the petrous bone (data not shown) or pituitary. PAS staining and Grocott staining were negative for both samples. The sample from the pituitary gland was examined by flow cytometry, showing no proliferative pattern of a specific lineage (data not shown).

As treatment, high-dose GC therapy (1 mg/kg/day of oral predonisolone) was initiated with a tapering course of 5 mg weekly. During the course of therapy, the patient did not present major side effects of GC. When the GC dose was reduced to 15 mg/day, tests to evaluate the curative effect were performed. MRI revealed size improvement and the normalized enhancement of the pituitary and involved lesion (Fig. 1B). There was no improvement in the loss of "bright spots" in the posterior lobe on T1-weighted imaging. Stimulation tests that were performed 3 days after MRI showed an improved TSH level and decreased PRL level. The patient was discharged with the prescription of desmopressin acetate (60 μg daily) and predonisolone (15 mg daily). Predonisolone has been gradually tapered and at 5 months after discharge it was reduced 8 mg daily. Baseline values of anterior pituitary hormones were examined, presenting the recovery of ACTH and further decrease of PRL (Table 3). At present, the patient has been seen in our outpatient clinic with close monitoring.

3. Discussion

Since Imura et al[3] described LINH as a new entity, which is an important cause of idiopathic CDI, there have been numerous reports of this entity in various clinical courses.[4] The definitive diagnosis of lymphocytic hypophysitis is made by biopsy,[5] but considering its invasiveness there are cases that are diagnosed by clinical manifestations. The typical clinical course of LINH includes selective effects on the posterior lobe of the pituitary and pituitary stalk.[6] On MRI, T1-weighed images reveal the absence of hyperintensity in the posterior lobe and thickening of the pituitary stalk. LINH constitutes the entity of lymphocytic hypophysitis, which is defined by autoimmune inflammatory process in pituitary. Lymphocytic hypophysitis is estimated to occur IN 1 in 9 million per year[7] and predominant in females in peripartum period[8] Although it is classified to LAH, LINH, and LPH based on the affected anatomical lesions, it has not been fully clarified whether these subtypes are relevant to each other or independent disease concepts. Some LINH cases are reported as a combination of hypopituitarism,[9] but chronological progression of these cases is not clear. Our case has significance not only because it presented anterior pituitary impairment 1 month after the onset of DI, but also we followed whole clinical course of LINH exacerbation with preforming pictorial and functional evaluations at all points in a single institution. Together with the positive result of anti-Rabphilin 3A antibody, this case provides indication about the onset mechanism and nature course of autoimmune hypophysitis. Overviewing through whole series of tests, on second-time admission, there was decrease of TSH, ACTH, and cortisol and elevation of PRL, suggesting the stalk compression and the existence of hypopituitarism. Subsequently after GC therapy, elevation of TSH and decrease of PRL were admitted and 5 months after discharge, ACTH level recovered. However, we could not tell prominent change as to GH, LH, and FSH. The reason that ACTH and cortisol had not changed after GC therapy compared with second-time admission would derive from the background that it was still under 15 mg daily GC

treatment. In support of this, 5 months after discharge, ACTH and cortisol had recovered under 8 mg GC treatment.

There are several points to mention regarding the present case. First, few previous studies traced the serial progression of LINH to panhypopituitarism in a single patient, performing functional and pictorial evaluation at all points. When functional impairment in the anterior lobe became prominent in the present patient, the enhanced lesion in the anterior lobe on MRI did not change from the primary admission. This suggests several scenarios regarding the onset of anterior lobe dysfunction. One is that the anterior lobe had already been affected by the first admission, and it was in the subsequent period that functional impairment became prominent. Another possible reason is that the anterior function was impaired because of mechanical compression of pituitary stalk and posterior lobe. Although the contrast effect in the anterior pituitary did not change between the first and second admissions, the maximum diameter of the stalk enlarged from 4.88 to 6.33 mm. In accord with the change, serum PRL was markedly elevated on second-time admission and decreased to normal range after stalk compression was released. However, reactions of anterior pituitary hormones in response to challenge test were preserved on second admission. Additionally, we could not observe apparent infiltration of lymphocytes in a sample from anterior pituitary, whereas massive infiltration was observed in a sample from petrous bone. Taken together, it is suggested that anterior pituitary dysfunction was triggered by mechanical pressure rather than direct inflammatory invasion from posterior pituitary. Although there have been several clinical case reports of supposed progression of LINH, we think this is the first case that the origin of LINH-combined anterior pituitary dysfunction was elucidated pathologically.

Second, the present patient was positive for anti-Rabphilin 3A antibody on the first admission. Rabphilin 3A is known to be involved with calcium-dependent exocytosis of secretory vesicles in neurons and endocrine cells,[10] and was recently reported to be a novel diagnostic marker of LINH. Considering that Rabphilin 3A is not detected in the anterior lobe,[2] this case may provide clues to investigate the origin of LPH.

Third, we did not choose GC therapy at the first admission based on the fact that its effect on LINH is still controversial.[11,12] Additionally, some studies have suggested that the proposed effect of GC is largely dependent on the timing of therapy.[11,13] In the present case, the diagnosis of LINH was made after 3 months when the patient first showed CDI symptoms, which led to our judgement that it was too late to start GC therapy. Considering that some hypophysitis cases show spontaneous recovery,[14] the contribution of GC therapy in this case requires further discussion.

4. Conclusion

Classical LINH presents with limited posterior lobe dysfunction. We could follow-up the outcome of progressive LINH by performing pictorial and functional evaluation continuously. Some LINH have potential of future progression to panhypopituitarsim and close monitoring of pituitary function is necessary after the onset of LINH. High-dose GC therapy is effective for case of LINH with involvement of extrapituitary lesion.

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