

A Case of Lymphocytic Infundibuloneurohypophysitis Showing Diabetes Insipidus Followed by Anterior Hypopituitarism Associated with Thrombasthenia

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Abstract. We report a case of a 42-year old male patient with diabetes insipidus followed by anterior hypopituitarism associated with thrombasthenia. The patient had been diagnosed with thrombasthenia since the age of 19. He was admitted and diagnosed as diabetes insipidus in 1995. Although T1-weighted image of magnetic resonance imaging (MRI) showed empty sella and partial pituitary stalk hypertrophy, the anterior pituitary functions were normal at that time. Three years later, he was re-admitted after an episode of general malaise and impotence in 1998. Endocrinological studies revealed adrenal insufficiency, hypothyroidism and hypogonadism. T1-weighted image of MRI demonstrated the thickening of pituitary stalk and neurohypophysis. Analysis of anti-pituitary antibodies by immunoblotting identified a major band at 61.5 kDa. The diabetes insipidus was controlled by desmopressin acetate and the shrinkage of pituitary stalk was seen after hormonal replacement therapy including glucocorticoid and thyroid hormone. We suggested that this case represented lymphocytic infundibuloneurohypophysitis, in which a chronic inflammatory process occurred in infundibulum and/or neurohypophysis and that hypopituitarism developed possibly due to damage to the pituitary portal vessels caused by a thickened pituitary stalk, although a pituitary biopsy was not done because of the risk of bleeding in thrombasthenia. The pituitary auto-antibodies in sera from patients with hypopituitarism may be helpful to characterize the patient with lymphocytic hypophysitis.

Key words: Anti-pituitary antibody, Diabetes insipidus, Hypopituitarism, Infundibuloneurohypophysitis, Thrombasthenia

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HYPOPITUITARISM is most commonly caused by pituitary adenomas or by other pituitary lesions such as cranial irradiation, head trauma and infection. However, in some patients other causes of pituitary dysfunction must be considered [1]. Lymphocytic hypophysitis is one of the causes of hypopituitarism, which is considered an autoimmune reaction in the anterior pituitary. Most cases occur in women, usually in relation to pregnancy [2]. The classical

presentation is an enlarged pituitary gland like a pituitary tumor in the early stage and the gland may atrophy in the later stages [3, 4]. Most patients with lymphocytic hypophysitis demonstrated either isolated or multiple anterior pituitary hormone(s) deficiency and ACTH and TSH secretion was thought to be impaired in 61.1% and 45.4%, respectively [2]. A few patients with lymphocytic hypophysitis who also had diabetes insipidus have been reported [5, 6]. Imura *et al.* have reported abnormal thickening of the pituitary stalk, enlargement of the neurohypophysis, or both on magnetic resonance imaging (MRI) in patients who had manifested idiopathic diabetes insipidus and postulated that this was possibly caused by lymphocytic

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infundibuloneurohypophysitis [7]. Since Saito *et al.* reported the first case of infundibuloneurohypophysitis in 1970 [8], there has been an increasing number of reports of infundibuloneurohypophysitis or infundibulohypophysitis manifesting anterior pituitary function disturbance [9–17]. In the present paper, we describe a male patient with diabetes insipidus associated with thrombasthenia. Three years after onset, he developed hypopituitarism. Lymphocytic hypophysitis, especially infundibuloneurohypophysitis was suggested to be the most probable cause of the pituitary disorder. In addition, we examined anti-pituitary antibodies using immunoblotting to confirm the autoimmune nature of this disease.

Case Report

A 42-year old man was admitted to our hospital complaining of thirst, polyuria and polydipsia in October 1995, suggesting diabetes insipidus. He had been diagnosed with thrombasthenia since the age of 19. He had not been on any medication except blood transfusion. He was diagnosed with central diabetes insipidus by laboratory tests (Table 1). Although T1-weighted image of magnetic resonance imaging (MRI) showed empty sella and partial pituitary stalk hypertrophy (Fig. 1), the anterior pituitary functions were normal (Fig. 2). After discharge, he was treated by desmopressin acetate. He was readmitted to our hospital after an episode of general malaise and impotence in December, 1998.

On physical examination, his blood pressure was 102/76 mmHg and pulse rate was 72/min, regular. Visual field and the acuity were normal, goiter was not palpable, and heart, lung and abdomen were normal. He had no axillary hair or effeminate pubic hair. Neurological examinations revealed no other

abnormalities.

Laboratory data on admission are shown in Table 2. Hematological data showed mild anemia (Hb: 12.4 g/dl). Bleeding time (Ivy) was 5.0 minutes (normal: 2–7 minutes) and activated partial thromboplastin time was 34.5 seconds (normal: 25.0–37.0 seconds). Serum transaminoferase level was slightly elevated (AST: 46 IU/L). Serum electrolyte levels were within normal limits. Serum LH, FSH, free T₃, free T₄, cortisol, testosterone, free testosterone, dihydroepiandrosterone (DHEA), androstenedione, urinary 17-OHCS, 17-KS and free cortisol were low, and serum prolactin was high. The levels of plasma ACTH and serum TSH were normal.

T1-weighted image of MRI demonstrated that the pituitary stalk and neurohypophysis had become markedly thicker, when compared to the MRI images from 1995 (Fig. 1).

The patient has been treated with testosterone depot (125 mg/2 week), glucocorticoid (30 mg of prednisolone/day) and levothyroxine sodium (50 µg/day). The impotence and general malaise started to improve. Plasma testosterone levels were increased to normal range. One month later, pituitary MRI demonstrated the shrinkage of pituitary stalk (maximal diameter change; from 10 mm to 8 mm).

Methods

Pituitary function tests

Provocative tests were performed on separate day as follows: A bolus injection of 500 µg of TRH, 100 µg of LHRH, 100 µg of GRH and 100 µg of CRH was performed simultaneously and multiple blood samples were collected to measure hormone concen-

Table 1. Endocrinological Findings on Admission (95/10)

Hypertonic Saline (5%, 10 min) Loading Test					
Time	0	10	20	30	min after saline
Plasma osmolality	293	302	305	300	mOsm/kg (275–295)
Na	144	145	147	147	mEq/L (135–147)
ADH	0.6	0.7	0.6	0.4	pg/ml (0.3–3.5)
Desmopressin Loading Test					
Time	0	1	2	3	hours after desmopressin
Urine osmolality	62	398	478	494	mOsm/kg (300–1250)

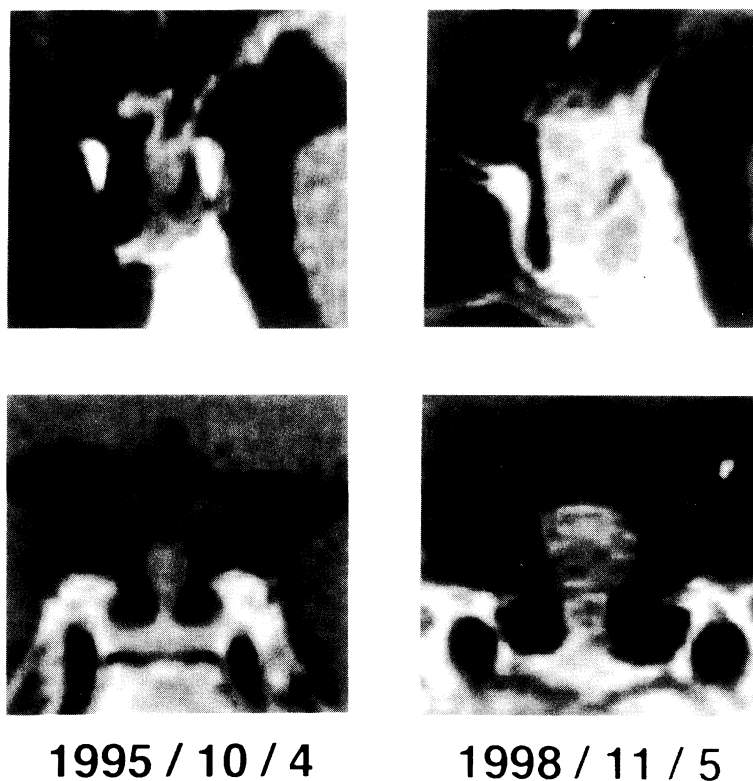


Fig. 1. Sagittal (upper panel) and coronal (lower panel) T1-weighted magnetic resonance imaging (MRI) findings. Note the marked enlargement (98/11/5) of pituitary stalk.

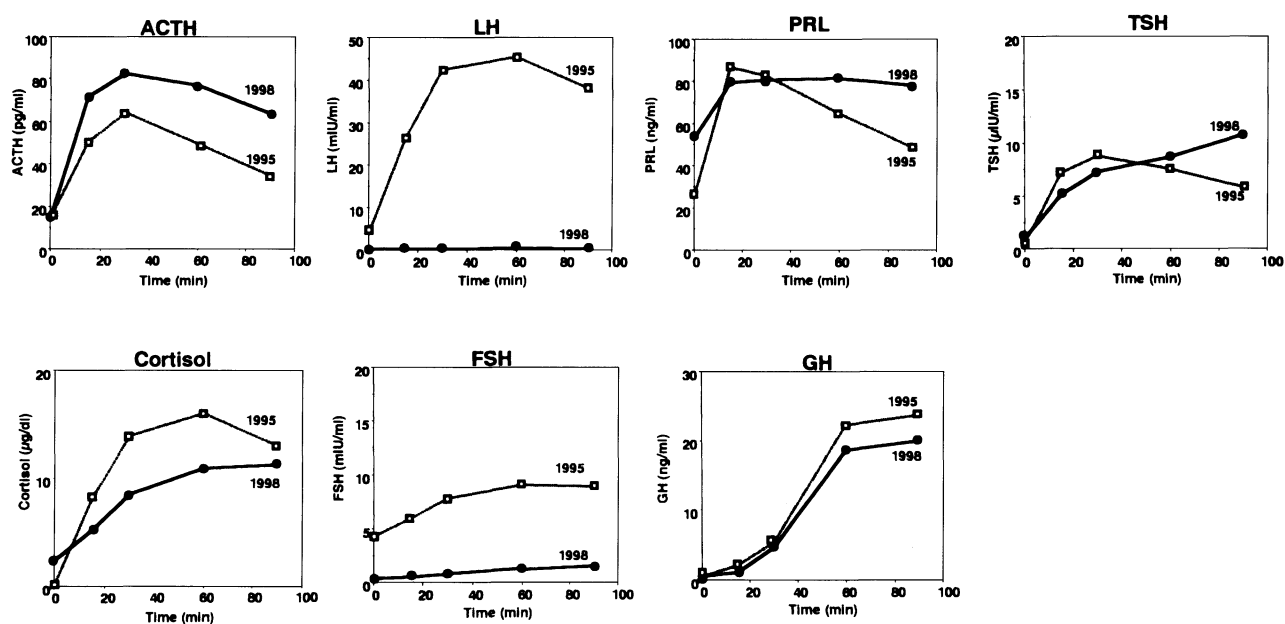


Fig. 2. Provocative tests of anterior pituitary functions. CRH (100 μ g), GRH (100 μ g), TRH (500 μ g) and LHRH (100 μ g) were injected intravenously as a bolus injection. Solid lines: 1998; broken lines: 1995.

Table 2. Laboratory Findings on Admission (98/12)

Peripheral blood		Endocrinological findings	
RBC	$418 \times 10^4/\mu\text{l}$	GH	0.56 ng/ml (<5)
Hb	12.4 g/dl	TSH	1.07 $\mu\text{U}/\text{ml}$ (0.34–3.5)
Ht	37.8%	LH	<0.25 mIU/ml (1.1–8.8)
WBC	5,100/ μl	FSH	0.40 mIU/ml (1.8–13.6)
Plt	$14.3 \times 10^4/\mu\text{l}$	PRL	53.4 ng/ml (0.1–26)
Blood Chemistry		ACTH	15.0 pg/ml (7.4–55.7)
TP	8.3 g/dl	Free T3	2.35 pg/ml (2.47–4.34)
Glucose	78 mg/dl	Free T4	0.57 ng/dl (1.0–2.1)
AlP	164 IU/L	Cortisol	2.4 $\mu\text{g}/\text{dl}$ (4.5–16.2)
T-bil	0.4 IU/L	Aldosterone	61 pg/ml (36–240)
ChE	297 IU/L	17-OHCS	1.8 mg/day (3.1–8.7)
ALT	26 IU/L	17-KS	1.3 mg/day (4.2–12.4)
AST	46 IU/L	Free cortisol	<10 $\mu\text{g}/\text{day}$ (35–160)
LDH	287 IU/L	Testosterone	88.0 ng/dl (410–1100)
CRN	0.7 mg/dl	Free testosterone	<0.5 pg/ml (18.0–42.0)
BUN	14 mg/dl	DHEA	1107 ng/ml (1300–5600)
Na	138 mEq/L	Androstendione	<0.10 ng/ml (0.99–2.68)
K	3.8 mEq/L	Others	
Cl	103 mEq/L	Anti-TPO Ab	0.2 U/ml (<0.3)
Ca	5.1 mEq/L	Anti-Tg Ab	<0.3 U/ml (<0.3)
P	2.2 mEq/L	ACE	14.7 IU/L (8.3–21.4)

trations before and for up to 90 min after injection. Repeated hormone loading test such as repeated LHRH test could not be performed because of patient's rejection. Plasma levels of ACTH, serum cortisol, LH, FSH, PRL, GH, TSH and testosterone were measured using commercially available kits. ACTH II IRMA kit was obtained from Mitsubishi Petrochemicals, Tokyo, Japan; EIA CORTISOL kit was purchased from Roche Diagnostic, Tokyo, Japan. GH and testosterone kits were from Eiken Chemical, Tokyo, Japan; and TSH RIA BEAD II and PRL RIA BEAD kits were purchased from Dynabot, Tokyo, Japan and the LH and FSH kits were obtained from Daiichi Radioisotope Laboratories, Tokyo, Japan.

Immunoblotting

Anti-pituitary antibodies were examined by immunoblot analysis as previously described by Crock *et al.* [18]. Briefly, normal human autopsy pituitary was homogenized in phosphate buffered saline with protease inhibitors (aprotinin, leupeptin, pepstatin and phenylmethylsulfonylfluoride) and centrifuged

at $400 \times g$ and then at $100,000 \times g$ to give cytosolic fraction. Pituitary cytosol preparations were fractionated on SDS-polyacrylamide gels by electrophoresis. The total protein loaded was constant at 50 $\mu\text{g}/\text{well}$. Separated proteins were transferred to polyvinylidene difluoride (PVDF) membranes and incubated with patients serum diluted 1 : 200 in TTBS solution (0.15 M NaCl/20 mM Tris-HCl, pH 7.6) overnight at 4°C. Reactivity to pituitary proteins was detected using biotin-conjugated goat antihuman IgG antiserum and a color reaction with ECL detection reagents (Amersham Pharmacia Biotech, Buckinghamshire, England).

Results

Pituitary function tests

The response of ACTH, cortisol, LH, FSH, PRL and TSH to hypothalamic hormones were normal in 1995. In contrast, the response of LH and FSH to LHRH was dramatically attenuated in 1998 compared with the responses in 1995 (Fig. 2). A

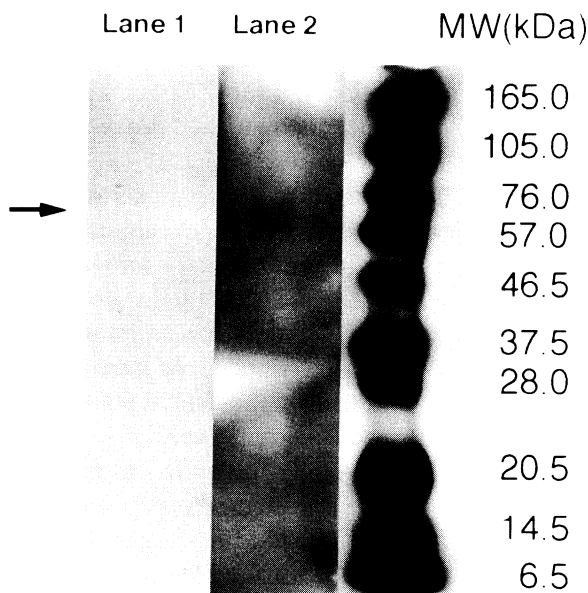


Fig. 3. Immunoblotting analysis of the patient's sera (1:200 dilution) with human pituitary antigens. Immunoblotting was performed as described in the Methods. Lane 1: normal subject serum, Lane 2: patient's serum (December 1998).

prolonged ACTH response and a blunted cortisol response to CRH was seen in 1998 compared with the responses in 1995. Furthermore, provocative tests demonstrated delayed GH and TSH response to hypothalamic hormones on both occasions. Basal PRL levels were high and it showed a delayed response to TRH in 1998.

Anti-pituitary antibodies

The result of anti-pituitary antibodies examined by immunoblot analysis are shown in Fig. 3. As shown in Fig. 3, no bands were seen in a control subject (Fig. 3, Lane 1). In contrast, a major band was identified at 61.5 kDa in the present patient (Fig. 3, Lane 2).

Discussion

The patient described above presented central diabetes insipidus and pituitary stalk swelling that was revealed by MRI, followed by an episode of hypopituitarism three years later. Neither pituitary surgery nor a pituitary biopsy was performed because

of thrombasthenia. The differential diagnosis of the pituitary lesion with panhypopituitarism includes pituitary adenoma, germinoma, granulomatous hypophysitis and lymphocytic hypophysitis [19, 20]. Pituitary adenoma was unlikely in this patient because such lesions are predominant in the pituitary stalk. Granulomatous hypophysitis may develop in patients with syphilis, tuberculosis, sarcoidosis and Langerhans' cell histiocytosis. However, a careful follow up and evaluation including serological tests, X-rays, and determination of tuberculin skin test and angiotensin converting enzyme did not reveal any sign of the above diseases. Suprasellar germinoma may be a candidate for this patient, however, it was unlikely as α -fetoprotein test was negative. Lymphocytic hypophysitis was the most probable diagnosis for this case, showing central diabetes insipidus followed by anterior pituitary dysfunction.

Lymphocytic hypophysitis most commonly occurs in the peri- or post-partum period [2]. Male patients are extremely rare and mild hyperprolactinemia is common [21–23]. Diabetes insipidus with lymphocytic hypophysitis may occur by direct inflammatory invasion from posterior lobe or destruction and/or compression of pituitary stalk [14]. In contrast, the term lymphocytic infundibuloneurohypophysitis has been coined by Imura *et al.* for the patients with diabetes insipidus and lymphocytic infiltration of the hypothalamic-neurohypophysial system [7]. Taken together the present history of preceding central diabetes insipidus followed by hypopituitarism in the patient and the MRI findings showing the thickening of the pituitary stalk but not in anterior pituitary gland, the proposed diagnosis is likely to be lymphocytic infundibuloneurohypophysitis rather than lymphocytic adenohypophysitis, and it is speculated that the hypopituitarism developed from the lesion of pituitary portal vessels. This speculation is the result of provocative tests showing the delayed response of ACTH, GH and TSH and the elevated PRL levels, although a pituitary biopsy was not done due to the risk of bleeding by thrombasthenia. The possibility that the pituitary gonadotroph was selectively lesioned by other mechanisms cannot be excluded because the response of LH and FSH to LHRH was dramatically attenuated compared with other pituitary hormones response.

The natural history of lymphocytic hypophysitis is variable, with some patients demonstrating spon-

taneous remission without therapy [24]. However, the majority of patients require active treatment, and supplemental therapy with glucocorticoid and/or thyroid hormone seems to reduce the mortality rate [2]. Impotence associated with a decreased libido has been the most common symptom found in male cases with lymphocytic hypophysitis [21, 23]. As the present case had severe impotence, testosterone as well as glucocorticoid and thyroid hormone has been replaced. Corticosteroid therapy has been advocated to reduce inflammation and has been effective in some patients [6, 25, 26], but in other reported instances, no benefit was achieved [27, 28]. In the present case, although pituitary hormone levels were not changed, glucocorticoid therapy seemed to be effective as shrinkage of the pituitary stalk was seen one month after the start of treatment. A recent study reported that corticosteroids administered in a case with lymphocytic hypophysitis revealing panhypopituitarism resulted in gradual recovery of all pituitary hormones, with MRI showing a reduction of two-thirds in pituitary mass [29]. However, five months after the end of corticoid treatment the patient relapsed with panhypopituitarism and increase of pituitary volume. Therefore, frequent follow-up MRI and hormonal examinations should be recommended even if pituitary recovery has been observed.

To date, in pituitary autoimmune diseases at least two target autoantigens, which are cytosolic proteins of 49 and 22 kDa, have been identified [1, 30–32]. The 49 kDa autoantigen might be related to ACTH deficiency from corticotroph destruction, which is the most frequent feature of lymphocytic hypophysitis [30]. In contrast, anti-GH antibodies identified a positive band with a molecular weight of 22 kDa, suggesting that anti-GH antibodies may be present in patients' sera [31]. In the present report, a 61.5 kDa cytosolic protein was identified as an autoantigen in

this patient. Although the reasons for the discrepancies among the results obtained from different laboratories are not known, the different sources of pituitary antigens and different methods utilized in immunoblotting may be responsible as we also observed a 20–22 kDa band in other patients with lymphocytic anterior hypophysitis or infundibuloneurohypophysitis using different pituitary antigens (unpublished observation). Further studies are needed to clarify the relationship between the pituitary antibodies and the genesis of lymphocytic hypophysitis.

It is well known that lymphocytic hypophysitis is often complicated with chronic thyroiditis. Moreover, lymphocytic hypophysitis may be associated with other disorders such as insulin dependent diabetes mellitus, adrenalitis, atrophic gastritis, pernicious anemia and lymphocytic parathyroiditis [2]. Very recent reports demonstrated cases complicated with Graves's disease and asymptomatic primary biliary cirrhosis [16, 32]. In the present report, the patient showed thrombasthenia. At least to our knowledge, this is the first case of lymphocytic infundibuloneurohypophysitis associated with thrombasthenia. The relation between lymphocytic infundibuloneurohypophysitis and thrombasthenia is unclear. However, in such a case because of the risks associated with the neurosurgical procedure, surgical intervention should be avoided whenever possible.

In summary, we report a case with diabetes insipidus followed by anterior hypopituitarism associated with thrombasthenia. Endocrinological studies revealed adrenal insufficiency, hypothyroidism and hypogonadism, and MRI findings demonstrated the thickening of pituitary stalk and neurohypophysis. Analysis of anti-pituitary antibodies by immunoblotting identified a major band at 61.5 kDa. We suggest that this case represents lymphocytic infundibuloneurohypophysitis.

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