

CASE REPORT

## Lymphocytic hypophysitis: Its expanding features

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**ABSTRACT.** Lymphocytic hypophysitis is classically defined as an inflammatory disorder confined to adenohypophysis. However, it has recently been indicated that infundibuloneurohypophysitis underlies some subsets of central diabetes insipidus (DI). Therefore, lymphocytic hypophysitis can be considered a syndrome including disorders of both the anterior pituitary (lymphocytic adenohypophysitis) and the posterior pituitary (lymphocytic infundibuloneurohypophysitis). We describe a 77-yr-old woman with lymphocytic hypophysitis presenting with headache, diplopia, general malaise and appetite loss. Head magnetic resonance imaging (MRI) demonstrated pituitary swelling and *dura mater* thickening on the *dorsum sella*. Endocrinological investigations revealed both anterior and posterior pituitary dysfunction associated with primary hypothyroidism

due to Hashimoto's thyroiditis. Headache and diplopia spontaneously disappeared, and anterior pituitary dysfunction, general malaise and appetite loss improved after taking 10 mg hydrocortisone daily, although ACTH hyposecretion persisted. Pituitary swelling was thereafter reduced but the *dura mater* thickening persisted. We suggest that this case may represent a variant of lymphocytic hypophysitis in which chronic inflammatory process involves both the anterior and the posterior pituitary gland, *infundibulum*, *dura mater* on the *dorsum sella* and cavernous sinus. Regarding expanding features of lymphocytic hypophysitis, it may be considered a syndrome including heterogeneous disorders, of which the pathogenesis remains to be elucidated. (J. Endocrinol. Invest. 24: 262-267, 2001)

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### INTRODUCTION

Lymphocytic hypophysitis is a relatively rare inflammatory disorder of the pituitary, which was first reported in a 22-yr-old woman by Goudie *et al.* in 1962 (1). Classically, lymphocytic hypophysitis has been considered to be confined to the anterior pituitary gland, and the terms lymphocytic hypophysitis and adenohypophysitis have been interchangeably used. It occurs mainly in women during late pregnancy and the post-partum period, with anterior pituitary swelling leading to hy-

popituitarism (2). There have been an increasing number of cases of lymphocytic hypophysitis because of the progress of magnetic resonance imaging (MRI) and of its better recognition among clinicians. It is now well recognized as a cause of hypopituitarism (2). On the other hand, Imura *et al.* (3) demonstrated that lymphocytic infundibuloneurohypophysitis is a cause of central diabetes insipidus (DI), in which the abnormal thickening of pituitary stalk and enlargement of the neurohypophysis were documented on MRI. However, there have recently been several reports of cases involving both adenohypophysitis and neurohypophysitis, some of which also involve other tissues surrounding the sella turcica (4-17). Here we report a case of lymphocytic hypophysitis presenting with ADH hyposecretion, diplopia and the thickened *dura mater* on the *dorsum sella*. The differential diagnosis from other disorders and the significance of atypical cases with lymphocytic hypophysitis, like the present case as a disease entity, will be discussed.

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*Key-words:* Lymphocytic hypophysitis, hypopituitarism, ADH hyposecretion, diplopia, *dura mater* thickening, Hashimoto's thyroiditis.

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## CASE REPORT

In October, 1998, a 77-yr-old woman was admitted to hospital presenting with headache and diplopia. Physical examination demonstrated that diplopia deteriorated on the right lateral gaze, indicating right VI nerve palsy. Head MRI showed swelling of the whole pituitary gland and thickening of the dura mater on the dorsum sella, while the cavernous sinus was intact (Fig. 1A, B). A tentative diagnosis of lymphocytic hypophysitis was made, but further examination could not be performed at that time. Headache spontaneously reduced, while diplopia persisted.

In September 1999, she was referred to our division for the evaluation of appetite loss and general malaise which had appeared one month earlier. Laboratory findings showed hypercholesterolemia (249 mg/dl) and hypoglycemia (69 mg/dl). Endocrinological examination revealed low  $T_4$ , low  $T_3$  and normal TSH level, low cortisol with undetectable level of ACTH, high PRL and relative low LH considering her menopausal state (Table 1). Simultaneous CRH, TRH, LHRH and GRH loading test was performed, which demonstrated no response of ACTH and cortisol, and delayed response in TSH, PRL, LH and GH (Fig. 2). Insulin-induced hypoglycemia (the lowest serum glucose 33 mg/dl) evoked no response of GH, ACTH and cortisol (Fig. 3). Rapid ACTH (0.25 mg 1-24 ACTH) infusion poorly stimulated cortisol secretion, but consecutive ACTH infusion test for 3 days showed normal cortisol elevation (data not shown). Hypertonic (5%) saline infusion test, which was performed after glucocorticoid replacement (hydrocortisone 10 mg

daily), revealed poor response of serum ADH, which was measured with radioimmunoassay kit (Mitsubishi Chemical Corp., Tokyo, Japan) (Fig. 4). Overnight urine osmolarity (417 mOsm/kg) was higher than serum osmolarity (283 mOsm/kg), suggesting the presence of ADH hyposecretion, although she had no complaints of thirst and/or polyuria (24-h urinary output and urine specific gravity were approximately 2 l and 1.020, respectively, both of which did not change after glucocorticoid replacement). Head MRI showed pituitary swelling, which was more slightly remarked than the year before (Fig. 1C). Thyroid ultrasonography demonstrated diffuse goiter (diameter 52 mm) compatible with Hashimoto's thyroiditis, which was confirmed by fine-needle aspiration biopsy (FNAB). Anti-thyroglobulin antibody was positive (0.4 U/ml; normal <0.3 U/ml), while anti-thyroperoxidase (TPO) antibody was negative. A test for antinuclear antibody was positive at a titer of 1:40 with a homogeneous pattern. Cerebrospinal fluid examination was normal. X-ray of the long bones and chest showed no abnormalities. A tuberculin skin test with purified protein derivatives (PPD) was positive and serum level of ACE was normal. Anti-pituitary antibody was negative, which was measured with indirect immunofluorescent antibody technique using rat pituitary cells as antigen (Sohgo Biomedical Laboratories, Saitama, Japan). Based on these findings, she was diagnosed to have hypopituitarism probably due to lymphocytic hypophysitis. She was administered 10 mg hydrocortisone daily, and thereafter her appetite loss

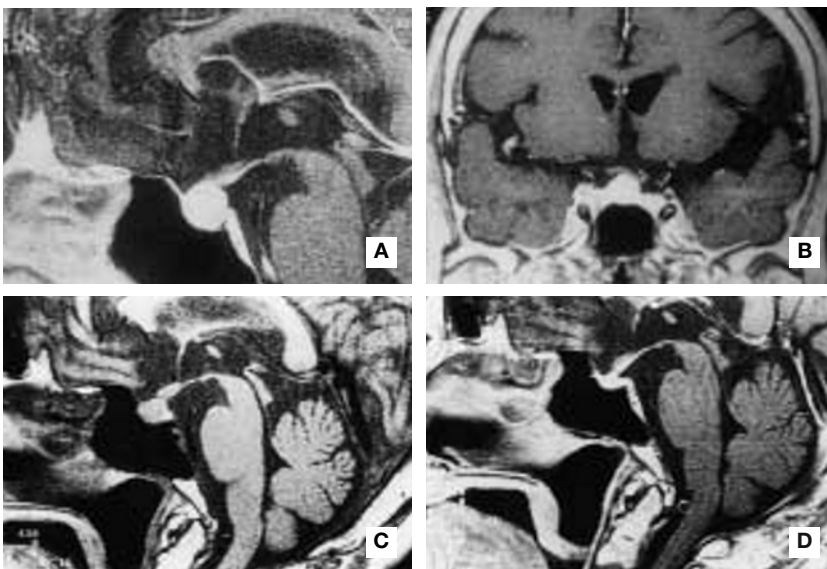


Fig. 1 - Sagittal and coronal T1-weighted MR images. A, B: Gd-enhanced sagittal (A) and coronal (B) MR images in October, 1998. They showed swelling of the whole pituitary gland and thickening of the dura mater on the dorsum sella, while the cavernous sinus was intact. C: Plain sagittal MRI in September, 1999. It showed pituitary swelling, which was more slightly remarked than last year (A). D: Gd-enhanced sagittal MRI in January, 2000. It showed the more remarkable reduction in pituitary size.

and general malaise gradually disappeared. In October, 1999, TSH, GH and LH showed higher levels and PRL lower levels than in August, while ACTH remained undetectable (Table 1). On the head MRI in January 2000, pituitary swelling showed a reduction in size (Fig. 1D). The head MRI, which was performed again in July 2000, showed no change in the pituitary size.

## DISCUSSION

In the present report, we described an elderly woman presenting with headache, diplopia, appetite loss and general malaise, who showed pituitary swelling and thickened *dura mater* on the *dorsum sellae*. Endocrinological investigations revealed the presence of both hypopituitarism and ADH hyposecretion. Headache and diplopia spontaneously improved. During the follow-up period, head MRI showed a spontaneous decrease of pituitary swelling even more marked after replacement therapy of hydrocortisone, when an improvement of hypopituitarism except for ACTH secretion was also observed. The diagnosis of lymphocytic hypophysitis was made based on the following reasons. Head MRI, which was performed in 1998, showed that the pituitary was heterogeneously enhanced by gadolinium (Gd)-DTPA and that normal pituitary was not visible, making the diagnosis of pituitary adenoma unlikely. X-ray of the long bones and chest, and laboratory findings such as

weakly positive skin PPD test and serum ACE within normal range indicated that the possibilities of tuberculosis, sarcoidosis and Langerhans cell histiocytosis were also unlikely. Pituitary swelling showed spontaneous reduction before replacement of glucocorticoid was given, as in the previous report (18). These findings suggest that lymphocytic hypophysitis is the most likely diagnosis in this case, although biopsy of adenohypophysis was not done because of spontaneous remission of pituitary swelling and the advanced age of the patient.

Endocrinological investigations revealed anterior pituitary dysfunction, ADH hyposecretion associated with primary hypothyroidism due to Hashimoto's thyroiditis. Hyperprolactinemia, delayed response of TSH, PRL, LH and GH in TRH, LHRH and GRH test, and ADH hyposecretion suggested the damage of the hypothalamus and/or pituitary stalk, which was probably due to involvement of inflammation in the hypothalamus and/or pituitary stalk or to compression of stalk by the swelling pituitary, although the inflammation of hypothalamus and/or pituitary stalk was not evident on head MRI. Urine concentration capacity seemed to be maintained with urine osmolarity higher than plasma osmolarity in common state. However, hypertonic (5%) saline infusion test revealed poor response of serum ADH to elevation of serum osmolarity (Fig. 4), indicating an impaired ADH secretory pool in response to high serum osmolarity. Therefore, it was consid-

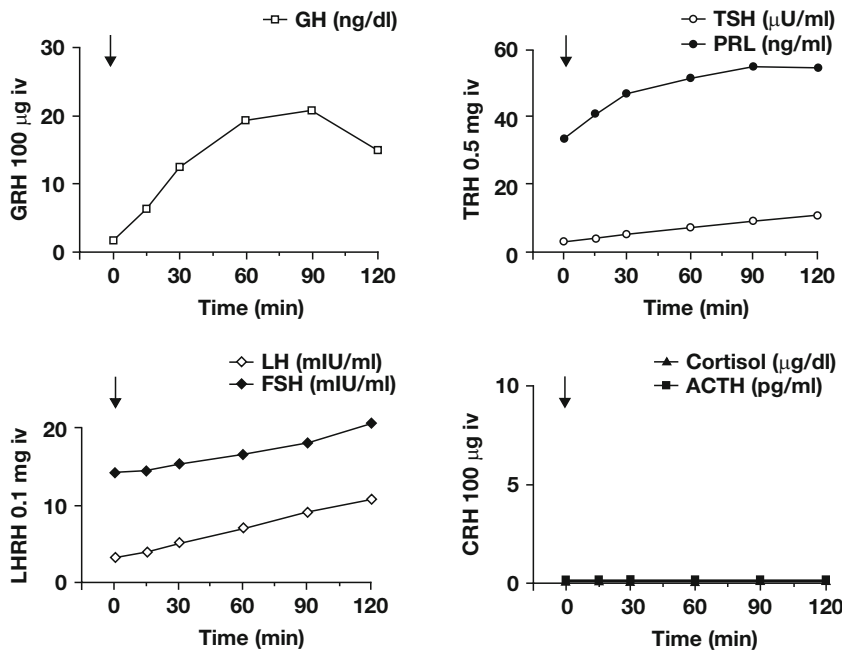


Fig. 2 - Simultaneous GRH, TRH, LHRH and CRH loading test. It demonstrated no response of ACTH and cortisol, and delayed response in TSH, PRL, LH and GH.

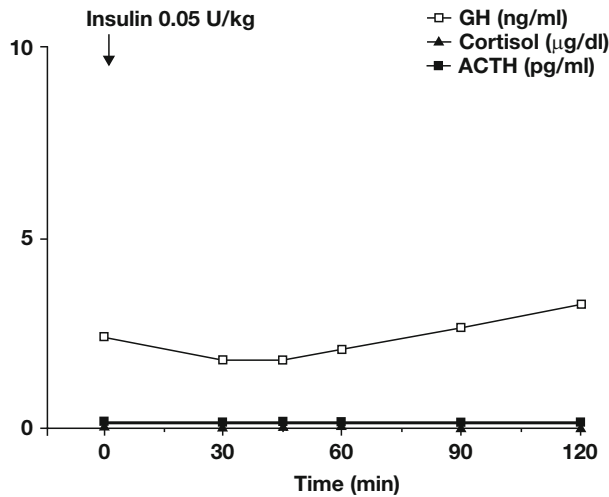


Fig. 3 - Insulin loading test. Insulin-induced hypoglycemia evoked no response of GH, ACTH and cortisol.

ered that not the term “diabetes insipidus” but the term “ADH hyposecretion” was appropriate to indicate the posterior pituitary function of this patient. Hypothyroidism was considered to be both primary and hypothalamic, since TSH level was within the normal range at admission, and showed an elevation above normal range two months after admission. Hypoadrenalism due to ACTH deficiency seemed to be caused mainly by the anterior pituitary damage considering that ACTH showed no response to CRH. Hyposecretion of ACTH persisted while other anterior pituitary hormone secretion was recovered. In general, the impairment of ACTH secretion is reported to be the most frequent pi-

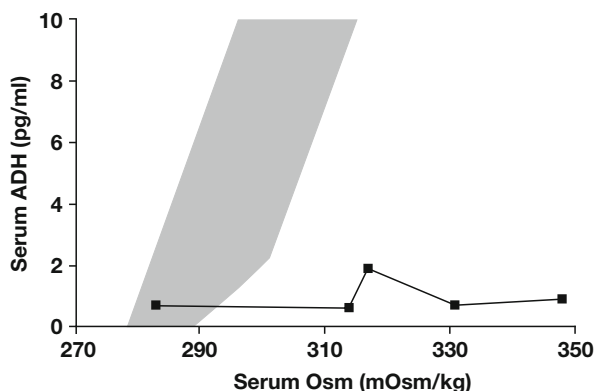


Fig. 4 - Hypertonic (5%) saline infusion test. It revealed poor response of serum ADH. The shaded area designates the range of serum ADH during 5% hypertonic saline infusions in normal subjects.

tuinary dysfunction in lymphocytic hypophysitis (61.1%), followed by TSH (45.4%), gonadotropins (38.9%), GH (36.1%) and PRL (36.1%) secretion impairment (19). Moreover, lymphocytic adenohypophysitis has also been described to be a cause of isolated ACTH deficiency (20). This case had characteristics of isolated ACTH deficiency, although it was not a typical one.

The thickened *dura mater* on the *dorsum sella*, which seemed to cause headache in this case, may be a variant of hypertrophic cranial pachymeningitis, which has been reported to complicate some cases with lymphocytic hypophysitis (8, 9). Diplopia in this case was considered to arise from the damage of right VI nerve within the cavernous sinus. Recently, many authors have reported lymphocytic hypophysitis in which the posterior pituitary and/or stalk (2, 4-8, 12), cavernous sinus (6-10), sphenoid sinus (12) and *dura mater* (8, 9) were involved together with the anterior pituitary. Similarly, the present paper reports a case in which the lesions involved were not only adenohypophysitis but also neurohypophysitis, *infundibulum* and/or hypothalamus, *dura mater* on the *dorsum sella*, and cavernous sinus.

In this case, a substitutive and not anti-inflammatory glucocorticoid dose was used for adrenal insufficiency due to ACTH deficiency considering that pituitary swelling was not as large to compress optic chiasma and spontaneously improved before admission to our hospital. In fact, the reduction in pituitary size after glucocorticoid replacement might be due to the natural course of the disease, considering that only a replacement dose of hydrocortisone was given. However, as some authors suggest, even a replacement dose of glucocorticoid might be effective in reducing the size of a pituitary mass in lymphocytic hypophysitis (7). It is interesting to follow-up head MRI to investigate whether such a reduction in pituitary size will lead to primary empty sella syndrome, considering the described association between primary empty sella syndrome and pituitary autoimmunity (21).

Although the etiology of lymphocytic adenohypophysitis still remains unknown, the complications of other autoimmune diseases such as Hashimoto's thyroiditis, silent thyroiditis and idiopathic adrenalitis suggest an autoimmune etiology for lymphocytic adenohypophysitis (19). Anti-pituitary antibodies were detected in only a small number of patients with lymphocytic adenohypophysitis (19). This case was possibly associated with Hashimoto's thyroiditis, considering typical ultrasonographic pattern, pathological diagnosis by FNAB and positive anti-thyroglobulin antibody, while anti-TPO antibody was negative.

This case was different from classical cases with

lymphocytic adenohypophysitis in that this patient was elderly, and that the chronic inflammatory process possibly involved the *infundibulum* and/or neurohypophysis, *dura mater* and cavernous sinus as well as adenohypophysis. In recent years, some cases have been reported, in which the inflammation invaded the pituitary from the cavernous sinus (Tolosa-Hunt syndrome) (13, 14) or from the orbit (fibrosing pseudotumor) (15). On the other hand, there have been several case reports of giant cell granulomatous hypophysitis involving the whole pituitary gland and cavernous sinus (16), and of necrotizing infundibulo-hypophysitis with the anterior and posterior pituitary involvement (17), in which the primary sites of inflammation were unclear. In the cases with lymphocytic hypophysitis involving both pituitary lobes and the surrounding structures (4-12), as in the present case, the primary lesion was unknown. Such cases may arise from an autoimmune process not to specific antigens but to nonspecific antigens such as substances which the pituitary may share with tissues around the *sella turcica*. Alternatively, it is possible that the disorders confined to adenohypophysitis or neurohypophysis may be caused by autoimmune processes based on unknown mechanisms specific to each lobe of the pituitary, and that in those associated with involvement of the surrounding structures around the *sella turcica* (atypical lymphocytic hypophysitis), the inflammation of other sites may simply extend into the anterior and/or posterior pituitary. Further studies are required to conclude whether classical cases of lymphocytic adenohypophysitis and of lymphocytic infundibuloneurohypophysitis may be pathogenetically different from atypical cases with lymphocytic hypophysitis as in the present case. In summary, we report a case of lymphocytic hypophysitis presenting with hypopituitarism, ADH hyposecretion, diplopia and *dura mater* thickening on the *dorsum sella*. Considering its expanding features, lymphocytic hypophysitis may be considered a syndrome including heterogeneous disorders.

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