A Case of Lymphocytic Infundibuloneurohypophysitis Associated with Systemic Lupus Erythematosus

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Abstract. A 27-year-old man was admitted to our hospital with facial erythema and general malaise. He had previously suffered from orbital myositis, central diabetes insipidus (DI), peripheral neuritis, and hypogonadotropic hypogonadism. Physical and immunological examinations revealed that he was suffering from systemic lupus erythematosus (SLE). Magnetic resonance imaging of the hypothalamic-pituitary region demonstrated a significant enlargement of the pituitary stalk and posterior pituitary. Endocrinological examinations showed that he had not only DI and hypogonadotropic hypogonadism but also hypoadrenalism and hypothyroidism, which were ascribed to the pituitary stalk lesion. Lymphocytic infundibuloneurohypophysitis associated with SLE was diagnosed. Administration of 30 mg/day of prednisolone for one month resulted in a marked reduction of the pituitary stalk thickening and posterior pituitary. It is recommended that a pharmacological dose of glucocorticoid be used in the treatment of lymphocytic hypophysitis patients who show significant thickening of the pituitary stalk and/or a large pituitary mass.

Key words: Lymphocytic infundibuloneurohypophysitis, SLE, Glucocorticoid, Diabetes insipidus (Endocrine Journal 49: 605-610, 2002)

LYMPHOCYTIC hypophysitis is a rare inflammatory disorder of the pituitary gland [1]. It is usually classified as lymphocytic adenohypophysitis or lymphocytic infundibuloneurohypophysitis, depending on whether the main lymphocytic lesion locates in the anterior pituitary or in the pituitary stalk and/or posterior pituitary [2]. The strong association of this disease with other autoimmune diseases (e.g., autoimmune thyroiditis, autoimmune adrenalitis, and pernicious anemia) in the early reported cases, along with histological findings showing heavy infiltration of lymphocytes and fibrosis, have suggested an autoimmune etiology of this disorder [2-4].

Imura et al. [5] reported abnormal thickening of the pituitary stalk, enlargement of the neurohypophyses, or both of these on magnetic resonance imaging (MRI) in patients who had manifested idiopathic diabetes insipidus (DI) for less than 2 years, suggesting that most cases of idiopathic DI might be caused by lymphocytic infundibuloneurohypophysitis. Since then, case reports of lymphocytic infundibuloneurohypophysitis have been increasing.

Although lymphocytic adenohypophysitis is frequently associated with autoimmune disease, only 3 cases of lymphocytic adenohypophysitis have been reported to be associated with systemic lupus erythematosus (SLE) [6-8]. We here describe the first case of lymphocytic infundibuloneurohypophysitis associated with SLE, and discuss the effect of prednisolone (PSL) treatment on pituitary stalk thickening in this patient.

Case Report

A 27-year-old man was admitted to Kochi Medical
School Hospital in April 2001. Eight years prior to admission (1993), he noticed double vision as well as swelling and pain in the left orbital region. At that time he was admitted to a hospital and diagnosed as orbitis of unknown etiology. He received glucocorticoid treatment, subsequent to which his symptoms disappeared. Two years later, he suffered from the same symptoms which were also cured with glucocorticoid. In 1997 when these same symptoms reappeared again, he was admitted to the same hospital and underwent biopsy of the extraocular muscle. Biopsy specimen showed infiltration of lymphocytes, suggesting nonspecific inflammation, and extraocular myositis was diagnosed. Glucocorticoid again relieved orbital swelling and pain. The patient was admitted to the Department of Internal Medicine in the same hospital, and underwent examinations that showed positive antinuclear antibodies and antidual stranded DNA antibody. At the time of admission, he complained of polyuria. His urine volume was 5000—9000 ml/day, and central diabetes insipidus (DI) was diagnosed. It was also revealed that he had peripheral neuritis and hypogonadotropic hypogonadism. It was not clear when these lesions occurred. Because he was not suffering from impotence, he did not receive testosterone administration. Since September 2000, however, he had been receiving injections of human chorionic gonadotropin (HCG) (5000 U) once a week, expecting to have a child. Subsequently, the patient had been receiving desmopressin for DI, and his general condition had been good until February 2001, when he noticed facial erythema and general malaise. In April of that year he had a high fever and headache, and consulted our Medical School Hospital, at which time SLE was suspected.

On physical examination, blood pressure was 110/70 mmHg and heart rate was 72 beats/min. He had butterfly rash on his face. Conjunctivae showed slight anemia but no jaundice. Eye movement and visual field were normal, but he noticed double vision when he looked upward and leftward. Gynecomastia was noted on both sides, which seemed to appear before receiving HCG. Patella and Achilles tendon reflexes were normal. Babinski reflex was detected in the left foot. Vibration sensation was impaired in both feet. No signs suggesting meningitis were noted. No muscle atrophy was noted, but muscle weakness was noted in both lower legs.

Laboratory examination showed no abnormalities in urine. Complete blood counts showed: hemoglobin 10.8 g/dl, white blood cell count 3200/μl, and platelet count 15.7×10^9/μl. Electrolytes were normal. Alanine aminotransferase and aspartate aminotransferase were 56 and 67 IU/l, respectively. Creatine phosphokinase, lactic dehydrogenase, and alkaline phosphatase were 77, 333, and 125 IU/l, respectively. Immunological examinations showed that antinuclear antibody was positive and of the diffuse and speckled type. Anti-DNA, anti-single stranded DNA, and double stranded DNA antibodies were 160 AU/ml, 708 IU/ml, and 400 IU/ml, respectively, and were all positive. Anti-Sm antibody was also high (×8). Immune complex level was also high (4.1 μg/ml). NK cell activity was low (3%). Complements were all low (CH50 8.9 U/ml, C3 57.4 mg/dl, C4 2.3 mg/dl). Anti-thyroglobulin antibody was positive (0.5 U/ml), but anti-thyroid peroxidase antibody was negative. Anti-pituitary antibodies were examined using Western blot method previously described (9). Antibodies to 29 kDa antigen of the human anterior pituitary cytosol was detected (Fig. 1).

The results of hormonal examination were: free T3 and free T4 levels were 2.0 ng/ml and 0.62 ng/dl, respectively, and were lower than the lower limit of the normal range. Urinary 17-OHCS, 17KS, and free cortisol were 1.9 mg/day, 2.0 mg/day and 5 μg/day, and all were low. Plasma cortisol, DHEA-S, testosterone, free testosterone, and estradiol were 2.0 μg/dl, 522 ng/ml, 23 ng/dl, 2.4 pg/ml, and less than 10 pg/ml, respectively, and all were very low. Anterior pituitary function was evaluated by intravenous injection of corticotropin-releasing hormone (CRH, 100 μg), thyrotropin-releasing hormone (TRH, 500 μg), growth hormone-releasing hormone (GRH, 100 μg), and luteinizing hormone-releasing hormone (LHRH, 100 μg). Baseline levels of ACTH (26 pg/ml), TSH (2.87 μIU/ml), and GH (0.12 ng/ml) were all normal. Baseline levels of LH (<0.25 mIU/ml) and FSH (<0.25 mIU/ml) were low, but PRL level (38 ng/ml) was high. ACTH showed rapid and good response, while cortisol response was poor (Fig. 2). TSH, PRL, and GH showed delayed responses. These responses were compatible with a lesion in the hypothalamus and/or pituitary stalk. However, no LH and FSH responses were observed, which suggested a lesion in the pituitary gonadotrophs.

MRI of the hypothalamic-pituitary region demon-
LYMPHOCYTIC HYPOPHYSISIS WITH SLE

MW(kDa)
165.0
105.0
76.0
57.0
46.5
37.5
20.5
14.5
6.5

Fig. 1. Antibodies to 29 kDa pituitary cytosolic antigen was detected by Western blot analysis. Right side bands show marker proteins. An arrow shows the size of the proteins.

A gadolinium-enhanced T1-weighted image showed high signal intensity of the pituitary stalk and the posterior pituitary (Fig. 3, upper panels). Lymphocytic infundibuloneurohypophysitis associated with SLE was diagnosed based on the above mentioned results and the diagnostic criteria for SLE set by the Japan Ministry of Health. The patient received 20 mg/day of hydrocortisone for several days, followed by 30 mg/day of PSL for the treatment of SLE. Intramuscular injection of HCG (5000 U, once every two weeks) and intranasal administration of desmopressin were continued. Serum testosterone level became normal (from 100 ng/ml to 300 ng/ml). One month administration of PSL resulted in a marked reduction of the thickening of the pituitary stalk and posterior pituitary (Fig. 3, lower panels). Complement levels were gradually improved. The patient has continued to receive the same dose of desmopression up to the time of this report.

Fig. 2. ACTH, cortisol, prolactin, TSH, GH, LH, and FSH responses to combined intravenous administration of CRH (100 μg), TRH (500 μg), GRH (100 μg), and LHRH (100 μg).
Discussion

This patient has been suffering from various disorders, most of which are autoimmune disorders. He first suffered from orbital myositis, followed by central DI, peripheral neuritis, hypogonadotropic hypogonadism, and SLE. He presented with both anterior and posterior pituitary dysfunction. In lymphocytic adenohypophysitis, the anterior pituitary is heavily infiltrated by lymphocytes with occasional plasma cells and inflammatory cells [2, 3]. The infiltrating lymphocytes are mainly T lymphocytes, and mostly CD4 positive cells. Fibrosis is also observed in many cases. In lymphocytic infundibuloneurohypophysitis, similar lesions are found in the pituitary stalk and/or posterior pituitary. In some rare cases a lesion is found in both the anterior pituitary and the infundibuloneurohypophysitis [10–13]. In these cases, lymphocytic panhypophysitis was diagnosed. Lymphocytic infundibuloneurohypophysitis usually causes central DI. According to our review on lymphocytic adenohypophysitis, central DI developed in 19.7% (30 cases) of 152 cases of lymphocytic adenohypophysitis [14]. DI may be caused by compression of the pituitary stalk by swollen adenohypophysitis. Ten of these 30 cases were likely to be lymphocytic panhypophysitis.

Anterior pituitary dysfunction has also been observed in some patients with lymphocytic infundibuloneurohypophysitis. According to our review on lymphocytic infundibuloneurohypophysitis, impairment of GH and gonadotropin secretion were found in 11 (39.3%) and 3 (10.7%) cases of 28 patients, respectively [14]. ACTH secretion was impaired in one case. Hyperprolactinemia was found in 5 cases (17.9%). Among cases of lymphocytic adenohypophysitis, impairments of ACTH, TSH, gonadotropin, GH, and PRL secretion were 60.9, 47.0, 42.2, 36.7, and 33.7%, respectively. Hyperprolactinemia was found in 35.2% of the cases [15].
In the present case, MRI showed significant thickening of the pituitary stalk. Responses of plasma 
ACTH, cortisol, and TSH, and PRL responses to CRH and TRH were compatible with the stalk le-
son, although LH and FSH responses to LHRH suggest-
a lesion of the pituitary gonadotrophs. These 
findings suggested that the main lesion was located in 
the infundibuloneurohypophysis, though partial in-
volvement of the anterior pituitary was also possible. 
As mentioned above, some previously reported cases 
suggested that lymphocytic inflammation occurred in 
both the anterior and posterior pituitary [10–13]. In 
these cases, some of the anterior pituitary hormones’ 
secretion were impaired [11, 13] which may also sug-
ject the involvement of anterior pituitary. However, 
as we did not perform successive LHRH administra-
tion test to examine the pituitary lesion in the present 
case, it cannot be concluded that lymphocytic inflam-
matory lesion occurred in the anterior pituitary. 
This patient presented with anti-pituitary antibody 
to 29 kDa antigen of the human anterior pituitary 
cytosol. This may also indicate that the inflamma-
atory lesion occurred in the anterior pituitary. Crock 
[16] detected an antibody to 49 kDa antigen at high 
frequency in patients with lymphocytic hypophysitis 
and isolated ACTH deficiency. Recently, they re-
ported that the 49 kDa antigen is alpha-enolase [17]. 
We detected the antibody to 22 kDa pituitary cyto-
sonic antigen at high frequency in patients with lympho-
cytic hypophysitis [9]. Therefore, it is likely that 
some different kinds of anti-pituitary antibodies are 
produced in patients with lymphocytic hypophysitis. 
In 20 to 56% of patients with lymphocytic adenohy-
pophysitis, the disease has been reported to be asso-
ciated with autoimmune disorders such as chronic 
thyroiditis, painless thyroiditis, autoimmune adrena-
litis, pernicious anemia, and type 1 diabetes mellitus, 
in which organ-specific antibodies are produced [2, 
15]. The patient in the present case presented with 
SLE, which usually develops non-organ specific anti-
bodies. Only 3 cases of lymphocytic adenohypo-
physitis have been associated with SLE [6–8]. Two 
cases of central DI have been reported in patients 
with SLE [18]. In these patients, however, MRI of 
sellar and parasellar areas were normal, and anti-
pituitary antibodies were negative. The present case 
showed not only anti-pituitary antibodies but anti-
thyroid peroxidase antibodies. Therefore, to our 
knowledge, this is the first case report of autoim-
une lymphocytic infundibuloneurohypophysis associated with SLE.

Glucocorticoid has been reported to be effective in 
the treatment of lymphocytic hypophysitis. Kristof 
et al. [19] reported that high dose methylpredni-
solone pulse therapy (120 mg methylprednisolone daily 
for 2 weeks, followed by a dose reduction to 80, 60, 
40, then 20 mg daily for 1 week each) improved 
anterior pituitary function in four of nine patients and 
DI in all of four patients. MRI findings also im-
proved in seven patients. According to our review 
of 158 cases with lymphocytic adenohypophysitis, 10 
(62.5%) of 16 patients to whom a pharmacological 
dose of glucocorticoid (PSL-equivalent dose ≥10 mg/day) was given showed reduction of pituitary 
mass (Table 1). Out of 36 patients to whom a physi-
ological dose of glucocorticoid (PSL-equivalent dose 
≥7.5 mg/day) was given, 16 (44.4%) showed reduc-
tion of pituitary mass. The cure rate of hormonal 
disorders was lower than that of pituitary mass. In 
the present case, 30 mg/day of PSL caused rapid 
reduction of thickening of the infundibuloneuro-
hypophysis. The patient is still suffering from DI and 
is taking desmopressin. As the patient is still taking 
15 mg/day of PSL, it is difficult to evaluate improve-

Table 1. Effect of glucocorticoids on the pituitary mass in patients with lympho-
cytic hyperplasia

<table>
<thead>
<tr>
<th>Dose of glucocorticoids</th>
<th>Total</th>
<th>Effective</th>
<th>Not-effective</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological dose*</td>
<td>16</td>
<td>10 (62.5%)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Supplementary dose**</td>
<td>36</td>
<td>16 (44.4%)</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Dose unknown</td>
<td>12</td>
<td>4 (33.3%)</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>30 (46.9%)</td>
<td>6</td>
<td>28</td>
</tr>
</tbody>
</table>

*: PSL-equivalent dose ≥10 mg/day
**: PSL-equivalent dose ≥7.5 mg/day
thickening of pituitary stalk, large pituitary mass and marked enhancement of the lesion on MRI. In the case of patients with chronic phase lymphocytic hypophysitis whose pituitary mass is small, the physiological dose of glucocorticoid may be recommended.

References