Lymphocytic hypophysitis in a patient with systemic lupus erythematosus

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ABSTRACT
A case of lymphocytic hypophysitis in a patient with systemic lupus erythematosus is described. A 20-year-old woman was admitted to our hospital with generalized myalgia and facial rash in May 1998. The patient had a medical history, physical examination, and laboratory findings compatible with systemic lupus erythematosus (SLE). Headache and nausea had developed 3 months previously and worsened over the following months. Hormonal investigation showed hypopituitarism except for prolactin. A magnetic resonance image of the brain showed a mass lesion in the pituitary fossa. A trans-sphenoidal surgical procedure was performed which revealed a dark-yellowish hematoma. Microscopic examination showed diffuse infiltration of lymphocytes and plasma cells with fibrosis in the anterior pituitary. Post-operatively the patient’s headaches and nausea resolved. This indicates that lymphocytic hypophysitis may be associated with SLE.

Introduction
Lymphocytic hypophysitis is a rare inflammatory disorder of the pituitary gland which is characterized by lymphocytic infiltration and fibrosis of the anterior pituitary (1). Most cases have been diagnosed in women during late pregnancy or the postpartum period. Patients usually present with symptoms of an expanding intrasellar mass or varying degrees of hypopituitarism. Although its causes are not known, it has been reported that lymphocytic hypophysitis is associated with autoimmune thyroiditis (2, 3), pernicious anemia (4), Grave’s disease (5), systemic lupus erythematosus (SLE) (6), and autoimmune diseases including the antipituitary (7), antimitochondrial (8), antiparietal (4) and antinuclear antibodies (9). Therefore, lymphocytic hypophysitis has been postulated to be an autoimmune disease primarily of pregnancy and the puerperium. Lymphocytic hypophysitis commonly manifests as a pituitary mass and pre-operatively has been misdiagnosed as a pituitary adenoma (7).

Our patient presented with an intrasellar mass and the pathologic findings during a transsphenoidal operation were compatible with lymphocytic hypophysitis. We describe an SLE patient with headache and nausea, in whom the presence of an intrasellar mass and pathologic findings indicated lymphocytic hypophysitis.

Case report
A 20-year-old woman was admitted to the Korea University Anam Hospital in May 1998 with a three-month history of facial rash, fever, generalized myalgia, hair loss and arthralgia. During the three months before admission, she had noted intermittent headache and nausea. No visual disturbances were present. There was no family history of autoimmune or endocrine problems.

On examination, the patient was severely distressed. Her heart rate was 70 beats per minute, her blood pressure 110/70 mm Hg, and she had a temperature of 36.2°C. Hair loss, malar rash, and a erythematos rash on the palms and soles could be seen. Ophthalmological examination showed normal visual fields. The remainder of the examination was normal.

Complete blood counts revealed: hemoglobin 10.6 g/dl, white blood cell count 2,960/mm³, and platelet count 106,000/mm³. Electrolytes and urinalysis were normal. Alanine aminotransferase was 107 IU/l and aspartate aminotransferase was 98 IU/l. The results of other laboratory evaluations were: antinuclear antibody (ANA) titer 1:40 (speckled pattern), anti-dsDNA antibody 20.44 U/ml (normal < 5.3 U/ml), negative anti-RNP antibody, negative anti-Sm antibody, reactive VDRL, negative anti-SS-A and anti-SS-B antibodies, erythrocyte sedimentation rate (ESR) 54 mm/hr (normal < 20 mm/hr), C3 55.5 mg/dl (normal 88 to 201 mg/dl), C4 15.0 mg/dl (normal 16 - 47 mg/dl). SLE was diagnosed based on the presence of malar rash, hair loss, leukopenia, positive ANA, and positive anti-dsDNA antibodies. Headache and nausea worsened one day after admission. Skull x-rays revealed an enlarged sella and magnetic resonance imaging (MRI) demonstrated a round mass lesion in the sella. T1- and T2-weighted images revealed high signal...
intensity of the pituitary mass (Fig. 1). A gadolinium-enhanced T1-weighted image showed high signal intensity within the mass (Fig. 2). Compared with the pre-enhanced film, evidence of definite enhancement was not seen. Further investigations of pituitary function were carried out. The basal hormone level revealed the following: growth hormone (GH) 4.12 ng/ml (normal 0-5), cortisol 4.52 µg/ml (normal 0-20), prolactin 90.3 ng/ml (normal 0-20), thyroid stimulating hormone (TSH) 1.13 IU/ml (normal 0-10), lutenizing hormone (LH) 2.86 mIU/ml (normal 5-25) and follicle stimulating hormone (FSH) 4.32 mIU/ml (normal 5-20). Dynamic tests of pituitary function were performed. TSH and prolactin responses to thyrotropin releasing hormone (TRH) (400 µg), LH and FSH responses to lutenizing hormone releasing hormone (LHRH) (100 µg), cortisol and GH responses to insulin (0.1 unit/kg body weight) were evaluated (Table I).

A trans-sphenoidal surgical procedure was performed and revealed a dark liquefied hematoma. After the hematoma was aspirated, the pituitary gland could be seen. A biopsy of the pituitary gland showed the infiltration of lymphocytes and plasma cells with fibrosis in the anterior pituitary (Fig. 3). Post-operatively, the patient’s headaches and nausea resolved. Two months later her hormone levels were as follows: cortisol 21.04 µg/ml, prolactin 125.74 ng/ml, TSH 1.77 IU/ml, LH 1.86 mIU/ml and FSH 2.28 mIU/ml. The patient is currently well and receiving prednisolone 15 mg and hydroxychloroquine 400 mg daily.

Discussion
Lymphocytic hypophysitis is a rare autoimmune disease, diagnosed either by surgical biopsy of the pituitary or at autopsy. Many of the patients reported previously had a large pituitary mass lesion, and most had various degrees of hypopituitarism (7-9). Our patient had no symptoms or signs of hypopituitarism, only headache and nausea. Dynamic pituitary function testing showed absent cortisol and growth hormone responses to insulin, impaired TSH response to TRH, and hyporesponses of FSH and LH to LHRH. She had an elevated prolactin level. Many have reported a mild elevation of prolactin attributed to either the disruption of hypothalamic transport of prolactin inhibitory factor by compression of the pituitary stalk, or to a direct effect of the inflammatory process on the prolactin cells, or to a lactotroph-stimulating antibody arising as a consequence of the inflammatory process (2, 4, 8-10). The cause of the elevated prolactin level in our patient is unclear; it could have been due to either lymphocytic hypophysitis or the SLE itself. Elevated serum prolactin levels have been reported in SLE patients (11, 12), and the persistently elevated prolactin levels in our patient after surgery may have been due to disease activity.

While the causes of lymphocytic hypophysitis are unclear, several findings suggest that autoimmunity is involved in the pathogenesis. Experimentally, lymphocytic hypophysitis has been induced by injecting pituitary tissues and adjuvants into footpads of the rat (13). The histologic features of this lesion were nearly identical to that seen in patients with lymphocytic hypophysitis. These results suggest that an autoimmune reaction may be implicated in the genesis of human lymphocytic hypophysitis. Similar

![Fig. 1. (a) T1-weighted image and (b) gadolinium-enhanced T1-weighted image demonstrating high signal intensity of the pituitary mass.](image-url)
results have been reported in rabbits (14). Also supporting an autoimmune pathogenesis is the reported association of thyroiditis (2, 3), adrenalitis (14), pernicious anemia (4), and Grave’s disease (5) in patients with lymphocytic hypophysitis. In 1993, Hasegawa et al. described the case of a young woman with SLE and lymphocytic hypophysitis (6). Our case represents the second report of an association between SLE and lymphocytic hypophysitis. Like Hasegawa’s patient, ours was unmarried and the onset of the disease was not related to pregnancy. The majority of cases to be reported have been seen during pregnancy or in the postpartum period.

The unique feature of our case was the presence of hematomata in the sella. In our patient, the hematoma may have been due to bleeding from the pituitary gland. Many cases previously reported manifested as a pituitary mass and had been misdiagnosed before surgery as a pituitary adenoma.

Cosman et al. (15) has suggested a management paradigm for lymphocytic hypophysitis based on the current understanding of this disease. If a patient develops a pituitary mass causing mild headache or visual symptoms, he should be monitored closely (including visual field examinations and CT scans) without surgical intervention. If the patient has severe headache or marked visual abnormalities, however, trans-sphenoidal surgery with biopsy should be performed. Hormone replacement therapy and corticosteroid therapy should be provided as needed.

In summary, our case demonstrates an association between systemic lupus erythematosus and lymphocytic hypophysitis. The evaluation of lymphocytic hypophysitis may be required in SLE patients with headache, hyperprolactinemia, a pituitary mass, and hypopituitarism.

References

Fig. 3. A biopsy of the pituitary gland showing infiltration of lymphocytes and plasma cells with fibrosis (Hematoxylin eosin stain, x100).