CLINICAL CASE SEMINAR

Distinct Radiological and Clinical Appearance of Lymphocytic Hypophysitis

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Lymphocytic hypophysitis is a rare inflammatory lesion of the pituitary gland. The disease shows a striking female predilection of approximately 9:1 and commonly affects young women during late pregnancy or in the postpartum period. Clinical presentation and radiological findings may mimic pituitary adenoma. We have reviewed the literature and report two cases of lymphocytic hypophysitis, neither of whom was neither pregnant or in the postpartum period; one of them (case 1) was a unique patient with empty sella associated with lymphocytic hypophysitis and diabetes insipidus established as a suprasellar mass.

Case Reports

Case 1

A 47-yr-old woman with two children presented with a 5-month history of polyuria-polydipsia (~15 liter/day), galactorrhea, and headache. She had been postmenopausal for 5 yr without hormone replacement therapy. Medical history showed that she lactated and had regular menses after the second delivery and had no history of peripartum or postpartum hemorrhage. On physical examination body mass index was 40 kg/m². The results of the physical examination were normal, except the patient was described as obese. Visual field test evaluated by computerized perimetry was normal.

Magnetic resonance (MR) of the pituitary gland showed a suprasellar mass (1×7×8 mm in diameter) with empty sella (Fig. 1, A and B). Central diabetes insipidus (DI) was diagnosed by the appropriate test. After the blood samples were obtained for baseline hormone values [free T₄, 4.8 pmol/L (normal, 3.3–5.5); free T₃, 19.3 pmol/L (normal, 9–24); TSH, 0.4 μU/mL (normal, 0.3–4.1); PRL, 98 μg/L (normal, 5–25); FSH, 3.2 mIU/L (normal, <20 for postmenopausal woman); LH, 0.2 mIU/L (normal, >20 for postmenopausal woman); estradiol, 36 pmol/L (normal, <108 for postmenopausal woman); cortisol, 913 nmol/L (normal, 190–660); ACTH, 7.9 pg/mL (normal, 1.3–12.3)], dynamic function tests of the pituitary gland were performed (Table 1), and hyperprolactinemia, secondary hypogonadism, and GH deficiency were diagnosed.

She was operated on by the transcranial approach because of a small increment in the size of the tumor on MR performed at 6-month interval. A mass lesion arising from the infundibulum and adherent to the right optic nerve was detected. The lesion could not be removed completely, and a biopsy was performed. Histopathological examination showed anterior and posterior (established by chromogranin and S-100 immunostaining) pituitary tissue heavily infiltrated by lymphocytes (positively stained by leukocyte common antigen), and the diagnosis was panhypophysitis (Fig. 2). During her follow-up, PRL levels progressively increased, and a disturbing galactorrhea could be managed by high doses (up to 20 mg/day) of bromocriptine SRO (5 mg bromocriptine mesylate as slow releasing tablets). Also, in addition to conjugated estrogen (0.625 mg/day), medroxyprogesterone acetate (5 mg/day), and desmopressin acetate (10 μg/day) intranasally, l-T₄ (100 μg/day) therapy was given for the management of secondary hypothyroidism developed after operation. Six months after the replacement therapy, she was well, with normal PRL and thyroid hormone levels and without any sign or symptom of secondary adrenal failure. The dose of bromocriptine SRO was lowered gradually (until 5 mg/day), and the patient was invited to regular clinical controls.

Diagnosis

Lymphocytic hypophysitis mainly affects women and typically presents during pregnancy or the postpartum period with symptoms referable to pituitary enlargement and later those of hypopituitarism (1). Commonly, lymphocytic hypophysitis presents with features of a mass lesion, with variable loss of anterior pituitary function and rarely with...
posterior pituitary involvement (2). In a few cases, chronic lymphocytic infiltration occurs in both hypophysis and infundibuloneurohypophysis (3). The most common radiological features of the lymphocytic hypophysitis are enlarged pituitary mass, which is characterized by homogeneous enhancement after gadolinium injection and thickened infundibulum on MR (1, 4, 5). Empty sella is an uncommon radiological appearance of lymphocytic hypophysitis, and to date, few patients have been reported (3). There are no definite biochemical or serological markers, and the diagnosis depends on the clinical suspicion and can only be clearly established by histological examination (1, 6).

### Discussion

Lymphocytic hypophysitis is a rare inflammatory disease of the anterior pituitary gland. The disease was first described by Goudie and Pinkerton in 1962 (7); since then, more than 120 cases have been reported. Although the etiology remains unknown, considerable evidence exists for an autoimmune pathogenesis (8, 9). In lymphocytic hypophysitis, the abnormalities appear to be confined to the anterior pituitary, with a small number of patients having clinical evidence of DI (1, 10), but, rarely, lymphocytic hypophysitis may also involve the infundibuloneurohypophyseal region (11).

Lymphocytic hypophysitis shows a striking female predilection of approximately 8.5:1 and commonly affects young women during late pregnancy or in the postpartum period (1, 12). However, it has also been described in postmenopausal women (2, 4, 13, 14). These two patients were neither pregnant nor in the postpartum period, and they are additional examples of lymphocytic hypophysitis during the postmenopausal period. We think that the occurrence of
lymphocytic hypophysitis without associated pregnancy is more frequent than that previously considered.

Besides partial or total hypopituitarism, hyperprolactinemia may be present in patients with lymphocytic hypophysitis, and in many of the patients elevated PRL levels may represent an endocrine marker of the disease (1). Although the second patient was normoprolactinemic, this suggestion is also supported in the first case with partial hypopituitarism and hyperprolactinemia. Stalk compression resulting in decreased dopamine delivery to the anterior pituitary may be a reason for hyperprolactinemia in this patient. However, an autoimmune mechanism involving the production of stimulating antibodies by plasma cells may lead to increased PRL secretion (15).

It was suggested that if inflammation of the pituitary gland is left untreated, the enlarged gland that produces a mass effect in the initial stages of the disease may shrink as glandular tissue is destroyed (6). It has been reported that some patients with presumed Sheehan’s syndrome but no clear history of postpartum hemorrhage or sepsis may have lymphocytic hypophysitis (1). In the second patient, although the medical history of inability to lactate and having no menses after the last delivery in combination with partial pituitary hormone deficiency is suggestive of Sheehan’s syndrome, she was diagnosed as having lymphocytic hypophysitis.

Sheehan’s syndrome, which occurs as a result of ischemic pituitary necrosis due to severe postpartum hemorrhage, is almost always characterized by empty sella and rarely DI (16). Although PRL deficiency and an absent PRL response to TRH stimulation have been reported as diagnostic and screening procedures in patients with Sheehan’s syndrome (17), we previously reported that Sheehan’s syndrome may be characterized by hyperprolactinemia (18). The lack of a typical medical history of suggesting Sheehan’s syndrome, such as postpartum hemorrhage, agalactorrhea, and amenorrhea during the postpartum period, clearly excludes Sheehan’s syndrome as a diagnosis in the first patient. The association of empty sella with lymphocytic hypophysitis in this patient led us to speculate that at least in some patients, lymphocytic hypophysitis may be an underlying disorder in patients with presumed Sheehan’s syndrome. To support this hypothesis, we believe that patients with lymphocytic hypophysitis should be followed for the development of empty sella. Empty sella may be primary or secondary in origin (19). Secondary empty sella is usually related to surgical treatment, radiotherapy, spontaneous infarction of pituitary tumors, bromocriptine therapy in prolactinoma, and

![Fig. 3. A, Patient 2. The coronal MR image demonstrates homogeneous uptake of gadolinium of pituitary gland. B, Patient 2. The sagittal MR image of thickened pituitary stalk and diffuse homogeneous uptake of gadolinium.](image1)

![Fig. 4. Photograph of hematoxylin-eosin-stained tissue from case 2, showing lymphocytic infiltration of anterior pituitary tissue.](image2)
T4 therapy in patients with primary hypothyroidism (20, 21). None of these causes was the case in the first patient.

It has been reported that lymphocytic hypophysitis should be strongly suspected if 1) symptoms occur during or soon after pregnancy; 2) ACTH and/or TSH deficiency is present with normal gonadotropin and GH secretion; and 3) contrast enhancement scans of the pituitary gland are positive (particularly gadolinium contrast on MR scanning) (10). These two cases represent an unusual presentation of lymphocytic hypophysitis with preserved ACTH and TSH secretion, but not gonadotropins, at the time of diagnosis. To our knowledge, lymphocytic hypophysitis, confirmed by histological diagnosis and empty sella, was not reported previously. Additionally, empty sella associated with panhypophysitis characterized by suprasellar mass and DI has never been reported previously. This unusual case provides additional insights into the presentation of lymphocytic hypophysitis.

Both spontaneous recovery of pituitary gland function and progressive and permanent hypopituitarism have been reported. Although the administration of bromocriptine can lower the high PRL level, the beneficial impact of this drug on the course of the disease is unproven (22). Addition of the deficient hormones is essential in the management of patients with lymphocytic hypophysitis. Corticosteroid therapy has been advocated and has been effective in some patients. Transphenoidal surgery is both diagnostic and therapeutic. However, surgical intervention may result in further deterioration of pituitary gland functions. It has been suggested that in the cases of suspected hypophysitis, a frozen section should be performed to confirm the diagnosis and to avoid aggressive resection of potentially viable pituitary tissue (1, 22).

In conclusion, lymphocytic hypophysitis is a rare disorder, and empty sella may be associated with this syndrome. It should be considered in the differential diagnosis of any pituitary mass that may extend to the suprasellar region, and lymphocytic hypophysitis should be suspected in the patients with empty sella, hyperprolactinemia, and hypopituitarism.

References