A Case of Lymphocytic Hypophysitis with Massive Fibrosis and the Role of Surgical Intervention

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Four weeks after a normal delivery, a 33-year-old woman was admitted to our hospital with visual disturbance, hypopituitarism, and diabetes insipidus. A homogeneously enhanced pituitary mass with suprasellar extension was observed. Presurgical steroid therapy was ineffective. A transsphenoidal approach revealed a firm white mass, which was histologically diagnosed as a lymphocytic hypophysitis with massive fibrosis. Lymphocytic hypophysitis shows a variety of clinical courses, and there are various problematic aspects concerning the histologic stage as well as the differential diagnosis. However, it is difficult to speculate concerning these without histologic studies. Cases with massive fibrosis, spontaneous resolution, or positive effects of steroids may be less likely.

KEY WORDS: Diabetes insipidus; Lymphocytic hypophysitis; Massive fibrosis; Pituitary tumor; Transsphenoidal approach

Lymphocytic hypophysitis is a distinct clinicopathologic entity of nonneoplastic inflammatory disorder affecting the adenohypophysis. It has been postulated to be an autoimmune disease primarily related to pregnancy and the puerperium. Although the true incidence of this disease is unknown, it has been suggested to be higher than previously thought [1,3], and at present more than 50 cases have been reported in the literature [15]. However, the natural history is still unknown, and the management of this disease is controversial. When gross visual impairment is absent, conservative treatment with steroids has been recommended by some authors recently [1,3,4,16,18].

This report describes a patient with lymphocytic hypophysitis who showed no improvement after presurgical steroid therapy. Transsphenoidal exploration yielded a diagnosis of lymphocytic hypophysitis with massive fibrosis. The role of surgical intervention in this disease is discussed.

Case Report
A 33-year-old housewife was admitted to our hospital with complaints of headaches, visual disturbance, and polyuria. Four weeks before admission, she had a full-term normal delivery of a healthy infant. Although she had suffered from infertility for 6 years, she was taking no medication. Her pregnancy was unremarkable until the ninth month, when she developed bitemporal headaches. Five days after the delivery, she experienced the onset of blurred vision in her left eye and loss of bitemporal visual fields. During the postpartum period, she had failure of lactation and complained of general fatigue, anorexia, polydipsia, and polyuria. She had no previous medical problem besides infertility; however, her sister and aunt suffered from rheumatoid arthritis and Hashimoto’s thyroiditis, respectively.

On admission, she showed a slightly lethargic appearance. She complained of general fatigue, anorexia, nausea, and dizziness, suggestive of hypopituitarism. Her urine volume was 5000–5500 mL/day (specific gravity 1.007–1.010), which increased to 4000 mL/day (1.005) after prednisolone was started. Ophthalmologic examination revealed a bitemporal hemianopsia and decreased visual acuity of the left eye (Vd: 1.2, Vs: 0.03). Optic atrophy was not observed. Other neurologic examination and routine laboratory examinations including serologic studies showed normal results.

Endocrine evaluation confirmed hypopituitarism: adrenocorticotropic hormone (ACTH) <5 pg/mL (normal, 9–52), thyroid-stimulating hormone (TSH) 0.15 μU/mL (normal, 0.34–3.5), luteinizing hormone (LH) <0.5 mIU/mL (normal, 5–20), follicle-stimulating hormone (FSH) 1.7 mIU/mL (normal 10–40), prolactin <1 ng/mL (normal, 1.4–14.6), however growth hormone (GH) was 2.6 ng/mL (normal, 0.66–3.68). They showed no response to the triple stimulation test (TSH, LH-RH, insulin). The plasma ADH level was 0.4 pg/mL.
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(normal, 0.3–3.5). Antipituitary antibodies, antinuclear antibodies, and anti-DNA antibodies were negative.

Skull x-ray showed no abnormalities. A computed tomographic (CT) study revealed a suprasellar isodense solid mass, which was enhanced homogeneously by the contrast medium (Figure 1). A magnetic resonance imaging (MRI) study showed an intrasellar and suprasellar isointense mass compressing the optic chiasm (Figure 2 left). The mass was enhanced homogeneously by Gd-DTPA agent (Figure 2 right). There were no other intrasellar or suprasellar masses, which may be the residual adenohypophysial or neurohypophysis. Angiogram showed no abnormalities except bilateral A1 elevation.

The patient was started on prednisolone (20 mg/day) for 2 weeks, and her headaches, general fatigue, and anorexia improved. However, visual disorders progressed gradually and her urine volume increased. The diagnosis at this point was nonfunctioning pituitary adenoma or lymphocytic hypophysitis. Because the visual symptoms as well as the size of the mass did not respond to the steroid therapy, and in order to establish a histologic diagnosis, transsphenoidal exploration of the sella was performed.

The sella was filled with an abnormally elastic hard dull white mass. It was avascular and was resected piecemeal. When more than half of the intrasellar mass was removed, there was a soft white region, that seems to show a normal residual pituitary, displaced superiorly adjacent to the abnormal region. No definite diagnosis was made on frozen section (chronic inflammation versus fibrous adenoma).

Pathologic study revealed massive fibrotic tissue accompanied by infiltration of some lymphocytes (Figure 3). Few adenohypophysial cells were distributed sparsely both singly and in small clusters throughout the fibrotic tissue. No granulomas or multinucleated giant cells were present. The lesion was characterized as a destructive chronic inflammatory lesion, and the diagnosis of lymphocytic hypophysitis with massive fibrosis was made.

After surgery, diabetes insipidus transiently became more prominent. It was controlled initially with occasional intramuscular injection of Pitressin, and later by DDAVP nose drops (desmopressin acetate). Both her visual acuity and visual fields were normalized (Vd; 1.2, Vs; 1.0) soon after the surgery. Her adenohypophysial function was not improved; therefore, replacement ther-
apy with hydrocortisone and thyroid hormone in addition to DDAVP nose drops was required.

Discussion
Lymphocytic hypophysitis is being recognized with increasing frequency as a pituitary mass lesion mimicking an adenoma. Although it has been reported that this disease is also seen in men [13,19] or post-menopausal women [7], the majority occurs in women during late pregnancy or during the postpartum period. It is well-known that this disease can cause hypopituitarism. In contrast with nonfunctioning pituitary adenomas, hypopituitarism generally develops more rapidly regardless of the size of the mass in patients with lymphocytic hypophysitis [3,10]. In addition, it tends to cause unusual patterns of endocrinologic abnormalities, e.g. isolated ACTH deficiency [8] or combined adrenal/thyroid deficiencies despite normal gonadal function [3,17]. Lymphocytic hypophysitis causes symptoms of an enlarged sellar mass such as visual disorders. It may also cause, albeit rarely, diabetes insipidus [6,7,10,12,14], cavernous sinus syndrome [14,19], or an occlusion of bilateral internal carotid arteries [6]. Our patient, who presented in the ninth month of pregnancy with visual disturbance, diabetes insipidus, and hypopituitarism, was strongly suspected of lymphocytic hypophysitis before surgery. Her laboratory data showed severe hypopituitarism, however, GH remained within the normal range.

Permanent diabetes insipidus presenting in lymphocytic hypophysitis before surgery has been reported, to our knowledge, in six cases [7,10,12,14]. As the neurohypophysis has been reported to be histologically normal in most cases of lymphocytic hypophysitis [3], the etiology of the diabetes insipidus is unknown. With the exception of one case [12], diabetes insipidus did not improve after the decompression by transphenoidal approach, including our case. It was suggested that diabetes insipidus may be due to the extent of inflammatory to [7] or direct destruction of the neurohypophysis, stalk, or hypothalamus.

The radiologic features of this lesion have been reported to be essentially identical to those of pituitary adenoma by neuroimaging studies—a homogeneous contrast-enhancing mass [3,9]. In our case, CT and MRI studies revealed an isodense well-enhanced mass, which is consistent with an adenoma. Therefore, though there are some clinical features that seem to be peculiar to lymphocytic hypophysitis, the diagnosis can be obtained only by histologic study of the surgical or autopsy specimen [1,7,9–11,18]. The differential diagnosis of lymphocytic hypophysitis may include: pituitary adenoma, Sheehan’s syndrome (pituitary necrosis), and other parasellar tumors or tumor-like lesions including granulomatous hypophysitis [3,4]. Among these para-
sellar lesions, nonfunctioning pituitary adenoma may be the most difficult to distinguish [3,9].

The histologic features of this lesion are characterized by diffuse lymphocytic infiltration, destruction of the normal organoid pattern, and replacement by a fibrosis. The degree of the lymphocytic infiltration and fibrosis differs from case to case, which seems to represent the various degrees of extent of destruction of the adenohypophysis and the stage of the lesion. In our case, the destruction of the adenohypophysis was severe, accompanied by massive fibrosis, whereas lymphocytic infiltration was not prominent. These findings seem to represent a chronic stage of an inflammatory lesion, which may also be similar to granulomatous hypophysitis, although granulomas and multinucleated giant cells were absent. In spite of the negative results of serologic studies, it may be difficult to distinguish, because the lesion was not totally examined. It is of interest that some authors have suggested that lymphocytic hypophysitis and granulomatous hypophysitis may be different phases of the same autoimmune process [13,14].

The natural history of lymphocytic hypophysitis is unknown, thus the management of this disease is still controversial [1,3,4,16]. Spontaneous resolution has been reported in some cases [1,2,5,11], and many asymptomatic cases may exist. Partial return of adenohypophysial function may occur, but it depends greatly upon the extent of adenohypophysial destruction [19]. On the other hand, some cases had a fulminating course and died of probable adrenal insufficiency [3]. At the present time, however, no predictive factors regarding the chronic course of this disease have been identified [15].

Most authors agree that the diagnosis of lymphocytic hypophysitis requires histologic study, however, it has been reported that surgical intervention is not always necessary [1,3–5,16]. This is because: (1) although the frequency is unknown, spontaneous resolution may occur. (2) Removal of the lesion, particularly when total removal was performed, may lead to an irreversible worsening of the preexisting hypopituitarism [9,11,12,16]. (3) Steroids or bromocriptine may be an effective medical treatment in some cases [1,4,18]. It has been proposed that patients of lymphocytic hypophysitis without gross visual impairment should be treated conservatively [3,5,16], including close observation, hormonal replacement, and steroid therapy [1,4,18]. Although steroids may suppress the inflammatory response and protect the remaining adenohypophysitis [4], there have been only few results to support this treatment and the efficacy is still controversial [3,17]. In our case when prednisolone was given (20 mg/day for 2 weeks) before surgery, her symptoms due to hypopituitarism apparently improved, whereas diabetes insipidus, which seemed to have been masked by the hypopituitarism, became more prominent. Although the dose and the duration of the steroids might have been insufficient [18], visual symptoms as well as the size of the mass did not show any improvement. Reusch et al [17] reported a case of lymphocytic hypophysitis unresponsive to a short course of dexamethasone. They suggested that the fibrosis in the lesion may not respond to steroids. Our case may also support this suggestion. In contrast to these cases, it was also suggested that in those cases showing spontaneous resolution of the mass and recovery of adenohypophysial function, the inflammation and the replacement by fibrosis had been mild. Steroids may be effective in such cases to suppress the inflammatory response.

Although lymphocytic hypophysitis is a distinct clinical entity, the natural history is unknown and various histologic stages and clinical courses seems to exist [1–4]. Without histologic study, it is not only difficult to distinguish them from an adenoma, but it is also difficult to speculate on the stage and course of the lesion. In cases with extensive destruction of the adenohypophysis and replacement by a massive fibrosis, sur-
gical intervention may be necessary, because spontaneous resolution and the effects of steroids are less likely. We believe that not only in cases with visual impairment, but also in cases that showed atypical features, such as diabetes insipidus or cavernous sinus syndrome, or that showed radiologic or neurologic deterioration during conservative treatment and observation, surgical intervention should be made without hesitation. Partial removal of the mass decompressing the surrounding structures by a transphenoidal approach seems to be the optimal surgical strategy, whereas total removal of the mass should be avoided [7,9,12,16].

The authors thank Dr. T. Sano (Department of Pathology, University of Tokushima School of Medicine) for his helpful comments on pathology.

References