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684 Recurrent Lymphocytic Hypophysitis: Case Report

Case Report

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ABSTRACT: OBJECTIVE AND IMPORTANCE: Lymphocytic hypophysitis is being recognized with increasing frequency, but the long-term course is not well known. Recurrence of lymphocytic hypophysitis after a long interval has never been reported.

CLINICAL PRESENTATION: A 53-year-old woman presented with central diabetes insipidus. Magnetic resonance imaging (MRI) revealed an intrasellar lesion. Transsphenoidal biopsy yielded a diagnosis of lymphocytic hypophysitis. Regression of the lesion was confirmed by follow-up MRI. The patient lived normally, with gradual improvement of diabetes insipidus, until she suddenly became aware of a visual defect, which developed into bitemporal hemianopsia 2 years after the biopsy. MRI revealed a large sellar lesion extending to the hypothalamus. However, the adenohypophysial function remained normal and the mild diabetes insipidus continued unchanged.

INTERVENTION: Prompt corticosteroid treatment was remarkably effective. The visual defect disappeared during steroid therapy, and a significant reduction of the lesion was revealed by MRI.

CONCLUSION: It is suggested that long-term follow-up with endocrinological and radiological studies may be necessary in cases of lymphocytic hypophysitis. Recurrent cases should be promptly treated with steroids when a definitive histological diagnosis had been confirmed.

KEY WORDS: Corticosteroid therapy; Lymphocytic hypophysitis; Pituitary gland; Recurrence; Transsphenoidal surgery

Lymphocytic hypophysitis is a rare chronic nonspecific inflammatory lesion of the pituitary gland mainly affecting the adenohypophysis. Nearly 100 cases have been reported, and characteristic features of this disease have become well known. The disease commonly affects women during late pregnancy or in the postpartum period and can cause hypopituitarism and visual disorders, mimicking nonfunctioning pituitary adenomas. Recent reports have demonstrated that the clinical features of lymphocytic hypophysitis are more complicated than previously thought, however, and that the natural history is variable. Thus, the management of this disease remains controversial. Although its efficacy in this disease remains uncertain, corticosteroid therapy has been recommended in recent reports. On the other hand, in some cases, radiological changes (including spontaneous resolution) during short-term follow-up has been well documented in the literature, but the long-term history of this disease remains poorly understood. We describe a case of lymphocytic hypophysitis, which we had previously reported, that showed recurrence 2 years after the transsphenoidal biopsy and was effectively treated with steroids. The natural history and the management of this disease are discussed.

CASE REPORT

A 53-year-old post-menopausal woman presented with polyuria (4000–7000 ml/d; specific gravity, 1.002) in November 1993. Her endocrinological diagnosis was central diabetes insipidus; however, the results of an adrenohypophysial function test, including a triple stimulation (thyrotropin-releasing hormone, 0.5 mg; luteinizing hormone-releasing hormone, 0.1 mg; regular insulin, 0.1 IU/kg) test, were normal except for growth hormone, which showed low response despite adequate hypoglycemia (<40 mg/dl). Although computed tomography failed to demonstrate the lesion, magnetic resonance imaging (MRI) disclosed an intrasellar mass lesion, which was poorly enhanced by gadolinium diethylene triamine penta-acetic acid (Fig. 1A). On the T1-weighted image, loss of the hyperintense signal of the neurohypophysis was observed but the pituitary stalk was not thickened. The patient underwent transsphenoidal biopsy in February 1994. A pathological examination demonstrated diffuse infiltration of lymphocytes and plasma cells associated with destruction of the adenohypophysis, fibrosis, and edema (Fig. 2). No granulomas or multinucleated giant cells were present. The diagnosis of lymphocytic hypophysitis was made. The patient did well postoperatively, and the diabetes insipidus gradually improved; therefore, desmopressin acetate became almost unnecessary 6 months after the biopsy. Although steroids were not used, regression of the lesion was revealed by MRI during the follow-up examination (Fig. 1B).

The patient suddenly became aware of a visual defect and a slight headache in June 1996, 28 months after the biopsy. At admission, a neurological examination revealed a bitemporal hemianopsia. The results of routine laboratory, cerebrospinal fluid, and serological examinations were normal. Antinuclear and other autoantibodies were negative, as were antipituitary antibodies (anticytoplasm and anticytere surface membrane) tested using the fluorescent antibody method. The results of the endocrinological examinations of the adenohypophysial hormones and the triple stimulation test were normal, except for the low response of growth hormone. The patient’s urine volume was 2000 to 4000 ml per day (specific gravity, 1.010) and had not shown a remarkable change for a year. Desmopressin acetate was occasionally used. The plasma antidiuretic hormone was 1.5 pg/ml (normal, 0.3–3.5 pg/ml). Computed tomography revealed an isodense sellar lesion with suprasellar extension, the margin of which was
enhanced by the contrast medium. On the T1-weighted image of MRI, a dumbbell-shaped isointensity lesion compressing the optic chiasm and extending to the hypothalamus was noted (Fig. 3A). The lesion showed irregular enhancement by gadolinium diethylene triamine penta-acetic acid (Fig. 3B). Recurrence of lymphocytic hypophysitis was suspected, and corticosteroid therapy was initiated at a daily dose of 30 mg of methylprednisolone for 1 week and at gradually decreasing doses during the next week. Steroid therapy was remarkably effective, resulting in the disappearance of the patient's headache and visual defect during the treatment at 1 month after recurrence. In addition, a significant reduction of the lesion was revealed by MRI (Fig. 3C) performed 2 weeks after the end of steroid therapy. The patient continued to do well, with slight diabetes insipidus that seldom required desmopressin acetate.

DISCUSSION
Recent reports have revealed that the clinical feature of lymphocytic hypophysitis is more complicated than previously thought. This patient, a postmenopausal woman, initially presented with diabetes insipidus and with visual disorder at the time of recurrence and did not show adenohypophysial dysfunction (12). A diagnosis of lymphocytic hypophysitis can be reliably obtained only by histological study, particularly in such atypical cases. The natural history of lymphocytic hypophysitis is variable (4,8,21), and no predictive factors regarding the chronological course of this disease have been identified (12). Radiological change may be observed in short-term follow-up studies (11,14). Furthermore, spontaneous resolution of the mass lesion and/or partial or total adenohypophysial function recovery has been reported (4,7,8,13,21). Recovery of adenohypophysial function in some cases may imply that some hypopituitarism may be caused secondarily by compression of residual tissue by inflammatory mass rather than by irreversible cellular destruction (5,21). It was also suggested that the gradual improvement of diabetes insipidus observed in the present case was a natural course of lymphocytic hypophysitis caused by a regression of inflammation of the neurohypophysial system. It has been suggested that the prognosis depends greatly on the extent of pituitary destruction by the inflammation (10,11,21). In contrast to these cases with various clinical courses in the short-term period, the long-term history of lymphocytic hypophysitis has been rarely reported. The pituitary has been suggested to become shrunken and atrophic at the chronic stage (9) and may cause empty sella syndrome at the end stage (13); however, a case of lymphocytic hypophysitis in which pituitary gland enlargement persisted for more than 10 years has been reported (9). It is well known that lymphocytic hypophysitis may be associated with other autoimmune conditions (5,13,21). In addition, albeit rarely, they may show recurrence. It was thus suggested that long-term observation is needed for patients with lymphocytic hypophysitis not only to perform hormonal replacement but for endocrinological and radiological follow-up studies.

A search of the literature failed to reveal a previous report of the recurrence of lymphocytic hypophysitis after a long interval. It is not likely that mild inflammation occurred for a long time in the present case, because regression of the lesion was confirmed by follow-up MRI. The autoantibodies examined in this case were always negative, and association with other autoimmune disorders was not seen. In addition to the pathogenesis of recurrence, it is also unclear why both adenohypophysial and neurohypophysial functions remained unchanged. Meanwhile, it needs to be emphasized that the histological diagnosis of lymphocytic hypophysitis should be carefully established because of the lack of specific histological markers (1,12,19). The histology of lymphocytic hypophysitis (lymphocytic infiltration, destruction of the adenohypophysis, and fibrosis) is nonspecific and may be observed in various other lesions. The same findings may be observed in adjacent compressed adenohypophysis in Rathke's cleft cyst and craniopharyngioma (7,19). Other inflammatory lesions, as well as secondary inflammatory response, such as previous hemorrhage in an occult adenoma (7), may exhibit similar findings. Furthermore, biopsy specimens are usually small fragments because it is necessary to avoid irreversible worsening of the preexisting hypopituitarism (13,5,11,16,21), and usage of steroids may have altered the original histology. In the present case, histological and immunohistochemical findings of the biopsy specimen, as well as radiological regression of the lesion after biopsy, suggest that the initial diagnosis of lymphocytic hypophysitis had been correctly established. On the other hand, although histological confirmation was not obtained, results of the examinations at the time of recurrence and a significant response to steroids indicated that the lesion was a recurrence of lymphocytic hypophysitis.

Although the management of lymphocytic hypophysitis is still controversial, conservative care with steroids has been recommended when gross visual disturbance is absent (1,3,5,6,10,16,20,21). Corticosteroid therapy has been advocated to reduce inflammation and protect the remaining adenohypophysitis (2,5,6,20), but its efficacy in this disease remains uncertain (10,18,21). It is suggested that steroids may be effective in the early stage of this disease when the pituitary becomes edematous, inflamed, and enlarged. However, when pituitary tissue is destroyed and replaced by fibrosis, steroids may not induce response (10,18). Therefore, in a case with a presumptive diagnosis of lymphocytic hypophysitis and without progressive compressive features, steroids should be attempted at an early stage (6). If the lesion does not respond to steroids, however, steroid therapy should not be continued, and transphenoidal surgery, which is both diagnostic and therapeutic in lymphocytic hypophysitis, should be performed.

In conclusion, we think that long-term follow-up may be needed for lymphocytic hypophysitis. When recurrence or radiological deterioration is recognized during follow-up, prompt steroid treatment should be
performed once a definitive histological diagnosis has been confirmed.

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REFERENCES


COMMENTS

In this case report of recurrent lymphocytic hypophysitis, Nishioha et al. call attention to several atypical aspects of the disease. First, this case involved a postmenopausal woman and contrasts with the more typical presentations that occur during pregnancy and/or the postpartum period. Second, this patient presented with diabetes insipidus. As a "rule," the inflammatory response in most morphologically verified cases has been observed to involve primarily the anterior pituitary; therefore, diabetes insipidus seldom occurs. Third, and most importantly, this report documents the occasionally unpredictable course of this condition and the potential for genuine clinical and radiographic recurrence. In each of these clinicopathological areas, this report illustrates that lymphocytic hypophysitis may not be as uniform and predictable a condition as is currently thought. Accordingly, and despite the apparent controversy surrounding this issue, we think that transphenoidal biopsy remains an important diagnostic step in the management of this disease.
Much has been written about lymphocytic hypophysitis during the last 8 years. There remains much to be learned about this disease. The cause is unknown, and the long-term course is not well documented. Autoantibodies have been sought but not often discovered. At the present time, this is not a useful diagnostic tool, but it remains interesting. To my knowledge, this is the first report of a recurrence with evidence revealed by magnetic resonance imaging that the process seems to have resolved.

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Hypophysitis is the common denominator for a collection of conditions of various origins and pathogenoses. It is important to differentiate lymphocytic from granulomatous giant-cell hypophysitis because, as far as we can judge from the literature, the two conditions seem to have different causes. The granulomatous, giant-cell hypophysitis may occur as a reaction to various local conditions, such as hemorrhages, pituitary adenomas, and Rathke’s cysts (2,3) (unpublished observation). We must assume that other conditions may be responsible for this histological variant whose pathogenesis, however, remains enigmatic in many cases.

Lymphocytic hypophysitis, on the other hand, seems to be an autoimmune disease analogous to the lymphocytic thyroiditis. There is supporting evidence for this interpretation. Patients have been described to have simultaneous lymphocytic inflammations of the pituitary and the adrenal or thyroid glands. I have recently observed a patient suffering from a combination of lymphocytic hypophysitis with Tolosa-Hunt syndrome (unpublished observation). That lymphocytic hypophysitis is often observed after pregnancy, a condition in which pituitary antibodies can be demonstrated with increased frequency with a complement consumption test (1), supports this interpretation.

We used to think that lymphocytic hypophysitis is a one-time event, precipitated, for example, by a pregnancy and ending either in a spontaneous cure or in a partial or total hypopituitarism. Many cases of Sheehan’s syndrome are not caused by ischemic infarction of the pituitary but by pre- or postpregnancy lymphocytic hypophysitis. Recurrences of surgically proven hypophysitis have not yet been reported. However, a review of the literature shows that a large percentage of the biopsied patients obviously underwent total hypophysectomies because postoperative panhypopituitarism was present. Therefore, no substrate for a manifestation of a continuing or recurring lymphocytic hypophysitis was present. This has changed. An increasing number of surgeons suspect that an exposed lesion may not be an adenoma and will thereby abstain from total mass
Figure 1. Coronal T1-weighted magnetic resonance image obtained at initial admission (A) and during the follow-up examination (B). At initial admission, a low-intensity intrasellar mass was noted (A). Regression of the lesion was observed after biopsy (B).

Figure 2. Photomicrograph of the surgical specimen, showing fibrous and edematous adenohypophysis with diffuse lymphocytic infiltration (hematoxylin and eosin stain; original magnification, ×240).

Figure 3. Coronal T1-weighted magnetic resonance images obtained at the time of recurrence (A and B) and 2 weeks after steroid therapy (C). A, dumbbell-shaped isointense lesion with suprasellar extension and compression of the optic chiasm. B, margin and inner portion irregularly enhanced by gadolinium diethylene triamine penta-acetic acid. C, significant regression of the lesion after steroid therapy.