Lymphocytic Adenohypophysitis Associated with Rathke’s Cleft Cyst

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Abstract
During the 8th month of her first pregnancy, a 40-year-old female suffered from visual disturbances. After treatment of pericarditis, which appeared 1 month after a normal delivery, she was referred to the neurosurgical department. She showed bitemporal hemianopsia, disturbance of visual acuity, and hypopituitarism. Initial computed tomography (CT) image showed a solid pituitary mass with suprasellar extension. However, 2 months later, the CT image changed to an enlarged partially cystic lesion. Transsphenoidal exploration of the sella demonstrated lymphocytic adenohypophysitis coexistent with Rathke’s cleft cyst. To our knowledge, such an association has never been reported previously. Presurgical diagnosis of lymphocytic adenohypophysitis still remains difficult and surgical intervention is necessary for definitive diagnosis. However, special attention is needed for the histological diagnosis of this lesion, particularly in clinically atypical cases.

Key Words: Pituitary gland; chronic inflammation; lymphocytic adenohypophysitis; Rathke’s cleft cyst; transsphenoidal surgery.

Introduction
Lymphocytic adenohypophysitis is a distinct clinicopathological entity consisting of a lesion showing chronic pituitary inflammation. This disease has been reported recently with increasing frequency [1–3], most cases being solid pituitary mass lesions mimicking pituitary adenoma in females during late pregnancy or during the postpartum period. The pathogenesis of lymphocytic adenohypophysitis is believed to be autoimmune, however, its natural history is still unknown and various clinical as well as histological features seem to exist [1,2,4]. In addition, computed tomography (CT) and magnetic resonance imaging (MRI) studies are not helpful in distinguishing lymphocytic adenohypophysitis from pituitary adenomas [2,5]. Thus, it remains difficult to obtain a correct diagnosis without surgical exploration, and the management of this disease is still controversial [1,2,4,6].

This article describes a case of lymphocytic adenohypophysitis associated with a Rathke’s cleft cyst. To our knowledge, such an association has never been reported. Possible mechanisms of such an association and the management of lymphocytic adenohypophysitis are discussed.

Case Report
A 40-yr-old female became aware of visual disturbance in her left eye during the 8th mo of her first pregnancy. One month after a full-term normal delivery of a healthy infant, she suffered from high fever, chest pain, and dyspnea. She was admitted to our hospital with a diagnosis
of pericarditis, myocarditis, and hepatitis C. Titers for viral (Coxsackie, ECHO, adeno, influenza, and so on) and bacterial (streptococcus, pneumococcus, and so on) showed normal results. In addition, autoantibodies (antinuclear, anti-DNA, anti-RNP, antmyocardial, and so on), rheumatoid factor (RF) test, and lupus erythematosus (LE) factor were all negative. Thus, etiology of the pericarditis/myocarditis remained uncertain. When her condition improved 1 mo later, she was referred to the neurosurgical department because of slowly progressive visual disturbance. She had no other previous medical problem.

She was lethargic and had failed to lactate. Neurological examination showed bitemporal hemianopia and disturbances of visual acuity: Vd; 0.05 (nc), Vs; 0.03 (nc). Other neurological examinations and routine laboratory examinations showed normal results apart from slight liver dysfunction (Table 1). Endocrinological evaluation revealed hypopituitarism: adrenocorticotropic hormone (ACTH) <5 pg/mL (normal, 9–52), luteinizing hormone (LH) <0.5 mIU/mL (normal, 5–20), follicle-stimulating hormone (FSH) <0.5 mIU/mL (normal, 10–40), prolactin <1.0 ng/mL (normal, 1.4–14.6), and cortisol <1.0 μg/dL (normal, 4.0–18.3). However, thyroid-stimulating hormone (TSH) 0.68 μU/mL (normal, 0.34–3.5) and growth hormone (GH) 1.8 ng/mL (normal, 0.66–3.68) were normal. These adrenohypophysial hormones showed no response to the triple stimulation (thyrotropin-releasing hormone, LH-releasing hormone, insulin) test. The plasma antidiuretic hormone was 0.8 pg/mL (normal, 0.3–3.5). Antipituitary (anticyttoplasm and anticytmembrane) antibodies were negative.

A CT image revealed a homogeneously enhanced solid pituitary mass with suprasellar extension (Fig. 1A). Two months later, however, the CT image changed to an enlarged partially cystic tumor (Fig. 1B). An MRI study showed an intrasellar and suprasellar partially cystic lesion compressing the optic chiasm (Fig. 2A). On the T1-weighted image, the solid portion of the lesion was hypointense and was enhanced by Gadolinium diethylenetriamine penta-acetic acid (Fig. 2B), whereas the cystic portion, located in the superoposterior part of the lesion, showed isointensity. There were no other intrasellar or suprasellar regions which may be the residual adenohypophysis or neurohypophysis. Differential diagnosis at this point included nonfunctioning pituitary adenoma
Transphenoidal approach. When the dura removed, the lesion was performed by a partial deroofing, craniopteroneal, and lateral approach. Following a partial delivery, Rathke's pouch and adenohypophysis were resected with intraoperative hemorrhage. Fanshawe et al. (1982) reported a partially solid, oligodendroglioma with homogenous enhancement of the solid portion of the lesion.

**FIG. 2** (a) Coronal T2-weighted MR demonstrating isointensity lesion compressing the optic chiasma. Sagittal gadolinium MR demonstrating an enlarged cystic mass.

**FIG. 1** (a) Initial enhanced CT image showing a solid pliarily mass. (b) Enhanced CT image 2 months after initial study demonstrating an enlarged cystic mass.
Fig. 3. (A) Photomicrograph of a surgical specimen obtained from solid portion of the lesion revealed diffuse and extensive infiltration of lymphocytes, with destruction of the glandular structures and replacement by fibrosis (H & E stain, ×130). (B) Photomicrograph of a surgical specimen obtained from cyst wall showing ciliated columnar epithelium (H & E stain, ×260).

Pathological examination demonstrated diffuse and extensive infiltration of lymphocytes associated with fibrosis (Fig. 3A). Some areas showed lymphocytic aggregates. By immunohistochemistry, lymphocytes infiltrating between residual adenohypophysial cells were predominantly positive for UCHL-1 (Dako, Denmark), whereas lymphocytes forming lymphoid follicles were mainly positive for L26 (Dako). Destruction of the glandular structure was prominent and a few nests of residual adenohypophysial cells were distributed sparsely. By immunohistochemistry, the proportion of the residual adenohypophysial cells were GH >> TSH > prolactin > FSH and LH > ACTH (all provided from NIDHH), and ACTH immunoreactive cells were only occasionally observed. On the other hand, the cyst surface was covered by ciliated columnar epithelium (Fig. 3B). The cyst was located in periphery of the lesion, whereas infiltration of lymphocytes and fibrosis were observed throughout the lesion. No adenomas, granulomas, or multinucleated giant cells were present. A diagnosis of lymphocytic adenohypophysitis with a Rathke’s cleft cyst was made.

The patient had transient diabetes insipidus but otherwise did well postoperatively. Her visual acuity and visual field improved immediately after surgery. However, endocrinological study revealed no improvement of her adenohypophysial dysfunction, therefore, hormone replacement with hydrocortisone was continued.

Discussion

Despite its characteristic features, difficulties in the presurgical diagnosis of lymphocytic adenohypophysitis have been pointed out by many authors [1,5,7,8]. Various atypical cases have been reported recently (e.g., male cases [9–11], postmenopausal female cases [7], cases showing presurgical diabetes insipidus [7,12,13],...
mater of the sella, which seemed normal, was opened, an abnormally elastic-hard, dull-white mass was exposed. During resection of the mass with sharp dissection, yellow mucoidal fluid flowed out from the cystic cavity behind the dull-white mass. Normal residual pituitary tissue was not observed.

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Discussion

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cavernous sinus syndrome [11,13], and the case described in this report which presented as a cystic tumor). In addition, the natural history of this disease is still unknown and various patterns of clinical courses seem to exist. Furthermore, histological findings differ from case to case. While some cases have been reported with slight destruction of the adenohypophysis and lymphocytic infiltration, others show complete disappearance of glandular structures accompanied by massive fibrosis [12,14]. Although it has been reported that, at the present time, no predictive factors regarding the chronological course of this disease have been identified [3], histological examination may offer more significant information. It seems appropriate to consider that the prognosis of this disease depends on the degree of hypophysial destruction [11]. Thus, histological examination of lymphocytic adenohypophysitis is necessary not only for establishing a definitive diagnosis, but it also provides a basis for speculation on the course and prognosis of this disease [12].

The management of lymphocytic adenohypophysitis has been controversial. When gross visual disturbance is absent, conservative treatment including steroids and hormonal replacement has been recommended in recent reports [1,2,4,6,8]. Although steroids are worth trying, their efficacy with regard to this disease still remains questionable [2,12,14]. We have previously reported that not only in patients with visual impairment, but also in patients who showed atypical features or who showed radiological or neurological deterioration during conservative treatment, surgical intervention should be made without hesitation [12]. To avoid irreversible worsening of the pre-existing hypopituitarism, partial removal of the mass decompressing the optic tract by a transsphenoidal approach is the optimal surgical strategy [5–7,12]. Thus, when lymphocytic adenohypophysitis is suspected before surgery and elastic-hard, dull-white tissue is exposed during transsphenoidal exploration, total removal of the mass must be avoided. We believe that the present case which showed atypical features, a partially cystic tumor, should also be included in this strategy.

To the best of our knowledge, coexistence of lymphocytic adenohypophysitis and Rathke's cleft cyst has never been reported previously. Although it may merely be a coincidence, one of these two lesions may have influenced the other. It is well known that Rathke's cyst accompanies some lymphocytic infiltration. Coexistence of granulomatous hypophysitis and Rathke's cyst has been reported by Albini et al. [15]. They suggested that the inflammatory process of granulomatous hypophysitis represents a foreign body reaction to leakage of cyst contents, with destruction of pituitary tissue. Granulomatous hypophysitis, which represents the giant-cell granulomas of unknown origin, is another mass-forming pituitary inflammatory lesion which is included in the differential diagnosis of lymphocytic adenohypophysitis. Granulomatous hypophysitis may be difficult to differentiate from lymphocytic adenohypophysitis even with histological studies, when typical multinucleated giant cells are absent in the small surgical specimen. In addition, it is of interest that some authors have reported that granulomatous hypophysitis and lymphocytic adenohypophysitis have common ultrastructural features, which may represent different stages of a single disease [10,13]. In the present case, however, initial CT image showed a solid mass, which then changed to a partially cystic lesion. Thus, it is inappropriate that lymphocytic adenohypophysitis was caused by preceding Rathke's cyst. On the other hand,
although it may be less likely, lymphocytic adenohypophysitis might have induced the retention cyst, the Rathke’s cyst. Chronic inflammation of the adenohypophysis may have stimulated and affected the growth of the pre-existent small Rathke’s cyst or cyst of the pars intermedia. Partial regression of the cystic portion of the lesion by steroids may support this hypothesis.

Another unique feature of this case was preceding pericarditis/myocarditis. Although an autoimmune process may also participate in pericarditis/myocarditis as a complication of collagen diseases, association with lymphocytic adenohypophysitis has never been reported. Since all the examination in relation to autoimmune disorders was negative in this case, correlation between pericarditis/myocarditis and lymphocytic adenohypophysitis was unknown.

In the present case, lymphocytes infiltrating between residual adenohypophysial cells were predominantly positive for UCHL-1, indicating that they are T-cells, whereas lymphocytes forming lymphoid follicles were mainly positive for L26, indicating that they are B-cells. These findings are identical to the previous report of Hashimoto et al. [16]. The lymphocytes are mostly T-cells, particularly CD4 cells, in most cases with lymphocytic adenohypophysitis [4,16,17]. On the other hand, the proportion of the residual adenohypophysial cells were GH >> TSH > prolactin > FSH and LH > ACTH. Although accurate ratio of these cells were undetectable, it seems that this result is compatible with endocrinological findings, which showed hypopituitarism apart from GH and TSH secretion.

Histological findings of lymphocytic adenohypophysitis are characterized by diffuse lymphocytic infiltration, destruction of the normal glandular structure, and replacement by fibrosis. Lack of granuloma, multinucleated giant cells, and epi-

thelioid histiocytes also are necessary for the diagnosis, however, these findings remain nonspecific. In addition, small surgical specimens may not present its representative features, especially when steroids have been used or the lesion is in its chronic stage. Furthermore, these nonspecific findings also are observed in adjacent compressed adenohypophysis in some cases of various pituitary lesions, including cranio-pharyngioma [18] and Rathke’s cleft cyst. Thus, histological diagnosis of lymphocytic hypophysitis is difficult and other lesions may easily be misdiagnosed. It has to be stressed that special attention is needed for the diagnosis of lymphocytic adenohypophysitis, particularly in clinically atypical cases.

References

Lymphocytic Hypophysitis with Rathke’s Cyst