NOTE

A Case of Cystic Lymphocytic Hypophysitis with Cacosmia and Hypopituitarism

SEONG JIN LEE, HYUNG JOON YOO, SUNG WOO PARK AND MOON GI CHOI

Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, Hallym University, ChunCheon, 200-704 Korea

Abstract. Lymphocytic hypophysitis is a rare inflammatory disease of the pituitary gland that is being increasingly recognized as a cause of hypopituitarism. This condition may be due to an autoimmune pituitary destruction which usually occurs in young women during pregnancy or in the immediate postpartum period. We describe a case of cystic pituitary mass in a thirty-eight year-old woman presenting with nausea, vomiting, cold intolerance, blurring of vision and the presence of disagreeable odors for a one-month period. She had secondary amenorrhea and galactorrhea for three months. Combined anterior pituitary stimulation test confirmed the diagnosis of hypopituitarism. Magnetic resonance imaging scan with enhancement showed a huge cystic sellar mass with suprasellar extension and thickening of the pituitary stalk. Transsphenoidal exploration was performed with preoperative diagnosis of pituitary macroadenoma with cystic necrosis. Histological examination revealed lymphocytic hypophysitis characteristic of diffuse, dense lymphocytes and plasma cells infiltration with surrounding interstitial reactive fibrosis. Postoperatively, the patient’s olfactory function returned to normal but combined anterior pituitary stimulation test showed persistence of hypopituitarism with mild hyperprolactinemia. Prednisolone, thyroxine and estrogen replacements were started and clinical symptoms were much improved. In summary, we report an extremely rare case of a woman with cystic lymphocytic hypophysitis with cacosmia and hypopituitarism, confirmed by histological examination.

Key words: Cystic lymphocytic hypophysitis, Cacosmia, Hypopituitarism, Magnetic resonance imaging


LYMPHOCYTIC hypophysitis is a rare inflammatory lesion of the pituitary gland, usually involving the adenohypophysis. Most cases are in young women during pregnancy or in the immediate postpartum period with a few in postmenopausal women and in men, suggestive of an autoimmune mechanism to this condition [1–4]. The clinical presentation and radiological findings may mimic pituitary macroadenoma in many cases. Patients often present with severe complications such as hypopituitarism. The diagnosis of this entity should be made by histological findings characteristic of massive infiltration of lymphocytes and plasma cells followed by necrosis or surrounding parenchymal fibrosis [5, 6]. Previously reported cases of lymphocytic hypophysitis have nonspecific, solid enlargement of the pituitary gland but only 5 cases of cystic lymphocytic hypophysitis have been described in English literature [7–9].

We report an extremely rare case of a woman with cystic lymphocytic hypophysitis with cacosmia and hypopituitarism, confirmed by histological examination.

Case Report

A thirty-eight year-old housewife presented with a one-month history of anorexia, nausea, vomiting, cold intolerance, blurring of vision and the presence of disagreeable odors. She had secondary amenorrhea and
galactorrhea for three months before visit to our hospital. She had no past medical history of seizure disorder or head injury, and had no family history of autoimmune or endocrine disorders. She delivered her last baby four years ago. On physical examination, pubic and axillary hairs were normally developed (Tanner stage V). Respiratory, abdominal and neurological examinations were completely unremarkable. Visual fields were intact.

The patient’s blood chemistry was normal, while her complete blood count demonstrated normocytic normochromic anemia with normal white blood cell and platelet counts. HIV serologic test was negative. None of the antibodies were detected against TSH receptor, microsome (thyroid peroxidase), thyroglobulin, gastric parietal cell, nucleus and mitochondria. All blood, sputum and urine cultures for bacteria, mycobacteria and fungi were negative.

Basal hormonal investigation showed secondary thyroid, adrenal and gonadal failure with elevated serum prolactin level at 45.3 ng/mL (normal: 1.3–20.8): GH 0.6 ng/mL (normal: <1.46), T3 81 ng/dL (normal: 85–185), T4 3.7 μg/dL (normal: 5.5–11.5), TSH 0.2 μIU/mL (normal: 0.3–5.0), cortisol 0.1 μg/dL (normal: 7–21) at 0800 h, ACTH 6.8 pg/mL (normal: 0–80), LH and FSH 0.1 mIU/mL (normal: 2.0–15.4) and 1.3 mIU/mL (normal: 1.7–8.5), respectively. Combined anterior pituitary stimulation test by intravenous injection of regular insulin (0.3 U/kg), TRH (400 μg) and LHRH (100 μg) confirmed the diagnosis of hypopituitarism (Table 1).

Magnetic resonance imaging (MRI) scan of the sellar region revealed a well-demarcated large sellar mass arising from the pituitary fossa of peripheral rim enhancement and cystic appearance with suprasellar extension and upward anterior displacement of the thickened pituitary stalk, suggestive of pituitary macroadenoma with cystic necrosis (Fig. 1). The optic chiasm was compressed, and was upwardly displaced by the pituitary mass. The diagnosis of hypopituitarism probably secondary to the huge cystic sellar mass was made. For confirmative diagnosis, transsphenoidal surgery was performed after preoperative prednisolone and thyroxine replacement.

At transsphenoidal exploration of the cystic sellar mass, a yellowish, firm cyst wall with fibrous tissue was exposed, and a cystic cavity filled with creamy, necrotic material was found. The wall of the cyst and macroscopically abnormal surrounding tissues were totally removed. Normal anterior pituitary gland could barely be in peripheral portion. Histological examination revealed necrosis with diffuse, dense infiltration of lymphocytes and plasma cells with interstitial reactive fibrosis intercalated by eosinophils and normal pituitary glandular cells, suggestive of a chronic inflammatory change (Fig. 2). Aggregates of foamy cells and macrophages were also noted. There was no evidence of neutrophils, giant cells, granulomatous or caseous necrosis, neoplastic cells, Rathke’s pouch remnant, craniopharyngioma or organisms including bacteria. The findings were compatible with lymphocytic hypophysitis with reactive fibrosis.

The patient’s olfactory function returned to normal but postoperative combined anterior pituitary stimulation test showed persistence of hypopituitarism with increased prolactin levels at 36.0 ng/mL. Prednisolone, thyroxine and estrogen replacements were started and clinical symptoms were much improved.

**Discussion**

Lymphocytic hypophysitis was first described by Goudie and Pinkerton in 1962; since then, more than 120 cases have been reported. Although the etiology remains to be clarified, considerable evidence exists for an autoimmune mechanism but our case had no features of autoimmune phenomenon [10, 11].

In lymphocytic hypophysitis, the inflammatory process usually appears to be confined to the adenohypophyseal region but the abnormalities may also involve the infundibulo-neurohypophyseal portion resulting in diabetes insipidus in a few patients [1, 12–15]. In some case reports, dense lymphocyte and plasma cell infiltration of the pituitary gland has been classified

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**Table 1.** Preoperative combined anterior pituitary stimulation test. Insulin (0.3 U/kg), TRH (400 μg) and LHRH (100 μg) were given intravenously.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Glucose (mg/dL)</th>
<th>GH (ng/mL)</th>
<th>ACTH (pg/mL)</th>
<th>Cortisol (μg/dL)</th>
<th>TSH (μU/mL)</th>
<th>FSH (mIU/mL)</th>
<th>LH (mIU/mL)</th>
<th>Prolactin (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>76</td>
<td>0.6</td>
<td>6.8</td>
<td>0.1</td>
<td>0.4</td>
<td>1.3</td>
<td>0.1</td>
<td>45.3</td>
</tr>
<tr>
<td>30</td>
<td>25</td>
<td>0.6</td>
<td>7.1</td>
<td>0.1</td>
<td>3.0</td>
<td>3.2</td>
<td>0.1</td>
<td>65.3</td>
</tr>
<tr>
<td>60</td>
<td>39</td>
<td>0.4</td>
<td>6.5</td>
<td>0.1</td>
<td>4.0</td>
<td>7.1</td>
<td>0.1</td>
<td>116.2</td>
</tr>
<tr>
<td>90</td>
<td>156</td>
<td>0.2</td>
<td>3.4</td>
<td>0.1</td>
<td>3.7</td>
<td>9.6</td>
<td>0.1</td>
<td>120.0</td>
</tr>
</tbody>
</table>
according to the site of infiltration: lymphocytic adenohypophysitis (LAH), infiltration confined to the adenohypophysis [16]; lymphocytic infundibuloneurohypophysitis (LINH), infiltration of the infundibulum and neurohypophysis [17]; lymphocytic panhypophysitis (LH), infiltration of both the adenohypophysis and neurohypophysis [18]. Because our patient preserved posterior pituitary function, we could diagnose our case as LAH by the above classification but it needs to be further followed to determine whether diabetes insipidus develops.

The endocrinological manifestation of lymphocytic hypophysitis can widely vary from only hyperprolactinemia probably due to stalk compression to hypopituitarism mimicking Sheehan’s syndrome [1]. Hyperprolactinemia is often presented in patients with lymphocytic hypophysitis including our case and, in many cases, elevated prolactin levels may provide a clue of this entity [1]. Stalk compression resulting in decreased dopamine delivery from the hypothalamus to the anterior pituitary gland is a major cause of hyperprolactinemia. However, an autoimmune mechanism involving the production of stimulating antibodies by plasma cells may lead to increased prolactin secretion [19]. Co-existing autoimmune disorders are described but the incidence is uncertain [1, 2, 5]. Stalk

Fig. 1. Preoperative (a) sagittal, (b) coronal, and (c) horizontal contrast-enhanced magnetic resonance imaging (MRI) scans showing a huge cystic sellar mass of low signal content and peripheral rim enhancement with suprasellar extension, thickening of the pituitary stalk and compression of optic chiasm.
compression as well as diffuse destruction by the inflammatory process contribute to the development of complete or partial anterior pituitary hormonal deficiencies. Selective loss of adenohypophyseal cells is likely to be the result of targeted autoimmune attack [20]. Although stalk compression was the primary insult for hyperprolactinemia and hypopituitarism in our case, massive necrosis with diffuse, dense infiltration of lymphocytes and plasma cells may suggest evidence for the co-existence of severe glandular destruction. Some patients spontaneously recover normal anterior pituitary function and a trial of corticosteroid administration to aid resolution has been advocated [4, 21]. In most patients, however, hypopituitarism persists even after intensive corticosteroid treatment.

Although unusual MRI scan findings such as peripheral rim enhancement and thickening of the pituitary stalk may strongly suggest lymphocytic hypophysitis, the clinical or radiological distinction between non-functioning pituitary macroadenoma and lymphocytic hypophysitis is very difficult in most cases [13, 22]. The most prominent radiological feature is the presence of pituitary stalk thickening [7, 23, 24]. Lymphocytic hypophysitis shows the enlargement of the pituitary gland with homogeneous enhancement and compression of optic chiasm [16]. Lymphocytic hypophysitis usually reveals a solid sellar mass without focal sign in the supra- or infrasellar region but the enlarged pituitary gland may extend into the suprasellar region or even the cavernous sinus in rare cases [12, 25]. LINH, in some cases, characteristically demonstrates the absence of the high signal of normal neurohypophysis on T1-weighted image as well as thickening of the pituitary stalk but no clear distinctive finding between lymphocytic hypophysitis and LINH can be made on MRI scan [17, 18]. There are thus many variations of MRI features of lymphocytic hypophysitis. Our patient had the peripheral rim enhancement and the thickened pituitary stalk with the normal signal of neurohypophysis on T1-weighted image at presentation.

Since Farah et al. first reported cystic lymphocytic hypophysitis, only 5 cases of cystic lymphocytic hypophysitis and 2 cases of cystic granulomatous hypophysitis have been described, while Puchner et al. reported 3 cases of lymphocytic hypophysitis with cystic craniopharyngioma [7–9, 26]. Although the evidence of Rathke’s cleft cyst or craniopharyngioma such as columnar epithelial layers or squamous metaplasia was not found in our case, the possibility remains that the histological findings of this patient’s pituitary tissue may be the secondary changes caused by some other cystic diseases. Xanthomatous hypophysitis, the least common form of primary hypophysitis, is also likely to be cystic on radiological or surgical evaluation but these lesions are defined only histologically by the presence of lipid-rich foamy histiocytes with variable numbers of lymphocytes [27]. Even though histological finding in our case revealed some aggregates of foamy cells and macrophages, it was compatible with lymphocytic hypophysitis. This overlapping feature should remind us that it is unclear whether lymphocytic and xanthomatous hypophysitis are truly distinct entities or different manifestations of the same disease. Therefore, our patient is of interest as is an extremely rare case of lymphocytic hypophysitis with cystic appearance, homogenous peripheral rim enhancement and the pituitary stalk thickening on Fig. 2. Histological findings. (a) Diffuse, dense infiltration of lymphocytes and plasma cells and (b) surrounding interstitial reactive fibrosis intercalated by normal pituitary glandular cells are shown.

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**Fig. 2.** Histological findings. (a) Diffuse, dense infiltration of lymphocytes and plasma cells and (b) surrounding interstitial reactive fibrosis intercalated by normal pituitary glandular cells are shown.
MRI scan.

Cacosmia, the presence of disagreeable or foul odors, may appear in certain psychic states and occasionally follows a head injury, especially to the uncal area. Our case had cacosmia but no history of head or brain injury. In addition, the patient’s olfactory function returned to normal after removal of cystic mass despite postoperative persistence of hypopituitarism. Therefore, in our case, it seems to be caused by the irritative process of the pituitary mass in the olfactory tract or medial part of temporal lobe.

In conclusion, lymphocytic hypophysitis should be included in the differential diagnosis of a cystic pituitary mass, and the confirmative diagnosis must be performed by surgical exploration and histological findings.

References


