NOTE

Symptomatic Rathke's Cleft Cyst Coexisting with Central Diabetes Insipidus and Hypophysitis: Case Report

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Abstract. We describe a 48-year-old female with acute onset of central diabetes insipidus followed by mild anterior pituitary dysfunction. Magnetic resonance imaging (MRI) revealed enlargement of the hypophysis-infundibulum accompanied by a cystic component. She underwent a transphenoidal exploration of the sella turcica. Histological examination showed foreign body type xanthogranulomatous inflammation in the neurohypophysis which might have been caused by rupture of a Rathke's cleft cyst. The MRI abnormalities and anterior pituitary dysfunction improved after a short course of corticosteroid administration, but the diabetes insipidus persisted. The histological findings in this case indicated the site of RCC rupture and the direction of the progression of RCC induced neurohypophysitis and adenohypophysitis.

Key words: Rathke's cleft cyst, Central diabetes insipidus, Hypophysitis


RATHKE'S cleft cysts (RCC), found in 2–33% of routine autopsy series [1, 2], are considered to arise in the remnants of Rathke's pouch, an invagination of the stomodeum [3, 4]. They are classically described as benign epithelial cysts containing mucoid material. Symptoms, when present, result from compression of the optic chiasm, hypothalamus or pituitary gland by these cysts [5–7]. But RCCs are occasionally accompanied by a foreign body inflammatory process around the cyst wall and some of these inflammatory processes involve the adjacent pituitary gland, resulting in panhypopituitarism [8–10].

We report a RCC patient who presented with diabetes insipidus (DI), in which anterior pituitary function was relatively preserved. The pathogenesis of the pituitary dysfunction is discussed herein.

Case Report

A 48-year-old Japanese woman presented with a history of sudden onset of polyuria and polydipsia in May, 1991. Her past history included oophorectomy for endometriosis and myoma uter. Initially she was diagnosed as having diabetes mellitus and managed with diet therapy. Six months later she was admitted to another hospital because of worsening polyuria and polydipsia. She was diagnosed as having central DI by means of the water deprivation and Carter-Robbins tests. MRI revealed enlargement of the hypophysis-infundibulum. She was admitted to the Department of Neurosurgery, Hiroshima University Hospital on December 11, 1991.

On admission, she was overweight at 53.5 kg, and was 154 cm tall. She was fully oriented and
her visual field was normal. Physiological and neurological examinations revealed no abnormalities. The urine volume was 3000–4000 ml/ day, and the specific gravity around 1.005. The white cell count was 10300, and C-reactive protein was 3.2 mg/dl, suggesting the existence of inflammation somewhere in her body. Plasma glucose was 148 mg/dl indicating mild diabetes mellitus. Serum treponema pallidum hemagglutination, purified protein derivatives (PPD), Rheumatoid factor, antinuclear antibody and antipituitary antibodies were negative. The chest and abdominal X-rays revealed no abnormalities. Her cerebrospinal fluid (CSF) cultures were negative for common bacteria, mycobacterium tuberculosis and fungi. Other laboratory studies were also within normal limits.

MRI demonstrated thickening of the pituitary stalk, and enlargement of the hypophysis accompanied by a small cystic lesion in the sella turcica. Hyperintensity of the posterior pituitary lobe was not seen in a T1 weighted sagittal image. Both the pituitary stalk and the hypophysis were strongly enhanced by Gadolinium (Fig. 1).

Anterior pituitary function was investigated with a set of three tests; insulin tolerance test, TRH (50 μg) test, and LHRH (100 μg) test. Serum GH, cortisol, TSH, PRL, LH and FSH were measured by radioimmunoassay as described previously [11]. The criteria for normal basal values and normal responses to stimuli used in this study were also described in the previous report [11]. GH, LH and TSH responses were compromised, while cortisol, PRL and FSH responses were well preserved (Table 1).

**Operation**

In order to obtain an exact diagnosis, transsphenoidal exploration was performed after obtaining informed consent. The floor and the dura mater of the sella turcica appeared intact. The color and texture of the pituitary gland also appeared to be normal. White mucus flowed from the cyst when the anterior pituitary was incised. Grayish granulation tissue posterior to the cyst was

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**Fig. 1.** Left: T1-weighted sagittal magnetic resonance imaging demonstrates thickening of the pituitary stalk and enlargement of the hypophysis associated with a small cystic lesion in the sella turcica. Right: Gd-DTPA enhanced sagittal magnetic resonance image. Note that the signals from both the pituitary stalk and the hypophysis are clearly increased.
Table 1. Pituitary functions pre- and post-operatively

<table>
<thead>
<tr>
<th></th>
<th>On admission</th>
<th>1 month after operation</th>
<th>4 months after operation</th>
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<tbody>
<tr>
<td></td>
<td>Base Peak</td>
<td>Base Peak</td>
<td>Base Peak</td>
</tr>
<tr>
<td>Insulin-induced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypoglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH ng/ml</td>
<td>3.2 4.8</td>
<td>1 3.1</td>
<td>0.62 7.6</td>
</tr>
<tr>
<td>Cortisol µg/dl</td>
<td>14 20.4</td>
<td>5.9 10.6</td>
<td>9.8 24.7</td>
</tr>
<tr>
<td>TRH (500 µg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH µU/ml</td>
<td>0.7 3.8</td>
<td>0.6 2.4</td>
<td>1.76 9.81</td>
</tr>
<tr>
<td>PRL ng/ml</td>
<td>9 33</td>
<td>5.9 13</td>
<td>7.2 25</td>
</tr>
<tr>
<td>LH-RH (100 µg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH mIU/ml</td>
<td>2.6 9.6</td>
<td>1.7 10</td>
<td>4.5 30</td>
</tr>
<tr>
<td>FSH mIU/ml</td>
<td>17 25</td>
<td>13 20</td>
<td>20 35</td>
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</table>

The values in brackets are standard normal values.

removed.

Histologic findings

Histologic examination of the surgically removed tissue revealed the cyst to be lined with ciliated columnar epithelium and to contain mucus. The continuity of the cyst wall was partially disrupted in some places (arrows). Lymphocytes, neutrophils, and a few foamy cells infiltrated the cyst and the surrounding area (Fig. 2a). Immunoperoxidase staining of the surgical specimens prior to the cyst wall was positive for both anti-neurofilament antibody and anti-glial fibrillary acidic protein (GFAP) antibody. This finding suggested that this specimen was obtained from the neurohypophysis (data not shown). Marked fibrosis, accompanied by capillary proliferation, and diffuse infiltration by lymphocytes, plasma cells and neutrophils were revealed in the neurohypophysis which was compatible with the prolonged chronic inflammation with granulation (Fig. 2b). Most of the cystic wall was destroyed by the inflammatory change and replaced by granulation or fibrous tissue, and a vestige of it remained in the neurohypophysis. The anterior pituitary lobe was infiltrated by foreign body reaction, consisting of a various inflammatory cells, i.e. lymphocytes, plasma cells and foammacrophages, but the anterior pituitary cells were relatively well preserved (Fig. 2c).

Immunohistochemical staining demonstrated that T (UCHL1; positive) and B lymphocytes (L26; positive) had infiltrated the anterior and posterior pituitary lobes. In these findings there was no evidence of autoimmune inflammation or specific inflammation, such as tuberculosis or sarcoid granuloma.

Postoperative course

Postoperatively, the patient developed general fatigue. A diagnosis of acute pituitary dysfunction was made. The patient was treated with intravenous injection of betamethasone (8 mg/day), which was tapered off over two days (total 14 mg) followed by the administration of cortisol acetate for 5 days.

In February, 1992 her anterior pituitary function was examined by a set of three tests. The responses of anterior pituitary hormones other than PRL were considerably impaired (Table 1). Diabetes insipidus was still present, but MRI showed that the hypophysis-infundibulum was remarkably decreased in size. She was discharged on a replacement therapy regimen of desmopressin acetate.

Four months after the surgery, the anterior pituitary function was investigated again. The GH response was still impaired, but those of cortisol, LH, FSH, TSH, and PRL had nearly normalized (Table 1). Thirty months after the surgery, she still needed desmopressin acetate treatment. MRI demonstrated slight atrophy of the infundibulo-hypophyseal structure and the continued absence of hyperintensity of the neurohypophysis in T1 weighted images (Fig. 3). Seven years after the surgery, MRI showed no recurrence, and the pituitary function test data were almost within normal limits, but the diabetes insipidus had persisted (Table 2).
Fig. 2. (a) Photomicrograph of the cyst lining composed of ciliated columnar epithelium. The continuity of the cyst wall was partially disrupted in some places (arrows). Lymphocytes, neutrophils, and a few foamy cells have infiltrated the cyst and the surrounding area (hematoxylin and eosin, × 115). (b) Photomicrograph of the neurohypophysis demonstrates high degrees of fibrosis, accompanied by various amounts of capillary proliferation (hematoxylin and eosin, × 152). (c) Photomicrograph of the anterior pituitary gland reveals pituitary cells to be relatively well preserved, but scattered inflammatory cells, i.e. lymphocytes, plasma cells and macrophages can also be seen (hematoxylin and eosin, × 115).

Table 2. Pituitary functions performed 7 years after surgery

<table>
<thead>
<tr>
<th>Function</th>
<th>Value</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>GH</td>
<td>0.8ng/ml</td>
<td>(0.0–6.0)</td>
</tr>
<tr>
<td>Somatomedin C</td>
<td>208ng/ml</td>
<td>(121–436)</td>
</tr>
<tr>
<td>ACTH</td>
<td>43pg/ml</td>
<td>(0–50)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>14.8µg/dl</td>
<td>(4.5–24.5)</td>
</tr>
<tr>
<td>TSH</td>
<td>1.91µU/ml</td>
<td>(0.50–3.70)</td>
</tr>
<tr>
<td>free T3</td>
<td>2.5pg/ml</td>
<td>(2.4–4.6)</td>
</tr>
<tr>
<td>free T4</td>
<td>1.3ng/dl</td>
<td>(0.8–1.4)</td>
</tr>
<tr>
<td>PRL</td>
<td>8ng/ml</td>
<td>(1–27)</td>
</tr>
<tr>
<td>LH</td>
<td>7.4mIU/ml</td>
<td>(8.7–38.0)</td>
</tr>
<tr>
<td>FSH</td>
<td>25.5mIU/ml</td>
<td>(26.2–113.3)</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.2pg/ml</td>
<td>(0.3–4.2)</td>
</tr>
</tbody>
</table>

The values in brackets are standard normal values.

Discussion

The patient presented with DI and mild anterior pituitary dysfunctions. MRI revealed enlargement of the hypophysis-infundibulum with a cystic component, ultimately diagnosed as RCC. Histologic examination revealed discontinuation of the epithelial line in the RCC, abundant inflammatory cells and fibrosis, compatible with granulomatous inflammation in the neurohypophysis, but the anterior pituitary gland
was relatively well preserved.

Granulomatous hypophysitis is histologically characterized by nodular aggregates of multinucleated giant cells, histiocytes and extensive plasma cell infiltration [12, 13]. Tuberculosis, syphilis, sarcoidosis and other systemic granulomatous diseases have also been considered as etiological factors in pituitary granulomas [14–17]. In our patient, tuberculosis and syphilis are unlikely because of the negative serology and the absence of a caseous granuloma. Systemic sarcoidosis is also unlikely because evidence of multi-organ involvement was lacking.

Recently Imura et al. reported a novel category of central DI called lymphocytic infundibuloneurohypophysitis (LINH), that is, self-limiting inflammation with infiltration of lymphocytes (mainly T lymphocytes) and plasma cells in the posterior lobe of the pituitary gland, and presenting with permanent DI with little or no anterior pituitary dysfunction [18]. Thickening and enlargement of the pituitary stalk or the neurohypophysis, or both were seen on MRI. RCC in our case might only coexist with LINH, but the presence of granulomatous change with infiltration of T and B lymphocytes and the coexistence of adenohypophysitis excluded LINH.

RCCs are occasionally accompanied with local and asymptomatic lymphoplasmatic inflammation, apparently induced by mucous secreted by goblet cells of the cyst wall [6, 19, 20]. In general, the cause of hypopituitarism in RCC cases is thought to be a mass effect on the pituitary or infundibulum [5–7]. In some cases, however, the hypopituitarism was caused by inflammation in the pituitary gland adjacent to the RCC [8–10].

In our case, the RCC was very small and unlikely to have exerted a compressive effect on the pituitary gland. On the other hand, disruption of the epithelial lining and contiguous granulomatous change in the neurohypophysis were demonstrated histologically. These findings strongly suggested that the RCC rupture had resulted in mucous spillage and triggered an inflammatory process in the pituitary gland. The stage of this process was more advanced in the neurohypophysis than in the adenohypophysis, probably reflecting the direction of spillage. To our knowledge this is the first reported case in which the histological findings indicated the RCC rupture site and the direction of the progression of inflammation.

Anterior pituitary function had been restored 4 months after transphenoidal surgery followed by a short course of steroid administration. This restoration might represent the natural course of this process. Surgical removal of the cyst contents and granulomatous tissue may, however, promote this natural healing process before destructive changes overwhelmed the whole pituitary gland.

It might have been better if we had not done surgical removal, and only used steroids to treat this patient, but foreign-body type hypophysitis as in our patient would not diminish as long as causative matter, e.g. the spilt contents of a ruptured RCC, remained in the hypophysis. So we should not administer steroids to treat foreign body type hypophysitis caused by ruptured RCC desultorily, and when steroid administration does not reverse the pituitary dysfunction, surgical removal should be considered.

The transphenoidal excision of a small RCC associated with hypophysitis, easily detected by MRI, should be kept in mind as a treatment option. In particular, surgical intervention may be justified in cases with a sudden onset of pituitary dysfunction, as in our case, but the nature of the association between these disorders should be clarified before surgery is selected as the first line treatment.

Acknowledgments

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References