Granulomatous Hypophysitis with Meningitis and Hypopituitarism

Mitsuaki Yoshioka, Norio Yamakawa, Hideaki Saito, Makoto Yoneda*, Toru Nakayama**, Mizuo Kuroki***, Tadashi Tsuchida*** and Masao Sekiya****

We report an unusual case of granulomatous hypophysitis in which visual impairment, meningitis and hypopituitarism in a 76-year-old female were associated with radiological evidence of a pituitary mass. The sellar lesion was indistinguishable from pituitary tumor on neuroimaging studies, but the recovery of visual acuity and visual field abnormalities together with the improvement of pituitary function after steroid administration indicated that the mass lesion was due to an inflammatory disease of the pituitary gland. The pituitary tissue obtained by transsphenoidal hypophysectomy revealed granulomatous inflammatory cell infiltration with epithelioid cells and scattered multinucleated giant cells. Although a causal relationship with meningitis was not ascertained, possible exposure of the CSF space to the autoimmune inflammatory process of the pituitary gland was likely in view of the positive pituitary antibody reaction and radiological evidence of suprasellar extension. This entity should be considered when evaluating patients with a pituitary mass, hypopituitarism and meningitis.

Key words: hypopituitarism, hemianopsia

Introduction

Giant-cell granulomatous hypophysitis is an uncommon disorder. The majority of reported cases come from necropsy materials since it is exceptional of find this pathological entity in surgically-obtained specimens. Thus, a comparatively limited number of clinical cases have been documented (1-6). Here, we describe a patient who presented with visual impairment, meningitis and hypopituitarism together with a radiologically-demonstrated intrasellar mass.

Case Report

A 76-year-old woman was seen in mid-May, 1990, at an ophthalmology clinic after having noted visual field abnormalities; she was referred to our hospital because of suspected intracranial lesions. On June 3, she experienced a febrile episode, after which she became unable to stand upright or to walk owing to extreme leg pain, and was admitted to our hospital the following day. Her blood pressure was 90/50 mmHg, pulse rate 84/min and regular, body temperature 36.9°C. She was somnolent. The dorsum of her left foot was reddened, swollen and tender, and the right thigh was also painful. There were no abnormalities in the chest or abdomen. Slight nuchal rigidity and urinary retention were noted. The erythrocyte sedimentation rate was 128 mm/h and white cell count 3,600/mm³. The C-reactive protein was 6.3 mg/dl. The total serum protein was 6.3 g/dl (albumin 2.8 g/dl). Serum sodium was 122 mEq/l, and chloride 93 mEq/l. VDRL (-), PPD test (+) and serum angiotensin-converting enzyme was 11.9 IU/l/37°C (normal 8.3-21.4). The chest X-ray was negative. Her cerebrospinal fluid (CSF) contained 160/mm³ white blood cells (mainly lymphocytes), protein 111 mg/dl, glucose 80 mg/dl and chloride 116 mEq/l. CSF cultures were negative for common bacteria, Mycobacterium tuberculosis and fungi. A computed tomography (CT) scan showed a highly contrast-enhanced intrasellar mass (Fig. 1). Perimetry revealed bitemporal hemianopsia. Endocrine studies showed a serum PRL level of 4.7 ng/ml (normal <15), GH level 0.7 ng/ml (normal <5), LH 0.5 mIU/ml and FSH 0.5 mIU/ml. The free thyroxine concentration was 0.5 ng/dl (normal 0.8-2.1), free triiodothyronine 1.7 pg/ml (normal 2.8-6.00) and TSH

From the Departments of Internal Medicine, *Neurology, **Ophthalmology, ***Neurosurgery and ****Pathology, Niigata Prefectural Central Hospital, Joetsu
Received for publication January 16, 1991; Accepted for publication June 29, 1992
Reprint requests should be addressed to Dr. Mitsuaki Yoshioka, the Department of Internal Medicine, Niigata Prefectural Central Hospital, 3–20, Ootemachi, Joetsu, Niigata 943, Japan
Yoshioka et al

Fig. 1. a) CT scan after intravenous administration of contrast medium showing a high density intrasellar lesion with well-defined, uniform enhancement. b) MRI, T1 sagittal scan after i.v. gadolinium-DTPA demonstrating a tumor-like lesion involving the pituitary with distinct enhancement up to the suprasellar region.

Table 1. Results of Pituitary Function Studies

<table>
<thead>
<tr>
<th>Time of day (hours)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHRH load (100 µg IV)</td>
<td>LH (mlU/ml)</td>
<td>0.5 ↓</td>
<td>0.5 ↓</td>
<td>0.5 ↓</td>
<td>0.5 ↓</td>
</tr>
<tr>
<td>FSH (mlU/ml)</td>
<td>0.5 ↓</td>
<td>0.8</td>
<td>1.5</td>
<td>2.0</td>
<td>2.2</td>
</tr>
<tr>
<td>TRH load (500 µg IV)</td>
<td>TSH (µU/ml)</td>
<td>0.8</td>
<td>1.8</td>
<td>2.5</td>
<td>2.4</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>4.7</td>
<td>11.0</td>
<td>8.9</td>
<td>7.6</td>
<td>6.8</td>
</tr>
<tr>
<td>Arginine load (0.5 gm. per kg. body weight)</td>
<td>GH (ng/ml)</td>
<td>0.7</td>
<td>0.5</td>
<td>1.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

obtained by highly sensitive radioimmunoassay was 0.77 µU/ml (normal 0.24–3.70). No serum antithyroglobulin or antimicrosomal antibodies were detected. The serum cortisol level was 1.3 µg/dl at 08:00 (normal 5–12) and 1.0 µg/dl at 20:00 (normal <5). Anti-pituitary antibodies against AtT20 cells were positive and GH3 cells were negative. The results of pituitary function studies were as follows. There were no LH and FSH responses to LHRH, nor any TSH response to TRH, nor any GH response to arginine. PRL responded slightly to intravenous TRH (Table 1).

Cefotaxime sodium and piperacillin sodium were given intravenously for the treatment of meningitis, although a bacterial cause was unlikely. Adrenocortical hypofunction was considered responsible for the hyponatremia and thus was evaluated by ACTH-Z test (3-day method). A normal response of urinary 17-OHCS to ACTH was obtained but the circadian rhythm of the blood cortisol level was found to be subnormal despite the fact that the hyponatremia had been corrected (Fig. 2). Daily intramuscular ACTH-Z injection was started, and produced dramatic clinical improvement on the second day in terms of recovery of appetite, disappearance of general malaise and rapid amelioration of

Fig. 2. Circadian rhythms of cortisol at the time of hospitalization when hemianopsia was conspicuous (solid lines) as compared to the time when hemianopsia improved (dashed lines).
Granulomatous Hypophysitis

Fig. 3. Photomicrographs of the surgical specimen. Left: Epithelioid cell granuloma with multinucleated giant cell. (HE stain, ×250); Right: granulation tissue containing granulomatous lesions. (HE stain, ×50)

the bitemporal hemianopsia. However, as anorexia and general malaise had returned in a few days, replacement therapy with corticosteroid and thyroid hormone was instituted and she remained almost free of clinical symptoms for several months thereafter. However, her visual fields eventually narrowed again. Magnetic resonance imaging (MRI) revealed a contrast-enhanced intrasellar mass with slight suprasellar extension (Fig. 1b). The patient underwent transsphenoidal excision of the pituitary mass on October 9, 1990. Abundant granulomatous tissue was observed with scattered epithelioid cells admixed with multinucleated giant cells (Fig. 3).

Discussion

Inflammatory diseases of the pituitary gland are roughly divided into two forms. Lymphocytic hypophysitis, which is characterized pathologically by diffuse infiltration of the gland with lymphocytes and plasma cells, commonly occurs in puerperants and pregnant women. Immunologic mechanisms have been implicated in the pathogenesis. The other form is giant cell granuloma or granulomatous hypophysitis. Histologically, it contains clusters of multinucleated giant cells and histiocytes and infiltrations with lymphocytes and plasma cells. This is a diagnosis by exclusion; i.e., tuberculosis, syphilis, sarcoidosis and other systemic granulomatous diseases are generally ruled out prior to making the diagnosis of granulomatous hypophysitis. The clinical features are characterized by a disproportionately severe pituitary dysfunction, despite less pronounced pituitary swelling than that seen in tumors of the pituitary gland, and rapid clinical deterioration (7). However, there are also reports claiming that these two inflammatory diseases are not separable into two distinct entities but merely represent different stages of a single disorder (8). In the present case, a profound pituitary hypofunction was noted in association with severely impaired vision and narrowed visual fields at the time of hospitalization. Vision improved quickly in the 2 weeks following steroid initiation while only a modest recovery of the hypopituitarism was attained. These differential responses to steroid would be indicative of an inflammatory process rather than a tumor. Tuberculosis and syphilis, authentic granulomaous disorders, which may reside in the pituitary gland, are unlikely in view of the negative serology, absent caseous granuloma and steroid-induced improvement. Systemic sarcoidosis is also unlikely because evidence for multi-organ-involvement was lacking. However, clinically solitary organ forms of sarcoidosis may precede systemic granulomatous manifestation and sometimes remain confined to a single organ for a prolonged period of time. This is particularly true in the case of sarcoid myelopathy in which progressive spinal cord symptoms may be the sole manifestation and even at autopsy involvement of areas other than the CNS may not be demonstrable. However, the presence of anti-pituitary antibody implies that an autoimmune inflammatory process rather than sarcoidosis is operative in this particular case.

To the best of our knowledge, there have been no reports on the concurrence of meningitis and granulomatous hypophysitis. With respect to lymphocytic hypophysitis, however, a case was reported, in which meningitis preceded the hypophysitis (9). The two diseases might possibly be causally related in terms of autoimmune mechanisms and in at least 4 of the 14 reported lymphocytic hypophysitis cases there might have been coexisting meningitis (10–13). It is our impression that in this particular case an autoimmune inflammatory process of the pituitary gland might somehow have extended into the CSF space, giving rise to meningitis. The radiological evidence of suprasellar extension of the mass supports this possibility. Hypophysitis, either lymphocytic or granulomatous, might therefore have a common pathogenetic basis, an autoimmune inflammatory process of the pituitary gland, and both could accompany a menin-
Yoshioka et al

gistic cellular response of the CSF. The constellation of pituitary mass, meningitis, and hypopituitarism together with positive anti-pituitary antibody thus points to autoimmune hypophysitis, a potentially treatable disorder.

References

8) McKeel DW. Common histopathologic and ultrastructural features in granulomatous and lymphoid adenohypophysitis. Program of the 65th annual meeting of the Endocrine Society 1983; Abstract 437.