Lymphocytic Hypophysitis, Pustulosis Palmaris et Plantaris and Eosinophilia

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We describe here a unique case of lymphocytic hypophysitis accompanied by pustulosis palmaris et plantaris and eosinophilia. The patient also suffered from panhypopituitarism with hyperprolactinemia and pituitary diabetes insipidus caused by lymphocytic hypophysitis. Complications of pustulosis palmaris et plantaris and eosinophilia with lymphocytic hypophysitis have not been reported previously. In the present case, the activities of the three diseases correlated well throughout the patient's course, suggesting that a common mechanism might possibly participate in their pathogenesis.

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Key words: diabetes insipidus, panhypopituitarism, hyperprolactinemia, pituitary tumor, magnetic resonance imaging

Introduction

Lymphocytic hypophysitis is a relatively rare disease which was first documented in 1962 (1). This disease is known to occur predominantly in females, and the majority of the patients have been diagnosed either during pregnancy or within 14 months after childbirth (2). Some patients may show symptoms caused by an expanding pituitary mass and may require surgical decompensation, and others may be identified by symptoms of hypopituitarism without any radiological abnormalities of the pituitary (3). Pathologically, infiltration of mononuclear cells at the pituitary is usually restricted to adenohypophysitis, so that the occurrence of diabetes insipidus due to the involvement of the posterior pituitary is very rare (2, 4). We describe here a unique patient with symptoms of an expanding pituitary mass along with diabetes insipidus, both of which became manifest 16 years after her last childbirth. This case also had the unusual complications of pustulosis palmaris et plantaris (PPP) and eosinophilia. Their activities correlated well with that of lymphocytic hypophysitis in the clinical course, suggesting that a common mechanism might participate in the pathogenesis of the three diseases and contribute to the unusual occurrence of lymphocytic hypophysitis so long after pregnancy.

Case Report

A 44-year-old Japanese woman was admitted to our hospital with complaints of headache, thirst, polyuria and polydipsia which had begun suddenly 5 months earlier. Her past history revealed that PPP occurred soon after her last uneventful delivery at age 28 and persisted to the present with repeated exacerbation and remission. At age 39, she began to notice pain and swelling over the left sternoclavicular joint whenever PPP became exacerbated. Her menstrual cycle had been regular until age 40, when a hysterectomy was performed after the diagnosis of uterine myoma. During the 10 months before admission, PPP had been aggravated and remained active along with a low grade fever and persistent eosinophilia (1,800–2,400/μL) in peripheral blood. On admission, her daily urine volume was as much as 6,400 mL. Physical examination revealed chronic periodontal infection without abnormal findings of the tonsils, pustulosis in the bilateral palmar and plantar region (Fig. 1A), and pain and swelling over the left sternoclavicular joint. The joint symptoms were diagnosed as due to pustulotic arthro-osteitis, since its activity was intimately related to that of PPP. A bone scan revealed an intense uptake at the corresponding joint (Fig. 1B). Neurologic examinations were totally unremarkable with normal visual acuity and no visual field defect. Galactorrhea or loss of axillary or inguinal hair were not observed. Laboratory examination revealed an
increased erythrocyte sedimentation rate (45 mm/hr), a negative CRP, moderate eosinophilia with 2.400/µl in peripheral blood, and bone marrow with 10.4% eosinocytes of 13.2×10³/µl of nucleated cells. Serum IgE was elevated with the value of 454 IU/ml (normal, 19–300 IU/ml). The blood chemical findings including liver and kidney functions were normal. Autoantibodies to the pituitary gland, thyroid gland, adrenal cortex or gastric parietal cells were not detected.

The results of endocrinological investigations on admission, in the absence of hormonal replacement therapy, are shown in Table 1. The responses of adrenocorticotropic hormone (ACTH), growth hormone (GH), thyroid-stimulating hormone (TSH), prolactin (PRL), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to a combined intravenous injection of insulin, thyrotropin-releasing hormone (TRH) and luteinizing hormone-releasing hormone (LHRH) were markedly impaired. Serum PRL concentration, which was high before stimulation, showed a modest increase after stimulation. These results

Table 1. Endocrine Investigations before Surgery

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<th>0 min</th>
<th>15 min</th>
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<th>45 min</th>
<th>60 min</th>
<th>90 min</th>
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<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>86</td>
<td>54</td>
<td>42</td>
<td>59</td>
<td>80</td>
<td>88</td>
<td>89</td>
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<tr>
<td>ACTH (pg/ml)</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
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<td>GH (ng/ml)</td>
<td>2.0</td>
<td>1.9</td>
<td>1.9</td>
<td>1.7</td>
<td>1.3</td>
<td>1.9</td>
<td>3.1</td>
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<tr>
<td>TSH (µU/ml)</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
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<td>&lt;0.1</td>
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<td>PRL (ng/ml)</td>
<td>62.0</td>
<td>118.0</td>
<td>110.9</td>
<td>112.0</td>
<td>80.4</td>
<td>66.3</td>
<td>63.8</td>
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<tr>
<td>FSH (mIU/ml)</td>
<td>4.0</td>
<td>6.4</td>
<td>8.3</td>
<td>9.4</td>
<td>10.2</td>
<td>11.2</td>
<td>11.2</td>
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<tr>
<td>LH (mIU/ml)</td>
<td>0.7</td>
<td>3.4</td>
<td>4.6</td>
<td>4.8</td>
<td>4.8</td>
<td>3.9</td>
<td>4.2</td>
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<tr>
<td>Cortisol (µg/dl)</td>
<td>10.1</td>
<td>13.7</td>
<td>12.2</td>
<td>11.0</td>
<td>9.3</td>
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Water deprivation and subsequent arginine vasopressin injection

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<th>10 h</th>
<th>10 h 30 min</th>
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<tr>
<td>Body weight (kg)</td>
<td>54.6</td>
<td>54.2</td>
<td>54.2</td>
<td>54.0</td>
<td>53.8</td>
<td>53.6</td>
<td>53.4</td>
<td>53.3</td>
<td>53.3</td>
<td>53.3</td>
<td>53.2</td>
<td>53.2</td>
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<td>Urine volume (ml/h)</td>
<td>260</td>
<td>60</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>80</td>
<td>140</td>
<td>160</td>
<td>60</td>
<td>5</td>
<td>5</td>
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<td>Plasma osmolality (mOsm/kg)</td>
<td>281</td>
<td>284</td>
<td>283</td>
<td>284</td>
<td>285</td>
<td>287</td>
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<td></td>
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<tr>
<td>Urinary osmolality (mOsm/kg)</td>
<td>111</td>
<td>257</td>
<td>302</td>
<td>279</td>
<td>303</td>
<td>272</td>
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<td>255</td>
<td>673</td>
<td>707</td>
<td>698</td>
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indicate the existence of panhypopituitarism with hyperprolactinemia. The results of a water deprivation study indicated the presence of pituitary diabetes insipidus due to vasopressin deficiency. Thyroid function tests were low normal with serum T4 6.3 μg/dl (normal, 6.6–10.8 μg/dl), T3 1.0 ng/ml (normal, 0.8–1.6 ng/ml) and free T4 0.98 ng/dl (normal, 1.06–2.00 ng/dl). No glucocorticoid deficiency was observed with urinary 17-hydroxycorticoïd 1.7 mg/day (normal, 1.6–8.8 mg/day) and 17-ketosteroid 3.8 mg/day (normal, 2.4–11.3 mg/day).

Magnetic resonance image (MRI) scanning revealed a large intrasellar mass with suprasellar and posterior extension and with the disappearance of high signal intensity of the posterior lobe on T1-weighted images (Fig. 2A). The mass was homogeneously enhanced after administration of gadolinium chelate (Fig. 2B). Transsphenoidal surgery was performed, and a large, extremely firm pituitary was subtotally resected. Microscopic examination of the specimen revealed a typical finding diagnostic of lymphocytic hypophysitis, with massive diffuse mononuclear cell infiltrate and interstitial fibrosis surrounding few persistent adenohypophyseal cells, but without granulomatous changes, such as epithelioid cells or multinucleated giant cells (Fig. 3). After surgery, the patient's PPP and pustulotic arthro-ostitis, which had been resistant to treatments for periodontal infection with incisal decompression and antibiotics, resolved spontaneously along with normalization of eosinocyte counts in peripheral blood and bone marrow (Fig. 4). Surface marker studies on peripheral lymphocytes at this time showed no abnormality with 38.0% CD4 and 28.4% CD8 (CD4/8 = 1.34). Human leukocyte antigen (HLA) phenotypes were A2, A31/w19, B35, B51/5, Cw3, DRw6, DRw52 and DQw7.

**Discussion**

This case may be unique since lymphocytic hypophysitis was diagnosed from an enlarged pituitary mass that was found 16 years after the last childbirth. An epidemiological survey revealed that lymphocytic hypophysitis occurs predominantly during pregnancy or soon after delivery, and all of the patients that showed a pituitary mass were diagnosed within 14 months after childbirth (1). Moreover, a search of the literature failed to find other reports of diabetes insipidus, PPP and eosinophilia complicating lymphocytic hypophysitis, as was found in the present case.
Lymphocytic hypophysitis is thought to be an autoimmune disease in nature because about 30% of the patients were found to have other organ-specific autoimmune diseases, such as Hashimoto's thyroiditis, nontuberculous Addison's disease and pernicious anemia (2-5), and because autoantibodies directed against pituitary cells were detected in some patients' sera (6, 7). In a recent animal study (8), a crucial role of T lymphocytes in the pathogenesis of lymphocytic hypophysitis was defined from the findings that the disease could be induced by an injection of recombinant rubella virus glycoprotein, but neonatal thymectomy prevented its occurrence. Involvement of T lymphocytes in lymphocytic hypophysitis was also suggested by clinical findings that CD4-positive helper T lymphocytes were increased in peripheral blood in a patient having both lymphocytic hypophysitis and pulmonary sarcoidosis, which returned to a normal range after hypophysectomy (5). Eosinophilia observed in the present case also might be caused by the action of T lymphocytes, because CD4-positive helper T lymphocytes are known to contain transcripts for interleukin-5 (IL-5) and to secrete it, which, in turn, causes proliferation of eosinocytes (9). The pathogenesis of PPP is not fully understood at present. However, oral cyclosporin A, a potent specific immunosuppressant for activated CD4-positive helper T lymphocytes, has been reported to be effective against persistent PPP (10), suggesting that T lymphocytes are also involved in its pathogenesis. In this context, one might hypothesize that lymphocytic hypophysitis, eosinophilia and PPP found in the present case were induced by a common mechanism modulated by activated CD4-positive helper T lymphocytes. In fact, the activities of the three diseases correlated well throughout the patient's course and seemed to be dependent on each other: symptoms of an expanded pituitary mass appeared in conjunction with the exacerbation of PPP and eosinophilia, and after hypophysectomy, PPP and eosinophilia resolved without any other treatment (Fig. 4). Unfortunately, this hypothesis was not verified by our clinical data, since no increase of CD4-positive T lymphocytes was observed in surface marker studies of peripheral lymphocytes performed postoperatively when the diseases abated. Autoantibodies to pituitary cells suggesting the participation of humoral immunity were also negative.

Nine cases of lymphocytic hypophysitis including the present case have been investigated for their HLA typing (4-6, 11-14). Race was reported in 8 patients, of whom 4 were white, 2 were black and 2 were Asian. In class I alleles, 6 patients shared the A2 phenotype and 3 patients shared the B35 phenotype. In class II alleles transcripts of which are known to present processed antigens to CD4-positive T lymphocytes (9), DR4 and DRw53 loci were shared by 3 patients, respectively.

Lymphocytic hypophysitis is known to cause a characteristic progressive hormone loss; the levels of GH and FSH/LH are reduced first, followed by levels of TSH and ACTH, and lastly PRL (2). Thus, about half of the cases presenting panhypopituitarism have been reported to be complicated with hyperprolactinemia (2) as observed in the present patient. The elevation of the prolactin level is generally ascribed to stalk compression by a pituitary mass (15) or residual lactotroph hyperplasia from recent pregnancy (16, 17). In the present case, although the precise mechanism of hyperprolactinemia remains unclear, it is likely to be the result of stalk compression or hypothalamic dysfunction rather than residual lactotroph hyperplasia, because MRI scanning showed an enlarged pituitary mass with suprassellar and posterior extension, and because 16 years had passed since her last pregnancy.

MRI scanning is known to be most useful for detecting an intrasellar mass caused by lymphocytic hypophysitis (2). In the present case, MRI also revealed an expanded pituitary mass with the disappearance of high signal intensity of the posterior lobe on T1-weighted images, which is a diagnostic finding.
frequently observed in diabetes insipidus (18). The occurrence of both diabetes insipidus and hyperprolactinemia in the present patient suggests that hypothalamic dysfunction probably exists in conjunction with pituitary damage. However, it remains unclear whether hypothalamic dysfunction is attributed to stalk compression by the pituitary mass or to the hypothalamic dysfunction of the inflammatory lesion. The gadolinium-enhanced MRI findings in lymphocytic hypophysitis have not been well documented to date. In the present case, the mass was homogeneously enhanced by the agent as shown in Fig. 2B. This is in sharp contrast to pituitary adenoma, in which enhancement by gadolinium is known not to occur. Since two recent case reports (19, 20) also documented the homologous enhancement of a pituitary mass by gadolinium in lymphocytic hypophysitis, this finding probably seems characteristic of the disorder and useful for its diagnosis.

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References