Central Diabetes Insipidus Due to Lymphocytic Infundibuloneurohypophysitis

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Lymphocytic infundibuloneurohypophysitis was recently reported by Kojima et al (1) and Imura et al (2) as a cause of idiopathic central diabetes insipidus. We report 2 patients with central diabetes insipidus who had abnormal findings on magnetic resonance imaging (MRI) that were compatible with this syndrome. One of the patients had bilateral enlarged salivary glands that showed an infiltration of activated T lymphocytes, as has been reported in the pituitary stalk among patients with lymphocytic infundibuloneurohypophysitis. Both patients had antibodies for the p24 antigen of the human T lymphocytic leukemia virus-1 (HTLV-1), as well as having the human leukocyte antigen (HLA)-A24 haplotype.

CASE REPORTS

Patient 1 was a 71-year-old Japanese man with bilateral swelling of his submandibular salivary glands. Six months before admission, a family member noted polydipsia. Three months before entry, he noted swelling of his submandibular glands. Weight loss, polyuria, and polydipsia developed. Physical examination on admission revealed bilateral enlarged submandibular glands (3 × 3 cm). Ophthalmologic examination was unremarkable. Routine laboratory analysis, tumor marker studies, and a chest radiograph revealed normal findings except for a low urine specific gravity (1.002), an elevated erythrocyte sedimentation rate (29 mm/h), and a positive tuberculin (PPD) skin test. Urine volume was 5 to 7 L per day. Autoantibodies, including rheumatoid factor, antinuclear antibody, anti-DNA antibody, anti-RNP antibody, anti-Sm antibody, anti-SS-A/Ro antibody, and anti-SS-B/La antibody, were all negative. A Western blot analysis for HTLV-1 antibodies revealed positive results for the p24 antigen, but not for p19, p53, or gp46. Serum angiotensin-converting enzyme activity was normal. A water deprivation test showed that the serum osmolality was 305 mOsm and the urinary osmolality was 365 mOsm after a 3% decrease in body weight. The plasma arginine vasopressin level was low (0.8 pg/mL) despite the high serum osmolality. Anterior pituitary hormones responded normally to stimulation tests with insulin or thyrotropin-releasing hormone. Basal levels of luteinizing hormone and follicle-stimulating hormone were normal. MRI demonstrated thickening of the pituitary stalk and enlargement of the neurohypophysis without high intensity of the posterior lobe on T1-weighted images that enhanced with gadolinium (Figure 1).

A biopsy specimen of the right submandibular gland revealed massive infiltration of T lymphocytes with small amounts of plasma cells, and fibrous components (Figure 2). Fluorescence-activated cell sorting of free cells from the specimen demonstrated CD1 0%, CD2 59%, CD3 55%, CD4 35%, CD7 49%, CD8 16%, CD10 2%, CD13 2%, CD14 1%, CD19 47%, CD20 48%, CD33 2%, and HLA-DR 72%, indicating that the dominant cells were activated T lymphocytes. The patient required 45 μg per day of desmopressin to control urine volume to between 1,200 mL and 1,500 mL per day. After 16 months, the dose was decreased to 15 μg per week.

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Patient 2 was a 58-year-old Japanese woman with xerostomia and polyuria. Urine volume was as much as 6 L per day, and the urine specific gravity was 1.003. The plasma arginine vasopressin level was low (0.7 pg/mL) after the administration of 5% saline (0.05 mL/min -1 · kg -1 body weight for 2 hours), even when the serum osmolality was 312 mOsm. Anterior pituitary hormones responded normally to stimulation. MRI demonstrated thickening of the pituitary stalk and enlargement of the neurohypophysis, compatible with a diagnosis of lymphocytic infundibuloneurohypophysitis (Figure 1). A Western blot analysis for HTLV-1 antibodies was positive for p24 only. The initial dose of desmopressin was 30 µg per day; 6 months later, the dose was decreased to 15 µg per day. Systemic disorders, such as sarcoidosis, Wegener’s granulomatosis, Langerhans type histiocytosis, and chronic extensive inflammation, as seen in Tolosa-Hunt syndrome, were excluded.

The HLA haplotypes were A11, A24 (9), B54 (22), B51 (5), and DR6 in patient 1, and A24 (9), B61 (40), B70, Cw3, DR4, and DR9 in patient 2.

DISCUSSION

Several disorders produce lymphocytic infiltration of the pituitary gland. Lymphocytic adenohypophysitis, which occurs primarily in pregnant woman, affects the anterior pituitary gland (3), causing complete or partial hypopituitarism. Diabetes insipidus is rare in this syndrome. Although an abnormal immune response is suspected, autoantibodies have not been detected (4). In contrast, diabetes insipidus was reported in 9 patients with lymphocytic infundibuloneurohypophysitis who had thickening of the pituitary stalk on MRI (2). Two of these patients who underwent biopsy had infiltration of activated T lymphocytes in the pituitary stalk. Of the 23 reported patients (5–13) with this disease, including our 2 patients, 20 were Japanese; 17 (74%) were women. Diagnostic criteria for this syndrome have been proposed (14). A third disorder that involves lymphocytic infiltration of the pituitary gland—necrotizing infundibulohypophysitis—has characteristics that overlap with the first two disorders, but the disorder also involves necrosis of the pituitary gland and stalk (15).

Our first patient met radiologic and endocrinologic criteria for lymphocytic infundibuloneurohypophysitis and also had lymphocyte infiltration of his salivary gland. A previous patient with lymphocytic infundibuloneurohypophysitis had elevated serum amylase and lipase levels; at autopsy, chronic pancreatitis with lymphocytic infiltration was seen (1). The salivary glands, pancreas, and pituitary stalk share similar secretory structures, raising the possibility that simultaneous lymphocytic infiltration can occur in these tissues.

Yamano et al (16) reported that 5 of 15 patients with Sjögren’s syndrome had anti-p24 antibody alone by West-
ern blotting, and they also demonstrated p24 antigen and A-type retrovirus differing from human immunodeficiency virus (HIV) and HTLV-1 in the epithelial cells of salivary glands from those patients. They suggested that a new retrovirus infection that has an antigen similar to p24 is involved in the pathogenesis of Sjögren’s syndrome. Bank et al (17) suggested that an autoimmune mechanism may depend on an HTLV-related endogenous sequence (HRES)-1 retrovirus infection, because an anti-HTLV-related endogenous sequence antibody cross-reacts with an anti-HTLV-1 p24 antigen. Although neither of our patients had keratoconjunctivitis, the changes in the salivary gland in patient 1 were similar to those of Sjögren’s syndrome.

Both patients in the present study had the A24 haplotype, as did 1 of the 2 patients previously analyzed for HLA type (10). HLA-A24 may correlate with beta-cell destruction in Japanese patients with insulin-dependent diabetes (18) and with HTLV-1-associated diseases (19). In our patients with lymphocytic infundibuloneurohypophysitis, swelling of the salivary glands, serum anti-HTLV-1 p24 antibody, and HLA-A24 suggest the possibility that lymphocytic infundibuloneurohypophysitis may depend on an abnormal immune response to a retroviral infection in patients with the HLA-A24 haplotype.

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