A 55-year-old man suffered from nasal obstruction, swelling of the salivary glands, and diplopia caused by markedly enlarged lacrimal glands. The diagnosis of primary Sjögren's syndrome was made by a positive Schirmer's test and nasal mucosal biopsy with severe lymphocyte infiltration. He was also found to have swelling of the whole pancreas and increased wall thickness in the common bile duct and the gall bladder. His serum was positive for an anti-carbonic anhydrase II antibody. Since carbonic anhydrase II is present in the ductal cells of various exocrine organs, this autoantibody is considered to be related to the pathogenesis of primary Sjögren's syndrome with a marked swelling of multiple exocrine organs.

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Introduction

Sjögren's syndrome is a chronic, slowly progressive autoimmune disease characterized by dysfunctions of exocrine glands with a classic sicca syndrome (1). This disorder can be classified into primary and secondary forms (2). The latter condition is associated with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and scleroderma. In patients with this disorder, salivary and lacrimal glands are primarily involved and these affected glands, which histologically show a marked infiltration of B cell-dominant lymphocytes, can be visualized by sialography, radionuclide scanning or MR imaging (3). Occasionally, the patients show enlargement of the glands affected. It is also known that mucous gland secretions in the respiratory and gastrointestinal tracts are extensively disturbed in Sjögren's syndrome. Additionally, it has been noted that patients with this syndrome sometimes experience chronic pancreatitis and primary biliary cirrhosis (4-6), but the pathogenesis of these disorders is still incompletely understood.

In this report, we describe a male patient with primary Sjögren’s syndrome who showed enlargement of multiple exocrine organs, with special attention to the involvement of the pancreas and the diffuse sclerotic changes in the pancreatic duct and the common bile duct.

Case Report

The male patient visited another hospital when he was 47 years old complaining of Raynaud’s phenomenon, morning stiffness and arthralgia of the hands, and rhinorrhea. Serological studies showed elevated levels of CRP and positive rheumatoid factor, so he was suspected to be suffering from some type of collagen disease. Oral administration of prednisolone (40 mg/day) was started and all these symptoms soon disappeared. The dose of prednisolone was then slowly decreased. At age 53, Raynaud’s phenomenon, nasal obstruction, and a swelling of the bilateral salivary glands appeared even though he was taking 5 mg prednisolone every other day. Prednisolone was increased to 15 mg/day, but his symptoms worsened and diplopia with bilateral exophthalmos appeared. At age 55 he was referred to our hospital.

On examination, a remarkable swelling of all salivary glands (especially both parotid glands), bilateral exophthalmos with diplopia (Fig. 1A), severe nasal obstruction, and Raynaud’s phenomenon were seen, but there was no arthropathy or sicca syndrome. Routine laboratory studies showed the following abnormalities: increased WBC count (11,610/µl: 50.0% neutrophils, 31.0% lymphocytes, and 12.0% eosinophils), elevated serum levels of ZTT (25.6 kunkel, normal: 4-12 kunkel), IgG (4,873 mg/dl, normal: 875-1,595 mg/dl) and IgE (900 IU/ml, normal <500 IU/ml), and an increased erythrocyte sedimentation rate (72 mm/h), but CRP (0.1 mg/dl), renal and liver function tests (BUN 14 mg/dl, creatinine 0.8 mg/dl, AST: 9 IU/l, ALT: 8 IU/l, total bilirubin: 0.2 mg/dl, γ-GTP: 18 IU/l, ALP: 126 IU/l, LDH: 146 IU/l), and serum amylase (total amylase: 185 IU/l). The diagnosis of primary Sjögren’s syndrome was made by a positive Schirmer’s test and nasal mucosal biopsy with severe lymphocyte infiltration.
Figure 1. Clinical picture and CT images of exocrine glands. A: Exophthalmos with bilateral swelling of lacrimal glands, B, C and D: Marked swelling of both lacrimal (arrowheads) (B), parotid (C) and submandibular glands (arrows) (D). E: Diffuse enlargement of pancreas and increased thickness of the common bile duct wall (arrowhead).
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48 IU/l, pancreas type: 19%, salivary type: 81%) were all normal. Among the serum autoantibodies examined, anti-SS-A antibody and anti-carbonic anhydrase II antibody (7) were positive, while anti-nuclear antibody, anti-SS-B antibody, anti-mitochondrial antibody and anti-smooth muscle antibody were undetectable.

CT revealed a marked swelling of the bilateral lacrimal glands and salivary glands (Fig. 1B, C, D), diffusely thickened nasal mucosa, enlargement of the whole pancreas, and increased wall thickness of the common bile duct and the gall bladder (Fig. 1E). Neither lymph node swelling nor hepatosplenomegaly was seen. Endoscopic retrograde cholangiopancreatography (ERCP) showed segmental narrowing and dilatation of the main pancreatic duct and an extrinsic stenosis of the inferior common bile duct (Fig. 2A). Swelling of the papilla Vateri was also observed. Gallium scintigraphy disclosed abnormal accumulation of the radioisotope in the bilateral nasal cavities and submandibular and lacrimal glands (Fig. 3A). RI sialography showed significantly reduced uptake of the radioisotope in the parotid glands.

Figure 2. ERCP findings before and after corticosteroid therapy. A: Pretreatment. Segmental narrowing of main pancreatic duct and marked stenosis of common bile duct (arrowhead) are seen. B: After treatment. Main pancreatic duct and common bile duct are well visualized.

Figure 3. Inflammatory findings. A: Gallium scintigram showing positive uptake of radioisotope on the nasal mucosa, bilateral lacrimal and submandibular glands. B: Biopsied nasal mucosa showing heavy infiltration of mononuclear cells (HE stain, ×75).
Concerning the sicca syndrome, although Schirmer’s test was positive, rose bengal’s test was negative in both eyes and the gum test showed only a slight hyperfunction of the salivary gland. The patient’s pancreatic exocrine and endocrine functions were normal (N-benzoyl-L-tyrosyl-P-aminobenzoic acid test: 83.6%, normal ≥70%; fecal chymotrypsin test: 54.5 U/g, normal ≥6.6 U/g; 75 g oral glucose tolerance test: vor 75 mg/dl, 120 minutes: 150 mg/dl; urinary C-peptide excretion: 112 μg/day, normal: 45–117 μg/day). Histologically, a marked infiltration of lymphocytes was seen on the minor salivary glands of the lip and nasal mucosa (Fig. 3B), but there was no infiltration of eosinophils. Additionally, a reactive proliferation of lymphocytes without atypical cells was observed in the superficial lymph nodes obtained from the right inguinal area. Immunohistochimical studies showed that these lymphocytes were composed of more T-cells than B-cells without monoclonality.

On the basis of these findings he was diagnosed with primary Sjogren’s syndrome, and the enlargement of the pancreas with segmental narrowing of the main pancreatic duct was considered to be caused by Sjogren's syndrome-related sclerosing pancreatitis. A high dose of corticosteroid therapy was started (steroid pulse therapy including an initial dose of methylprednisolone 1 g/day 3 times, then tapering from prednisolone 60 mg/day to 20 mg/day during the following year). All his symptoms, including exophthalmos with diplopia, gradually improved. After one year, CT showed a significant regression in the swelling of multiple exocrine organs including the pancreas, and ERCP also revealed a remission of the diffuse sclerotic changes in both the common bile duct and the pancreatic duct (Fig. 2B).

Discussion

Sjogren’s syndrome is characterized clinically by dry mouth (xerostomia) and dry eyes (xerophthalmia) and the presence of both disorders is usually called the sicca syndrome (1). Our patient lacked any apparent sicca syndrome but satisfied two of the three major diagnostic criteria of Sjogren’s syndrome proposed by the Japanese research committee for this disorder in 1977: severe infiltration of mononuclear cells in the minor salivary glands and an abnormal sialographic finding. This patient showed marked swelling of the salivary and lacrimal glands, so lymphoma or pseudolymphoma developing secondarily to Sjogren’s syndrome was considered to be a differential diagnosis.

The histopathological findings of biopsied tissues consisting of nasal mucosa, lip and a lymph node strongly suggested that the swelling of exocrine glands was ascribable to a chronic inflammation with severe lymphocyte infiltration. The term Mikulicz-type Sjogren’s syndrome was previously used to indicate the phenomenon of multiple exocrine gland swelling caused by severe inflammation-related lymphocyte infiltration, and the clinical picture of our patient seems to coincide well with the concept of Mikulicz-type Sjogren’s syndrome. Mikulicz’s syndrome was originally defined as painless symmetrical swelling of lacrimal and salivary glands (8). The underlying diseases in this syndrome were known to consist of lymphoproliferative disorders, tuberculosis, sarcoidosis and other chronic inflammatory diseases including Sjogren’s syndrome, but the terms “Mikulicz’s syndrome” and “Mikulicz-type Sjogren’s syndrome” have not recently been used, possibly because of the obscure disease entity reflected by the term.

The present patient also had enlargement of the whole pancreas on CT, and a diffuse sclerotic change of the main pancreatic duct and marked narrowing of the distal part of the common bile duct were observed on ERCP. Several reports (3-5) have indicated that patients with Sjogren’s syndrome sometimes experience complications with pancreatitis. Pancreatic exocrine function as examined by a secretin test was reported to be disturbed in 28.6 to 54.5% of patients with Sjogren’s syndrome, while 12.5 to 90.0% of the patients evaluated by a pancreozymin-secretin test were also found to have reduced function (6). Histopathological studies of the pancreas were carried out in six patients with Sjogren’s syndrome (4); changes in acinar cells were noted in four and lymphocytic infiltration with fibrosis was seen in three. Recently, a unique form of pancreatitis, referred to as sclerosing pancreatitis or autoimmune pancreatitis (9-14), has been described: this disorder is characterized by an irregular narrowing of the pancreatic duct, swelling of the pancreatic parenchyma, hypergammaglobulinemia, lymphoplasmacytic infiltration and a favorable response to corticosteroids. Imaging studies of the pancreas indicated that the pancreatic lesion in our patient coincided with sclerosing or autoimmune pancreatitis. Although the therapeutic effect of corticosteroids for Sjogren’s syndrome is still controversial, this therapy is very effective for the pancreatitis seen in patients with this syndrome (13). In the present patient, corticosteroids markedly relieved the pancreatitis, as evidenced by ERCP findings (11).

In Sjogren’s syndrome several autoantibodies, including SS-A, SS-B and α-fodrin, have been identified as disease-related antibodies (1). Among them the antibody to carbonic anhydrase II was occasionally detectable in the sera of patients with this disease (7, 15, 16), although it was also found in the sera of patients with other collagen diseases: systemic lupus erythematosus, progressive systemic sclerosis and dermatomyositis (17). Originally, carbonic anhydrase II was reported to be an enzyme of an interspecies cross-reactive antigen (15), and its histological localization was shown to be in the ducts of a variety of exocrine glands, including salivary, lacrimal and pancreatic glands, the biliary tract and unirnferous distal tubules (16). It has recently been proposed that the presence of an anti-carbonic anhydrase II antibody is a useful hallmark for the diagnosis of autoimmune cholangitis (18). The antibody to carbonic anhydrase II was positive in our patient and all of the affected organs in this patient are known to have intracellular distributions of this enzyme. These findings suggest that anti-carbonic anhydrase II antibody plays a pathological role in the development of this unique form of primary Sjogren’s syndrome, although the exact mechanism of diffuse swelling of multiple exocrine glands including the pancreas remains unclear. Fur-
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	her studies are necessary to reveal the pathological process of this autoimmune-related extensive exocrinopathy.

References