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IgG4-Related Sclerosing Disease Incorporating Sclerosing Pancreatitis, Cholangitis, Sialadenitis and Retroperitoneal Fibrosis with Lymphadenopathy

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Key Words
Autoimmune pancreatitis · IgG4 · Cholangitis, sclerosing · Sialadenitis, sclerosing · Retroperitoneal fibrosis

Abstract
Background and Aims: Autoimmune pancreatitis is usually associated with elevated serum IgG4 concentrations, and sometimes with sclerosing cholangitis and Sjögren's syndrome. This study aimed to elucidate the proposed entity of IgG4-related sclerosing disease. ***Methods:*** Subjects were patients with autoimmune pancreatitis (n = 26), sclerosing sialadenitis (n = 5), chronic alcoholic pancreatitis (n = 20), sialolithiasis (n = 34), Sjögren's syndrome (n = 50), and primary sclerosing cholangitis (n = 3). Sections of various organs and tissues of these patients were examined immunohistochemically using antibodies to CD4-T, CD8-T, and CD20-B cell subsets and IgG4, and serum IgG4 concentrations were measured. ***Results:*** Patients with autoimmune pancreatitis were associated with sclerosing cholangitis (n = 23), sclerosing sialadenitis (n = 2), retroperitoneal fibrosis (n = 2), and abdominal (n = 5) and cervical (n = 4) lymphadenopathy. They demonstrated infiltrations of more abundant IgG4-positive plasma cells in the pancreas, peripancreatic retroperitoneal tissues, extrahepatic bile duct, gallbladder, stomach, minor salivary gland, and abdominal lymph nodes compared with those of other diseases ($p < 0.01$). Such infiltrations were also observed in the minor salivary gland and submandibular gland of patients with sclerosing sialadenitis ($p < 0.01$). Serum IgG4 concentrations were significantly elevated in patients with autoimmune pancreatitis and sclerosing sialadenitis ($p < 0.01$). ***Conclusion:*** We propose a new clinicopathological entity of IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy.

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Introduction

Many cases of autoimmune pancreatitis, in which autoimmune mechanisms are involved in pathogenesis, have been reported in Western countries as well as in Japan [1, 2]. The condition is characterized clinically and morphologically by diffuse enlargement of the pancreas, diffuse irregular narrowing of the main pancreatic duct, increased levels of serum γ-globulin or IgG, presence of autoantibodies, and responsiveness to steroid therapy [2].

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Autoimmune pancreatitis has occasionally been observed in association with Sjögren's syndrome [3, 4], primary sclerosing cholangitis [3, 4] or retroperitoneal fibrosis [5, 6]. Serum concentrations of IgG4 are significantly and specifically raised in patients with autoimmune pancreatitis [7]. It is also called lymphoplasmacytic sclerosing pancreatitis due to its characteristic histological features [7, 8].

By examining 6 resected specimens of autoimmune pancreatitis, we have reported that diffuse infiltrates of CD4- or CD8-positive T lymphocytes and IgG4-positive plasma cells were apparent, and accompanied by marked interstitial fibrosis and obliterated phlebitis throughout the pancreas [9]. As similar inflammatory processes have been observed in the various organs of patients with autoimmune pancreatitis, we preliminarily reported that, rather than being a disorder confined to the pancreas, autoimmune pancreatitis might represent a pancreatic lesion occurring as part of a systemic disease with extensive organ involvement [10].

On the basis of this hypothesis, since 2002 we have prospectively investigated various organs of patients with autoimmune pancreatitis and other sclerosing diseases, and propose a new clinicopathological entity of IgG4-related sclerosing disease.

Materials and Methods

Subjects were patients with autoimmune pancreatitis (n = 26), sclerosing sialadenitis (Kuttner's tumor; n = 5), chronic alcoholic pancreatitis (n = 20), sialolithiasis (n = 34), Sjögren's syndrome (n = 50), and primary sclerosing cholangitis (n = 3). Histological confirmation of the diagnoses was available for all patients other than 10 with autoimmune pancreatitis. The clinical course of the patients with autoimmune pancreatitis and sclerosing sialadenitis was investigated.

Serum IgG4 concentrations were measured by single radial immunodiffusion (The Binding Site, Birmingham, UK) [7] in 73 patients: autoimmune pancreatitis (n = 17); sclerosing sialadenitis (n = 5); chronic alcoholic pancreatitis (n = 20); sialolithiasis (n = 21), and Sjögren's syndrome (n = 10). Serum IgG4 concentrations were measured before steroid therapy in patients with autoimmune pancreatitis, sclerosing sialadenitis and Sjögren's syndrome.

To examine the specificity of localization of abundant IgG4-positive plasma cells in autoimmune pancreatitis and other diseases, we prospectively examined the histopathological findings of biopsy specimens from the stomachs and salivary glands of the subjects. Most of the other materials were collected by chart review. All these specimens from the various organs or tissues of subjects were fixed in 10% formaldehyde. Serial sections (4 μm thick) were cut from paraffin-embedded tissue blocks. Sections were immunostained using antibodies to CD4-T (Novocastra, Newcastle upon Tyne, UK), CD8-T (Dako Cytomation, Glostrup, Denmark), and CD20-B (Dako Cytomation) cell subsets and IgG4 (The Binding Site) antibodies using the avidin-biotin-peroxidase complex (ABC). The number of immunoreactive inflammatory cells was counted per high power field. Five fields were analyzed per case and counts were averaged. Examined tissues or organs were: 30 pancreases (6 resected and 4 biopsied autoimmune pancreatitis and 20 resected chronic alcoholic pancreatitis); 26 resected retroperitoneal peripancreatic tissues (6 autoimmune pancreatitis and 20 chronic alcoholic pancreatitis); 29 resected extrahepatic bile ducts (8 autoimmune pancreatitis, 20 chronic alcoholic pancreatitis and 1 primary sclerosing cholangitis); 28 resected gallbladders (8 autoimmune pancreatitis and 20 chronic alcoholic pancreatitis); 11 hepatic tissues (3 resected autoimmune pancreatitis, 1 biopsied sclerosing sialadenitis, 4 resected chronic alcoholic pancreatitis and 3 resected and 2 biopsied primary sclerosing cholangitis); 36 gastric mucosa (6 resected and 4 biopsied autoimmune pancreatitis, 3 biopsied sclerosing sialadenitis, 16 resected chronic alcoholic pancreatitis, 6 biopsied Sjögren's syndrome and 1 biopsied primary sclerosing cholangitis); 67 biopsied minor salivary glands (3 autoimmune pancreatitis, 4 sclerosing sialadenitis, 10 sialolithiasis and 50 Sjögren's syndrome); 38 resected submandibular glands (2 autoimmune pancreatitis, 4 sclerosing sialadenitis and 34 sialolithiasis); 27 resected abdominal lymph nodes (6 autoimmune pancreatitis, 1 sclerosing sialolithiasis and 20 chronic pancreatitis), and 8 biopsied cervical or mediastinal lymph nodes (1 autoimmune pancreatitis, 3 sclerosing sialadenitis and 14 Sjögren's syndrome).

For statistical analyses, the Kruskal-Wallis test was employed, followed by the Mann-Whitney U test. p values of <0.01 were considered significant.

Results

Autoimmune pancreatitis (n = 26; 21 men, 5 women; average age 68.2 years) was diagnosed according to the following criteria: irregular narrowing of the main pancreatic duct on endoscopic retrograde pancreatography (n = 26); pancreatic enlargement on ultrasonography or computed tomography (n = 25); increased serum γ-globulin (n = 12); presence of autoantibodies (n = 14); characteristic histological findings in the pancreas (n = 10), and clinical improvement with steroid therapy (n = 14). Six patients underwent pancreatoduodenectomy and 3 underwent laparotomy with pancreatic biopsy due to suspicion of pancreatic tumor, and 1 underwent pancreatic biopsy under ultrasonography. The most common presenting symptom was obstructive jaundice (n = 20). Sclerosing cholangitis was observed in 23 patients (2 intrahepatic bile duct, 1 upper and middle bile duct and 20 lower bile duct). Swelling of the salivary glands was observed concurrently with the occurrence of autoimmune pancreatitis in 2 patients. Autoimmune pancreatitis occurred in 2 patients during follow-up of sclerosing sialadenitis. Retroperitoneal fibrosis occurred 1 year after the develop-

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