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Original Paper

The Natural Course of Autoimmune Pancreatitis

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KEY WORDS:
Autoimmune pancreatitis; Natural course; Steroid therapy; IgG4; Imaging study

ABBREVIATIONS:
Autoimmune Pancreatitis (AIP); Computed Tomography (CT); Ultrasonography (US); Magnetic Resonance Cholangio-pancreatography (MRCP); Endoscopic Retrograde Cholangio-pancreatography (ERCP); Antinuclear Antigen (ANA)

ABSTRACT

Background/Aims: Since autoimmune pancreatitis (AIP) responds dramatically to steroid therapy, most AIP patients are promptly treated with steroids when the diagnosis of AIP is made. Therefore, the natural course of AIP is unclear. This study aimed to evaluate the clinical course of AIP patients without steroid therapy and assess the indications for steroid therapy in these patients.

Methodology: Clinical features were retrospectively assessed in 12 patients who were followed for more than 6 months after the diagnosis of AIP without steroids.

Results: Six patients were later treated with steroids due to exacerbation of AIP. Five of them developed obstructive jaundice due to bile duct stenosis. Segmental enlargement progressed to diffuse enlargement in 4 patients. Serum IgG and/or IgG4 levels increased with AIP progression. In 4 patients, swelling of the salivary glands preceded AIP. Radiological and clinical features responded well to steroid therapy. Spontaneous improvement occurred in 3 patients. Four asymptomatic patients with segmental pancreatic enlargement have demonstrated no changes without steroid therapy until now.

Conclusions: About half of the segmental AIP cases progressed and needed steroid therapy, which was effective. Asymptomatic segmental AIP cases without biliary lesions may be followed without steroid therapy with periodic laboratory and imaging studies.

INTRODUCTION

Autoimmune pancreatitis (AIP) is a particular type of pancreatitis that is thought to have an autoimmune etiology (1,2). During the past 10 years, a number of new clinicopathological aspects of AIP have been clarified, and AIP is now considered to be a discrete entity worldwide (3,4). As patients with pancreatic cancer and AIP share many features, such as a pancreatic mass, painless jaundice, new-onset diabetes mellitus, and elevated tumor markers, several AIP patients have been surgically resected on suspicion of pancreatic cancer (1,5). Recently, as the concept of AIP has become increasingly accepted, most AIP patients are promptly treated with steroids when the diagnosis of AIP is made, since AIP responds dramatically to steroid therapy (6-10). Therefore, the natural course of AIP is unclear, although there are some reports that several AIP patients improved spontaneously (11,12). It is also questionable whether steroid therapy is indispensable for all AIP patients.

This study evaluated the clinical course of AIP patients without steroid or surgical therapy and assessed the indications for steroid therapy in AIP patients.

METHODOLOGY

Patients

From April 1990 to April 2008, 48 patients were diagnosed as having AIP according to the Diagnostic Clinical Criteria for AIP 2006 (13). Initial therapy consisted of surgery on suspicion of pancreatic cancer (resection (n=6) and by-pass surgery with pancreatic biopsy (n=4)), and steroids (n=34). Steroid therapy was given due to obstructive jaundice due to stenosis of the bile duct (n=25), diffuse enlargement of the pancreas (n=4), associated retroperitoneal fibrosis (n=3), abdominal pain (n=1), and enlargement of the pancreatic body and tail (n=1). Steroid therapy was added in 1 patient after resection and in 1 patient after by-pass surgery for late occurrence of an extra-pancreatic lesion (retroperitoneal fibrosis and systemic lymphadenopathy, respectively). The patients were followed with laboratory studies, including serum IgG or IgG4 levels and imaging studies, such as computed tomography (CT), ultrasonography (US), and magnetic resonance cholangiopancreatography (MRCP), periodically every 3-6 months. Endoscopic retrograde cholangiopancreatography (ERCP) was performed repeatedly in cases in which precise evaluation of the pancreatic or biliary duct was necessary.

Methods

Of the 48 patients, 12 patients were followed for more than 6 months after the diagnosis of AIP without steroid or surgical therapy. The patients were divided into two groups (those who later underwent

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steroid therapy due to exacerbation of AIP, and those who were followed without steroid or surgical therapy), and their clinical features were assessed retrospectively.

Statistical Analysis

Statistical analysis was performed by Mann-Whitney's U-test or Fisher's exact test. In all tests, corrected p values of <0.05 were considered statistically significant.

RESULTS

One patient had secondary obstructive jaundice due to lower bile duct stenosis, but he was treated only with percutaneous transhepatic biliary drainage for 12 months, since he died at that time due to associated advanced pulmonary cancer. No significant changes were observed in pancreatic and bile duct stenoses or enlargement of the pancreas during the follow-up period.

Overall, 6 of the other 11 patients were later given steroid therapy due to exacerbation of AIP during the follow-up period of 6 to 35 months after the initial diagnosis of AIP. At the time of the initial diagnosis of AIP, 5 patients had segmental enlargement of the pancreas (head (n=3), body (n=1) and tail (n=1)), and 1 patient had diffuse enlargement of the pancreas. ERCP showed irregular narrowing of the main pancreatic duct in accordance with the pancreatic enlargement. Pancreatic segmental enlargement in 4 asymptomatic patients was detected incidentally on US or CT. Five patients later developed obstructive jaundice due to stenosis of the lower (n=4) and intrahepatic (n=1) bile duct. In 4 patients, segmental enlargement (head (n=2), body (n=1) and tail (n=1)) progressed to diffuse enlargement **(Figure 1a-d)**. In case 2, a segmental pancreatic head lesion progressed along with progression of lower bile duct stenosis. In case 4, the diffuse pancreatic lesion progressed along with progression of stenosis of the intrahepatic bile duct. Spontaneous improvement occurred in 2 patients. In Case 1, enlargement of the pancreatic tail improved and disappeared spontaneously 15 months after the initial diagnosis, but the pancreas was enlarged diffusely 13 months later. In cases in which the serum IgG and/or IgG4 levels were measured serially, they increased along with progression of the AIP. In case 1, the serum IgG and IgG4 levels decreased in accordance with spontaneous improvement of the AIP. In case 2, antinuclear antigen (ANA) changed from negative to positive (x160) when the AIP progressed (14). In 3 patients, preceding diabetes mellitus progressed as the AIP occurred. In 4 patients, swelling of the salivary glands preceded AIP, and all of the salivary gland lesions were initially diagnosed on biopsy as sclerosing sialadenitis; later immunohistochemical examination retrospectively revealed infiltration of abundant IgG4-positive plasma cells in the salivary glands. In all 6 patients, the radiological findings of both the pancreatic and biliary lesions and the clinical features improved markedly after steroid therapy **(Table 1)**.

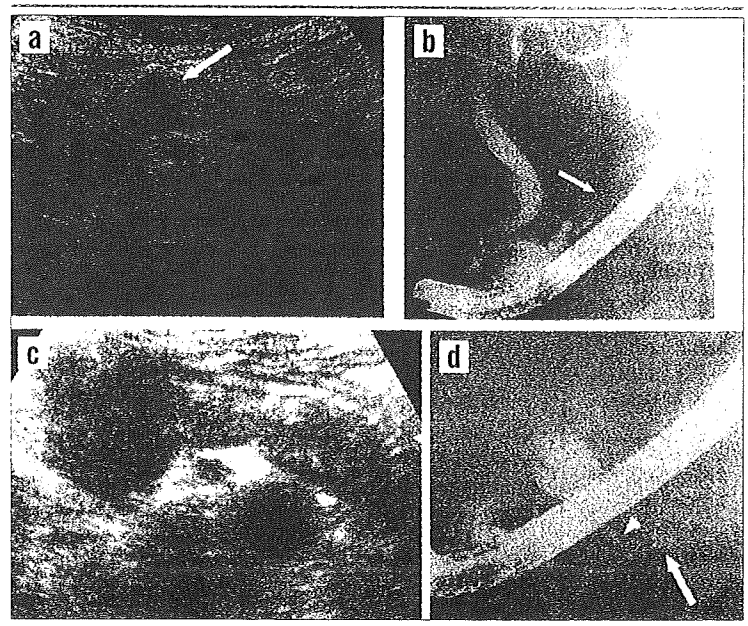

FIGURE 1 Case 5. **(a)** Segmental hypoechoic swelling in the pancreatic body was detected on US. **(b)** Segmental narrowing of the main pancreatic duct in the pancreatic body on ERCP. **(c)** Six months later, the lesion progressed to diffuse enlargement of the pancreas. **(d)** Six months later, extensive narrowing of the main pancreatic duct and stenosis of the lower bile duct were detected on ERCP.

Five patients were followed without steroid therapy for 6, 7, 12, 24 and 25 months, respectively, and 4 of these patients are still being followed. Swelling of the salivary glands preceded AIP in 1 patient. Segmental pancreatic enlargement was incidentally detected on US or CT in 3 asymptomatic patients. One patient was found to have diffuse enlargement of the pancreas while being investigated for general malaise, and one patient was found to have segmental swelling of the pancreatic body while being treated for acute pancreatitis. The diffuse enlargement of the pancreas without involvement of the biliary tract improved spontaneously 1 year later, and it did not recur for 1 year, after which the patient was lost to follow-up. Four patients with segmental pancreatic enlargement and irregular narrowing of the main pancreatic duct (head (n=1) and body (n=3)) but without involvement of the biliary tract demonstrated no changes during 6 to 25 months of follow-up without steroid therapy.

There were no statistically significant differences in clinical features between the 6 patients who were finally treated with steroids and the 5 patients who did not require steroids during followed up. However, serum IgG and IgG4 levels were higher and sclerosing sialadenitis was more common in steroid-treated patients **(Table 2)**.

DISCUSSION

AIP is a fibroinflammatory disease that is characterized histologically by fibrosis with dense infil-

TABLE 1 Clinical Course of 6 Cases of Autoimmune Pancreatitis who were Finally Treated with Steroids

Case 1 (66, m)	1993.4	1995.7	1998.7	1999.2	2000.3	2001.4 Steroid	2001.6	2001.9
Symptom								
Pancreatic swelling			Segmental (tail)	Improved	Disappeared	Diffuse	Improved	
Bile duct stenosis			none	none	none	none		none
Salivary gland swelling	+	+	+	+	+	+		Improved
BHL		+	+	+	+	+		Improved
DM		+	Progressed					Improved
IgG (mg/dL)	2349	2894	3166	2150	2020	2980		1270
IgG4 (mg/dL)						1240		220
ANA	-		-			-		

Case 2 (69, f)	1998.3	1998.11 Steroid	1998.12	1999.2
Symptom	Abdominal pain	Icterus		Improved
Pancreatic swelling	Segmental (head)	progressed		Improved
Bile duct stenosis	Lower	progressed		Improved
DM	+	progressed		Improved
IgG (mg/dL)	1640	2640		1060
IgG4 (mg/dL)		298		118
ANA	-	x 160		x 20

Case 3 (70, f)	2002.5	2002.8	2003.9	2004.2	2004.8 Steroid	2004.8	2004.10
Symptom					Icterus		Improved
Pancreatic swelling			Normal	Segmental (head)	Diffuse	Improved	
Bile duct stenosis			none	Lower	Progressed	Improved	
Salivary gland swelling	+	+	+	+	+	Improved	
Lacrymal gland swelling		+	+	+	+	Improved	
IgG (mg/dL)			2440	2320	2594		1580
IgG4 (mg/dL)			825	595	1030		259
ANA			x 20		x 20		x 20

Case 4 (69, m)	2002.4	2003.12	2004.3	2004.6	2004.7 Steroid	2004.9
Symptom		Malaise	Icterus	Improved		Improved
Pancreatic swelling		Diffuse	Progressed	Improved		Improved
Bile duct stenosis		Intrahepatic Lower	Progressed	Improved		Improved
Salivary gland swelling	+	+	+	+		Improved
DM	+	Progressed				Improved
IgG (mg/dL)				1770		1190
IgG4 (mg/dL)				418		59
ANA				-		-

Case 5 (65, f)	2004.12	2007.7	2008.1	2008.2 Steroid	2008.4
Symptom			Icterus		Improved
Pancreatic swelling		Segmental (body)	Diffuse		Improved
Bile duct stenosis		none	Lower		Improved
IgG (mg/dL)	1690		1829		1060
IgG4 (mg/dL)		228	274		177
ANA		-	-		-

Case 6 (59, m)	2007.5	2007.9	2008.2	2008.2 Steroid	2008.4
Symptom			Icterus		Improved
Pancreatic swelling		Segmental (head)	Diffuse		Improved
Bile duct stenosis		None	Lower		Improved
Salivary gland swelling	+	+	+		Improved
IgG (mg/dL)		2030	2580		929
IgG4 (mg/dL)		750	970		309
Rheumatoid factor		-	x 45		-
ANA		-	-		-

BHL: bilateral hilar lymphadenopathy, ANA: antinuclear antibody, DM: diabetes mellitus.

tration of lymphocyte and IgG4-positive plasma cells in the pancreas (1,2). AIP patients also have various extrapancreatic lesions such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis (1,15). Steroid therapy is very effective for the extrapancreatic lesions, as well as the pancreatic lesions, in AIP patients, and steroid therapy has become standard therapy for AIP (6-10). Since steroid therapy is given to most AIP patients soon after the diagnosis, the natural course of AIP without therapy is unclear, and the effect of steroid therapy on the natural history of AIP is unknown. Therefore, whether asymptomatic patients, most of whom present with segmental pancreatic changes, should be treated with steroids is questionable.

The present study showed that the disease worsened in 6 of 11 AIP patients during follow-up and required steroid therapy; 5 of the 6 patients developed obstructive jaundice. The biliary lesion in AIP patients is sclerosing cholangitis, which consists of transmural fibrosis with infiltration of abundant lymphocytes and IgG4-positive plasma cells and is quite similar to the histological findings in the pancreas; thus, the development of the biliary lesion appears to involve the same mechanism as the progression of the pancreatic lesion in patients with AIP. Four patients with segmental AIP progressed to diffuse enlargement. The period between the initial diagnosis of AIP and progression ranged from 6 to 35 months. Spontaneous improvement was observed in 3 patients, including 1 patient who relapsed and developed diffuse enlargement 13 months after complete remission. Several reported AIP cases have shown progression from the segmental type to the diffuse type during observation without therapy, including: a segmental head lesion that progressed to the diffuse type in 2 months (16); a segmental head lesion that progressed to the diffuse type in 12 months (17); and a segmental pancreatic body and tail lesion that progressed to the diffuse type in 24 months (12). There have also been reports of relapse in the remnant pancreas after resection, including: relapse in the remnant pancreatic head 1 year after distal pancreatectomy (18), and relapse in the remnant pancreatic body and tail 4 months after pancreatoduodenectomy (19). Steroid therapy was effective for these lesions that had progressed or relapsed. These findings indicate that the segmental inflammation may advance to subsequent diffuse changes throughout the pancreas or develop repeatedly at different sites and at different times in some AIP patients. Diffuse change of the pancreas seems to be the final appearance of AIP, and whether this inflammatory process affects the gland diffusely or segmentally may merely reflect the stage of the disease.

On the other hand, several cases of spontaneous regression of AIP have been reported over a period of 2 to 60 months (11,12). Wakabayashi *et al.* (12) reported 4 AIP patients showing spontaneous regression; they had negative immunoserologic tests and had no biliary lesions. Kubota *et al.* (20) also reported that AIP patients who were seronegative for IgG4, had no obstructive jaundice, and had segmental pancreatic enlargement had a greater tendency toward spontaneous remission. Although there were no statistically significant differences in the clinical features between patients finally treated with steroids and patients who did not require steroids during follow-up, this might be due to the small number of cases studied. Serum IgG and IgG4 levels were higher and the extrapancreatic lesion of sclerosing sialadenitis was more common in steroid-treated patients. Furthermore, serological findings, including the serum IgG and IgG4 levels, changed in accordance with the progression or regression of the pancreatic lesions. It has been reported that serum IgG4 levels reflect disease activity of AIP, and that AIP patients with several extrapancreatic lesions have higher IgG4 levels than those with no lesions (21,22). Since the histological appearances of various extrapancreatic lesions, which involves fibrosis and dense infiltration of lymphocytes and IgG4-positive plasma cells, in AIP patients is quite similar to that seen in the pancreas, AIP appears to be a pancreatic lesion of an IgG4-related systemic disease (1,23,24). Therefore, patients with multiple extrapancreatic lesions may have greater disease activity.

TABLE 2 Clinical Features of Patients with Autoimmune Pancreatitis Finally Treated with Steroids and Followed Without Steroids

	Treated with steroids (n=6)	Followed without steroids (n=5)	*p* value
Follow-up period	8.0 (6.0-15.5)*	12.0 (6.5-24.5)	0.579
Age on diagnosis	67.5 (63.5-69.2)	56.0 (50.5-71.0)	0.232
Male/female	3/3	5/0	0.181
Serum IgG (mg/dL)	2030.0 (1665.0-2743.0) (n=5)	1847.5 (n=4)	0.327
Serum IgG4 (mg/dL)	595.0 (n=3)	318.5 (n=4)	0.479
Extrapancreatic lesion +/-	4/2	1/4	0.242

*Median (quartile range).

It is generally accepted that the indications for steroid therapy in AIP are having symptoms, such as obstructive jaundice due to stenosis of the bile duct or abdominal pain, and other associated extrapancreatic lesions, such as retroperitoneal fibrosis (1,6-10). It is not known whether the present segmental cases that are being followed without steroid therapy may progress in the future. However, in all patients who were later treated with steroids due to AIP exacerbation, the radiological findings of both the pancreatic and biliary lesions and the clinical features improved markedly. Given these findings, asymptomatic segmental AIP cases without biliary lesions may be followed without steroid therapy with periodic laboratory and imaging studies. However, cases with higher serum IgG4 levels or extrapancreatic lesions appear to be more likely to progress.

In conclusion, although about half of segmental AIP cases progress and need steroid therapy, asymptomatic segmental AIP cases without biliary lesions may be followed without steroid therapy with periodic laboratory and imaging studies.

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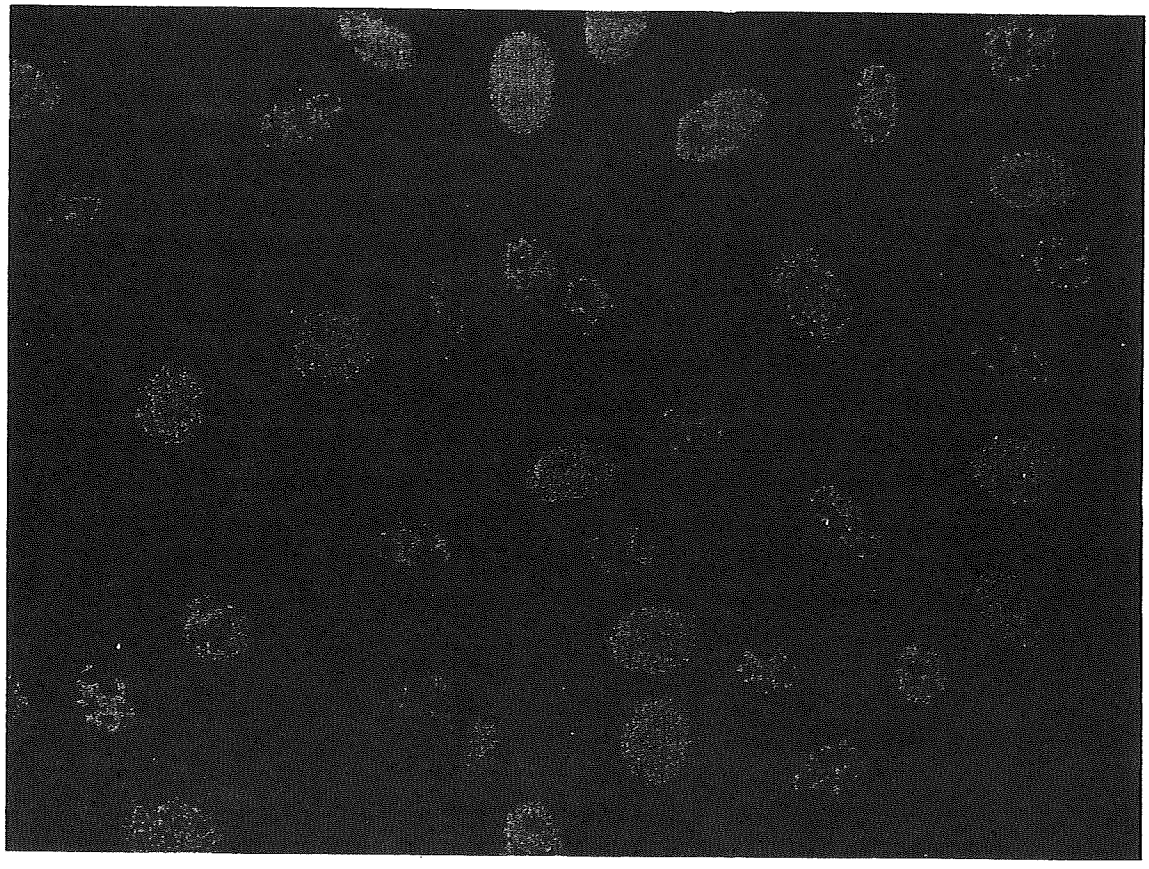
K. Conrad, E.K.L. Chan, M.J. Fritzler, R.L. Humbel,
P. von Landenberg, Y. Shoenfeld (Eds.)

From Pathogenesis to Therapy of Autoimmune Diseases

Report on the 9th Dresden Symposium on Autoantibodies held in Dresden on September 2–5, 2009



AUTOANTIGENS, AUTOANTIBODIES, AUTOIMMUNITY
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PABST

IgG4-related sclerosing disease

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Introduction

Yoshida et al. proposed the concept of autoimmune pancreatitis (AIP) in 1995 [1], and AIP has become a distinct entity recognized worldwide. In AIP patients, serum IgG4 levels are frequently and significantly elevated, and various extrapancreatic lesions are present. Based on histological and immunohistochemical examination of various organs of AIP patients, we have found dense infiltration of IgG4-positive plasma cells and T lymphocytes, as well as fibrosis in the peripancreatic retroperitoneal tissue, bile duct wall, gallbladder wall, periportal area of the liver, salivary glands, as well as the pancreas. Furthermore, all of the extrapancreatic lesions associated with AIP, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, show infiltration of abundant IgG4-positive plasma cells. Both the pancreatic and the extrapancreatic lesions of AIP respond well to steroid therapy. Therefore, we proposed the existence of a novel clinicopathological entity, an "IgG4-related sclerosing disease", and suggested that AIP is a pancreatic lesion of this systemic disease [2–5]. At present, IgG4-related sclerosing disease has been noted in hepatology, cholangiology, rheumatology, urology, nephrology, respirology, endocrinology, pathology, and radiology, as well as pancreatology.

IgG4-related sclerosing disease

IgG4-related sclerosing disease is a systemic disease characterized by extensive IgG4-positive plasma cell and T lymphocyte infiltration of various organs. Clinical manifestations are apparent in organs such as the pancreas, bile duct, gallbladder,

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salivary gland, retroperitoneum, and etc. where tissue fibrosis with obliterative phlebitis is pathologically induced. AIP is not simply a pancreatitis but it is a pancreatic lesion reflecting an IgG4-related sclerosing disease. Some inflammatory pseudotumors may be involved in this disease. In some cases, only 1 or 2 organs are clinically involved, while in others, 3 or 4 organs are affected (Fig. 1). The disease occurs predominantly in elderly males, is frequently associated with lymphadenopathy, and responds well to steroid therapy. Serum IgG4 levels and immunostaining with anti-IgG4 antibody are useful in making the diagnosis. The precise pathogenesis and pathophysiology of IgG4-related sclerosing disease remain unclear. Since malignant tumors are frequently suspected on initial presentation, IgG4-related sclerosing disease should be considered in the differential diagnosis to avoid unnecessary surgery [2–5].

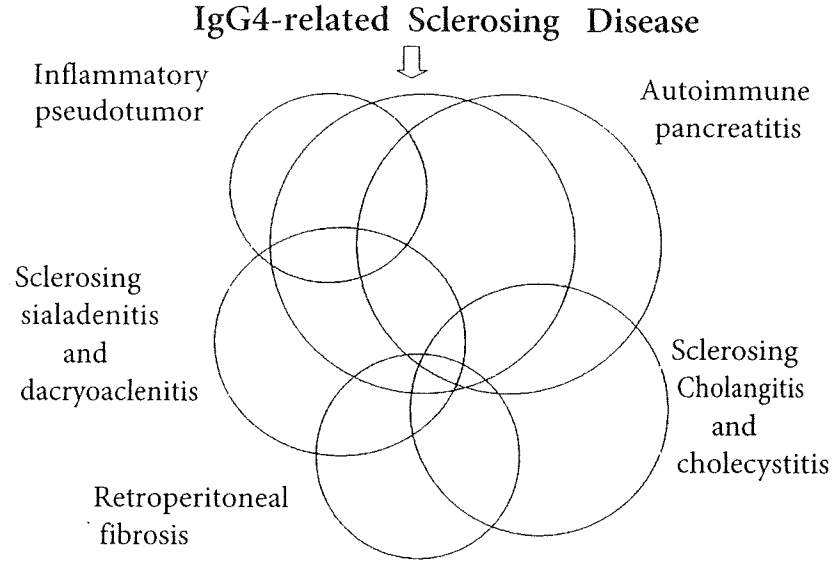

Figure 1. Schematic illustration of IgG4-related sclerosing disease.

Multifocal fibrosclerosis is an uncommon fibroproliferative systemic disorder with multiple manifestations, including sclerosing cholangitis, fibrosis of the salivary glands, retroperitoneal fibrosis, Riedel's thyroiditis, and fibrotic pseudotumor of the orbit [6]. The histopathology of the extrapancreatic lesions associated with AIP strongly suggests that multifocal fibrosclerosis is an IgG4-related sclerosing disease [2].

Autoimmune pancreatitis

Concept and clinical features

AIP is a unique form of pancreatitis in which autoimmune mechanisms are suspected to be involved in the pathogenesis. AIP occurs more commonly in elderly males. In our 57 AIP Patients, the mean age of the patients was 66.5 years (range, 25–83 years), and the male-to-female ratio was 4:1. The major clinical symptom is obstructive jaundice due to associated sclerosing cholangitis (70 % in our series). Failure of pancreatic exocrine or endocrine function is frequently seen. Up to 50 % of AIP patients present with glucose intolerance [7].

Pathogenesis

Levels of serum IgG4, a subtype of IgG, are frequently elevated, and they are particularly high in AIP. Dense infiltration of IgG4-positive plasma cells is seen in various organs of AIP patients. These findings suggest that IgG4 plays a major role in the pathogenesis of AIP, although the trigger for the IgG4 elevation or its pathogenetic role in AIP has not been clearly disclosed.

Although the actual effector cells of AIP have not been clearly delineated, there is an increased number of activated CD4- and CD8-positive T cells bearing HLA-DR among the peripheral blood lymphocytes and in the pancreas of AIP patients [8]. Zen et al. reported that the expression of Th2 cytokines (IL-4, IL-5, and IL-13) and regulatory cytokines (IL-10 and TGF-β) was up-regulated in the affected tissues of patients with IgG4-related sclerosing pancreatitis and cholangitis, and they suggested that the predominant Th2 and regulatory immune reactions might play an important role in its pathogenesis [9].

Diagnosis

It is of utmost importance that AIP be differentiated from pancreatic cancer, as some AIP patients in which pancreatic cancer is suspected undergo unnecessary laparotomy or pancreatic resection. Since there is currently no diagnostic serological marker for AIP, AIP should be diagnosed on the basis of the presence of a combination of abnormalities unique to AIP. The Japanese "Diagnostic Criteria for Autoimmune Pancreatitis" were revised in 2006 [10]. They consisted of three items: 1) radiological imaging showing diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas; 2) laboratory data demonstrating abnormally elevated levels of serum gammaglobulin or IgG, or IgG4, or the presence of autoantibodies; and 3) histological examination of the pancreas showing lymphoplasmacytic infiltration and fibrosis. The diagnosis of AIP is made when either all 3 criteria are present or criterion 1 together with either criterion 2 or criterion 3 is present.

Radiologically, pancreatic enlargement is usually hypoechoic, sometimes with scattered hyperechoic spots on ultrasonography (Fig. 2). On dynamic CT, there is delayed enhancement of the enlarged pancreatic parenchyma. Typical AIP patients show diffuse enlargement of the pancreas, the so-called sausage-like appearance. Since inflammatory and fibrous changes involve the peripancreatic adipose tissue, a capsule-like rim surrounding the pancreas, which appears as a low density on CT, is detected in some cases. Pancreatic calcification or a pseudocyst is rarely seen. Cases of focal enlargement of the pancreas are sometimes difficult to differentiate from pancreatic cancer. Endoscopic retrograde cholangiopancreatography (ERCP) discloses an irregular, narrow main pancreatic duct (Fig. 3). In patients with segmental narrowing, absence of upstream dilatation of the main pancreatic duct is characteristic.

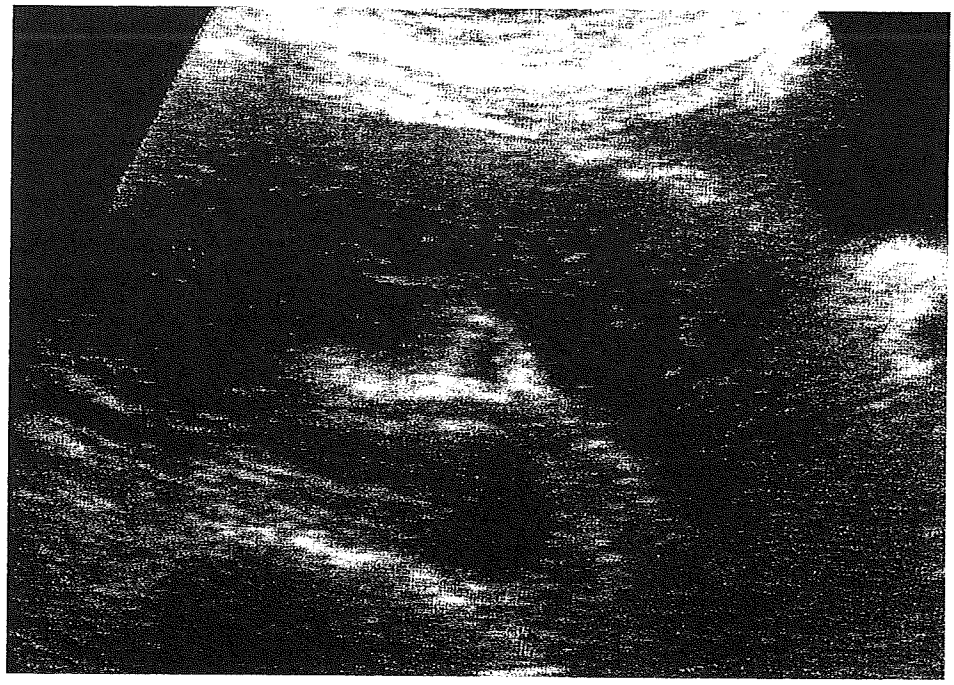

Figure 2. Diffuse hypoechoic enlargement of the pancreas on US in a patient with autoimmune pancreatitis.

In our AIP patients, hypergammaglobulinemia (>2.0 g/dl) and elevated serum IgG levels (> 1800 mg/dl) are detected in 33 % and 56 %, respectively, while autoantibodies, including antinuclear antibody and rheumatoid factor, were present in 44 % and 16 %. According to the report by Okazaki et al., anti-lactoferrin antibody, anti-carbonic anhydrase-II (CA II) antibody, anti-pancreatic secretory trypsin inhibitor (PSTI) antibody, and anti-smooth muscle antibody were detected in 75 %, 55 %, 25 %, and 15 % of their 54 AIP patients, but anti-SSA or anti-SSB antibody, anti-glutamic acid dehydrogenase (GAD) antibody, and anti- mitochondrial antibody (AMA) were rarely observed [11]. Serum IgG4 levels are rather significantly

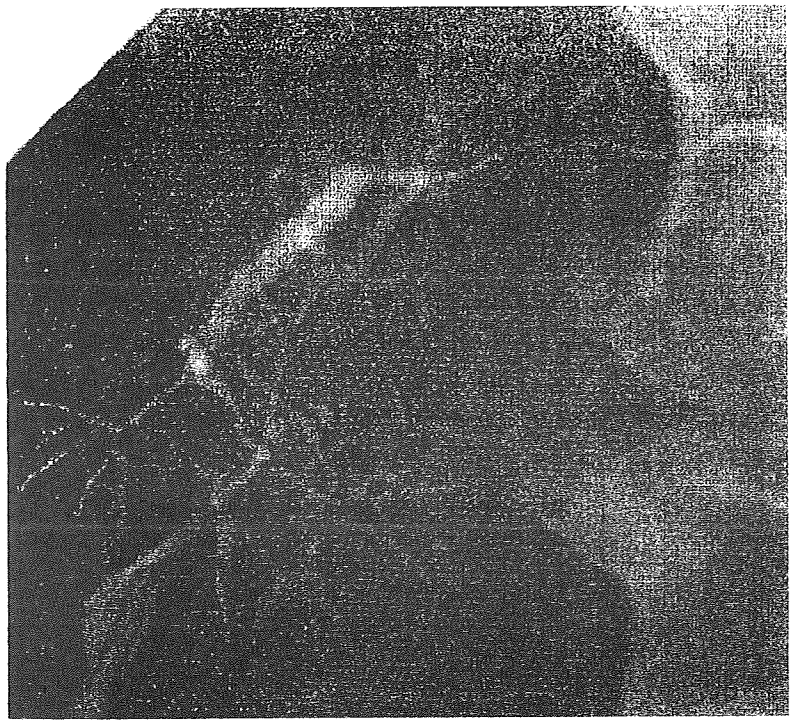

Figure 3. Irregular narrowing of the main pancreatic duct on ERCP in a patient with autoimmune pancreatitis.

and specifically high (>135 mg/dl) in AIP patients [12]. The sensitivity of elevated serum IgG4 levels was 80 % in our series.

Histologically, dense infiltration of T lymphocytes and IgG4-positive plasma cells with fibrosis is detected in the pancreas of AIP patients (Fig. 4). The pancreatic duct is narrowed by periductal fibrosis and lymphoplasmacytic infiltration. Another characteristic histological finding is obliterative phlebitis involving minor and major veins, including the portal vein. Such an inflammatory process widely and intensely involves the contiguous soft tissue and peripancreatic retroperitoneal tissues.

Treatment and prognosis

AIP responds dramatically well to corticosteroid. Oral steroid is a standard therapy for AIP. The indications for steroid therapy in AIP are symptoms such as obstructive jaundice due to sclerosing cholangitis, abdominal pain, and the presence of other associated systemic diseases, such as retroperitoneal fibrosis.

Before steroid therapy is started, endoscopic or percutaneous transhepatic biliary drainage must be done in cases with obstructive jaundice, and glucose levels must be controlled in cases with diabetes mellitus. Oral predonisolone is usually started at 0.6mg/kg/day, and then it is tapered by 5 mg every 1–2 weeks. Serological

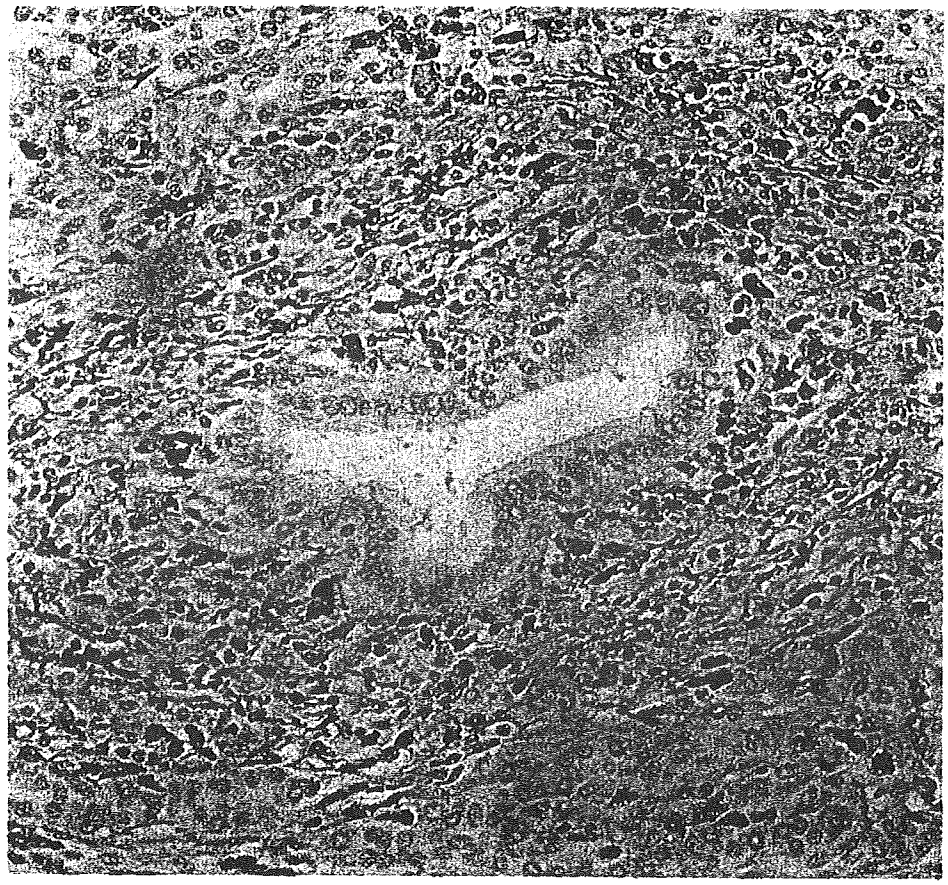

Figure 4. Dense infiltration of IgG4-positive plasma cells in the pancreas of a patient with autoimmune pancreatitis (IgG4 immunostaining).

and imaging tests are followed periodically after commencement of steroid therapy. Usually, pancreatic size is normalized within a few weeks, and biliary drainage becomes unnecessary after 1–2 months. Patients in whom complete radiological improvement is documented can stop their medication. To prevent relapses, continued maintenance therapy with prednisolone 5 mg/day is sometimes required. In half of steroid-treated patients, impaired exocrine or endocrine function improved. About 20–30 % of AIP patients relapse during maintenance therapy or after steroid medication is stopped and they should be retreated with high-dose steroid therapy [13].

The long-term prognosis of AIP is not well known. Recurrent attacks of AIP resulting in pancreatic stone formation have been reported in some cases [14].

IgG4-related sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is progressive despite conservative therapy, and it involves the intra- and extrahepatic bile ducts, resulting in liver cirrhosis. The effect of steroid therapy is questionable, and liver transplantation currently provides the greatest hope for a possible cure. PSC occurs during the 30s–40s and is frequently associated with inflammatory bowel disease [15]. Pancreatography is not abnormal in most PSC cases.

Stenosis occurred in the lower part of the common bile duct in 70 % of our AIP patients. When stenosis is found in the intrahepatic or the hilar hepatic bile duct, the cholangiographic appearance is very similar to that of PSC. Elevation of serum IgG4 is frequently observed in patients with IgG4-related sclerosing cholangitis, and it responds dramatically to steroid therapy, unlike PSC. Clinically, patients with IgG4-related sclerosing cholangitis are older at diagnosis than patients with PSC. The histological appearance is transmural fibrosis, dense fibrosis with infiltration of T lymphocytes and IgG4-positive plasma cells and obliterative phlebitis in the bile duct wall and the periportal area of the liver, in contrast to PSC. Given the age at onset, associated diseases, pancreatographic findings, response to steroid therapy, prognosis, and IgG4-related serological and immunohistochemical data, IgG4-related sclerosing cholangitis is a different disease from PSC (Table 1) [16].

Table 1. Clinicopathological differences between sclerosing cholangitis with autoimmune pancreatitis and PSC.

	cholangitis with AIP	**PSC**
Age	elderly	young and elderly
Steroid responsiveness	good	poor
Prognosis	good	poor
Associated diseases	sclerosing diseases	ulcerative colitis
Serum IgG4 elevation	frequent	rare
IgG4-positive plasma cell infiltration	dense	few
Extensive wall thickening	occasional	rare
Sclerosing cholecystitis	occasional	rare
Narrowing of the main pancreatic duct	always	none
Stenosis of the bile duct	lower	intrahepatic
	segmental	multiple, beaded pruned-tree

IgG4-related sclerosing cholecystitis

Thickening of the gallbladder was detected on US and/or CT in 32 % of our AIP patients. Dense infiltration of IgG4-positive plasma cells and lymphocytes, as well as transmural fibrosis, was detected in the gallbladder wall [17].

IgG4-related sclerosing sialadenitis and dacryoadenitis

Swelling of the bilateral salivary glands was present in 25 % of our AIP patients, and it was associated with cervical or mediastinal lymphadenopathy. Swelling of the bilateral lacrymal glands was associated in one AIP patient. Swelling of the salivary and lacrymal glands and the lymph nodes improved after steroid therapy. In the salivary glands of these patients, dense infiltration of IgG4-positive plasma cells and fibrosis were detected (Fig. 5A, 5B).

Mikulicz's disease is a unique condition that refers to bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands. Patients with Mikulicz's disease lack anti-SS-A and anti-SS-B antibodies, but frequently have elevated serum IgG4 levels. Infiltration of many IgG4-positive plasma cells into the lacrimal and salivary glands has been detected in Mikulicz's disease. Thus, Mikulicz's disease appears to be salivary gland lesions of IgG4-related systemic disease [18, 19].

IgG4-related retroperitoneal fibrosis

Retroperitoneal fibrosis was present simultaneously or metachronously in 7 % of our AIP patients. Dense infiltration of IgG4-positive plasma cells and obliterative phlebitis were found in both the pancreas and the retroperitoneal fibrous mass. Both the retroperitoneal fibrosis and AIP resolved after steroid therapy [20].

IgG4-related inflammatory pseudotumor

Some IgG4-related inflammatory pseudotumors of the liver [21], lung [22], and hypophysis [23], which were characterized by dense infiltration of IgG4-positive plasma cells and lymphocytes intermixed with fibrosis and obliterative phlebitis, have been reported in patients with or without AIP. Steroid therapy is effective for these IgG4-related inflammatory pseudotumors.

IgG4-related lymphadenopathy

In a study using gallium-67 scintigraphy, pulmonary hilar gallium-67 uptake was found in 41 (80.4 %) of 51 AIP patients [24]. In our series, abdominal

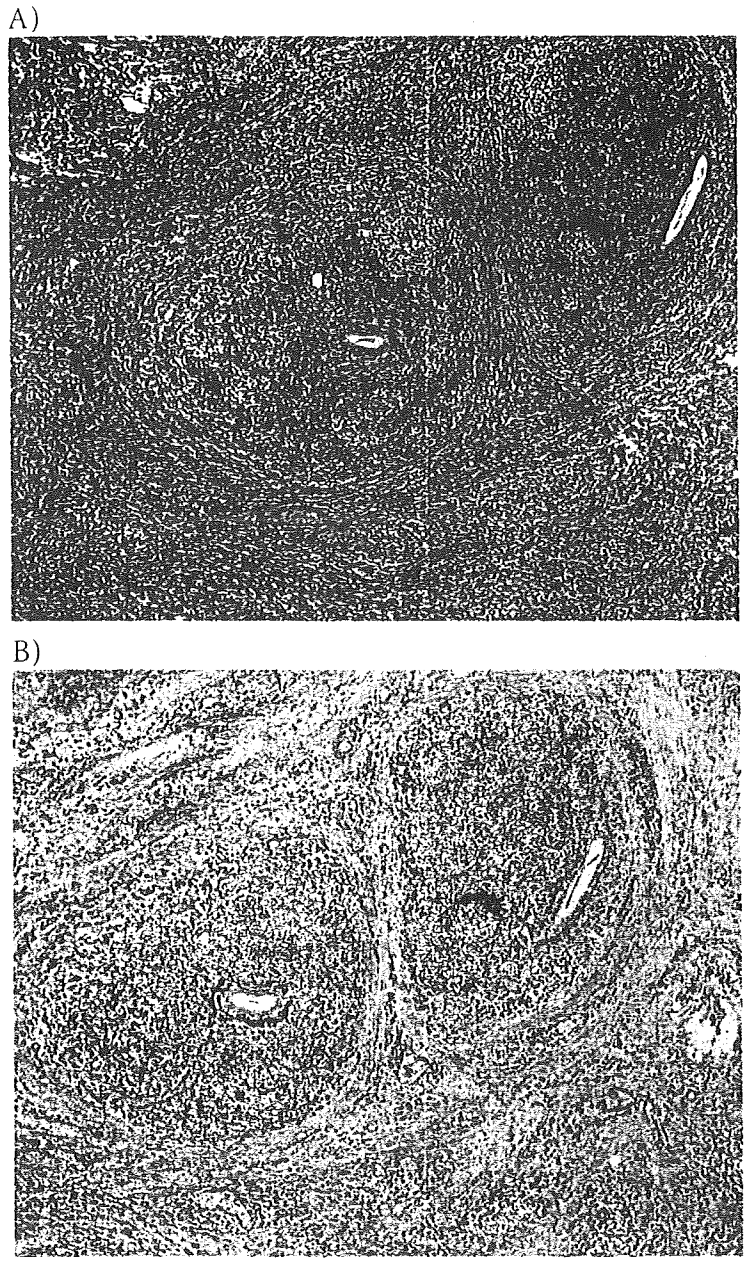

Figure 5. Histology of IgG4-related sclerosing sialadenitis. **(A)** Fibrosis and lymphoplasmacytic infiltration in the salivary gland. **(B)** Dense infiltration of IgG4-positive plasma cells (IgG4 immunostaining).

lymphadenopathy of up to 2 cm in diameter was observed in 5 of 8 patients at laparotomy, and cervical or mediastinal lymphadenopathy of up to 1.5 cm in diameter was observed on CT in 33 %. In all these cases, the lymphadenopathy disappeared after steroid therapy. Dense infiltration of IgG4-positive plasma cells was detected in swollen abdominal and cervical lymph nodes.

Other IgG4-related sclerosing diseases

Some cases of interstitial pneumonia [25], tubulointerstitial nephritis [26], prostatitis [27] and aortitis [28] may be included in IgG4-related sclerosing disease.

Conclusions

IgG4-related sclerosing disease is a new clinicopathological systemic entity. It is characterized by extensive IgG4-positive plasma cell and T lymphocyte infiltration of various organs, and major clinical manifestations are apparent in the organs, in which tissues fibrosis with obliterative phlebitis is pathologically induced. As steroid therapy is effective, accurate diagnosis is necessary.

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patients, clinicians should become familiar with subtle CF clinical manifestations, including pancreatic, intestinal, and hepatic involvement.

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Rapid Changes in Sclerosing Cholangitis Associated With Autoimmune Pancreatitis

To the Editor:

Autoimmune pancreatitis (AIP) is a recently described clinical entity whose pathogenesis may involve autoimmune mechanisms. Sclerosing cholangitis is frequently associated with AIP, and the major initial symptom of AIP is obstructive jaundice caused by this stenosis.[1–3] We report here an AIP case showing rapid progression of sclerosing cholangitis in the hilar bile duct within 2 days.

CASE REPORT

A 59-year-old man with obstructive jaundice was admitted to our hospital. Abdominal ultrasonography showed diffuse hypoechoic enlargement of the pancreas. On magnetic resonance cholangiopancreatography, stenosis was detected in the lower bile duct, but the main pancreatic duct was not seen. Serum IgG and IgG4 levels were elevated to 2438 mg/dL (normal, <2000 mg/dL) and 970 mg/dL (normal, <135 mg/dL), respectively. Laboratory testing revealed elevated total bilirubin (10.1 mg/dL; normal, <1.0 mg/dL) and alkaline phosphatase (841 IU/L; normal, 115–359 IU/L) levels. Endoscopic retrograde cholangiopancreatography demonstrated diffuse narrowing of the main pancreatic duct and stenosis of the lower bile duct, and an endoscopic nasobiliary drainage (ENBD) tube was inserted into the common bile duct (Fig. 1A). The patient's condition was diagnosed as AIP. On the following day, approximately 300 mL of bile was excreted from the ENBD tube, and the total bilirubin level decreased to 9.0 mg/dL. However, on the next day, the amount of excreted bile decreased to 80 mL, and the total bilirubin level increased to 11.6 mg/dL. Because cholangiography via the ENBD tube showed stenosis of the hilar bile duct in addition to that of the lower bile duct (Fig. 1B), oral prednisolone therapy (30 mg/d) was started. On the seventh day after the start of steroid therapy, stenosis of both the hilar and the lower bile duct improved (Fig. 1C), the enlarged pancreas decreased to normal size, and the ENBD tube was withdrawn. The patient has been treated with maintenance prednisolone (5 mg/d) to the present time, 6 months later.

DISCUSSION

Autoimmune pancreatitis is frequently associated with several extrapancreatic lesions. Sclerosing cholangitis is most frequent in extrapancreatic lesions of