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Systemic extrapancreatic lesions associated with autoimmune pancreatitis

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Autoimmune pancreatitis (AIP) is frequently associated with sclerosing cholangitis (SC). SC with AIP has a cholangiographic appearance that is often confused with primary sclerosing cholangitis (PSC) but only the former responds well to corticosteroid therapy. Detailed study of cholangiographic findings allows discrimination of SC with AIP from PSC. Band-like strictures, a beaded or pruned-tree appearance, and diverticulum-like outpouching were significantly more frequently observed in cases of PSC. In contrast, segmental strictures, dilation after confluent stricture, and strictures of the lower common bile duct were significantly more common in SC with AIP. The other systemic extrapancreatic lesions associated with AIP found in the literature were Sjögren's syndrome, ulcerative colitis, retroperitoneal fibrosis, sialadenitis, thyroiditis, and idiopathic thrombocytopenic purpura. In a comparison of the clinical course and laboratory data of our cases, gamma-globulin, IgG, and IgG4 levels were significantly higher in patients with AIP with systemic extrapancreatic lesions than those without them. In our immunohistochemical study, marked infiltration of IgG4+ plasma cells was frequently observed in the pancreas, liver, bile duct, and salivary glands of the AIP patients examined. In contrast, the degree of infiltration of IgG4+ plasma cells around the bile duct in the portal areas and the extrahepatic bile duct with PSC was significantly lower than with AIP. These results also suggest that AIP is a disease state clearly different from PSC. In addition, the normal epithelia of the pancreatic ducts, bile ducts, gallbladder, and salivary gland ducts reacting with the patients' sera was detectable by the anti-IgG4 antibody. Therefore, AIP may also affect extrapancreatic organs, and the sera of AIP patients may contain an IgG4 autoantibody to various organs.

Key words: autoimmune pancreatitis, IgG4, sclerosing cholangitis, primary sclerosing cholangitis, immunohistochemistry

Introduction

Autoimmune pancreatitis (AIP) is often associated with various systemic extrapancreatic lesions.[1–5] Some of these systemic extrapancreatic lesions show pathological findings similar to those in the pancreas.[3–5] We support the concept of multifocal fibrosclerosis[6,7] or IgG4-related autoimmune diseases,[8] of which pancreatic lesions are manifestations. The concept of AIP was first published in 1961 by Sarles et al.,[9] and since then it has occasionally been treated in Western countries as a manifestation of multifocal fibrosclerosis.[7] IgG4 is reported to be a useful marker for discriminating AIP from other pancreatic diseases.[8] We previously reported that serum IgG4 is a useful marker for distinguishing sclerosing cholangitis with AIP from primary sclerosing cholangitis (PSC).[10] The concept of IgG4-related autoimmune diseases was first proposed by Kamisawa et al.,[8] who showed that a number of IgG4 antibody-stained plasma cells could be recognized in a number of organs in the human body.

This report describes systemic extrapancreatic lesions associated with AIP, mainly based on our experience of (1) characteristic findings of sclerosing cholangitis with AIP, (2) a review of AIP cases with the other systemic extrapancreatic lesions, (3) a comparison of clinical data between AIP with and without systemic extrapancreatic lesions, and (4) an immunohistochemical analysis of AIP using anti-IgG4 antibody and patients' sera.

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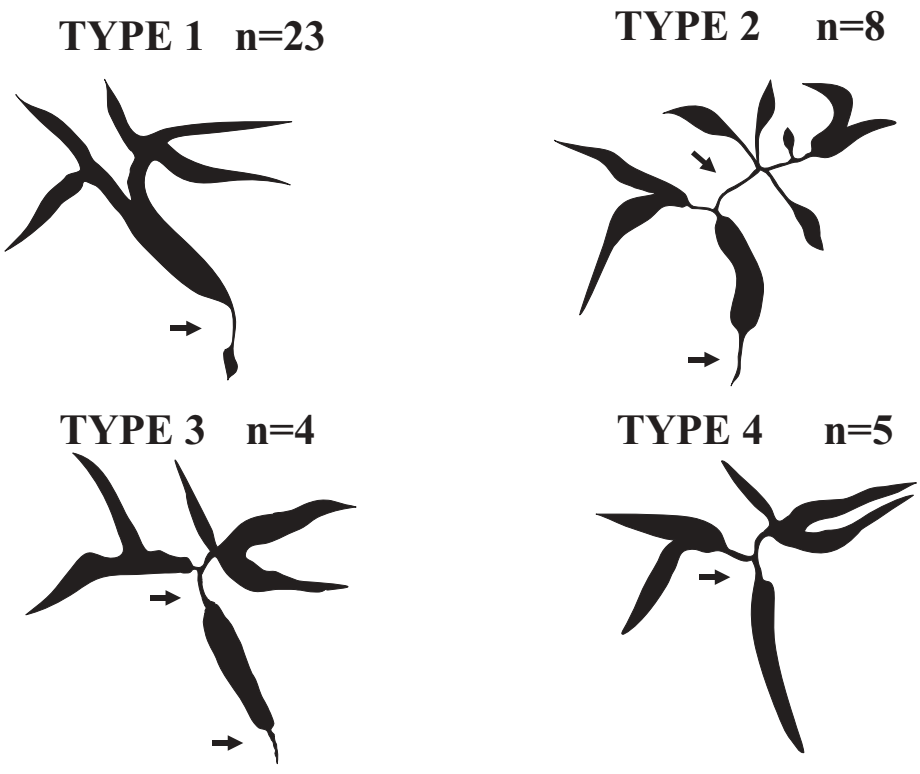

Fig. 1. Classification of cholangiogram in sclerosing cholangitis with autoimmune pancreatitis (AIP) (n = 40). Type 1, stenosis was present in the distal common bile duct alone. Type 2, stenoses were diffusely distributed in the intrahepatic and extrahepatic bile ducts. Type 3, stenosis was localized to both the hilar hepatic area and the distal common bile duct. Type 4, strictures were evident in the hilar area only

Sclerosing cholangitis

Sclerosing cholangitis with AIP has a cholangiographic appearance that is similar to that of PSC. Based on a review of Japanese case reports of PSC with chronic pancreatitis,[11–13] it is our suspicion that most of these cases were sclerosing cholangitis with AIP because pancreatography showed diffuse narrowing of the main pancreatic duct with an irregular wall, and corticosteroid administration was an effective therapy for the sclerosing changes in both the pancreas and the biliary tract.

We have reported that sclerosing cholangitis associated with AIP constitutes a clinical entity that is different from PSC.[10] Sclerosing cholangitis with AIP differs from PSC in the presenting complaints, cholangiographic findings, associated diseases, levels of IgG4, and clinical course.[10,14] Sclerosing cholangitis with AIP, as well as the pancreatic changes, responds well to treatment with a corticosteroid or to biliary drainage.[10] In contrast, PSC is a progressive disease, regardless of therapy, that involves the intra- and extrahepatic bile ducts and leads to biliary cirrhosis. The efficacy of corticosteroid therapy for PSC is questionable,[15,16] and liver transplantation is the only effective treatment. Therefore, it is necessary to discriminate between these two diseases before making therapeutic decisions.

Cholangiogram of sclerosing cholangitis with AIP

We have presented evidence that the cholangiogram of sclerosing cholangitis with AIP of the main pancreatic duct could be classified into four types.[17] In our classification of the cholangiographic changes of AIP, stenosis was present in the distal common bile duct alone in type 1, stenoses were diffusely distributed in the intrahepatic and extrahepatic bile ducts in type 2, stenosis was localized to both the hilar hepatic area and the distal common bile duct in type 3, and strictures were evident in the hilar area only in type 4 (Fig. 1).

When a diagnosis of AIP can be established, unnecessary surgical operations based on a misdiagnosis of pancreatic carcinoma can usually be avoided. However, biliary strictures because of AIP have a cholangiographic appearance that is similar to that of other biliary diseases. Type 1 cholangiographic findings in our classification are often misdiagnosed as pancreatic carcinoma, type 2 findings are often confused with PSC, and types 3 and 4 may be misdiagnosed as cholangiocarcinoma.

Comparison of cholangiographic findings: PSC vs. sclerosing cholangitis with AIP

Cholangiographic findings for PSC vs. sclerosing cholangitis with AIP are compared in Table 1.[14] Each

Table 1. Comparison of cholangiographic findings: primary sclerosing cholangitis (PSC) vs. sclerosing cholangitis (SC) with AIP (From [14], with permission)

1. Length of stricture

	Band-like stricture		Segmental stricture		Dilation after confluent stricture	
Score	PSC	SC with AIP	PSC	SC with AIP	PSC	SC with AIP
0	11	36	19	0	25	23
1+	6	0	5	22	3	4
2+	12	0	5	14	1	9
P value	PSC > SC with AIP, $P < 0.001$		PSC < SC with AIP, $P < 0.001$		PSC < SC with AIP, $P < 0.05$	

2. Characteristic findings of PSC

	Beaded appearance		Pruned-tree appearance		Diverticulum-like outpouching		Shaggy appearance	
Score	PSC	SC with AIP	PSC	SC with AIP	PSC	SC with AIP	PSC	SC with AIP
0	16	36	11	36	19	36	25	32
1+	4	0	5	0	9	0	2	2
2+	9	0	13	0	1	0	2	2
P value	PSC > SC with AIP, $P < 0.01$		PSC > SC with AIP, $P < 0.001$		PSC > SC with AIP, $P < 0.01$		n.s.	

3. Region of stricture

	Stricture of hepatic hilar region		Stricture of lower CBD	
Score	PSC	SC with AIP	PSC	SC with AIP
0	22	26	17	4
1+	4	3	6	2
2+	3	7	6	30
P value	n.s.		PSC < SC with AIP, $P < 0.001$	

PSC, primary sclerosing cholangitis; SC, sclerosing cholangitis; AIP, autoimmune pancreatitis; n.s., not significant; CBD, common bile duct

cholangiogram was scored for specifically defined characteristics, including stricture length, and the characteristic findings and region(s) of stricturing. A band-like stricture, a beaded appearance, a pruned-tree appearance, and a diverticulum-like formation were only found in PSC. Long stenosis, segmental stricture, and a long stricture with prestenotic dilatation were significantly more common in sclerosing cholangitis with AIP. In a few cases in both groups, a shaggy appearance and stricture of the hilar region were present. Stricture of the distal common bile duct was also observed in both groups, but was significantly more frequent among patients with sclerosing cholangitis with AIP. Some characteristic findings of cholangiograms for PSC and sclerosing cholangitis with AIP are shown schematically in Fig. 2.

Discriminant analysis was performed after the selection of variables by the step-wise method (Table 2).[14] This method selected band-like stricture, pruned-tree appearance, and stricture of the distal common bile duct as variables. When the discriminant function formula was applied to all cases, the median and the 5th and 95th percentiles were 5.64, 0.016, and 11.5, respectively, for PSC, and 5.73, 6.72, and 0.10, respectively, for sclerosing cholangitis with AIP. Therefore, 96% of PSC and 96% of sclerosing cholangitis with AIP were correctly classified by the discriminant function formula.

Other systemic extrapancreatic lesions associated AIP

Review of AIP cases with other systemic extrapancreatic lesions

We reviewed the documentation of other systemic extrapancreatic lesions associated with cases of AIP in the Japanese and English literature (Table 3).[18] The diseases which were frequently found to be associated with AIP were Sjögren's syndrome, ulcerative colitis, and retroperitoneal fibrosis. Occasionally, sialadenitis,

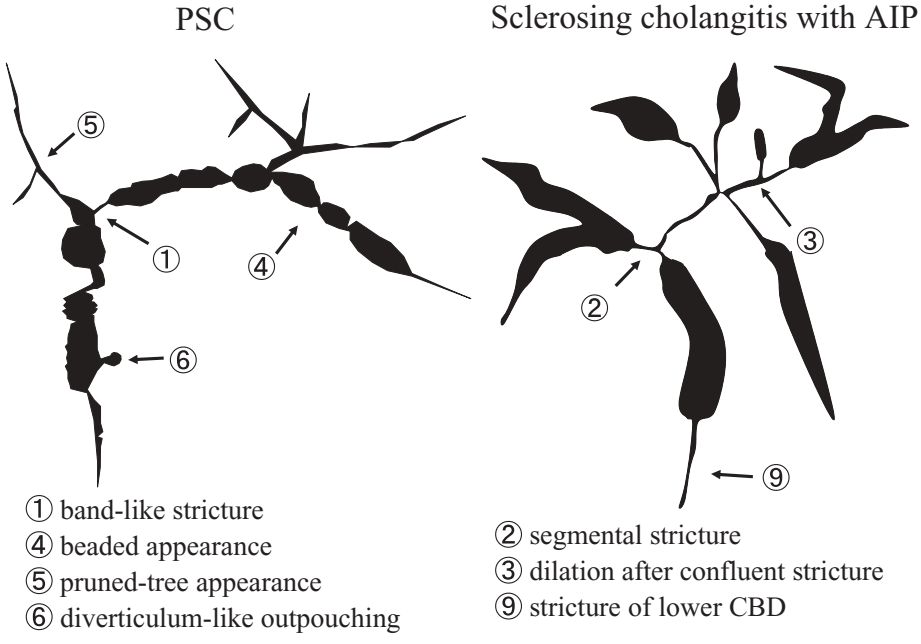

Fig. 2. Schematic illustration of a comparison of cholangiographic findings: primary sclerosing cholangitis (*PSC*) vs. sclerosing cholangitis with AIP. *CBD*, common bile duct

Table 2. Discriminant analysis (From [14], with permission)

Variables	Discriminant coefficients	Odds ratio	*P* value
Age	–0.0941976	0.910103	0.00620678
Band-like stricture	3.40993	30.2631	0.0000214291
Pruned-tree appearance	1.215125	3.37113	0.148121
Stricture of distal third of CBD	–3.02868	0.0483797	0.00000961773

The odds ratio for age estimates that for each additional year of age, the odds for having primary sclerosing cholangitis instead of sclerosing cholangitis with autoimmune pancreatitis decrease by a factor of about 9%
Discriminant *P* value = 0.954393
Discriminant function formula constant = 6.21049
$Z = 6.21049 - 0.0941976 \times (\text{age}) + 3.40993 \times (\text{band-like stricture}) + 1.21525 \times (\text{pruned-tree appearance}) - 3.02868 \times (\text{stricture of distal third of common bile duct})$

Table 3. Review of AIP cases with systemic extrapancreatic lesions (From [18], with permission)

	Western countries ($n = 172$)	Japan ($n = 132$)	
Sjögren's syndrome	13	24	$P < 0.01$
IBD			
UC	14	5	NS
CD	4	0	NS
Total	18	5	$P < 0.05$
Retroperitoneal fibrosis	9	8	NS
Sialadenitis	5	4	NS
Thyroid disease	4	1	NS
ITP	2	3	NS
RA	2	1	NS
Interstitial pneumonia	0	3	NS
Tubulointerstitial nephritis	1	2	NS
SLE	0	2	NS
Automimmune hepatitis	0	2	NS
Orbital pseudotumor	2	0	NS
Malignant lymphoma	2	0	NS

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; ITP, idiopathic thrombocytopenic purpura; RA, rheumatoid arthritis; SLE, systematic lupus erythematosus; AIH, autoimmune hepatitis

thyroiditis, and idiopathic thrombocytopenic purpura were also found to complicate AIP. The incidence of AIP-associated Sjögren's syndrome was significantly higher in Japan (24/132 cases; 18.2%) than in Western countries (13/172 cases; 7.6%) ($P < 0.01$), whereas the incidence of AIP-associated inflammatory bowel disease (IBD) was significantly higher in Western countries (18/172 cases; 10.5%) than in Japan (5/132 cases; 3.8%) ($P < 0.05$).

In our study, enlargement of the submandibular gland was observed in four cases, but all these cases lacked anti-SSA and -SSB auto-antibodies, which are specific for Sjögren's syndrome. A total of 90% of patients with Sjögren's syndrome are middle-aged women, whereas AIP is common in elderly men. These results were the same as those reported by Kamisawa et al.[5] Hamano et al.[19] also reported that serum IgG4 levels in patients with Sjögren's syndrome were significantly lower than those in patients with AIP. We therefore believe that the enlargement of the submandibular gland associated with AIP is different from typical Sjögren's syndrome. Lachrymal and salivary gland swellings associated with AIP have been considered to be Mikulicz disease and Küttner tumor.[20,21]

None of our cases had AIP associated with IBD. The cases of AIP diagnosed in Europe and the USA, on the other hand, showed two subsets of unique pathological findings.[22,23] One exhibited lymphoplasmacytic sclerosing pancreatitis, and the other showed idiopathic duct-centric chronic pancreatitis or AIP with granulocytic epithelial lesions. Both reports showed that the latter occurred predominantly in a group of patients who were younger and more commonly suffering from ulcerative colitis or Crohn's disease. These reports may offer an explanation for the different incidences of IBD associated with AIP in Japan and in Western countries.

Comparison of clinical course and laboratory data between patients with AIP with and without systemic extrapancreatic lesions

In our cases, there were no significant differences between the two groups in age, sex, extent of narrowing of the main pancreatic duct, or enlargement of the pancreas.[18] Gamma-globulin levels were significantly higher in patients with AIP with systemic extrapancreatic lesions than in those without (3.0 ± 1.2 vs. 1.8 ± 1.2; $P < 0.05$). IgG levels were also significantly higher among patients with systemic extrapancreatic lesions than among those without (3032 ± 975 vs. 2010 ± 1244; $P < 0.05$), as were IgG4 levels (727 ± 813 vs. 227 ± 197; $P < 0.05$). When encountering cases of AIP with elevated gamma-globulin, IgG, and IgG4 levels, the possible coexistence of other systemic extrapancreatic lesions should therefore be considered.

Maintenance steroid therapy (dose 3–10 mg) was required for 6 patients with associated extrapancreatic lesions. The ratio of cases requiring maintenance steroid therapy was significantly higher among those with systemic extrapancreatic lesions (6/8) than among those without (7/23; $P < 0.05$).[18]

Immunohistochemical study of AIP using anti-IgG4 antibody

Immunohistochemical analysis of AIP patients' tissue

To examine which extrapancreatic organs are affected, various tissues or organs obtained from AIP patients were studied immunohistochemically with an anti-IgG4 antibody. The results are summarized in Table 4.[24] Marked infiltration of IgG4+ plasma cells was observed in the pancreas, liver, bile duct, and salivary glands of many of the AIP patients examined.

In contrast, the degree of infiltration of IgG4+ plasma cells around the bile duct in the portal areas of patients with PSC was significantly lower than in those with AIP. IgG4+ plasma cell infiltration around the extrahepatic bile duct as well as the intrapancreatic bile duct was also significantly lower. These results also suggest that AIP is a disease state which is clearly different from PSC. Kamisawa et al.[5] stained the salivary glands of Sjögren's syndrome patients with an anti-IgG4 antibody and found that plasma cells were negative for IgG4. We also stained the salivary glands of Sjögren's syndrome patients with an anti-IgG4 antibody and the results were the same as those described by Kamisawa et al.[5] Thus, AIP may affect the salivary glands by a mechanism which is different from that occurring in Sjögren's syndrome.

Immunohistochemical analysis of AIP patients' sera

IgG4+ plasma cell infiltration may not indicate that the infiltrated organ is targeted. To prove the presence of an autoantibody to pancreas or extrapancreatic organs or both, the serum of AIP patients' was reacted with various normal organs or tissues extracted for other diseases, and any positive reaction was detected by staining with an anti-IgG4 antibody (Table 5).[24] The epithelia of pancreatic duct, bile duct, gallbladder, and salivary gland duct, in particular, showed a strong reaction, which correlated relatively well with the clinical features of the patients. It is suggested that patients' sera contain an autoantibody to the respective epithelial cells, inducing an inflammatory cell infiltration. Furthermore, following glucocorticoid therapy the IgG4 antibody from the patients' sera showed decreased reactivity with these tissues.[24]

Table 4. Immunohistochemical analysis of tissues of AIP patients and control groups (From [24], with permission)

	Score				
	0	1	2	3	*P* value*
Pancreatic duct walls					
AIP (*n* = 5)	1	1	1	2	$P < 0.05$
Chronic pancreatitis (*n* = 6)	5	1	0	0	
Intrahepatic bile duct in the portal areas					
AIP (*n* = 11)	0	2	8	1	$P < 0.05$
PSC (*n* = 10)	5	5	0	0	
Extrahepatic and intrapancreatic bile duct					
AIP (*n* = 8)	1	3	1	3	$P < 0.05$
PSC (*n* = 4)	3	1	0	0	
Salivary gland					
AIP (*n* = 3)	0	0	1	2	$P < 0.05$
Sjögren's syndrome (n = 5)	5	0	0	0	
Gastric mucosal layer					
AIP (*n* = 7)	5	1	1	0	NS
Chronic gastritis (*n* = 3)	3	0	0	0	
Duodenal musosal layer					
AIP (*n* = 6)	2	3	1	0	NS
PSC (*n* = 3)	2	0	1	0	
Colonic mucosal layer					
AIP (*n* = 6)	2	2	0	2	NS
PSC (*n* = 7)	5	1	1	0	

Counting the number of IgG4-positive plasma cells in the high power field
*Score 0 = 0, Score 1 < 20, 20 ≦ Score 2 ≦ 50 or 50 < Score 3
The Mann-Whitney test was used to calculate two-sided *P* values

Table 5. IgG4 immunoreactivity of normal tissues incubated with the serum of AIP patients and the control group (From [24], with permission)

	AIP (*n* = 6)				Control (*n* = 6)				
	0	1	2	3	0	1	2	3	*P* value*
Duct epithelium in pancreas	0	5	1	0	6	0	0	0	$P < 0.05$
Acinar cells in pancreas	6	0	0	0	6	0	0	0	NS
Islet cells in pancreas	6	0	0	0	6	0	0	0	NS
Hepatocytes	6	0	0	0	6	0	0	0	NS
Intrahepatic bile duct epithelium	1	4	1	0	6	0	0	0	$P < 0.05$
Extrahepatic and intrapancreatic bile duct	0	1	4	1	6	0	0	0	$P < 0.05$
Epithelium in gallbladder	0	1	4	1	6	0	0	0	$P < 0.05$
Duct epithelium in salivary gland	0	1	0	5	6	0	0	0	$P < 0.05$
Acinar cells in salivary gland	6	0	0	0	6	0	0	0	NS
Squamous epithelium in esophagus	4	1	1	0	6	0	0	0	NS
Mucosal epithelium in stomach	3	3	0	0	6	0	0	0	NS
Mucosal epithelium in small intestine	6	0	0	0	6	0	0	0	NS
Musosal epithelium in large intestine	6	0	0	0	6	0	0	0	NS
Epithelial cells in lung	5	1	0	0	6	0	0	0	NS

*IgG4-positive cells were evaluated as Score 0 = 0–5%, Score 1 = 6–20%, Score 2 = 21–50%, or Score 3 = more than 50%
The Mann-Whitney test was used to calculate two-sided *P* values

Conclusion

AIP is often associated with various systemic extrapancreatic lesions such as sclerosing cholangitis and sclerosing sialadenitis. However, these diseases associated with AIP are different from both PSC and Sjögren's syndrome. Recently, prostatitis and lymphocytic hypophysitis associated with AIP have also been reported.[25,26] An increasing number of organs have been included in the category of IgG4-related autoimmune diseases. If patients with systemic extrapancreatic lesions are encountered, we should therefore not focus on any par-

ticular aspect, but rather on the possibility of a syndrome complex. In managing patients with AIP with high gamma-globulin, IgG, and IgG4 levels, an attempt should also be made to detect the existence of other systemic extrapancreatic lesions that would require steroid treatment.

In addition, in order to make a precise diagnosis of AIP in difficult cases, we should examine extrapancreatic lesions such as enlargement of the submandibular gland, retroperitoneal fibrosis, and sclerosing cholangitis.[27]

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