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Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis

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Background. Autoimmune pancreatitis is a unique form of chronic pancreatitis characterized by high serum IgG4 concentrations and abundant IgG4-bearing plasma cell infiltration in the pancreatic lesion, and it has been reported to be associated with a variety of extrapancreatic lesions, leading us to postulate the concept of a systemic inflammatory disease. To confirm this, we clarified the exact distribution of these extrapancreatic lesions and provide a panoramic view of them. ***Methods.*** The frequency, distribution, clinical characteristics, and pathology of five extrapancreatic lesions were determined in 64 patients with autoimmune pancreatitis by examining clinical and laboratory findings. ***Results.*** The most frequent extrapancreatic lesion was hilar lymphadenopathy (80.4%), followed by extrapancreatic bile duct lesions (73.9%), lachrymal and salivary gland lesions (39.1%), hypothyroidism (22.2%), and retroperitoneal fibrosis (12.5%). No patients had all five types of lesions. Patients with hilar lymphadenopathy or lachrymal and salivary gland lesions were found to have significantly higher IgG4 levels than those without (P = 0.0042 and 0.0227, respectively). Patients with three lesions were found to have significantly higher IgG4 levels than those with no lesion, suggesting that patients with multiple extrapancreatic lesions have active disease. Similar to pancreatic lesions, extrapancreatic lesions have a characteristic histological finding of abundant IgG4-bearing plasma cell infiltration, and they respond favorably to corticosteroid therapy. ***Conclusions.*** Autoimmune pancreatitis was recognized as a systemic inflammatory disease. Furthermore, recognition of these characteristic findings will aid in the correct diagnosis of this disease.

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Introduction

A unique form of chronic pancreatitis occurring predominantly in elderly men and characterized by minimal abdominal pain, irregular narrowing of the pancreatic duct, and swelling of the pancreatic parenchyma has been referred to by various designations, including chronic inflammatory sclerosis of the pancreas,[1] lymphoplasmacytic sclerosing pancreatitis,[2] chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct,[3,4] autoimmune chronic pancreatitis,[5,6] sclerosing pancreaticocholangitis,[7] autoimmune-related pancreatitis,[8–10] and sclerosing pancreatitis.[11,12] This disease is now generally referred to as autoimmune pancreatitis, based on the clinical features of various serum autoantibodies, hypergammaglobulinemia, histological evidence of lymphoplasmacytic inflammation and fibrosis, and a favorable response to glucocorticoid treatment.[13–21] The exact cause and pathogenesis of autoimmune pancreatitis have not been clarified. In addition, this disease has been frequently misdiagnosed as pancreatic cancer, leading to unnecessary surgery.[22,23] It is therefore imperative that it be correctly diagnosed.

The most characteristic feature of this disease is high serum IgG4 concentrations, found in more than 90% of patients, which reflects disease activity[11] and infiltration of abundant IgG4-bearing plasma cells in the pancreatic lesion.[12,18] Serum assay for IgG4 provides a useful tool for the diagnosis and monitoring of this disease. Histological findings of abundant IgG4-bearing plasma cells are also a histological hallmark of this disease, and can be used to differentiate between this disease and malignant conditions.

Other prominent features of this disease involve a variety of extrapancreatic complications seen in sclerosing cholangitis,[2,7,17,19,20] Sjögren's syndrome, as manifested by lachrymal and salivary gland swellings,[18,24] hypothyroidism,[25] hilar lymphadenopathy,[26] retroperitoneal fibrosis,[12,17,27–29] interstitial pneumonia,[30,31] and tubulointerstitial nephritis.[32,33] Some of these extrapancreatic lesions show pathological findings similar to those of pancreatic lesions, including infiltration of abundant IgG4-bearing plasma cells.[12,18,26–29] This disease may involve widespread inflammatory lesions similar to pancreatitis, suggesting the possibility of a systemic disease such as multifocal fibrosclerosis,[2,12,18] IgG4-related autoimmune disease,[34] or IgG4-associated multifocal fibrosis.[35] However, most reports about extrapancreatic lesions have been published as reports on single cases or a small series of cases, or restricted to specific lesions. To confirm whether various extrapancreatic lesions are a systemic manifestation of inflammatory lesions characteristically found in autoimmune pancreatitis, it is necessary to clarify their exact distribution and provide a panoramic view of these lesions by examining a sufficient number of patients. Only a few detailed reports have addressed these issues.[36] Therefore, in the present study, we clarified the distribution and characteristics of five extrapancreatic lesions found in this disease by examining the clinical features of 64 patients with autoimmune pancreatitis.

Methods

Between September 1994 and June 2005, we treated and followed 64 patients with autoimmune pancreatitis: 53 men and 11 women aged 38–79 years (median age, 62.4 years). Diagnosis was based on the diagnostic criteria for autoimmune pancreatitis proposed by the Japanese Pancreas Society.[37]

In addition to ordinary blood tests, serum levels of IgG subclasses and circulating immune complexes were measured by single radial immunodiffusion assays (Binding Site, Birmingham, UK) and the monoclonal rheumatoid factor method (Immune complex mRF Nissui, Nissui Pharmaceutical, Tokyo, Japan) in all 64 patients.[11]

Lachrymal and salivary gland lesions were determined by physical examination, computed tomography (CT), magnetic resonance imaging (MRI), and gallium-67 citrate (Ga-67) scintigraphy.[26]

We measured serum levels of free T3 (2.5–4.2 ng/l), free T4 (1.0–2.0 ng/dl), and thyroid stimulating hormone (TSH) (0.2–4.0 mIU/l). We defined hypothyroidism as a high TSH state, and separated the subjects into two groups according to the following conditions: (1) clinical hypothyroidism with low free T4; and (2) subclinical hypothyroidism with normal free T4.[25] In addition, we measured anti-thyroglobulin (anti-Tg) antibody (Tg-Ab kit; Eiken, Tokyo, Japan; <0.7 IU/Ml), and anti-thyroid peroxidase (anti-TPO) antibody (TPOAb kit; Cosmic, Tokyo, Japan; <0.1 IU/Ml).

We determined hilar lymphadenopathy by thin-sliced CT in 50 patients and by Ga-67 scintigraphy in 49 patients. Ga-67 scintigraphy was performed just before corticosteroid therapy and repeated after 4 weeks of corticosteroid therapy. A whole-body scan with a single head rectangular gamma camera (SNC-510R, Shimadzu, Kyoto, Japan) was obtained after intravenous injection of 111 MBq of Ga-67 citrate. A positive image was defined by finding both (1) a normal or greater than normal amount of hepatic uptake, or (2) deletion of or a marked decrease in uptake after 4 weeks of corticosteroid therapy.[26]

Bile duct and retroperitoneal fibrosis lesions were determined by abdominal CT in all patients. For further examination of bile duct lesions, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), and intraductal ultrasonography (IDUS) were performed in 63, 39, and 40 patients, respectively.[38,39] We excluded stenosis of the lower bile duct from extrapancreatic lesions in this study, because lower bile duct lesions are frequently influenced by pancreatic lesions.

All participants provided written informed consent for invasive tests such as ERCP, and prior to the taking of serum samples. The institutional ethics committee granted permission for the study.

Statistical analysis of differences was performed by χ-squared analysis or Fisher's exact test, the Mann-Whitney test, or the Kruskal-Wallis method and the Bonferroni method. Corrected $P < 0.05$ was accepted as statistically significant. All reported P values are two-sided.

Results

A summary of the clinical findings of all patients, including results of serological tests and extrapancreatic lesions, is provided in Table 1.

Serological tests

A high serum IgG4 concentration (>135 mg/dl) was found in 59 of 64 (92.2%) patients (median, 617.5 mg/dl). Five patients with normal IgG4 concentrations had either antinuclear antibodies or rheumatoid factor. A high serum circulating immune complex concentration (>4.2 μg/ml) was found in 43 of 64 (67.2%) patients (median, 6.45 μg/ml).

Table 1. Extrapancreatic lesions of patients with autoimmune pancreatitis included in the study

Case	Age	Sex	IgG4	IC	Hilar lymph-adenopathy	Extrapancreatic bile duct lesions	Hypothyroid state	Lachrymal gland swelling	Salivary gland swelling	Retroperitoneal fibrosis
1	63	M	248	5.9	+	+	+	+	–	–
2	50	M	758	41.6	+	+	+	–	+	–
3	69	M	635	3.4	+	+	+	–	+	–
4	69	M	1705	9.9	+	+	+	–	+	–
5	73	F	758	51.4	+	+	–	–	+	–
6	79	M	1950	35.1	+	+	–	–	+	–
7	56	M	265	4.7	+	+	–	–	–	+
8	69	F	1150	58.4	+	+	+	–	–	–
9	59	M	965	11.9	+	+	+	–	–	–
10	62	M	825	4.1	+	+	+	–	–	–
11	68	M	725	7.1	+	+	–	–	–	–
12	58	M	1830	12.1	+	+	–	–	–	–
13	61	M	227	10.1	+	+	–	–	–	–
14	75	M	965	2	+	+	–	–	+	+
15	56	M	486	32.7	+	+	–	–	+	–
16	59	M	78	4.1	+	+	–	–	–	+
17	67	M	1430	16	+	+	NA	+	+	–
18	53	F	227	6.3	+	+	–	–	–	–
19	59	M	206	6	+	+	–	–	–	–
20	57	M	213	2.5	+	+	–	–	–	–
21	51	M	216	3.5	+	+	–	–	–	–
22	63	F	137	6.3	+	+	–	–	+	–
23	62	M	305	8.5	+	–	+	–	+	+
24	63	M	2855	42	+	–	–	+	+	+
25	67	M	1525	3.4	+	–	–	–	–	–
26	67	M	725	3.4	+	–	–	–	+	–
27	76	F	420	2	+	–	+	–	+	–
28	65	M	730	5.5	+	–	–	+	+	–
29	51	M	730	6.3	+	–	–	+	+	–
30	76	M	975	9.4	+	–	–	+	+	–
31	67	M	1185	20.9	+	–	–	–	+	–
32	75	F	730	4.2	+	–	–	–	–	–
33	65	M	2570	12.5	+	NA	–	–	+	+
34	68	M	880	12.2	+	NA	+	+	–	–
35	68	M	600	17.7	+	NA	–	–	+	–
36	67	M	500	15.4	+	NA	–	–	–	–
37	74	M	433	3.5	+	NA	–	–	–	–
38	73	M	1150	18.2	+	NA	NA	–	–	+
39	50	F	808	53	+	NA	–	–	–	–
40	76	F	808	27.8	+	NA	–	–	–	–
41	51	M	1045	8.9	+	NA	NA	–	–	–
42	73	M	774	3.3	–	+	–	–	–	–
43	71	M	780	3.6	–	+	NA	–	–	–
44	56	M	156	6.6	–	+	–	–	+	–
45	48	M	379	8.2	–	–	–	–	–	–
46	68	M	222	5.4	–	–	–	–	–	–
47	65	F	42	2	–	NA	–	–	–	–
48	70	M	265	2.2	–	NA	–	–	–	–
49	38	M	446	46	–	NA	–	–	+	–
50	72	M	22	2	–	NA	+	–	–	–
51	61	F	81	18.3	–	NA	–	–	–	–
52	40	M	450	5.3	NA	+	NA	+	+	–
53	66	M	1270	12.2	NA	+	NA	–	+	–
54	48	M	965	14.3	NA	+	NA	–	–	–
55	64	M	156	2.1	NA	+	NA	–	–	–
56	56	M	154	3	NA	+	NA	–	–	–
57	51	M	8	2	NA	+	–	–	–	–
58	63	M	550	2.7	NA	+	–	–	–	–
59	52	M	1655	43	NA	+	–	–	–	–
60	54	M	1015	16.4	NA	+	–	–	–	–
61	67	M	310	2.2	NA	NA	+	–	–	–
62	63	M	165	2.5	NA	NA	NA	–	–	+
63	59	M	136	5.2	NA	NA	–	–	–	–
64	62	F	394	13.9	NA	NA	–	–	–	–

IC, immune complex; +, positive; –, negative; NA, not available

Extrapancreatic lesions

Figure 1 summarizes the distribution and frequency of five extrapancreatic lesions.

Lachrymal and salivary gland lesions. Lachrymal and salivary gland swellings were found in 8 (12.5%) and 23 (25.9%) patients, respectively. Both lesions were found in 6 (9.4%) patients, and one or the other was found in 25 (39.1%) patients. Almost all lesions were bilateral, symmetric, and painless swellings that drastically decreased in number, resulting in the recovery of the exocrine function, after corticosteroid therapy. Specimens from extracted salivary glands or from lip salivary glands characteristically showed abundant IgG4 plasma cell infiltration. In two patients, the lesions preceded the pancreatitis by 15 years, or they appeared 3 years after the resolution of pancreatitis. Other patients showed these lesions simultaneously or within 1 year of the occurrence of a pancreatic lesion. We found no significant difference in age or in the male : female ratio between patients with these lesions and those without. Twenty-five patients with either lachrymal or salivary gland lesions had significantly higher IgG4 and circulating immune complex (CIC) levels than those with no lachrymal or salivary gland swellings (P = 0.0227 and P = 0.0383, respectively) (Table 2).

Thyroid lesions. We evaluated thyroid function and the presence of anti-Tg and anti-TPO antibodies in 54 patients. Hypothyroidism (high TSH level) was found in 12 patients (22.2%); clinical hypothyroidism with a low free T4 level was found in 9 patients; and subclinical hypothyroidism with a normal free T4 level was found in 3 patients. Either anti-Tg antibody or anti-TPO antibody was found in 22 patients (40.7%), and the frequency of anti-Tg antibody (33.3%) exceeded that of anti-TPO antibody (18.5%). We found no significant differences in age, sex, serum IgG4 level, or serum CIC level between patients with hypothyroidism and those without (Table 2). We did not find Riedel's thyroiditis, manifested as fibrosing changes, in any patients. Long-term corticosteroid therapy resulted in the normalization of TSH and free T4 levels and the disappearance of autoantibodies in some patients who had received no thyroid hormone supplements.

Hilar lymphadenopathy. We evaluated the presence of hilar lymphadenopathy by Ga-67 scintigraphy and thin-sliced chest CT in 51 patients. Thin-sliced CT disclosed hilar lymph node swelling in patients with a positive hilar Ga-67 uptake. Hilar lymphadenopathy, determined by hilar Ga-67 uptake and thin-sliced CT, was found in 41 patients (80.4 %) and disappeared after 4 weeks of corticosteroid therapy. Patients with hilar lymphadenopathy showed significantly higher IgG4 levels than those without (P = 0.0042) (Table 2). Three patients showed apparent bilateral hilar lymphadenopathy (BHL) by chest roentgenography and had been given a diagnosis of sarcoidosis in other hospitals. However, they had normal serum levels of angiotensin-converting enzyme (ACE) and showed no other typical symptoms of sarcoidosis.

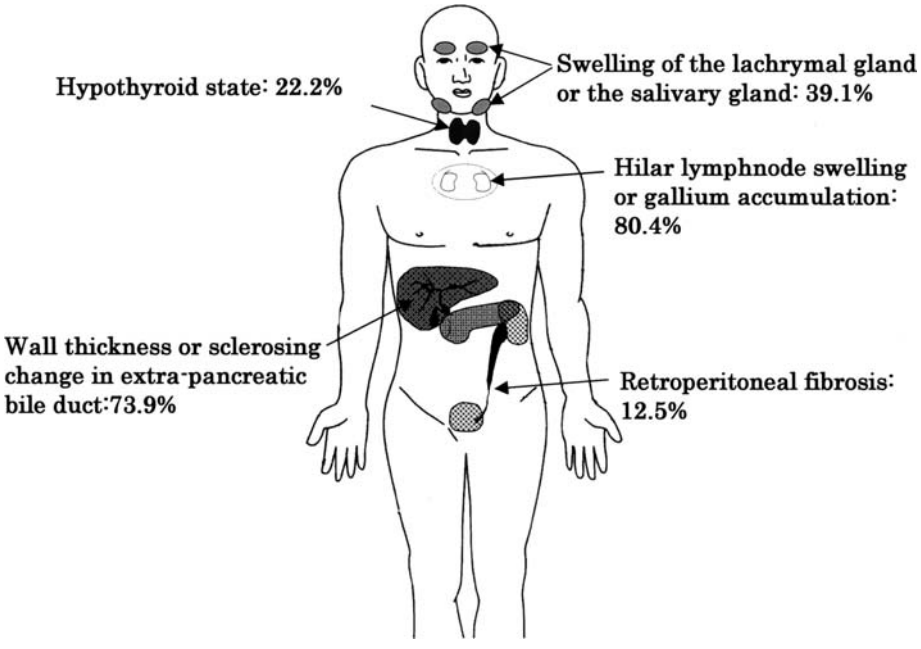

Fig. 1. Distribution of five extrapancreatic lesions seen in patients with autoimmune pancreatitis

Table 2. Comparison of various parameters between the positive and negative groups for various extrapancreatic lesions

	Positive	Negative	*P* value
Wall thickening or sclerosing change in extrapancreatic bile duct			
n	34	12	—
Age	60.0	67.0	0.1265
Sex (male/female)	30/4	10/2	0.9999
IgG4	680.0	730.0	0.4018
Immune complex	6.3	5.9	0.7639
Swelling of either lachrymal gland or salivary gland			
n	25	39	—
Age	66.0	61.5	0.1814
Sex (male/female)	22/3	31/8	0.5052
IgG4	730.0	394.0	0.0227
Immune complex	9.9	5.2	0.0383
Hypothyroid state			
n	12	42	—
Age	67.5	63.0	0.1731
Sex (male/female)	10/2	33/9	0.9999
IgG4	696.5	525.0	0.5324
Immune complex	7.2	6.45	0.5599
Either hilar lymphnode swelling or hilar gallium accumulation			
n	41	10	—
Age	65.0	66.5	0.8492
Sex (male/female)	33/8	8/2	0.9999
IgG4	730.0	243.5	0.0042
Immune complex	8.9	4.5	0.0919
Retroperitoneal fibrosis			
n	8	56	—
Age	62.5	67.0	0.8231
Sex (male/female)	8/0	45/11	0.3807
IgG4	635.0	617.5	0.5492
Immune complex	9.3	6.3	0.7071

Extrapancreatic bile duct lesions. We evaluated the presence of extrapancreatic bile duct lesions such as wall thickening by EUS or IDUS and sclerosing change by ERCP, and determined these in 46 patients. ERCP disclosed narrowing or sclerosing change of the bile duct system in only 17 patients (26.6%). However, EUS or IDUS disclosed wall thickening or sclerosing change in 34 patients (73.9%), who required drainage procedures. Biopsy specimens from thick bile duct wall showed abundant IgG4 plasma cell infiltration. We found no significant differences in age, sex, serum IgG4 level, or serum CIC level between patients with bile duct lesions and those without (Table 2).

Retroperitoneal fibrosis. Retroperitoneal fibrosis was found in eight patients (12.5%), all of whom were male. All eight patients presented with hydronephrosis caused by narrowing of the urethra or thick fibrosing tissues around the abdominal aorta and iliac artery. Six of eight patients showed lesions at different points in relation to pancreatitis: three after the occurrence of the pancreatic lesion, and three before. We found no significant differences in age, sex, serum IgG4 level, or serum CIC level between patients with retroperitoneal fibrosis and those without (Table 2).

Correlations among the five extrapancreatic lesions

No patients had all five types of extrapancreatic lesions. We found 4 lesions in 6 patients (9.4%), 3 in 14 patients (21.9%), 2 in 17 patients (26.6%), one in 20 patients (31.3%) and none in 7 patients (10.9%). We divided the 64 patients into five groups according to the number of extrapancreatic lesions, and examined the differences in IgG4 and CIC levels among them. We found a significant difference in IgG4 values ($P = 0.0427$), but no significant difference in CIC values ($P = 0.3121$) by the Kruskal-Wallis method. Furthermore, we found a significant difference in IgG4 values between the group with no lesions and that with three lesions by the Bonferroni method ($P = 0.049$) (Fig. 2), and found a tendency for patients with multiple lesions to have higher IgG4 values than those with few lesions. IgG4 values were comparable between the group with four lesions and that with two lesions (Fig. 2).

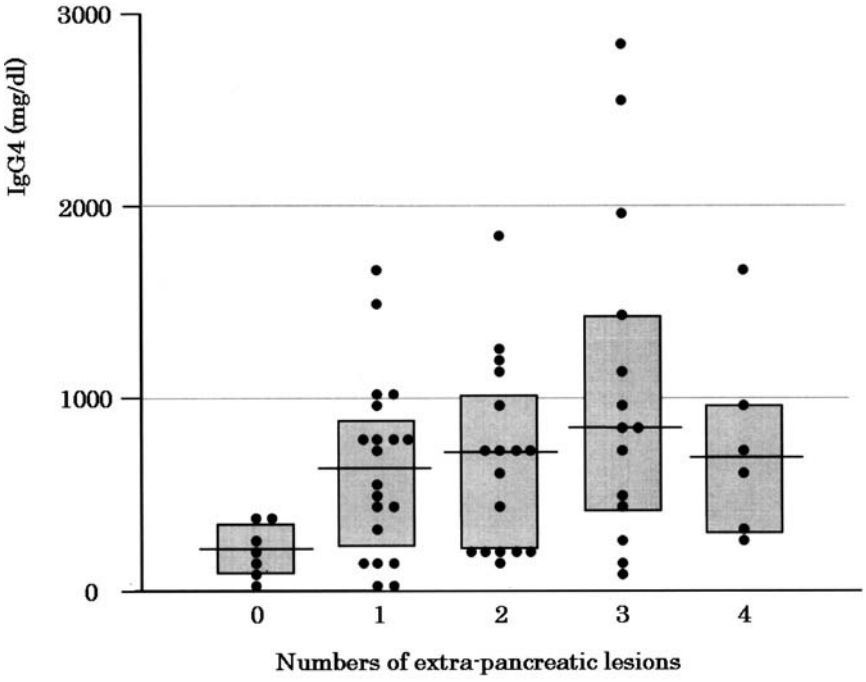

Fig. 2. Scattergram of serum IgG4 values according to the number of extrapancreatic lesions in patients with autoimmune pancreatitis. The bottom and top edges of the *boxes* are the 25th and 75th percentiles, respectively. *Bar* indicates median values

Discussion

Many studies have shown that autoimmune pancreatitis is associated with extrapancreatic lesions such as lachrymal and salivary gland swelling,[2,18,24,40–43] sclerosing cholangitis,[2,7,17,19,20,44–49] retroperitoneal fibrosis,[12,17,27–29] interstitial pneumonia,[30,31] gastric ulcer,[50] and tubulointerstitial nephritis.[32,33] We have reported a close association with this disease between hilar lymphadenopathy and thyroid lesions.[25,26] The findings of these extrapancreatic lesions suggest that autoimmune pancreatitis is a pancreatic manifestation of a systemic disease such as multifocal fibrosclerosis.[2,12,18,34,35,51,52] To confirm this hypothesis, we examined the prevalence, distribution, and detailed characteristics of five extrapancreatic lesions in 64 patients with this disease.

In previous reports, lachrymal and salivary gland lesions are common complications of Sjögren's syndrome; however, in the present study, the most frequent extrapancreatic lesion was hilar lymphadenopathy (80.4%), followed by extrapancreatic bile duct lesions (73.9%), lachrymal and salivary gland lesions (39.1%), hypothyroidism (22.2%), and retroperitoneal fibrosis (12.5%).

Hilar lymphadenopathy has sometimes been diagnosed as sarcoidosis. Our three patients showed apparent BHL by chest roentgenography, but they had normal serum ACE values and showed no other symptoms typical of sarcoidosis. Significant Ga-67 hilar uptake mimicking the finding of sarcoidosis resulted from the hilar lymphadenopathy, but faded away after corticosteroid therapy. We should clarify in the future whether hilar lymphadenopathy is a specific finding for this disease or is generally found in autoimmune diseases. If Ga-67 scintigraphy cannot be used, the common modalities of thin-sliced CT or multidetector CT will disclose these lesions.

Extrapancreatic bile duct lesions are the next most frequent extrapancreatic lesion (73.9%). We excluded stenosis of the lower bile duct from extrapancreatic lesions in this study, because lower bile duct lesions are frequently influenced by the pancreatic lesion, pancreatic head swelling. ERCP disclosed a narrowing or sclerosing change in extrapancreatic bile ducts in only 17 patients (26.6%), but IDUS and EUS disclosed wall thickening of the bile duct system in most patients who required a drainage procedure. It is sometimes difficult to differentiate these extrapancreatic bile duct lesions from bile duct malignancies or primary sclerosing cholangitis.[19,45–47] These lesions may precede the pancreatitis[44] or appear after resolution of the pancreatitis, making differentiation more difficult. A favorable response to corticosteroid therapy and a histological finding of abundant IgG4-bearing plasma cell infiltration in the duct wall should support a diagnosis of extrapancreatic lesion associated with autoimmune pancreatitis.[48,49]

Thyroid lesions showed atypical findings of Hashimoto's thyroiditis with regard to age and sex and a preponderance of anti-Tg antibody,[53] though some lesions associated with autoimmune pancreatitis have been possibly included in Hashimoto's thyroiditis. We

also identified a favorable response of the hypothyroid state to corticosteroid therapy in some patients, suggesting that these thyroid lesions respond to corticosteroid therapy. These lesions possibly have a pathological background similar to those of pancreatitis or other extrapancreatic lesions, though we could not confirm the pathology of the thyroid lesions. It is postulated that autoimmune pancreatitis is a pancreatic manifestation of multifocal fibrosclerosis that includes Riedel's thyroiditis.[51] However, we did not find severe fibrosis in the thyroid lesions, which contradicts the supposed presence of Riedel's thyroiditis.

Previous reports have indicated a close association between Sjögren's syndrome and autoimmune pancreatitis.[18,21,26,40] However, the lachrymal and salivary gland lesions found in the latter disease present with several symptoms that are atypical of Sjögren's syndrome, including bilateral painless swelling, a preponderance of salivary gland lesions, and a favorable response to corticosteroid therapy, resulting in a recovery of exocrine function. Abundant IgG4-bearing plasma cell infiltration is a characteristic histological finding for this condition that is not found in Sjögren's syndrome.[18] Accordingly, the lachrymal and salivary gland lesions found in this disease should be differentiated from Sjögren's syndrome. Recently, Mikulicz disease and Küttner tumor, which are considered to be Sjögren's syndrome-like diseases, have been reported to be associated with high serum IgG4 concentrations or abundant IgG4-bearing plasma cell infiltration,[41,42] suggesting a close association between these Sjögren's syndrome-like diseases and the lachrymal and salivary gland lesions found in autoimmune pancreatitis.

A common characteristic feature of these five extrapancreatic lesions is a favorable response to corticosteroid therapy, similar to pancreatic lesions. In the pathology of bile duct lesions, retroperitoneal fibrosis, and lachrymal and salivary gland lesions, abundant IgG4-bearing plasma cell infiltration is a characteristic finding. Accordingly, these extrapancreatic lesions have the same pathological background as pancreatic lesions, suggesting that autoimmune pancreatitis is a systemic disease with widespread inflammatory lesions.

In addition to these five types of extrapancreatic lesions, autoimmune pancreatitis has been reported to be associated with interstitial pneumonia,[30,31] hepatic pseudotumor,[45] gastrointestinal lesions,[50] and tubulointerstitial nephritis.[32,33] We will describe further the characteristics and distribution of these additional lesions in the future. The outstanding feature is that different extrapancreatic lesions sometimes appear at different periods. In some cases, lachrymal and salivary gland lesions preceded pancreatitis by 15 years, or they appeared 3 years after the resolution of pancreatitis. In six of eight patients, retroperitoneal fibrosis appeared at a different time from pancreatitis. Thus, metachronous lesions appear to result in the heterogeneous distribution and variable frequency of the extrapancreatic lesions generally found in this disease.

We found that patients with three lesions had significantly higher IgG4 levels than those with no lesions, and patients with multiple lesions tended to have higher IgG4 values than those with few lesions. These results are the same as those previously reported.[36] Patients with many extrapancreatic lesions possibly have a more active disease state than those with few lesions. Patients with hypothyroidism, retroperitoneal fibrosis, or extrapancreatic bile duct lesions showed lower serum elevations of IgG4 than those with lachrymal and salivary gland lesions. Previous studies have found abundant IgG4-bearing plasma cell infiltration in these tissues, similar to lachrymal and salivary gland lesions. It is unclear why patients with a specific distribution of extrapancreatic lesions show lower serum levels of IgG4. IgG4 values were comparable between the group with four lesions and that with two lesions, suggesting that the addition of hypothyroidism, retroperitoneal fibrosis, or extrapancreatic bile duct lesions did not necessarily induce marked elevation of IgG4.

Recognition of various extrapancreatic lesions should also aid in the correct diagnosis of this disease. In the past, many patients with this disease have been misdiagnosed as having malignant diseases, leading to unnecessary surgeries.[11,23,24,54] If association with a variety of extrapancreatic lesions is a characteristic feature of this disease, recognition of these lesions in addition to measurement of IgG4 may support a correct diagnosis. We have found many possible designations or first diagnoses for these extrapancreatic lesions, including Sjögren's syndrome, Hashimoto's thyroiditis, sarcoidosis, primary sclerosing cholangitis, bile duct cancer, pancreatic cancer, primary retroperitoneal fibrosis, and urethral tumor. It is possible that these lesions correspond to extrapancreatic lesions associated with autoimmune pancreatitis. It is recommended that pancreatic lesions be investigated and serum IgG4 values be measured in patients with these designations.

A limitation of this study was that the five lesion types were examined by different methods and modalities. If we had used other methods and modalities for the five types of lesions or focused on other lesions, the prevalence of these five types and the spectrum of extrapancreatic lesions would be changed. Because this study was retrospective, each case did not always provide sufficient information, we could not check extrapancreatic lesions completely (Table 1), and different methods and modalities were used for individual lesions.

In conclusion, many patients with autoimmune pancreatitis characteristically present with a variety of

extrapancreatic lesions, including extrapancreatic bile duct lesions, lachrymal and salivary gland lesions, hilar lymphadenopathy, hypothyroidism, and retroperitoneal fibrosis, suggesting that this disease should be recognized as a systemic inflammatory disease. Furthermore, recognition of these characteristic findings should aid in the correct diagnosis of this disease.

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