Prevalence and Distribution of Extra-Pancreatic Lesions Complicated with Autoimmune Pancreatitis

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Abstract

Purpose: 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 has been reported to be associated with a variety of extra-pancreatic lesions, leading us to postulate the concept of systemic inflammatory disease. To confirm this, we attempted to clarify the exact distribution of and provide a panoramic view of these extra-pancreatic lesions. **Methods:** The frequency, distribution, clinical characteristics, and pathology of five extra-pancreatic lesions were determined in 64 patients with autoimmune pancreatitis by examining clinical and laboratory findings. **Results** The most frequent extra-pancreatic lesion was hilar lymphadenopathy (80.4%), followed by extra-pancreatic bile duct lesions (73.9%), lachrymal and salivary gland lesions (39.1%), hypothyroidism (22.2%), and retroperitoneal fibrosis (12.5%). No patients had all of five 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, 0.0227, respectively). Patients with 3 lesions were found to have significantly higher IgG4 levels than those with no lesion, suggesting that patients with multiple extra-pancreatic lesions represent an active state of the disease. Similar to pancreatic lesions, extra-pancreatic lesions have a characteristic histological finding of abundant IgG4 bearing plasma cell infiltration, and they respond favorably to corticosteroid therapy. **Conclusion:** Autoimmune pancreatitis can be recognized as systemic inflammatory disease. Furthermore, recognition of these characteristic findings will aid in correct diagnosis of this disease.

Key Words: autoimmune pancreatitis, IgG4, extra-pancretic lesion, systemic inflammatory disease

Introduction

A unique form of chronic pancreatitis characterized by an elderly male preponderance, 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 pancreatico-cholangitis [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 this disease is correctly diagnosed.

The most characteristic feature of this disease is high serum IgG4 concentrations found in over 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 in differentiating between this disease and malignant conditions.

Other prominent features of this disease involve a variety of extra-pancreatic complications seen in sclerosing cholangitis [2, 7, 17, 19, 20], Sjögren's syndrome, as manifest 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 extra-pancreatic 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 systemic disease such as multifocal fibrosclerosis [2, 12, 18], IgG4-related autoimmune disease [34], or IgG4-associated multifocal fibrosis [35]. However, most reports regarding extra-pancreatic lesions have been published as reports on single cases or a small series of cases, or restricted to specific lesions. To confirm whether or not a variety of extra-pancreatic lesions are a systemic manifestation of inflammatory lesions characteristically found in autoimmune pancreatitis, it is necessary to clarify the exact distribution of and provide a panoramic view of these lesions by examining a sufficient number of patients. There have been only a few detailed reports addressing these issues [36]. Therefore, in the present study, we attempted to clarify the distribution and characteristics of five extra-pancreatic 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). The diagnosis was based on the diagnostic criteria for autoimmune pancreatitis proposed by 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, United Kingdom) and the monoclonal rheumatoid factor method (Immune complex mRF Nissui,Nissui Pharmaceutical, Tokyo, Japan) for all 64 patients [11].

Lesions were determined for lachrymal and salivary glands by physical examination, CT, 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 addditoin, we measured anti-thyroglobulin (anti-Tg) antibody (Tg-Ab kit; Eiken, Tokyo; <0.7 IU/ML), and anti-thyroid peroxidase (anti-TPO) antibody (TPOAb kit; Cosmic, Tokyo; <0.1 IU/ML).

We determined hilar lymphadenopathy by thin-sliced CT for 50 patients and by Ga-67 scintigraphy for 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, 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].

Lesions of bile duct and retroperitoneal fibrosis were determined by abdominal CT for 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 the stenosis of the lower bile duct from extra-pancreatic lesions in this study, because lower bile duct lesion is frequently influenced by pancreatic lesion.

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 for differences was performed by Chi-square analysis or Fisher's exact test, the Mann-Whitney test, or the Kuskal-Wallis method and the Bonferroni method. A level of corrected $P<0.05$ was accepted as statistically significant. All reported P values are 2-sided.

Results

A summary of clinical findings for all patients, including serological tests and extra-pancreatic lesions, is provided in **table 1**.

Serological tests

High serum IgG4 concentration (>135mg/dL) was found in 59 of 64 (92.2%) patients (median 617.5 mg/dL). Five patients with normal IgG4 concentrations had either anti-nuclear antibodies or rheumatoid factor. High serum circulating immune complex concentration (>4.2 μg/mL) was found in 43 of 64 (67.2%) patients (median 6.45 μg/mL).

Extra-pancreatic lesions

Figure 1 summarizes the distribution and frequency of these extra-pancreatic 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 either of two lesions 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, lesions had preceded pancreatitis 15 years previously, or had appeared 3 years after the resolution of pancreatitis. Other patients showed these lesions simultaneously or within one year of the occurrence of 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. A 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, gender, serum IgG4 level, and serum CIC level between patients with hypothyroid state and those without (**table 2**). We did not find Riedel's thyroiditis manifest as fibrosing changes in any patients. Long-term corticosteroid therapy resulted in the normalization of TSH and FT4 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 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 roentogenography 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.

Extra-pancreatic bile duct lesions

We evaluated the presence of extra-pancreatic bile duct lesions such as wall thickness 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 thickness 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, gender, serum IgG4 level, and 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 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 the occurrence of pancreatitis. Three patients showed it after the occurrence of pancreatic lesion, and other 3 patients did it before. We found no significant differences in age, gender, serum IgG4 level, and serum CIC level between patients with retroperitoneal fibrosis and those without (**table 2**).

Correlations among five extra-pancreatic lesions

No patients had all five types of extra-pancreatic 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 5 groups according to the number of extra-pancreatic 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 Kuskal-Wallis method. Furthermore, we found a significant difference in IgG4 values between the group with no lesions and that with 3 lesions by the Bonferroni method (p=0.049) (figure 2), and found a tendency that patients with multiple lesions have higher IgG4 value compared with that with a few lesions. IgG4 values of the group with 4 lesions were comparable to that with 2 lesions (figure 2).

Discussion

Many studies have shown that autoimmune pancreatitis is associated with extra-pancreatic 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 tuburointerstitial nephritis [32, 33]. We have reported a close association between hilar lymphadenopathy and thyroid lesions with this disease [25, 26]. The findings regarding these extra-pancreatic 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 extra-pancreatic lesions in 64 patients with this disease.

In previous reports, lachrymal and salivary gland lesions have been popular complications as a Sjögren's syndrome; however, in the present study the most frequent extra-pancreatic lesion was hilar lymphadenopaty (80.4%), followed by extra-pancreatic 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 given a diagnosis of sarcoidosis. Our three patients showed apparent BHL by chest roentogenography, but they had normal serum ACE values and showed no other typical symptoms of sarcoidosis. Significant Ga-67 hilar uptake mimicking the finding of sarcoidosis resulted from the hilar lympadenopathy, but faded away after corticosteroid therapy. We should clarify in future whether hilar lymphadenopathy is a specific finding for this disease or is generally found in other autoimmune diseases. If Ga-67 scintigraphy can not be used, common modalities of thin-sliced CT or multi detector CT will disclose these lesions.

Extra-pancreatic bile duct lesions are next frequent extra-pancreatic lesion (73.9%). We excluded the stenosis of the lower bile duct from extra-pancreatic lesions in this study, because lower bile duct lesion is frequently influenced by pancreatic lesion, pancreatic head swelling. ERC disclosed a narrowing or sclerosing change in extra-pancreatic bile ducts in only 17 patients (26.6%), but IDUS and EUS disclosed wall thickness of bile duct system in most patients who required a drainage procedure. It is sometimes difficult to differentiate these extra-pancreatic 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 extra-pancreatic lesion associated with autoimmune pancreatitis [48, 49].

Thyroid lesions showed atypical findings of Hashimoto's thyroiditis with regard to age, gender 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 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 extra-pancreatic lesions, though we could not confirm the pathology of the thyroid lesions. It is postulated that autoimmune pancreatitis is a pancreatitic 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 this 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 extra-pancreatic 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 extra-pancreatic 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 extra-pancreatic lesions, autoimmune pancreatitis has been reported to be associated with interstitial pneumonia [30, 31], hepatic pseudotumor [45], gastrointestinal lesions [50], and tuburointerstitial nephritis [32, 33]. We will describe further the characteristics and distribution of these additional lesions in future. The outstanding feature is that different extra-pancreatic lesions sometimes appear at different periods. In some cases, lachrymal and salivary gland lesions precede pancreatitis by 15 years, or they appear 3 years after the resolution of pancreatitis. In six of eight patients, retroperitoneal fibrosis appeared at a different time from that of pancreatitis. Thus, metachronous lesions appear to result in the heterogeneous distribution or various frequencies of extra-pancreatic lesions generally found in this disease.

We found that patients with 3 lesions have significantly higher IgG4 levels than those with no lesions and found a tendency that patients with multiple lesions have higher IgG4 value compared with those with a few lesions. These results were same as those of the previous report [36]. Patients with many extra-pancreatic lesions possibly represent a more active state of the disease than those with few lesions. Patients with hypothyroidism or retroperitoneal fibrosis or extra-pancreatic 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 that of lachrymal and salivary gland lesions. It is unclear why patients with a specific distribution of extra-pancreatic lesions show lower serum levels of IgG4. IgG4 values of the group with 4 lesions were comparable to that with 2 lesions, suggesting that the addition of hypothyroidism or retroperitoneal fibrosis or extra-pancreatic bile duct lesions necessary did not induce marked elevation of IgG4 values in some cases.

Recognition of a variety of extra-pancreatic lesions should also aid in correct diagnosis of this disease. In the past, many patients with this disease have been misdiagnosed to have malignant diseases, leading to unnecessary surgeries [11, 23, 24, 54]. If association with a variety of extra-pancreatic 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 extra-pancreatic 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 the extra-pancreatic lesions associated with autoimmune pancreatitis. It is recommended to examine the pancreatic lesions or to measure serum IgG4 values for patients with these designations.

The limitation of this study was that the five lesions were examined by different methods and modalities. If we use another methods and modalities for individual 5 lesions or focused on another lesions, the prevalence for these 5 lesions and the spectrum of extra-pancreatic lesions will be changed. Because this study was retrospective one and each case could not always provide sufficient information, we could not check extra-pancreatic lesions completely as shown in table 1, and had used different methods and modalities for individual lesions.

In conclusion, many patients with autoimmune pancreatitis characteristically present with a variety of extra-pancreatic lesions, including extra-pancreatic bile duct lesions, lachrymal and salivary gland lesions, hilar lymphadenopathy, hypothyroid state 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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Figure Legends

Figure 1. Distribution of major extra-pancreatic lesions seen in patients with autoimmune pancreatitis.

Figure 2. Scattergram of serum IgG4 values according to the number of extra-pancreatic 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.

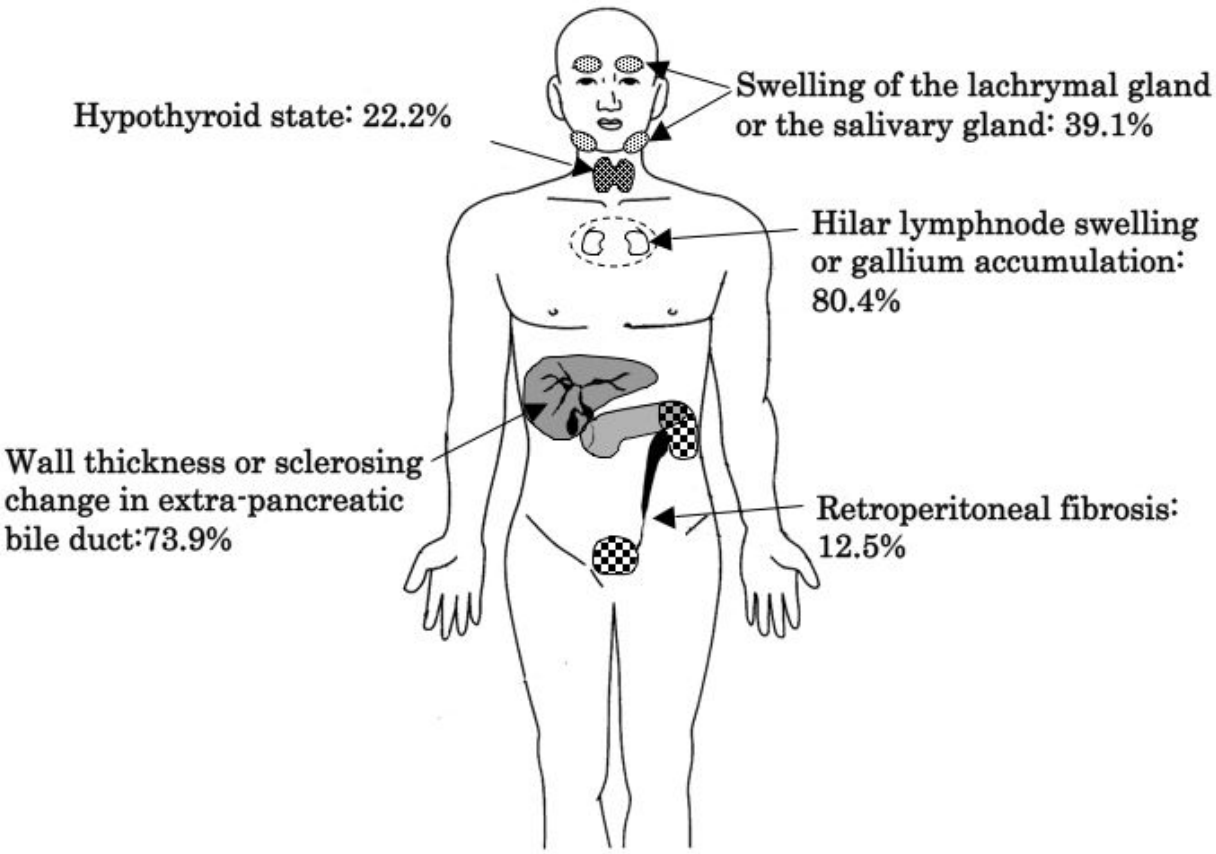
Hypothyroid state: 22.2%
Swelling of the lachrymal gland or the salivary gland: 39.1%
Hilar lymphnode swelling or gallium accumulation: 80.4%
Wall thickness or sclerosing change in extra-pancreatic bile duct:73.9%
Retroperitoneal fibrosis: 12.5%

Figure 1

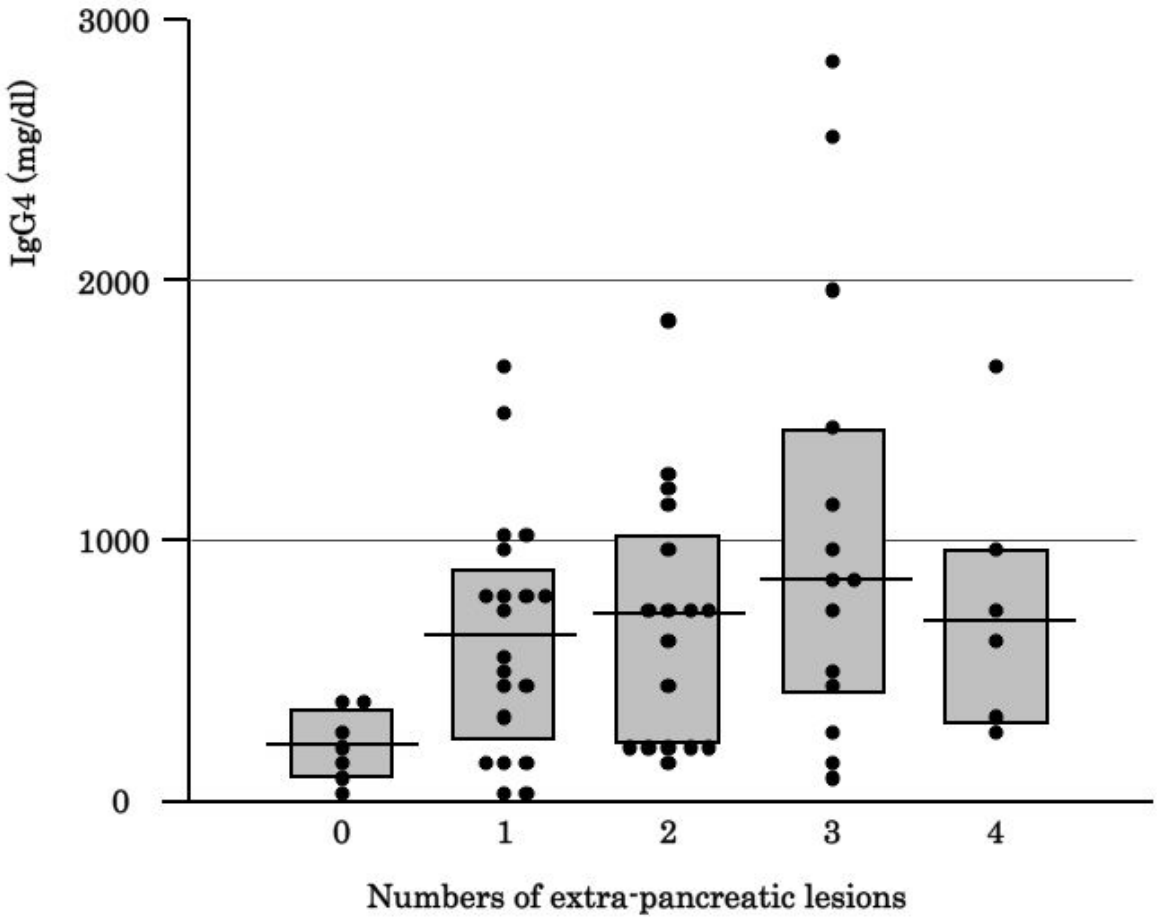
3000
2000
1000
0
IgG4 (mg/dl)
0
1
2
3
4
Numbers of extra-pancreatic lesions

Figure 2

Table 1. Extra-pancreatic lesions of patients with autoimmune pancreatitis included in the study

Case	Age	Sex	IgG4	IC	Hilar lymph-adenopathy	Extra-pancreatic 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

Table 2 Comparison of various parameters between positive group and negative group for various extra-pancreatic lesion

	Positive	Negative	p value
Wall thickness or sclerosing change in extra-pancreatic 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