more frequent in SIgG4-negative AIP patients (38%, $p = 0.01$). Steroid therapy was effective in both groups, but relapse was detected only in SIgG4-positive patients. SIgG4-positive AIP patients frequently underwent steroid therapy, and SIgG4-negative AIP patients were sometimes followed conservatively (31%, $p = 0.019$) (Table 1). Six SIgG4-positive AIP patients who were followed conservatively at first were later treated with steroids because of exacerbation of AIP. There were no significant differences in clinical findings between 5 slightly lower SIgG4 patients and 8 extremely lower SIgG4 AIP patients (Table 2).

Serum IgG4 and IgG levels were significantly higher in SIgG4-positive AIP patients ($p < 0.001$). There were no differences in presence of autoantibodies, serum IgE, and amylase levels, and peripheral eosinophil count (Table 3).

Radiologically, pancreatic diffuse swelling was frequently detected in SIgG4-positive AIP patients (51%, $p = 0.027$), and segmental swelling of the pancreatic body and/or tail was more frequent in SIgG4-negative AIP patients (46%, $p = 0.018$). FDG-PET revealed intense FDG uptake in all patients, and there were no differences in maximum SUV. On DWI, high signal intensity was detected in all patients, and there were no differences in ADC values (Table 4).

Sclerosing extrapancreatic lesions, especially sclerosing cholecystitis and sclerosing sialadenitis, were frequently detected in SIgG4-positive AIP patients (51%, $p = 0.008$). Acute pancreatitis was more frequent in SIgG4-negative AIP patients (23%, $p = 0.45$). Ulcerative colitis was associated in one SIgG4-positive and SIgG4-negative AIP patient, respectively. There were no significant differences in frequencies of diabetes mellitus and pancreatic exocrine dysfunction (Table 5).

Salivary gland and lacrimal gland functions

Salivary Na^+ concentration increased significantly in both SIgG4-positive AIP patients and SIgG4-negative AIP patients compared with controls ($p < 0.001$), but it was significantly higher in SIgG4-positive AIP patients than in SIgG4-negative AIP patients ($p = 0.034$). The salivary $\beta 2$ microglobulin concentration increased significantly in both SIgG4-positive AIP patients ($p < 0.001$) and SIgG4-negative AIP patients ($p = 0.003$) compared with controls, but it was significantly higher in SIgG4-positive AIP patients than in SIgG4-negative AIP patients ($p = 0.024$) (Table 6).

On Schirmer's test, tear secretion dysfunction was detected only in 5 SIgG4-positive AIP patients; the average level of the lower of the two eyes' test results was significantly lower in SIgG4-positive AIP than in SIgG4-negative AIP patients ($p = 0.015$) (Table 7).

Histological and immunohistochemical findings

The 5 resected and the 5 biopsied pancreatic specimens of SIgG4-positive AIP patients revealed LPSP with abundant infiltration of CD3-positive T lymphocytes and IgG4-positive plasma cells (Fig. 1a), and abundant infiltration of IgG4-positive plasma cells was detected in the peripancreatic retroperitoneal regions and peripancreatic lymph nodes. EUS-FNA of 3 SIgG4-positive AIP patients could not confirm the diagnosis due to inadequate materials.

Table 1 Clinical differences between SIgG4-positive and SIgG4-negative AIP patients

	SIgG4-positive	SIgG4-negative	*p* value
Number of patients	45	13	
Age at diagnosis (years), mean ± SD (range)	63.7 ± 10.2 (27–83)	61.5 ± 20.7 (29–83)	0.610
Male/female	36/9	7/6	0.077
Alcohol intake +/−	3/32 (9%)	1/12 (8%)	>0.999
Smoking +/−	21/14 (60%)	6/7 (46%)	0.516
Present and/or past history of allergic diseases +/−	11/26 (30%)	2/6 (33%)	>0.999
Initial symptoms			
Obstructive jaundice	35 (78%)	4 (31%)	0.002
Abdominal pain	3 (7%)	5 (38%)	0.010
Asymptomatic	7 (16%)	4 (31%)	0.243
Therapy			
Steroid	36 (80%)	6 (46%)	0.031
Responsiveness	36/36 (100%)	6/6 (100%)	>0.999
Relapse	5/36 (14%)[a]	0/6 (0%)[b]	>0.999
Resection	5 (11%)	2 (15%)	0.647
Bypass operation	3 (7%)	1 (8%)	>0.999
Follow-up	2 (4%)	4 (31%)	0.019

[a] Observation period: 50.2 ± 38.6 (6–173) months

[b] Observation period: 57.3 ± 45.4 (8–140) months

Table 2 Clinical differences between slightly lower SIgG4 and extremely lower SIgG4 AIP patients

	Slightly lower SIgG4	Extremely lower SIgG4	*p* value
Number of patients	5	8	
Age at diagnosis (years), mean ± SD (range)	70.4 ± 10.5 (63–83)	57.3 ± 23.8 (29–83)	0.464
Male/female	2/3	5/3	0.592
Alcohol intake +/−	0/5 (0%)	1/7 (13%)	>0.999
Smoking +/−	2/3 (40%)	4/2 (67%)	>0.999
Present and/or past history of allergic disease +/−	1/3 (25%)	1/3 (25%)	>0.999
Initial symptoms			
Obstructive jaundice	2 (40%)	2 (25%)	>0.999
Abdominal pain	0	5 (63%)	0.075
Asymptomatic	3 (60%)	1 (12%)	0.216
Acute pancreatitis +	0	3 (38%)	0.230
Ulcerative colitis	0	1 (12%)	>0.999
Therapy			
Steroid	0	6 (75%)	0.021
Responsiveness		6 (100%)	
Relapse		0	
Resection	1 (20%)	1 (12%)	>0.999
Bypass operation	1 (20%)	0	0.384
Follow-up	3 (60%)	1 (12%)	0.216

Table 3 Serological differences between SIgG4-positive and SIgG4-negative AIP patients

	SIgG4-positive ($n = 45$)	SIgG4-negative ($n = 13$)	*p* value
Serum IgG4, mg/dl (range)	604.2 ± 526.0 (144–2490)	62.4 ± 40.5 (11–123)	<0.001
Serum IgG, mg/dl[a] (range)	2344.8 ± 966.3 (1220–5580)	1396.2 ± 277.4 (984–1836)	<0.001
Autoantibody +/−	20/24 (45%)	7/5 (58%)	0.552
Serum IgE >580 IU/ml +/−	10/13 (43%)	1/6 (14%)	0.214
Serum IgE (IU/ml)[a]	838.4 ± 1022.8	1429.1 ± 3266.7	0.212
Eosinophils >600/mm^3 +/−	3/33 (8%)	3/10 (23%)	0.321
Eosinophils (cell/mm^3)	283.3 ± 214.6	354.0 ± 247.6	0.377
Elevation of serum amylase +/−	12/33 (27%)	4/9 (31%)	0.739
Serum amylase (IU/l)	199.8 ± 305.3	242.6 ± 313.3	0.399

[a] Mean ± SD

Two resected, 1 biopsied, and 1 EUS-FNA (19G-needle) pancreatic specimen of SIgG4-negative AIP patients revealed LPSP with abundant infiltration of T lymphocytes and IgG4-positive plasma cells. However, abundant infiltration of IgG4-positive cells was not detected in the peripancreatic retroperitoneal region or peripancreatic lymph nodes in 2 resected pancreatic materials. The number of IgG4-positive plasma calls infiltrating the resected or biopsied pancreas was not significantly different in the SIgG4-positive AIP (55.5 ± 23.9/hpf) and SIgG4-negative AIP (31.6 ± 24.6/hpf); the average number of IgG4-positive plasma cells in the pancreas was only 15/hpf in resected AIP, with a serum IgG4 level of 43 mg/dl (Fig. 1b). EUS-FNA of 2 SIgG4-negative AIP patients could not confirm the diagnosis because of inadequate materials. In the pancreas of 1 surgically biopsied and 1 EUS-FNA (19G needle) specimen, marked fibrosis (Fig. 2a) and abundant infiltration of CD20-positive B lymphocytes (Fig. 2b) rather than CD3-positive T lymphocytes (Fig. 2c), and destruction of acinar cells were detected, but few IgG4-positive plasma cells were observed (Fig. 2d), and neutrophilic infiltration was not detected (Table 8).

The number of IgG4-positive plasma cells infiltrating the gastric mucosa was significantly higher in S. IgG4-positive AIP than in SIgG4-negative AIP patients ($p = 0.004$) (Table 9).

Discussion

AIP is considered to be closely related to IgG4 serologically and histopathologically. In this study, 13 of 58 AIP patients had normal IgG4 levels. The rate of elevated

Table 4 Radiological differences between SIgG4-positive and SIgG4-negative AIP patients

	SIgG4-positive	SIgG4-negative	*p* value
Number of patients	45	13	
Pancreatic swelling			
Diffuse	23 (51%)	2 (15%)	0.027
Segmental			
Head	16 (36%)	5 (38%)	>0.999
Body and/or tail	6 (13%)	6 (46%)	0.018
FDG-PET			
FDG uptake +/−	8/0 (100%)	5/0 (100%)	0.107
Maximum SUV[a] (range)	3.5 ± 1.0 (2.2–5.6)	4.7 ± 1.0 (2.9–5.2)	
Diffusion-weighted MRI			
High signal intensity +/−	8/0 (100%)	5/0 (100%)	
ADC values ($\times 10^{-3}$ mm^2/s)[a] (range)	1.03 ± 0.14 (0.84–1.21)	1.00 ± 0.11 (0.88–1.15)	0.558

FDG fluorine-18 fluorodeoxyglucose, *PET* positron emission tomography, *SUV* standardized uptake value, *ADC values* apparent diffusion coefficient values

[a] Mean ± SD

Table 5 Associated diseases of SIgG4-positive and SIgG4-negative AIP patients

	SIgG4-positive	SIgG4-negative	*p* value
Number of patients	45	13	
Extrapancreatic lesions +	23 (51%)	1 (8%)	0.008
Sclerosing cholangitis +	4 (9%))	1 (8%)	>0.999
Sclerosing cholecystitis +	14 (31%)	0	0.025
Sclerosing sialadenitis +	14 (31%)	0	0.025
Retroperitoneal fibrosis +	3 (7%)	0	>0.999
Acute pancreatitis	2 (4%)	3 (23%)	0.045
Ulcerative colitis +	1 (2%)	1 (8%)	0.401
Diabetes mellitus +	18 (40%)	3 (23%)	0.338
Pancreatic exocrine dysfunction +/−	6/0 (100%)	1/2 (33%)	0.083

Table 6 Differences of sialochemistry between SIgG4-positive and SIgG4-negative AIP patients

	SIgG4-positive ($n = 18$)	SIgG4-negative ($n = 7$)	Controls ($n = 30$)
Na^+ (mEq/l)	32.6 ± 12.2*, **	21.7 ± 3.9*	13.7 ± 8.2
β2-microglobulin (mg/dl)	2.7 ± 1.3*, ***	1.5 ± 0.3****	1.0 ± 0.6

Mean ± SD

* $p < 0.001$ compared with controls

** $p = 0.034$ compared with SIgG4-negative patients

*** $p = 0.024$ compared with SIgG4-negative patients

**** $p = 0.003$ compared with controls

Table 7 Differences of Schirmer's test between SIgG4-positive and SIgG4-negative AIP patients

	SIgG4-positive ($n = 9$)	SIgG4-negative ($n = 5$)	*p* value
Schirmer's test (mm)	5.4 ± 2.4	11.9 ± 0.1	0.015

Mean ± SD

serum IgG4 levels in AIP patients was 78%, which was similar to the 68% [8] to 81% [1] recently reported in the literature. Although serum IgG4 levels sometimes fluctuate, they were measured at least more than twice in AIP patients without an elevated serum IgG4 level on the first examination.

There was no difference in age at diagnosis between SIgG4-positive AIP patients and SIgG4-negative AIP patients, and the female ratio tended to be higher in SIgG4-negative AIP patients. SIgG4-negative AIP patients were less likely to have obstructive jaundice but more frequently with abdominal pain and acute pancreatitis; they also more frequently showed segmental swelling of the pancreatic body and/or tail, but were less likely to have associated sclerosing extrapancreatic lesions. Although the relationship between AIP and allergic aspects is reported [23], there was no difference in allergic manifestations between the 2 groups. No SIgG4-negative AIP patients relapsed after steroid therapy. Finally, SIgG4-negative AIP patients were sometimes followed conservatively. Ghazale et al. [24] compared 34 AIP patients with elevated serum IgG4 levels and 11 AIP patients without elevated serum IgG4 levels, and

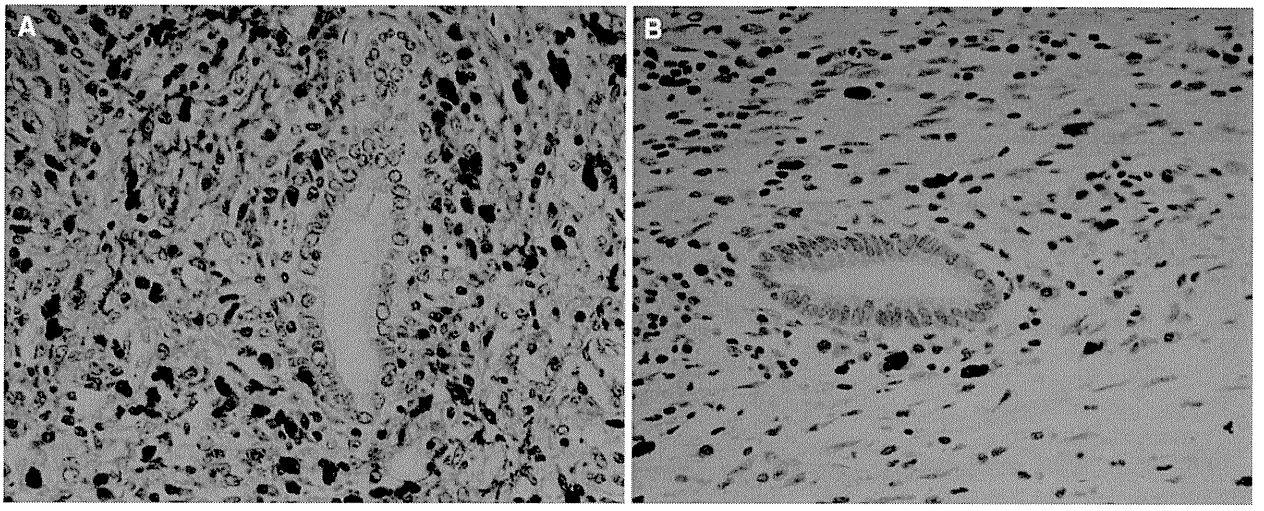

Fig. 1 **a** Abundant infiltration of IgG4-positive plasma cells in the pancreas of SIgG4-positive AIP patient (IgG4 immunostaining). **b** IgG4-positive plasma cells infiltrating the pancreas of SIgG4-negative AIP patient (IgG4 immunostaining). Note the number was less than that of SIgG4-positive AIP patient

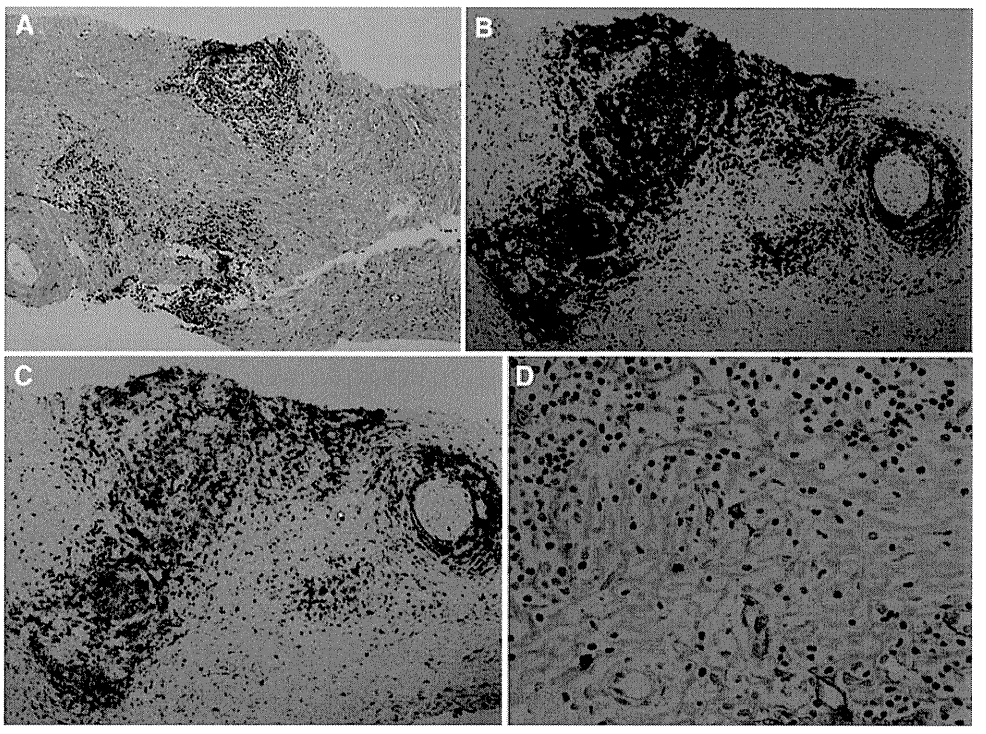

Fig. 2 Surgically biopsied specimen of the pancreas of SIgG4-negative AIP patient. **a** Marked fibrosis with lymphocytic infiltration was detected. Immunohistochemically, **b** infiltration of CD20-positive B lymphocytes was more dominant than **c** that of CD3-positive T lymphocytes. **d** Few IgG4-positive plasma cells were observed (IgG4 immunostaining)

they reported that AIP patients with normal IgG4 levels were more likely to be female (45 vs. 9%, $p = 0.01$) and less likely to present with extrapancreatic lesions (65 vs. 27%, $p = 0.03$).

Recently, another type of AIP was reported under the name of IDCP [9] or AIP with GEL [10]. It is histologically characterized by ductal epithelial granulocytic infiltration and less presence of IgG4-positive cells, a feature not seen in LPSP. IDCP is sometimes detected in Western countries, but it appears uncommon in Japan and Korea [2]. Although the clinical features of IDCP have not been fully clarified, IDCP appears to affect younger patients and may not have a male preponderance, with no involvement of other organs other than inflammatory bowel disease [3, 9, 10]. Serum IgG4 levels are rarely elevated in IDCP patients [3]. Italian AIP patients had a lower average age (43.4 years), a relatively high proportion of women (38%), a high rate of segmental swelling of the pancreas (63%), a low

Table 8 Histological findings of the pancreas of SIgG4-positive and SIgG4-negative AIP patients

	SIgG4-positive ($n = 13$)	SIgG4-negative ($n = 8$)
Resection	LPSP ($n = 5$)	LPSP ($n = 2$)
Biopsy	LPSP ($n = 5$)	LPSP ($n = 1$)
		Fibrosis with abundant infiltration of B lymphocytes ($n = 1$)
EUS-FNA	Inadequate materials ($n = 3$)	LPSP ($n = 1$)
		Fibrosis with abundant infiltration of B lymphocytes ($n = 1$)
		Inadequate materials ($n = 2$)

Table 9 Differences in the number of IgG4-positive plasma cells infiltrating the gastric mucosa of SIgG4-positive and SIgG4-negative AIP patients

	SIgG4-positive ($n = 17$)	SIgG4-negative ($n = 7$)	p value
Number of IgG4-positive plasma cells (/hpf) mean ± SD (range)	7.0 ± 5.5 (0–20)	1.4 ± 0.9 (0–3)	0.004

prevalence of serum IgG4 elevation (50%), frequent associations with acute pancreatitis (32%) and ulcerative colitis (30%), and rare involvement of other organs [25]. This clinical profile of Italian AIP patients suggests that a fair proportion of Italian AIP patients had IDCP. Sah et al. [26] reported that 3 of 4 IDCP patients presented with acute pancreatitis. Clinical profiles of SIgG4-negative AIP patients are similar to those of IDCP or Italian AIP patients, except for young age and frequent association with ulcerative colitis.

Both inflammatory and neoplastic lesions accumulate FDG on FDG-PET, and showed high signal intensity on DWI. Findings on FDG-PET and DWI were quite similar in SIgG4-positive and SIgG4-negative AIP. In the present study, histological examination of the pancreas was performed in 8 SIgG4-negative AIP patients. LPSP was diagnosed in 4 patients. EUS-FNA of 2 SIgG4-negative AIP patients could not confirm the diagnosis due to inadequate materials, including a 33-year-old male patient with ulcerative colitis. Asian diagnostic criteria can diagnose IDCP from pancreatic imaging and steroid responsiveness. Since histological examination of an adequate pancreatic specimen is necessary to diagnose IDCP, it is possible that IDCP is included in some of the SIgG4-negative AIP patients. On the other hand, in the pancreas of 2 SIgG4-negative AIP patients, marked fibrosis and abundant infiltration of B lymphocytes rather than T lymphocytes, and destruction of acinar cells were detected, but few IgG4-positive plasma cells were observed, and neutrophilic infiltration was not detected. This histology may be another type of SIgG4-negative AIP other than LPSP and IDCP.

Salivary gland function was impaired in all AIP patients, but the degree of impairment was less in SIgG4-negative AIP patients. Lacrimal gland function was impaired only in SIgG4-positive AIP patients. In 2 resected SIgG4-negative AIP patients, abundant infiltration of IgG4-positive cells was confined to the pancreas, and it was not detected in the peripancreatic retroperitoneal region or peripancreatic lymph nodes. Although abundant infiltration of IgG4-positive plasma cells is sometimes detected in the gastric mucosa of AIP patients [5, 27, 28], IgG4-positive plasma cells rarely infiltrated the gastric mucosa of SIgG4-negative AIP patients. It has been reported that serum IgG4 levels reflect disease activity of AIP, and extrapancreatic lesions tend to be more common in patients with higher serum IgG4 levels [7, 29]. Given these findings, though AIP is a systemic disease exhibiting IgG4-related phenomena throughout various organs, these phenomena tended to be rather confined to the pancreas in SIgG4-negative AIP patients. The greatest weakness of this study is that the number of histologically confirmed cases and SIgG4-negative AIP patients is too small to be conclusive. Although AIP is a rare disease, further prospective studies are necessary to clarify this issue.

In conclusion, SIgG4-negative AIP showed different clinicopathological features from SIgG4-positive AIP. Some SIgG4-negative AIP cases are LPSP that is rather confined to the pancreas. SIgG4-negative AIP may include IDCP or sclerosing pancreatitis other than LPSP or IDCP, but further studies are needed to clarify this issue.

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Systemic Involvement of IgG4-related Sclerosing Disease

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Abstract: A novel clinicopathological entity of "IgG4-related sclerosing disease" has been proposed, based on histological and immunohistochemical examination of various organs of patients with autoimmune pancreatitis (AIP). This is a systemic disease that is characterized by extensive IgG4-positive plasma cell and T lymphocyte infiltration of various organs. Clinical manifestations are apparent in organs where tissue fibrosis with obliterative phlebitis is pathologically induced. AIP may be a pancreatic lesion reflecting an IgG4-related sclerosing disease. This disease includes AIP, IgG4-related sclerosing cholangitis, IgG4-related cholecystitis, IgG4-related sialadenitis, IgG4-related retroperitoneal fibrosis, IgG4-related tubulointerstitial nephritis, IgG4-related interstitial pneumonia, IgG4-related prostatitis, and IgG4-related inflammatory pseudotumor. Many cases are associated with IgG4-related lymphadenopathy. Most IgG4-related sclerosing diseases have been found to be associated with AIP, but IgG4-related sclerosing diseases without pancreatic involvement have been reported. In some cases, only 1 or 2 organs are clinically involved, while in others 3 or 4 organs are affected. The disease occurs predominantly in elderly males and responds well to steroid therapy. Serum IgG4 levels and immunostaining with anti-IgG4 antibody are useful in making the diagnosis. Since malignant tumors are frequently suspected on initial presentation, IgG4-related sclerosing disease should be considered in the differential diagnosis to avoid unnecessary surgery.

Keywords: IgG4-related sclerosing disease, autoimmune pancreatitis, IgG4, sclerosing cholangitis, retroperitoneal fibrosis.

INTRODUCTION

Autoimmune pancreatitis (AIP) is a recently described particular type of pancreatitis in which the pathogenesis may involve autoimmune mechanisms. In AIP patients, serum IgG4 levels are frequently and significantly elevated, and various extrapancreatic lesions are present [1, 2]. Based on histological and immunohistochemical examination of various organs of AIP patients, we proposed the existence of a novel clinicopathological entity, an "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, salivary gland, retroperitoneum, kidney, lung, prostate, 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 [3-5].

On 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) done in AIP patients, abnormal FDG uptake has been observed in various extrapancreatic lesions [6]. Furthermore, many IgG4-related sclerosing diseases of organs other than the pancreas have been recently reported. Although the nomenclature differs, IgG4-related sclerosing disease has been noted in hepatology, cholangiology, rheumatology, urology, nephrology, respiro-logy, endocrinology, pathology, and radiology, as well as pancreatology. Based on our experience of AIP patients, this review focuses on the clinical, laboratory, imaging, and histopathological features of IgG4-related sclerosing disease, including AIP.

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IgG4-RELATED SCLEROSING DISEASE

Serum IgG4 Levels in Various Diseases

We measured serum IgG4 levels at the time of initial evaluation of 468 patients with suspicion of pancreatobiliary, allergic or immunological diseases. The median serum IgG4 levels were as follows: 301.5 mg/dl in AIP, 20.0 mg/dl in chronic pancreatitis, 88.5 mg/dl in idiopathic pancreatitis, 34.0 mg/dl in pancreatic cancer, 35.5mg/dl in biliary tract cancer, 357.0 mg/dl in Mikulicz's disease, 19.0 mg/dl in Sjogren's syndrome, and 47.5 mg/dl in chronic sialoadenitis. The median serum IgG4 level of AIP was significantly greater than any other biliary-pancreatic diseases ($p<0.01$), and the median serum IgG4 level of Mikulicz's disease was significantly greater than other salivary gland diseases ($p<0.01$). Difference of the median serum IgG4 levels between AIP and Mikulicz's disease was not significant (Table **1**, Fig. **1**) [7]. Yamamoto *et al.* reported that serum IgG4 levels in Mikulicz's disease were 1111.0 mg/dl which were significantly higher than 88.8 mg/dl in Sjogren's syndrome [8].

Distribution of IgG4-positive Plasma Cells in the Organs of Various Diseases

We counted number of IgG4-positive plasma cells per high power field in various organs of patients with AIP, sclerosing sialadenitis, chronic alcoholic pancreatitis, Sjogren's syndrome, and primary sclerosing cholangitis.

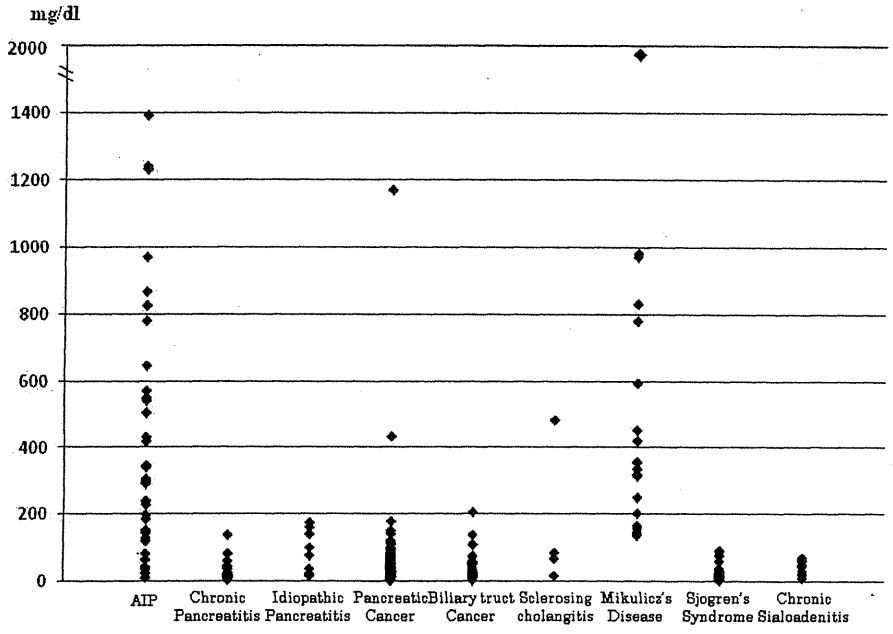

Fig. (1). Serum IgG4 levels in various diseases [7].

Infiltrating IgG4-positive plasma cells in the pancreas, peripancreatic retroperitoneal tissue, extrahepatic bile duct, gallbladder, stomach, minor salivary gland, and abdominal lymph node were more abundant in AIP patients compared with those of other diseases ($p<0.01$). Such infiltrations were also observed in the minor salivary gland and submandibular gland of patients with sclerosing sialadenitis ($p<0.01$) (Table 2) [4]. Yamamoto *et al.* also reported that numerous IgG4-positive plasma cells infiltrated the salivary and lacrimal glands of Mikulicz's disease patients, but there were not observed in those of patients with Sjogren's syndrome [8].

IgG4-Related Sclerosing Disease

We have found dense infiltration of IgG4-positive plasma cells and CD4- or CD8-positive T lymphocytes, as well as fibrosis in the peripancreatic retroperitoneal tissue, bile duct wall, gallbladder wall, periportal area of the liver, salivary glands, and 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. Serum IgG4 levels were significantly and frequently elevated in patients with AIP or sclerosing sialadenitis. Both the pancreatic and the extrapancreatic lesions of AIP respond well to steroid therapy [9-13].

Therefore, we proposed the existence of a novel clinicopathological entity, an "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, salivary gland, retroperitoneum, kidney, lung, prostate, and etc. where tissue fibrosis with

Table 1. Serum IgG4 Levels in Various Patient Groups

	Pancreatobiliary Diseases						Salivary Gland Diseases			Others	Total
	AIP	Chronic Pancreatitis	Idiopathic Pancreatitis	Pancreatic Cancer	Bile Duct Cancer	Sclerosing Cholangitis	Mikulicz's Disease	Sjogren's Syndrome	Chronic Sialoadenitis		
Number of patients	39	18	8	116	34	4	18	32	10	189	468
Range IgG4 (mg/dl)	11-1390	4-137	17-174	<3-1170	<3-206	17-473	137-1910	4-92	10-71	<3-472	<3-1910
Median IgG4 (mg/dl)	301.5	20.0	88.5	34.0	35.5	76.0	357.0	19.0	47.5	34.0	38.0
IgG4 >135mg/dl	30/39 (77%)	1/18 (6%)	3/8 (38%)	5/116 (4%)	2/34 (6%)	1/4 (25%)	18/18 (100%)	0/32 (0%)	0/10 (0%)	15/189 (8%)	75/468 (16%)

AIP: autoimmune pancreatitis Ref. [7].

Table 2. Number of IgG4-positive Plasma Cells Per High Power Field in the Organs of Various Diseases

	AIP	Sclerosing Sialadenitis	Chronic Pancreatitis	Sjogren's Syndrome	PSC
Pancreas	52.0 (n=10)	NE	0.9 (n=20)[a]	NE	NE
Retroperitoneum	70.0 (n=6)	NE	0.15 (n=20)[a]	NE	NE
Bile duct	58.0 (n=8)	NE	0.045 (n=20)[a]	NE	1 (n=1)
Gallbladder	25.0 (n=8)	NE	0.045 (n=20)[a]	NE	NE
Liver	12 (n=3)	10 (n=1)	0.01 (n=4)	NE	1 (n=3)
Stomach	8.0 (n=10)	4 (n=3)	1.25 (n=16)[a]	0.025 (n=6)[a]	1 (n=1)
Minor salivary gland	20 (n=3)	38 (n=4)	NE	1.105 (n=50)[b]	NE
Submandibular gland	50 (n=2)	45 (n=4)	NE	NE	NE
Abdominal LN	45.0 (n=6)	20 (n=1)	3.3 (n=20)[a]	NE	NE
Cer/Med LN	80 (n=1)	55.0 (n=3)	NE	4.5 (n=4)	NE

[a]: $p<0.01$ compared with AIP, [b]: $p<0.01$ compared with sclerosing sialadenitis
The values are medians.
LN: lymph node; Cer/Med: cervical or mediastinal; PSC: primary sclerosing cholangitis; NE: not.
Ref. [4].

obliterative phlebitis is pathologically induced. AIP is not simply a pancreatitis but it is a pancreatic lesion reflecting an IgG4-related sclerosing disease. Most IgG4-related sclerosing diseases have been found to be associated with AIP, but IgG4-related sclerosing diseases without pancreatic involvement have been reported. 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. **2**). 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 [3-5].

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 [14]. As the histopathological findings of these disorders are similar, fibrotic changes with lymphoplasmacytic infiltration and occasional phlebitis, it is suggested that they are all interrelated and probably different manifestations of a common disorder of fibroblastic proliferation. Several cases of pancreatic pseudotumor or chronic pancreatitis associated with multifocal fibrosclerosis have been reported. The histopathology of the extrapancreatic lesions associated with AIP strongly suggests that multifocal fibrosclerosis is an IgG4-related sclerosing disease [15].

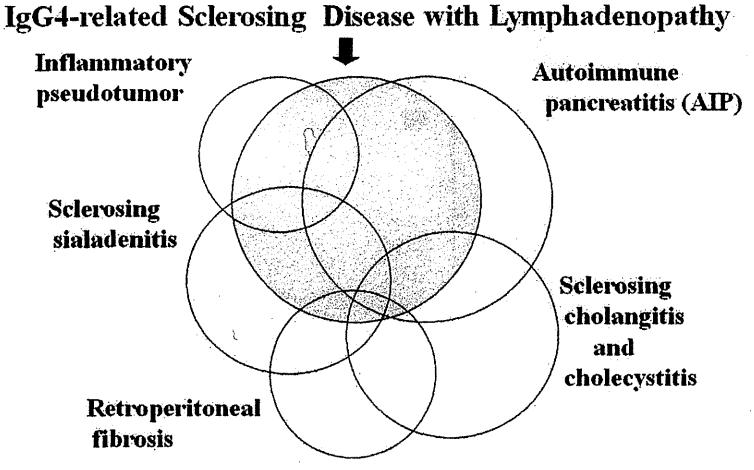

Fig. (2). Schematic illustration showing the relationship of IgG4-related sclerosing disease.

Table 3. Clinical and Radiological Differences Between Patients with Autoimmune Pancreatitis Exhibiting High or Low Serum IgG4 Levels

	Serum IgG4 ≥ 220 mg/dl	Serum IgG4 < 220 mg/dl	P Value
Number of cases	23	17	
Age on diagnosis (yr); median (quartile range)	66.0 (64.0-68.0)	68.0 (56.0-77.0)	.7527
Male/female	19/4	13/4	.7024
Enlargement of the pancreas diffuse/segmental	12/11	8/9	.9999
Obstructive jaundice +/-	21/2	11/6	.0532
Sclerosing cholangitis +/-	12/11	0/17	.0002
Sclerosing cholecystitis +/-	11/12	2/15	.0204
Sclerosing sialadenitis +/-	8/15	3/14	.2972
Retroperitoneal fibrosis +/-	3/20	0/17	.2480
Diabetes mellitus +/-	9/14	5/12	.7385
Number of extrapancreatic lesions median (quartile range)	1.0 (1.0-2.0)	0.0 (0.0-0.5)	.0003

Ref. [16].

EXTRAPANCREATIC LESIONS AND FUNCTION OF ORGANS IN AUTOIMMUNE PANCREATITIS

Serum IgG4 Levels and Extrapancreatic Lesions in Autoimmune Pancreatitis

We examined whether there is a correlation between serum IgG4 levels and associated extrapancreatic lesions in AIP patients. The mean serum IgG4 level of the 40 AIP patients was 411±448 mg/dl. Based on the ROC curve data, the optimal cutoff value for the serum IgG4 to distinguish between AIP patients with and without extrapancreatic lesions was 220 mg/dl; 18 (78%) of 23 patients whose serum IgG4 was ≥ 220 mg/dl had extrapancreatic lesions, while 4 (24%) of 17 patients whose serum IgG4 was < 220 mg/dl had extrapancreatic lesions ($p<0.01$). No significant differences between the 2 groups in age, gender, the frequency of pancreatic enlargement or obstructive jaundice, and associated sialadenitis, retroperitoneal fibrosis, and diabetes mellitus were identified. Sclerosing cholangitis and cholecystitis were more frequent in patients with serum IgG4 levels ≥ 220 mg/dl than in those with a lower serum IgG4 level ($p<0.01$ and $p<0.05$, respectively). The number of associated extrapancreatic lesions was significantly greater in patients with a high serum IgG4 level (Table **3**) [16].

Pancreatic Endocrine and Exocrine Function in Autoimmune Pancreatitis Before and After Steroid Therapy

Glucose tolerance was normal (n=18), borderline (n=6), and diabetes mellitus (DM, n=34 (60%)) in 58 AIP patients. DM was concomitant with onset of AIP in 26 patients, and worsening of pre-existing DM in 8 patients. Pancreatic exocrine function examined by BT-PABA test was reduced in 11 (92%) of 12 AIP patients. Impaired pancreatic exocrine function improved after steroid therapy in 4 of 8 patients treated. The 4 patients also showed treatment-related improvement in endocrine function (Fig. **3**). HbA1c decreased more than 0.5% in 38% of 16 patients 3 months after starting steroid and in 87% 1 year after (Fig. **4**) [9-13].

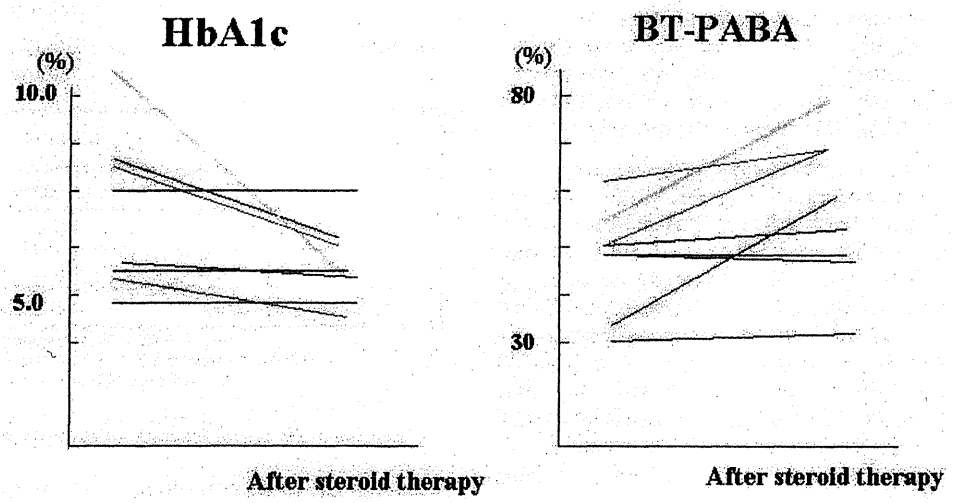

Fig. (3). Changes in HbA1c (%) and BT-PABA (%) of AIP patients before and after steroid therapy.

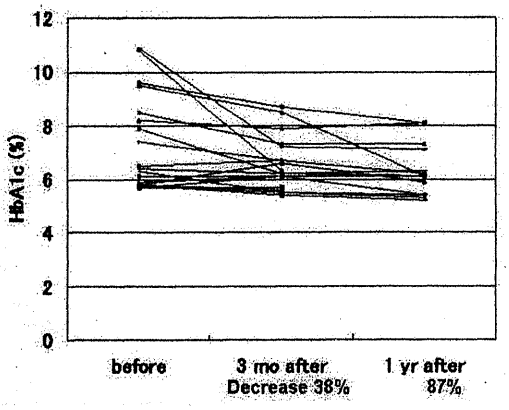

Fig. (4). Changes in serum HbA1c (%) of AIP patients before and after 3 months and 1 year of steroid therapy [12].

Salivary Gland Function of Autoimmune Pancreatitis in Relation to Elevation of Serum IgG4

To examine the differences in salivary gland function between AIP patients in relation to presence or absence of elevated serum IgG4 concentration, we divided 14 AIP patients into 2 groups with high (>135 mg/dL) and low serum IgG4 concentration, and performed sialochemistry, and submandibular and parotid gland scintigraphy.

Serum IgG4 concentration was elevated in 10 patients. Bilateral submandibular glands swelling was detected in 5 patients with high serum IgG4, but was not detected in patients with low serum IgG4. In submandibular and parotid gland scintigraphy, both ratio of cumulative peak count (PCR) and ratio of washout (WR) in high serum IgG4 group were significantly lower than that in controls ($p<0.01$). In low serum IgG4 group, PCR in submandibular gland scintigraphy, and PCR and WR in parotid gland scintigraphy were significantly lower than that in controls ($p<0.05$, $p<0.01$ and $p<0.05$). In submandibular gland scintigraphy, PCR in high serum IgG4 group was significantly lower than that in lower serum IgG4 group ($p<0.05$) (Table **4**).

Salivary gland function impaired in AIP patients with or without elevation of serum IgG4 concentration, but it impaired more in patients with high serum IgG4 than in those with low serum IgG4 [9, 17, 18].

Table 4. Submandibular Gland Function Examined by Scintigraphy

	No. of Cases	PCR (%)	WR (%)
Autoimmune pancreatitis			
high serum IgG4	10	10.4±8.0 ** #	45.6±27.7 **
low serum IgG4	4	23.3±8.5 *	56.4±28.4
Controls	14	35.1±8.2	87.6±9.0

PCR: Ratio of cumulative peak count, WR: Ratio of washout.
**: $p<0.01$ compared with controls, *: $p<0.05$ compared with controls.
#: $p<0.05$ compared with low serum IgG4 group Ref. [17].

Lacrimal Gland Function in Autoimmune Pancreatitis

We investigated lacrimal gland function in AIP patients, and determined changes after steroid therapy by Schirmer's test. Dysfunction of tear secretion was found in at least one eye in 7 (64%) of 11 patients. The average lower level in both eyes was 4.3±1.5 mm in the 7 patients with lacrimal gland dysfunction, which was significantly lower than the 8.2±2.4 mm in patients with normal lacrimal gland function ($p<0.01$). There were no significant differences between the two groups in age at diagnosis of AIP, sex ratio, and the presence of swelling of the lacrimal glands and the salivary glands (Table **5**).

Although there was no significant difference, mean serum IgG4 levels and mean salivary Na+ and β2 microglobulin levels were lower in patients with normal lacrimal gland function. After steroid therapy, lacrimal gland function improved in 3 of 5 patients with impaired lacrimal gland function, though the degree of improvement was not marked compared to the improvement of salivary gland function [19].

Table 5. Clinical Differences Between Autoimmune Pancreatitis Patients with Normal and Impaired Lacrimal Gland Function

	Normal Lacrimal Gland Function (n=4)	Lacrimal Gland Dysfunction (n=7)	p Value
Schirmer's test* (mm)	8.2±2.4	4.3±1.5	.005
Age* (years)	64.2±6.5	61.8±9.4	.749
Male/Female	2/2	5/2	.575
Swelling of lacrimal glands +	1 (25%)	0 (0%)	.363
Swelling of salivary glands +/-	1 (25%)	4 (57%)	.545
Serum IgG4* (mg/dl)	368.8±356.4	899.1±730.7	.185
Na+ in saliva* (mEq/l)	19.4±8.4	24.2±18.5	.334
β2 microglobulin in saliva* (mg/l)	1.6±0.8	2.8±1.4	.161

*: mean±SD Ref. [18].

IgG4-RELATED SCLEROSING CHOLANGITIS

IgG4-related sclerosing cholangitis is frequently associated with AIP, but some cases of IgG4-related sclerosing cholangitis without AIP have been reported. In many AIP cases, the stenosis is located in the lower part of the common bile duct. When stenosis is found in the intrahepatic or the hilar hepatic bile duct, the cholangiographic appearance is very similar to that of primary sclerosing cholangitis (PSC) [20, 21].

We compared clinicopathological characteristics of AIP patients with sclerosing cholangitis (SC) associated with AIP with those of 4 PSC patients. Men were significantly more commonly affected by SC with AIP than by PSC. Patients' age at diagnosis was significantly older in those with SC with AIP. Among the initial symptoms, obstructive jaundice was most frequently observed in SC patients with AIP. Elevated serum IgG4 levels were frequent in SC patients with AIP, but it not in the 2 PSC patients examined. Sclerosing diseases were frequently associated with SC with AIP. Ulcerative colitis was present in only 2 young PSC patients (Table **6**).

Table 6. Clinical Differences Between Sclerosing Cholangitis with Autoimmune Pancreatitis and Primary Sclerosing Cholangitis

	SC with AIP	PSC	P Value
Average age (years)	63.8	39.2	<0.01
Male/female	29/5	1/3	<0.05
Obstructive jaundice +/-	30/4	0/4	<0.01
Elevated serum IgG4 +/-	26/30	0/2	
Associated sclerosing disease +/-	20/14	0/4	<0.05
Associated ulcerative colitis +/-	0/34	2/2	<0.01

SC with AIP: sclerosing cholangitis with autoimmune pancreatitis.
PSC: primary sclerosing cholangitis Ref. [22].

Thirty-two SC patients with AIP were treated with steroid therapy, and all of them showed a good response. All PSC patients were treated with ursodeoxycholic acid, and 1 patient underwent steroid therapy for associated ulcerative colitis. Cholangiographic findings progressed gradually in 3 PSC patients, and 1 patient ultimately required liver transplantation. All SC patients with AIP had a favorable outcome without liver failure.

On pancreatography, narrowing of the main pancreatic duct was detected in all SC patients with AIP, but no abnormal findings were detected in any of the PSC patients. On cholangiography, the intrahepatic bile duct was involved in all PSC patients, but it was involved in only 4 SC patients with AIP. Segmental stenosis of the lower bile duct was observed in all SC patients with AIP, but it was not detected in any of the PSC patients. Extensive involvement of the bile duct, showing widespread wall thickening of the middle and upper bile duct where stenosis was not obvious on cholangiography, was detected only in 14 SC patients with AIP, though there was no significant difference between the two groups. A diffusely distributed, beaded and pruned-tree appearance was detected only in PSC patients. A long stricture was detected in the hepatic hilar region in all 4 SC patients with AIP involving the intrahepatic bile ducts (Table 7).

Table 7. Cholangiopancreatographic Differences Between Sclerosing Cholangitis with AIP and Primary Sclerosing Cholangitis

	SC with AIP	PSC	P Value
Narrowing of the main pancreatic duct +/-	34/0	0/4	<0.01
Stenosis of the intrahepatic bile duct +/-	4/30	4/0	<0.01
Stenosis of the lower bile duct +/-	34/0	0/4	<0.01
Extensive bile duct wall thickening	14/20	0/4	NS
Beaded appearance	0/34	2/2	<0.01
Pruned-tree appearance	0/34	3/1	<0.01

SC with AIP: sclerosing cholangitis with autoimmune pancreatitis.
PSC: primary sclerosing cholangitis Ref. [22].

In PSC, the hilar bile duct displayed diffuse fibrosis with moderate lymphoplasmacytic infiltration. The liver of PSC patients showed the features of biliary cirrhosis, and fibro-obliterative lesions characterized by onion skin-like periductal fibrosis with predominantly lymphocytic infiltration were observed around the intrahepatic bile duct. However, infiltration of IgG4-positive plasma cells was not detected in the bile duct or liver. The histological findings of SC associated with AIP included transmural fibrosis and dense lymphoplasmacytic infiltration of the bile duct wall, along with lymphoplasmacytic infiltration and fibrosis in the periportal area of the liver. Compared with PSC, lymphoplasmacytic infiltration was more dense, the degree of fibrosis was less severe, and the onion skin-like appearance was not observed. Dense infiltration of IgG4-positive plasma cells was detected in the bile duct wall and the periportal area, as well as in the pancreas, of patients with AIP. Given these findings, IgG4-related sclerosing cholangitis is a different disease that is distinct from PSC [22, 23].

IgG4-RELATED SCLEROSING CHOLECYSTITIS

Thickening of the gallbladder wall 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 of 6 of 8 examined patients [24].

IgG4-RELATED SCLEROSING SIALADENITIS

Mikulicz's disease is a unique condition that refers to bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands [25]. Although Mikulicz's disease has been considered a subtype of Sjogren's syndrome, there are several differences between the two diseases. 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 [26].

Swelling of the salivary glands was present in 24% of our AIP patients, and it was associated with cervical or mediastinal lymphadenopathy. Swelling of both the salivary glands and the lymph nodes improves after steroid therapy. Histopathology of the salivary glands of these patients is sclerosing sialadenitis which consisted of fibrosis and infiltration of IgG4-positive plasma cells and lymphocytes. Degree of fibrosis is less compared with that in the pancreas of AIP. Sclerosing sialadenitis and Mikulicz's disease, could be salivary gland lesions of IgG4-related systemic disease [26, 27]. In our series, swelling of the salivary glands preceded AIP in 8 patients.

IgG4-RELATED RETROPERITONEAL FIBROSIS

The pathognomonic feature of retroperitoneal fibrosis is a thick retroperitoneal fibrotic mass covering the abdominal aorta and compressing the ureters [28]. Retroperitoneal fibrosis was present simultaneously or metachronously in 8% 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 [29]. Neild *et al.* [30] reported the histological

findings of 12 patients with idiopathic retroperitoneal fibrosis, which showed, to varying degrees, fibrosis and intense inflammatory cell infiltration with T lymphocytes and IgG4-positive plasma cells, as well as venulitis and obliterative arteritis; biopsy of the mass after steroid therapy revealed decreased infiltration of IgG4-positive plasma cells. Some cases of retroperitoneal fibrosis are the retroperitoneal lesions of IgG4-related systemic disease. Retroperitoneal fibrosis occurs preceding, concomitant with, and subsequent to AIP.

IgG4-RELATED TUBULOINTERSTITIAL NEPHRITIS

Tubulointerstitial nephritis is sometimes associated with AIP [31]. Some AIP cases show several nodular lesions in the kidney mimicking metastatic tumors [32]. Takahashi *et al.* [33] reported that, of 40 AIP patients, 14 (35%) had renal involvement (12 with parenchymal involvement and 5 with extraparenchymal involvement); the renal lesions regressed after steroid therapy, but they progressed without steroid therapy. Cortical renal lesions were observed in 7 (14%) of our 49 AIP patients on CT [34].

Immunohistochemically, dense infiltration of IgG4-positive plasma cells was detected in the renal interstitium. Furthermore, in some AIP cases, membranous nephropathy showing IgG4-positive deposits in the glomeruli or tubular basement membrane have been reported [35]. These IgG4-positive lesions decreased with improvement of renal function after steroid therapy.

IgG4-RELATED INTERSTITIAL PNEUMONIA

Interstitial pneumonia showing X-ray findings such as an interstitial pattern, ground-glass appearance, and honeycombing is sometimes associated with AIP. On high-resolution CT of the lung, dense alveolar consolidation and air bronchograms in bilateral perihilar regions have been reported [36]. Some cases had respiratory failure, and steroid therapy is effective in improving respiratory function and radiological findings. In biopsy specimens, dense infiltration of IgG4-positive plasma cells was detected in the thickened alveolar septum [36, 37]. Hirano *et al.* [37] reported that, of 30 AIP patients, 4 had pulmonary involvement during follow-up.

IgG4-RELATED PROSTATITIS

IgG4-related prostatitis has recently been reported in patients with or without AIP. Patients show lower urinary tract symptoms, and prostate enlargement is evident on digital rectal examination. The symptoms and radiological findings improved after steroid therapy. Histologically, the prostate showed dense infiltration of IgG4-positve plasma cells and lymphocytes, obliterative phlebitis, and gland atrophy with dense fibrosis [38].

IgG4-RELATED INFLAMMATORY PSEUDOTUMOR OF THE LIVER, LUNG, AND HYPOPHYSIS

One type of inflammatory pseudotumors is categorized as a plasma cell-rich type (plasma cell granuloma) [39]; although the pathogenesis of the plasma cell granuloma type is not known. Some IgG4-related inflammatory pseudotumors of the liver [40] and lung [41], which are characterized by dense infiltration of IgG4-positive plasma cells and lymphocytes intermixed with fibrosis and obliterative phlebitis, have been recently reported in patients with or without AIP. Four cases of hypophysitis in association with AIP have been reported; they all presented with hypopituitarism and swelling of the pituitary lesion [41, 42]. In one case [42], abundant infiltration of IgG4-positive plasma cell was demonstrated in the pituitary tumor. 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 [43]. In our series, abdominal 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% of our AIP patients. In all these cases, the lymphadenopathy disappeared after steroid therapy. Dense infiltration of IgG4-positive plasma cells was detected in all abdominal lymph nodes and cervical lymph nodes, but fibrosis was rarely observed. When bilateral hilar lymphadenopathy is marked, sarcoidosis is suspected clinically [44].

CONCLUSION

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. AIP is a pancreatic lesion of this systemic disease. As steroid therapy is effective, accurate diagnosis is necessary.

ACKNOWLEDGEMENT

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Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis

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IgG4-related disease is a recently recognized multi-organ disorder characterized by high levels of serum IgG4 and dense infiltration of IgG4-positive cells into several organs. Although the pancreas was the first organ recognized to be affected by IgG4-related disorder in the syndrome of autoimmune pancreatitis, we present here clinicopathological features of 23 patients diagnosed as having renal parenchymal lesions. These injuries were associated with a high level of serum IgG4 and abundant IgG4-positive plasma cell infiltration into the renal interstitium with fibrosis. In all patients, tubulointerstitial nephritis was the major finding. Although 14 of the 23 patients did not have any pancreatic lesions, their clinicopathological features were quite uniform and similar to those shown in autoimmune pancreatitis. These included predominance in middle-aged to elderly men, frequent association with IgG4-related conditions in other organs, high levels of serum IgG and IgG4, a high frequency of hypocomplementemia, a high serum IgE level, a patchy and diffuse lesion distribution, a swirling fibrosis in the renal pathology, and a good response to corticosteroids. Thus, we suggest that renal parenchymal lesions actually develop in association with IgG4-related disease, for which we propose the term 'IgG4-related tubulointerstitial nephritis.'

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KEYWORDS: autoimmune pancreatitis; corticosteroid; fibrosis; IgG4; tubulointerstitial nephritis

IgG4-related disease represents a recently recognized group of multi-organ diseases characterized by a high level of serum IgG4 and dense infiltration of IgG4-positive cells into multiple organs.[1–3] The condition was first described in relation to the pancreas (that is, autoimmune pancreatitis (AIP)),[4] and has since been expanded to various organ systems. At present, many other inflammatory conditions affecting multiple organs are considered to fall within the category of IgG4-related disease,[1–3] including sclerosing cholangitis,[5] sialadenitis,[2,6] retroperitoneal fibrosis,[7] interstitial pneumonitis,[8] inflammatory pseudotumor,[1–3] and periaortitis.[9] Although much attention is now being focused on these conditions, and the number of case reports of IgG4-related disease has been increasing, there are still few clinicopathological data on the involvement of organs other than the pancreas. The aim of this study was to elucidate the clinicopathological characteristics of renal parenchymal lesions associated with IgG4-related disease.

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RESULTS

Patient profiles

Patients were all Japanese (20 men and 3 women) with an average age of 65.2 ± 10.1 (40–83) years at the time of diagnosis of renal disease. Although seven patients fulfilled the criteria for Sjögren's syndrome, as revised by the Japanese Ministry of Welfare in 1999, none of them met the criteria for systemic lupus erythematosus, anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis, rheumatoid arthritis, or sarcoidosis. None of the organ specimens showed any evidence of malignant lymphoma by the DNA PCR method or immunohistochemistry. At the time of diagnosis of renal involvement, one patient had been treated with low-dose corticosteroid (prednisolone 2.5 mg daily) because of AIP (patient 5 in Table 1). Three patients had been treated with the corticosteroid because of AIP (patients 19 and 22 in Table 1) or idiopathic thrombocytic purpura (patient 8 in Table 1), but the treatment was discontinued when they developed renal involvement. The other 19 patients had not received corticosteroids or immunosuppressants before the appearance of renal lesions.

Clinical features

Of the 23 patients, 22 (95.7%) had some accompanying extrarenal lesions: sialadenitis in 19 (82.6%), lymphadenopathy in 10 (43.5%), AIP in 9 (39.1%), dacryoadenitis in 7 (30.4%), lung lesions (interstitial pneumonitis and nodular lesions) in 6 (26.0%), and others in 3 (pseudotumor of the liver, prostatitis, and idiopathic thrombotic purpura) (Table 1). Among the extrarenal lesions, 15 (represented in bold in Table 1) had been recognized before diagnosis of the renal lesions, and 10 of these 15 lesions in patients 3, 5, 8, 19, and 22 had improved with steroid therapy, or spontaneously, at the time of diagnosis of the renal lesions. The other 39 lesions were diagnosed at the same time as the renal lesions. Clinical symptoms were mostly associated with extrarenal lesions, such as gland swelling and lymphadenopathy. Fever, arthralgia, skin eruption, and edema were observed in 3, 5, 1, and 2 patients, respectively. In 21 of the 23 patients, the renal lesions were observed by physicians because of urinary abnormalities, renal dysfunction, and/or abnormalities revealed by radiological examinations, including computed tomography (CT) and gallium citrate scintigraphy, during follow-up or further examinations of the IgG4-related extrarenal lesions. In patients 13 and 14, renal lesions were observed because of renal dysfunction in the absence of extrarenal lesions. The results of renal histological and laboratory findings alerted the attending physicians to IgG4-related disease, who then carried out measurements of serum IgG4 levels and IgG4 immunostaining. (Additional gallium citrate scintigraphy showed gallium-67 accumulation of both the salivary glands in patient 13.)

Laboratory findings at the time of diagnosis of the renal lesions

Urinary protein excretion was <0.3 g/day in 19 of the 23 patients (Table 1). Urinary protein excretion >1.0 g/day was shown in two patients with membranous nephropathy (patients 14 and 22). Hematuria (urinary red blood cells >3 per h.p.f. (high-power field)) was shown in eight patients. Although mostly mild, hematuria with urinary red blood cells >20 per h.p.f. was evident in three patients with glomerular lesions (patients 14, 22, and 23). Hematological examinations revealed anemia (hemoglobin <10.0 g/dl) in only one patient (hemoglobin 9.0 g/dl in patient 20). Although white blood cell counts were within the normal range in most patients (mild leukocytosis was observed in 2 patients), eosinophila (eosinophils >5%) was observed in 11 patients (47.8%). Platelet counts were within the normal range in all patients. Renal function varied from normal to renal failure (serum creatinine 0.67–6.87 mg/dl). Elevated creatinine levels (serum creatinine >1.2 mg/dl) were shown in 13 of the 23 patients. Abnormal liver function at the time of diagnosis of the renal lesions was observed in three patients; AST (aspartate transaminase) 53 IU/l (range: 13–33), ALT (alanine transaminase) 101 IU/l (range: 10–47), ALP (alkaline phosphatase) 914 IU/l (range: 115–359) in patient 4, AST 16 IU/l, ALT 20 IU/l, ALP 573 IU/l in patient 5, and AST 55 IU/l, ALT 115 IU/l, ALP 1690 IU/l in patient 22. Pancreatic swelling due to AIP had improved by this time in patients 5 and 22, and no patient showed CT abnormalities in the liver or pancreatobiliary system.

All patients showed elevated levels of serum IgG (2721–8841 mg/dl, mean 4836 ± 1499 mg/dl, normal range 870–1700). Although serum IgA and IgM levels were within the normal ranges in all patients, elevation of the serum IgE level (272–4442 IU/ml, normal range <250 IU/ml) was observed in 10 of 14 evaluated patients (71.4%). Serum IgG4 levels before steroid therapy ranged from 587 to 4630 mg/dl (mean 1520 ± 909, normal range <105 mg/dl). In 16 of the 23 patients (69.6%), the serum CH50 level was found to be decreased, together with a reduction in the serum level of C3, C4, or both. In two patients (nos 20 and 21), only the C3 level was decreased. The rheumatoid factor was positive in 7 of 18 evaluated patients (38.9%). Although anti-nuclear antibodies were positive in 69.6%, anti-SS-A, anti-SS-B, anti-Sm, and anti-RNP antibodies were all negative, and the levels of anti-DNA antibodies were not increased in any of the patients. The level of CRP was <1.5 mg/dl in 22 of the 23 patients, and 8.7 mg/dl in 1 patient (patient 7). Cryoglobulin, M-protein, myeloperoxidase-ANCA, and proteinase-3-ANCA were not observed in any of the patients.

Imaging studies

CT revealed abnormal renal parenchymal lesions in 16 of the 23 patients (69.6%) (Table 1). Among them, diffuse swelling of the bilateral kidneys was evident in seven patients. Patchily distributed hypoattenuated lesions in the renal cortex, being single or multiple, round or wedge shaped, were found in 10 patients (Figure 1). Renal pelvic tumor and calicectasis were observed in addition to the renal parenchymal lesions in patients 2 and 4, respectively. In patient 1, thickening of the renal pelvic wall was observed, although no renal

Table 1 | Clinicopathological features of 23 patients with IgG4-related tubulointerstitial nephritis

No	Age/sex	Renal biopsy findings	U-Pr/U-B	Cr at biopsy	IgG (*N*:870–1700)	IgG4 (*N*<105)	IgE (*N*<250)	Low CH50	Low C3	Low C4	ANA	RF	Extrarenal lesions	Renal CT findings	Tx of pre-/post-biopsy	Cr at 1 M after Tx	References
1	58/F	TIN	0.23 g/day/(±)	0.67	7319	4630	4442	(−)	(−)	(−)	(−)	(+)	La, Sa, AIP, Ly	Thickening of renal pelvis	(−)/PSL40	0.59	
2	76/F	TIN	(−)/(−)	0.69	2721	769	267	(−)	(−)	(−)	(+)	(−)	La, Sa, Ly, Lu	Pa, pelvic tumor	(−)/PSL20	0.64	
3	76/M	TIN	(−)/(−)	0.71	3486	1030	NA	(+)	(−)	(+)	(−)	(−)	***Sa***, AIP	Pa	(−)/(−)	0.69	Saeki *et al.*[33,34]
4	40/F	TIN	(−)/(−)	0.74	3450	2400	272	(+)	(−)	(+)	(−)	(+)	La, Sa, Lu	Pa, S, calicectasis	(−)/Pulse+PSL60	0.58	Shimoyama *et al.*[35]
5	52/M	TIN	(−)/(−)	0.80	3180[a]	1430[a]	NA	(−)	(−)	(−)	(−)	(+)	***Sa***, ***AIP***, ***Lu***	Pa	PSL2.5/PSL10	0.7	Nakamura *et al.*[36]
6	56/M	TIN+mesPGN	(+)/(−)	0.9	5680	1920	248	(+)	(+)	(+)	(+)	(−)	La, Sa, Ly	Pa	(−)/PSL50	0.9	Yamamoto *et al.*[37]
7	70/M	TIN	(±)/(−)	0.9	3496	623	NA	(+)	(+)	(+)	(+)	(−)	AIP	S	(−)/PSL30	0.8	
8	61/M	TIN	(−)/(−)	1.09	6569	730[a]	1049[a]	(+)	(+)	(+)	(+)	NA	***Sa***, ***AIP***, ***ITP***, Ly	Pa	(−)/PSL60[b]	0.97	Saeki *et al.*[14,33,34]
9	74/M	TIN	(+)/(−)	1.1	4387	1320	560	(+)	(+)	(+)	(+)	(+)	***Sa***	S	(−)/PSL30	0.9	Nakada *et al.*[38]
10	58/M	TIN	(−)/(−)	1.15	2850	1470	456	(−)	(−)	(−)	(+)	NA	Pseudo-tumor (liver)	Pa	(−)/PSL30	1.06	
11	62/M	TIN+IgAGN	(−)/(±)	1.3	8194	NA	704	(+)	(+)	(+)	(+)	(+)	La, Sa, AIP, Ly	S	(−)/Pulse+PSL30	1.1	
12	75/M	TIN	(+)/(−)	1.34	5380	587	NA	(+)	(+)	(+)	(+)	(+)	Sa, Ly, Lu	Pa	(−)/PSL30	1.14	
13	68/M	TIN	(−)/(−)	1.37	2995	670	2323	(+)	(+)	(+)	(+)	(−)	Sa	Normal	(−)/PSL40	1.19	Saeki *et al.*[14,33]
14	83/M	TIN+MN	2.3 g/day/(3+)	1.48	3144	924	32	(+)	(+)	(+)	(+)	NA	(−)	Normal	(−)/PSL40	1.39	Saeki *et al.*[39]
15	60/M	TIN	(−)/(−)	1.7	8841	1028	NA	(+)	(+)	(+)	(+)	(−)	***Ly***, ***Lu***, Sa	Normal	(−)/PSL30	NA	Takamura *et al.*[40]
16	60/M	TIN+mesPGN	(+)/(±)	1.75	5188	305[a]	NA	(+)	(+)	(+)	(+)	(+)	Sa, Ly	S	(−)/PSL50	1.55	Saeki *et al.*[14,33,34]
17	61/M	TIN	NA	2.0	8005	2390	858	(+)	(+)	(+)	(+)	(−)	Sa, Ly	S	(−)/unknown	NA	
18	55/M	TIN	(+)/(−)	2.1	5040	1780	NA	(−)	(−)	(−)	(+)	(+)	***AIP***, Sa	Pa	(−)/PSL40	1.3	Saeki *et al.*[33]
19	69/M	TIN	0.25 g/day/(±)	2.36	4001	1340	NA	(+)	(+)	(+)	(−)	NA	***AIP***	Normal	(−)/PSL30[b]	2.1	
20	64/M	TIN	NA	2.9	5100	1360	92	(−)	(+)	(−)	(+)	(−)	La, Sa	Normal	(−)/PSL50	NA	
21	76/M	TIN	0.3 g/day/(+)	5.4	2963	1800	125	(−)	(+)	(−)	(−)	(−)	***Sa***	Normal (nonenhanced)	(−)/PSL40	2.9	
22	78/M	TIN+MN	1.4 g/day/(2+)	6.17	3731	1860	NA	(+)	(+)	(−)	(−)	(−)	***Sa***, ***AIP***	Pa	(−)/PSL20[b]	HD	Saida *et al.*[10]
23	68/M	TIN+endocap	(2+)/(2+)	6.87	4661	1120	335	(+)	(+)	(+)	(+)	(−)	La, Sa, Ly, Lu, P	S (nonenhanced)	(−)/PSL30	1.45	

Abbreviations: ANA, antinuclear antibody; Cr, serum creatinine (mg/dl); CT, computed tomography; endocap, endocapillary hypercellularity; IgAGN, IgA nephropathy; IgG, serum IgG (mg/dl); IgE, serum IgE (IU/ml); IgG4, serum IgG4 (mg/dl); Low CH50,C3,C4, low titer of serum CH50,C3,C4; M, month; mesPGN, mesangioproliferative glomerulonephritis; MN, membranous nephropathy; NA, not available; pre-/post-biopsy, pre-renal biopsy/post-renal biopsy; RF, rheumatoid factor; TIN, tubulointerstitial nephritis; Tx, treatment; U-B, hematuria; U-Pr, proteinuria.

[a]Value under steroid therapy. AIP, autoimmune pancreatitis; ITP, idiopathic thrombocytic purpura; La, dacryoadenitis; Lu, lung lesion; Ly, lymphadenitis; P, prostatitis; Pa, patchy lesion; PSL, prednisolone mg/day; S, diffuse swelling; Sa, sialadenitis (bold and italic extrarenal lesions were diagnosed before diagnosis of renal lesion).

[b]History of steroid treatment. HD, hemodialysis.

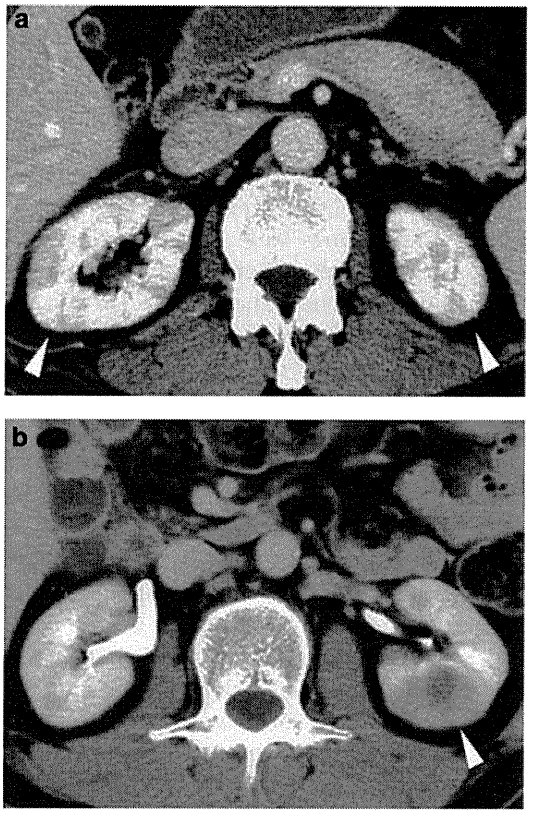

Figure 1 | Contrast-enhanced renal CT findings in patients with IgG4-related nephropathy. (**a**) Multiple wedge-shaped low-attenuation lesions in both renal cortices are evident (arrows, patient 3); (**b**) A tumor-like less-enhanced mass (arrow) is evident in the left kidney (patient 8). CT, computed tomography.

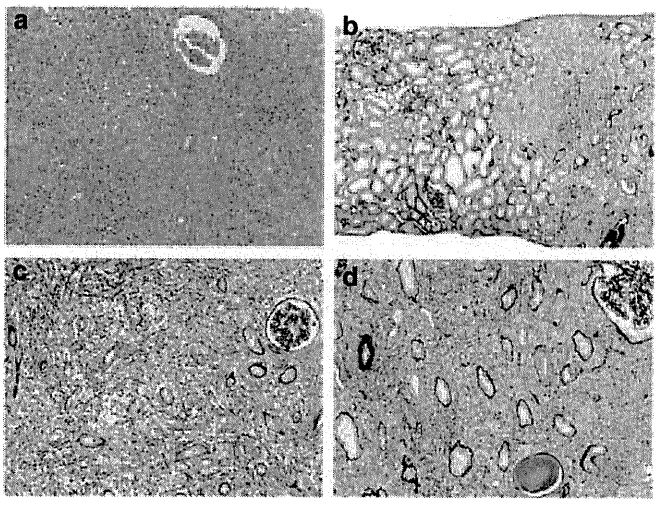

Figure 2 | Light microscopy findings in the renal tissues. (**a**) Diffuse marked renal interstitial inflammation consisting of lymphocytes and plasma cells with fibrosis is demonstrated, and most tubules are diminished (patient 8, HE; original magnification × 200); (**b**) Patchy distribution of dense lymphoplasmacytic infiltrates with irregular fibrosis, showing a clear margin (patient 16, PAM-Masson; original magnification × 80); (**c**, **d**) Collagen fibers exhibit a swirling pattern or an arabesque outline in a PAM-stained preparation, and the inflammatory cells show infiltration into the collagen fibers (panel **c**; patient 13, PAM-Masson; original magnification × 200, panel **d**; patient 21, PAM-Masson; original magnification × 250). HE, hematoxylin and eosin; PAM, periodic acid-methenamine.

parenchymal lesion was evident. Gallium citrate scintigraphy was performed before therapy in 17 patients (nos 2–9, 11–18, and 21), and all but 2 (nos 2 and 14) showed gallium-67 accumulation in both the kidneys. Gallium citrate scintigraphy performed during therapy showed no gallium-67 accumulation in the kidneys (patients 10 and 21).

Renal pathology

Tubulointerstitial nephritis was a dominant feature in all patients (Table 1). Light microscopy demonstrated dense cell infiltration with fibrosis and tubular atrophy. The infiltrate was predominantly composed of plasma cells and lymphocytes, and also eosinophils in some patients. Distribution of the lymphoplasmacytic infiltration was not only diffuse but also patchy, sometimes with a clear margin (Figure 2a and b). Tubule atrophy or diminishment developed according to the severity of cell infiltration and fibrosis. In the fibrotic interstitium, collagen fibers exhibited a swirling pattern or an arabesque outline in periodic acid-methenamine silver-stained preparations, and inflammatory cells infiltrated the collagen fibers, producing a characteristic pattern (Figure 2c and d). On light microscopy, the glomeruli were unremarkable in 18 patients, except for evidence of focal global sclerosis. One patient (no. 14) showed membranous nephropathy. Mild mesangioproliferative glomerulonephritis was evident in three patients (nos 6, 11, and 16), and focal segmental endocapillary hypercellularity was observed in one (no. 23). Direct immunofluorescence was evaluated in 14 patients (nos 1, 2, 5, 6, 9, 10, 11, 13, 14, 16, 18, 19, 21, and 22). In three patients (nos 1, 18, and 21), deposition of immunoglobulins and complement components was not confirmed in the glomeruli or the interstitium. In the patient with membranous nephropathy (no. 14), diffuse and global IgG and C3 deposits along the glomerular capillary walls, and focal deposits of IgG and C3 along the tubular basement membranes were observed. In patient 22, no deposition was observed in the glomeruli, and parts of the tubular basement membranes were positive for C3 deposition. Although the glomeruli on light microscopy were also unremarkable in the patient, electron microscopy revealed segmental subepithelial deposits on the glomerular basement membranes, and therefore, we diagnosed the patient as having tubulointerstitial nephritis with membranous nephropathy.[10] In three patients with mild mesangioproliferative glomerulonephritis (nos 6, 11, and 16), no apparent deposit was evident on the tubular basement membranes. In two of these patients (nos 6 and 16), mild IgG and IgA deposits (IgA was not dominant) were observed in the mesangial areas. In the other patient (no. 11), dominant IgA deposition was observed in the mesangial area, and we diagnosed the patient as having tubulointerstitial nephritis with IgA nephropathy. In four of

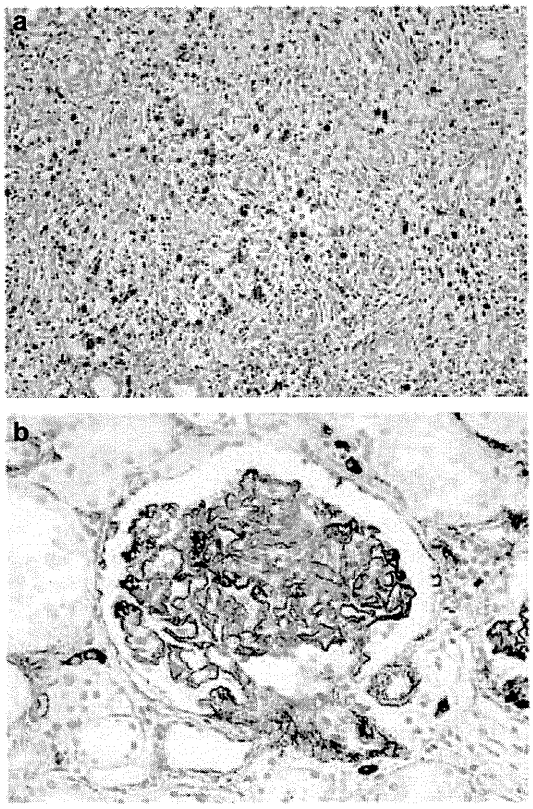

Figure 3 | Immunostaining of IgG4 in renal tissues.
(**a**) Numerous IgG4-positive plasma cells are evident in the renal interstitium (patient 13, original magnification ×250); (**b**) In the patient with membranous nephropathy (patient 14), diffuse staining of glomerular capillary walls is also shown in addition to the IgG4-positive infiltrating plasma cells in the renal interstitium (original magnification ×400).

the other six patients (nos 5, 9, 13, and 19), segmental staining for IgG or C3 was shown in the glomeruli, with no deposits on the tubular basement membrane; faint or mild segmental mesangial staining for IgG in patients 5, 9, and 19, and mild segmental staining for C3 along the glomerular capillary wall in patient 13. In the other two patients (nos 2 and 10), nonspecific faint segmental staining for C3 was evident on the tubule basement membranes, without any deposits in the glomeruli.

Immunostaining for IgG4 revealed infiltration of numerous IgG4-positive plasma cells (IgG4-positive plasma cells/IgG-positive plasma cells >40%; IgG4-positive plasma cells >10 per h.p.f.) into the renal interstitium (Figure 3a). In the patient with membranous nephropathy (no. 14), IgG4 immunostaining also showed diffuse reactivity in the glomerular capillary walls, and focal staining of the tubule basement membrane, in addition to the infiltrating plasma cells (Figure 3b).

Treatment and course

The treatment regimen was decided according to the opinion of each attending physician (Table 1). Of the 23 patients, 21 were treated with prednisolone (initial dose 10–60 mg/day) for renal lesions. Intravenous methylprednisone pulse therapy (500–1000 mg for 3 days) was also conducted in three patients. One patient (no. 3) was followed up without therapy because both AIP and renal lesions improved spontaneously. Among patients treated with corticosteroid, the clinical data after 4 weeks were evaluable in 19. In 18 of those patients, abnormalities of renal function, complement level, and imaging features were all improved by therapy. Extrarenal lesions were also improved. In one patient with renal failure (no. 22), renal function did not recover, and maintenance hemodialysis became necessary.

DISCUSSION

Lesions of the kidney associated with IgG4-related disease include those affecting the renal parenchyma, and lesions of other areas.[7,11] Renal parenchymal lesions associated with IgG4-related disease were first described in 2004 as case reports of tubulointerstitial nephritis associated with AIP.[12,13] Thereafter, the number of case reports of tubulointerstitial nephritis associated with IgG4-related disease has been increasing,[14–18] although most of such cases have been accompanied by AIP and their number is still limited.

The clinicopathological features of IgG4-related disease have been described most extensively for cases with pancreatic involvement (that is, AIP).[19–22] It predominantly affects middle-aged to elderly men. The clinical symptoms are mild and the condition usually comes to clinical attention because of imaging abnormalities of the pancreas or obstructive jaundice. In most patients, extrapancreatic lesions, such as sclerosing cholangitis, sclerosing sialadenitis, lymphadenopathy, and retroperitoneal fibrosis occur during the clinical course, sometimes simultaneously and often metachronously.[23] Laboratory examinations reveal characteristically increased levels of serum IgG and IgG4 (increased serum IgG4 is observed in 68–90% of Japanese patients with AIP),[22] and a recent study has shown that the serum IgE level is also frequently elevated.[24] Antinuclear antibodies and rheumatoid factor are often positive, but anti-SSA and anti-SSB antibodies are negative,[21] and hypocomplementemia is observed in 17–36% of the patients.[25] CT scan or magnetic resonance imaging shows diffuse pancreatic enlargement or focal masses. Corticosteroid therapy is usually quite effective for normalizing pancreatic lesions, and also the clinical and laboratory parameters. Histopathologically, dense lymphoplasmacytic infiltration, swirling or storiform fibrosis, and abundant IgG4-positive plasma cell infiltration revealed by IgG4 immunostaining are characteristic, and several studies have shown that IgG4-related disease shows similar pathological features, regardless of the specific type of organ involved.[8,26] In this study, we diagnosed 23 patients as having renal parenchymal lesions associated with IgG4-related disease on the basis of the renal pathological features described above, in addition to high levels of serum IgG4. As an elevated serum IgG4 level is characteristic of IgG4-related disease, but not diagnostic (sensitivity 75%, specificity 93% in AIP),[20] histopathological examination including IgG4

immunostaining is useful for diagnosis of this disease in addition to an elevated serum IgG4 level. Although 14 of the 23 patients did not have any pancreatic lesions, the clinical features were quite uniform and similar to those shown in AIP. Our results suggested that renal parenchymal lesions actually developed in association with IgG4-related disease, but not in association with AIP.

Tubulointerstitial nephritis is caused by various factors, including infections, drug reactions, urinary tract obstruction, autoimmune conditions, plasma cell dyscrasias, and metabolic disorders. Many patients in the present series showed hypergammaglobulinemia, hypocomplementemia, and positivity for anti-nuclear antibodies, being reminiscent of systemic lupus erythematosus, but none of them met the criteria for it. Although seven of the patients fulfilled the ordinary criteria for Sjögren's syndrome, typical Sjögren's syndrome does not show elevation of the serum IgG4 level and abundant IgG4-positive plasma cell infiltration.[3] Recent studies have shown that there are considerable differences between IgG4-related disease and Sjögren's syndrome, although distributions of the involved organs are similar,[2,3] and therefore it is important to recognize IgG4-related disease and to distinguish it from Sjögren's syndrome.[27] The clinical symptoms, laboratory findings such as hypocomplementemia, a low CRP level and negativity for ANCA, and also radiological findings, differed from those of drug-induced tubulointerstitial nephritis, infection, and ANCA-related vasculitis. The clinicopathological features of tubulointerstitial nephritis associated with IgG4-related disease are thus unique and distinct from those of other renal diseases.

Despite the characteristic clinicopathological features, the pathogenesis of IgG4-related disease remains poorly understood, although autoimmune or allergic mechanisms have been discussed.[5,19,20] Cornell *et al.*[28] demonstrated IgG4 immune-complex deposition in the renal tubule basement membranes of patients with tubulointerstitial nephritis associated with AIP, suggesting an immune-complex mechanism. In the present series, an apparent deposition of immune complex on the tubular basement membranes was evident in only one of the patients with membranous nephropathy by direct immunofluorescence. On the other hand, the relationship between glomerular lesions and IgG4-related disease is also poorly understood. Although the major pathological feature of this disease is tubulointerstitial nephritis, the glomeruli were also affected in a small number of cases in this study, and this has also been described previously,[12,15,29,30] membranous nephropathy being the most frequent feature among them. The significance of IgG4 has been documented in idiopathic membranous nephropathy, in which the predominance of Th2 cytokines is a common feature,[31,32] and also in IgG4-related disease,[5] suggesting a possible relationship between them. In view of the possible association of renal lesions with IgG4-related disease, glomerular lesions should be examined closely in addition to interstitial lesions. Further large-scale and detailed clinicopathological studies including electron microscopy examinations will be necessary to elucidate the pathogenesis of IgG4-related renal lesions.

As the concept of IgG4-related disease was proposed relatively recently, it remains largely unrecognized by most clinicians. However, accurate diagnosis of IgG4-related disease is very important because steroid therapy is usually quite effective.[19–22] In this study, the renal lesions had improved with corticosteroid therapy in most patients at the time of the 4-week follow-up. However, renal function did not recover in one patient (no. 22) with renal failure.[10] Although in this study we were unable to characterize the clinicopathological differences between patients with better or worse renal function, because it was a retrospective analysis and only one patient showed worsened renal function after treatment, it is important to be aware that renal failure may also occur in IgG4-related disease if the diagnosis is delayed. Nephrologists should be aware of the condition in patients with tubulointerstitial nephritis, and measure the serum IgG4 level, especially when there is associated sialadenitis, lymphadenopathy, hypergammaglobulinemia, eosinophilia, hypocomplementemia,[41] and a patchy lesion distribution. In addition, clinicians should be vigilant for the development of renal lesions at any time when following the course of involvement of other organs in patients with any IgG4-related disease, such as AIP. In five of the present patients, renal lesions developed during remission of the condition in other organs.

In conclusion, renal parenchymal lesions associated with IgG4-related disease appear to have characteristic clinicopathological features in comparison with those of other renal diseases, and therefore we propose the term 'IgG4-related tubulointerstitial nephritis' for this condition.

MATERIALS AND METHODS

Patients and methods

A total of 153 patients with suspected IgG4-related disease were collected retrospectively from 22 collaborating institutions in Japan between September 2004 and August 2009, among whom 30 were diagnosed as having renal parenchymal abnormalities by their physicians. Among these 30 patients, we diagnosed 23 as having renal parenchymal lesions associated with IgG4-related disease. (In Table 1, patients nos 3, 4, 5, 6, 8, 9, 13–16, 18 and 22 have been previously reported in references 10, 14, and 33–40.) The diagnosis was based on a high serum IgG4 level (>135 mg/dl) and numerous infiltration of IgG4-positive plasma cells into the renal interstitium (IgG4-positive plasma cells/IgG-positive plasma cells $>40\%$; IgG4-positive plasma cells >10 per h.p.f.) with fibrosis. Although the serum IgG4 level was not measured in one patient, we also diagnosed this patient as having renal parenchymal involvement associated with IgG4-related disease because of the presence of tubulointerstitial nephritis with infiltration of numerous IgG4-positive plasma cells into the renal interstitium with typical AIP and Mikulicz's disease. In the other 7 of 30 patients, renal parenchymal abnormalities were diagnosed on the basis of radiographic abnormalities. Five of these patients were diagnosed as having IgG4-related sialadenitis and dacryoadenitis and showed multiple hypoattenuating lesions in the renal cortex by contrast-enhanced