

Retroperitoneal Fibrosis: A Clinicopathologic Study With Respect to Immunoglobulin G4

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Abstract: The possible involvement of immunoglobulin G4 (IgG4) in the pathogenesis of idiopathic sclerosing lesions has been suggested. In this study, a clinicopathologic analysis was performed to reveal characteristics of retroperitoneal fibrosis relating to IgG4. The study involved 17 patients with retroperitoneal fibrosis. Immunohistochemistry revealed numerous IgG4-positive plasma cell infiltrates in 10 cases (IgG4-related), but only a few positive cells in 7 cases (non-IgG4-related). All patients with IgG4-related retroperitoneal fibrosis were male, whereas all except 1 with unrelated lesions were female. Histologically, eosinophilic infiltration (> 5 cells per high-power field) and obliterative phlebitis were commonly observed in IgG4-related lesions. Serologically, serum IgG and IgG4 concentrations were significantly higher in the IgG4-related cases, with the IgG4 concentrations all over 135 mg/dL (the upper limit of the normal range). Steroid therapy was performed in 13 cases, and was effective irrespective of IgG4. Three patients had recurrence during the follow up. Five of 10 IgG4-related cases had sclerosing lesions at other sites. The only tests that reliably distinguish the 2 groups were serum IgG4 levels or IgG4/IgG ratio in the plasma cells in a tissue biopsy. The only major clinical difference was the striking male predominance in IgG4-related cases. In conclusion, this study revealed that retroperitoneal fibrosis could be classified as IgG4-related or not. This distinction seems important to help better characterize the biology/pathogenesis of both groups and better predict the possibility of other IgG4-related processes at other anatomic sites.

Key Words: IgG4, periaortitis, multifocal fibrosclerosis, autoimmune pancreatitis, fibrosis

(*Am J Surg Pathol* 2009;33:1833–1839)

Retroperitoneal fibrosis is an idiopathic sclerosing lesion involving soft tissue or organs in the retroperitoneum. Retroperitoneal fibrosis is now considered a heterogeneous disease entity, with the possible involvement of autoimmune disorders or viral infections in its pathogenesis.^{1,14} Patients with retroperitoneal fibrosis sometimes have idiopathic sclerosing lesions in other organs such as the bile duct (sclerosing cholangitis) and salivary glands (chronic sclerosing sialadenitis), a condition referred to as multifocal fibrosis.¹²

Recently, a close relationship between multifocal fibrosis and immunoglobulin G4 (IgG4) has been suggested.⁸ In 2001, Hamano et al⁵ reported that patients with sclerosing pancreatitis, also called autoimmune pancreatitis, have high-serum IgG4 concentrations. The same group also revealed that autoimmune pancreatitis is pathologically characterized by numerous IgG4-positive plasma cell infiltrates.⁶ Since then, similar sclerosing lesions containing many IgG4-positive plasma cells have been identified in various organs, and a systemic disease entity named IgG4-related disease was proposed. Irrespective of the organ involved, patients with IgG4-related diseases have similar clinicopathologic characteristics. The clinical characteristics are male predominance, a frequent association with IgG4-related diseases in other organs, and steroid responsiveness. The pathologic characteristics are diffuse lymphoplasmacytic infiltration with irregular fibrosis, occasional infiltration by eosinophils, obliterative phlebitis, and numerous IgG4-positive plasma cells.^{3,10,17}

Several cases of IgG4-related retroperitoneal fibrosis have been reported, some associated with autoimmune pancreatitis, and some not. Steroid therapy was effective for IgG4-related retroperitoneal fibrosis the same as for IgG4-related diseases in other organs.^{4,19} However, important issues remain unresolved, including (1) whether all cases of retroperitoneal fibrosis are related to IgG4,

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and if not, (2) whether the clinicopathologic characteristics of IgG4-related cases are different from those of non-IgG4-related cases.

In this study, we performed a clinicopathologic analysis using 17 cases of retroperitoneal fibrosis to reveal clinicopathologic differences between IgG4-related and non-IgG4-related cases.

PATIENTS AND METHODS

Case Selection

A total of 17 cases, in which the original diagnosis was retroperitoneal fibrosis, were selected from the pathology files of our hospitals in Japan, and the consultation file of 1 author (Y.Z) for the period between 1990 and 2005. The patients were 11 males and 6 females with an average age of 62 years (range: 30 to 78 y). One patient was reported in a earlier case report.¹⁹ Seven patients underwent a needle biopsy, 9 patients underwent a surgical biopsy, and 1 patient underwent a left nephrectomy.

The diagnosis of retroperitoneal fibrosis was based on a histologic examination of biopsied or surgically resected specimens. All the cases examined involved lymphoplasmacytic infiltration and fibrosis to some degrees. No atypical features suggestive of neoplasia were identified in lymphoid cells or spindle-shaped stromal cells. Biopsies are not sufficient to completely exclude the possibility of neoplastic lesions. However, all patients were sufficiently followed up (follow-up period: average, 39 mo; range, 5 to 138 mo). No neoplastic lesions were detected in the retroperitoneum of any patients during the follow-up period.

Classification of Retroperitoneal Fibrosis

Retroperitoneal fibrosis was classified as IgG4-related and non-IgG4-related on the basis of pathologic features. Our earlier studies revealed that most patients with IgG4-related diseases had a IgG4/IgG-positive plasma cell ratio of more than 30%.^{10,17,18} In contrast, the ratio was less than 10% for non-IgG4-related diseases. Therefore, we diagnosed IgG4-related retroperitoneal fibrosis in patients having diffuse IgG4-positive plasma cell infiltration and an IgG4/IgG-positive cell ratio greater than 30%.

Clinical Examination

We compared clinical characteristics between patients with IgG4-related and non-IgG4-related retroperitoneal fibrosis. Age, sex, clinical symptoms, presence or absence of sclerosing lesions at other locations, and response to steroids were examined in each case. The retroperitoneal fibrosis was classified into 3 types on the basis of the location: (1) periaortic/arterial, involving connective tissue around the abdominal aorta or first branches like iliac and supramesenteric arteries; (2) periureteral, showing mass lesions along the ureters or renal pelvis with or without ureteral obstruction; and (3) plaque-like, having a plaque-like mass broadly involving

the retroperitoneum. All locations were described in cases involving other sites or multiple sites of the retroperitoneum. A serological examination was performed regarding serum IgG and IgG4 concentrations, and antinuclear antibodies using serum before starting the steroid therapy. Serum IgG and IgG4 concentrations were not available for 1 patient, a consultative case.

Pathologic Examination

Formalin-fixed and paraffin-embedded sections were prepared and used for the histopathologic examination. Four-micron sections were cut for hematoxylin and eosin (H&E), Elastica van Gieson, and immunohistochemical staining, and for in situ hybridization.

Histologic features were compared between IgG4-related and non-IgG4-related cases. We examined the degree of inflammation in the retroperitoneum (0, minimal inflammatory cell infiltration; 1+, focal accumulation of inflammatory cells; 2+, between 1+ and 3+; 3+, diffuse inflammatory cell infiltration). We also examined the following 7 histologic features: plasma cell infiltration [more than 10 per high-power field (hpf)], neutrophilic infiltration (more than 10 per hpf), eosinophilic infiltration (more than 5 per hpf), lymph follicles with a germinal center, obliterative phlebitis, granuloma, and presence of multinucleated giant cells. Other characteristic histologic features were described in each case.

Immunohistochemistry

Immunostaining of IgG, IgG4, CD3, CD20, and CD79 α were performed by an autostainer (HX System Benchmark, Ventana Medical Systems, Tucson, AZ). Primary antibodies used were a rabbit monoclonal antibody against human IgG (Dako Cytomation, Glostrup, Denmark), a mouse monoclonal antibody for human IgG4 (ZYMED Laboratory, Inc, San Francisco, CA), a rabbit monoclonal antibody for human CD3 (LAB VISION corporation, Fremont, CA), a rabbit monoclonal antibody for human CD20 (Abcam, Tokyo, Japan), and a mouse monoclonal antibody for CD79 α (Dako Cytomation). Sections were pretreated with proteinase (IgG and IgG4) or a heated plate (CD3, CD20, and CD79 α). IgG-positive or IgG4-positive plasma cells were counted in 3 different hpfs (10 $\times$ eyepiece and 40 $\times$ lens) with intense inflammation, and the ratio (percentage) of IgG4-positive plasma cells/IgG-positive plasma cells was calculated in each case. Specimens of tonsil were used as positive controls. Negative controls were evaluated by replacing the primary antibody with similarly diluted nonimmunized mouse serum.

In Situ Hybridization

In situ hybridization of κ -chain and λ -chain was performed by an autostainer (HX System Benchmark) as per the manufacturer's instructions. Specific probes for κ -chain and λ -chain were obtained from Ventana Medical Systems. Specimens of gastric marginal zone B-cell lymphoma (MALToma) and tonsillitis were used as positive and negative controls, respectively.

TABLE 1. The Number of IgG-positive or IgG4-positive Plasma Cells and the Ratio of IgG4/IgG-positive Plasma Cells in Patients With Retroperitoneal Fibrosis

	IgG4-related (n = 10)	Non-IgG4-related (n = 7)	P
IgG-positive plasma cells (/hpf)	109 (41-206)	53 (3-743)	0.03
IgG4-positive plasma cells (/hpf)	68 (24-144)	3 (0-12)	< 0.001
IgG4/IgG-positive plasma cell ratio (%)	62% (35-76%)	4% (0-10%)	< 0.001

hpf indicates high-power field; IgG, immunoglobulin G.

Statistical Analysis

The statistical analysis was performed using the Mann-Whitney *U* test. A probability of $P < 0.05$ was considered statistically significant.

RESULTS

Pathologic Features

On the basis of immunostaining of IgG4, the 17 cases could be classified as either IgG4-related (cases 1 to 10) or non-IgG4-related (cases 11 to 17). Numbers of IgG and IgG4-positive plasma cells, and ratios of IgG4/IgG-positive plasma cells are shown in Table 1. Values were significantly higher in cases of IgG4-related retroperitoneal fibrosis (Fig. 1A). The pathologic features of IgG4-related and non-IgG4-related cases are compared in Table 2. The degree of inflammation was more pronounced in the IgG4-related cases, although not significantly ($P = 0.061$) (Figs. 1B, C). Lymph follicles were well developed in 5 cases of IgG4-related retroperitoneal fibrosis (Fig. 1D). Eosinophilic infiltration (> 5 /hpf) was observed in 5 of 10 (50%) patients with IgG4-related retroperitoneal fibrosis (Fig. 1E). Compared to surgical cases only, obliterative phlebitis was more frequently observed in IgG4-related cases (100% vs. 25%, $P = 0.009$) (Fig. 1F).

Immunostaining of CD3, CD20, and CD79 α revealed a mixture of T and B cells in each lesion. In situ hybridization of κ -chain and λ -chain also showed the polyclonality of plasma cells in all cases.

Overall, IgG4-related retroperitoneal fibrosis was more inflammatory in nature and diagnosed based only on H&E staining especially in surgical cases. However, 1 unrelated case (case 15) had intense sclerosing inflammation with obliterative phlebitis and some eosinophils resembling IgG4-related disease except for the many multinucleated giant cells and low number of IgG4-positive plasma cells.

Clinical Features

Clinical characteristic of IgG4-related and non-IgG4-related cases are compared in Table 3. All the patients with IgG4-related retroperitoneal fibrosis were more than 50 years old. In contrast, 3 of 7 patients with non-IgG4-related lesions were less than 50 years of age ($P = 0.525$). Interestingly, the patients with IgG4-related fibrosis were all male; whereas all but one of the patients

with non-IgG4-related lesions were female ($P < 0.001$). Regarding locations of retroperitoneal fibrosis, periaortic/arterial involvement was observed in 8 (80%) and 6 (86%), periureteral involvement in 5 (50%) and 3 (43%), and plaque-like lesions in 1 (10%) and 1 (14%) of the IgG4-related and non-IgG4-related patients, respectively. Patient 3 also had a separate sclerosing lesion around the renal capsule, and patient 6 showed perirectal involvement. Regarding location and shape on radiologic images, there was no significant difference between the 2 groups. Four IgG4-related cases (cases 1, 4, 5, and 8) and 3 non-IgG4-related cases (cases 11, 12, and 17) involved hydronephrosis related to retroperitoneal fibrosis.

Serological Examinations

Serum concentrations of IgG and IgG4, and anti-nuclear antibodies were compared between the IgG4-related and non-IgG4-related patients (Table 4). No difference was observed in IgG concentrations between the 2 groups. IgG4 concentrations and the IgG4/IgG ratio were significantly higher in the IgG4-related cases than unrelated cases. Especially, all the IgG4-related patients had concentrations of more than 135 mg/dL, which is a diagnostic threshold commonly used for autoimmune pancreatitis. There was no significant difference regarding antinuclear antibodies between the groups.

Extraretroperitoneal Lesions

Five patients with IgG4-related retroperitoneal fibrosis had other sclerosing lesions at extraretroperitoneal sites (Table 3). Those lesions were diagnosed on high-serum IgG4 concentrations and characteristic radiologic findings.⁷

Treatment and Recurrence

Steroid therapy was performed in 13 (8 IgG4-related and 5 non-IgG4-related) cases at first presentation (Table 5). The average follow-up period was 39 months. Three patients (cases 1, 2, and 11) were found to have recurrences during follow up. Patient 1 underwent a left nephrectomy on suspicion of a renal pelvic tumor, which was pathologically diagnosed as pseudotumorous retroperitoneal fibrosis with pelvic involvement. Seventeen months later, he was found to have a similar lesion around the right renal pelvis, which was effectively treated

by steroids. Patient 2 was first diagnosed with retroperitoneal fibrosis 14 years ago, and treated with steroids. This patient has had 2 recurrences, and both of which

responded well to steroid therapy. Patient 11 had a recurrence 5 months after the first treatment with steroids. Then, this patient underwent ureteral stenting.

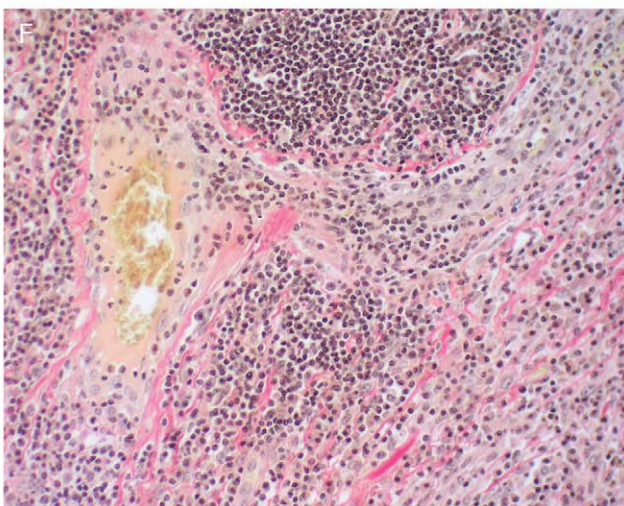
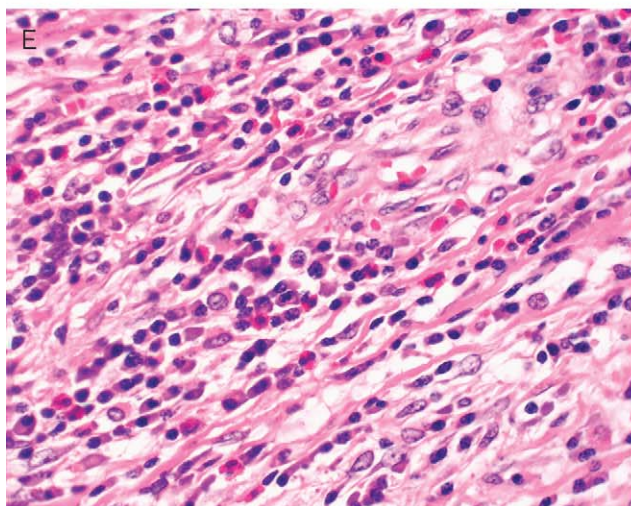
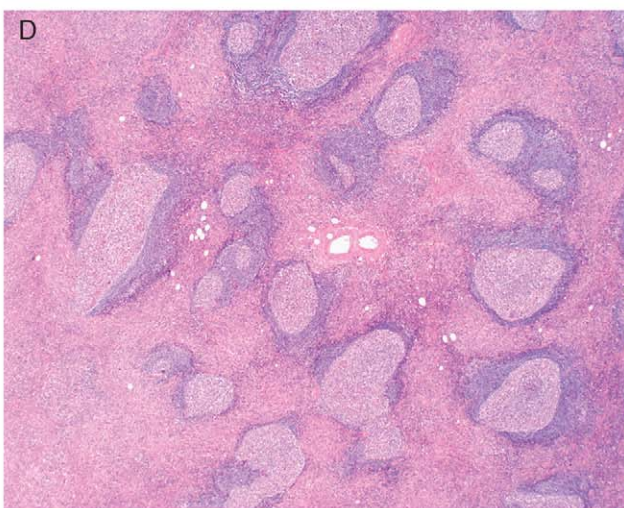
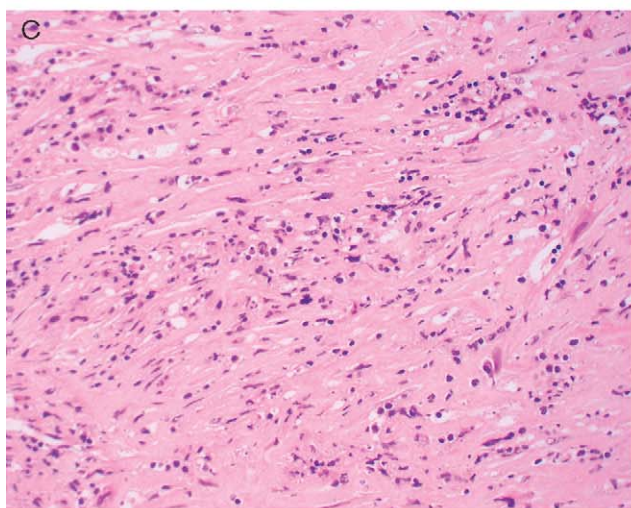
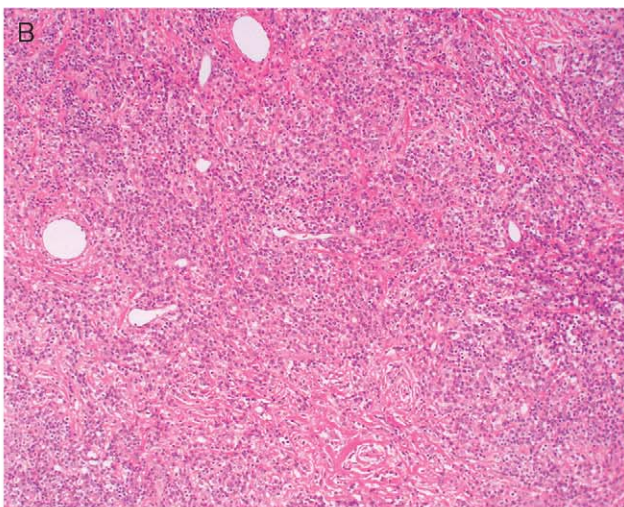
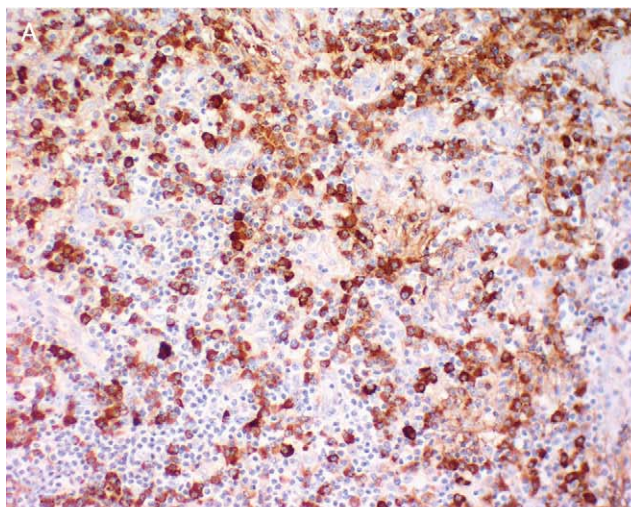


TABLE 2. Histological Features of IgG4-related and Non-IgG4-related Retroperitoneal Fibrosis

	IgG4-related (n = 10)	Non-IgG4-related (n = 7)	P
Inflammation (mild/moderate/severe)	1/5/4	4/2/1	0.061
Lymph follicles	5 (50%)	2 (29%)	0.391
Lymph follicles (surgical cases)*	5/6 (83%)	1/4 (25%)	0.801
Plasma cells (> 10/hpf)	10 (100%)	6 (86%)	0.232
Eosinophils (> 5/hpf)	5 (50%)	1 (14%)	0.141
Neutrophils (> 5/hpf)	0	0	Identical
Multinucleated giant cells	2 (20%)	2 (29%)	0.691
Russell bodies	5 (50%)	1 (14%)	0.141
Obliterative phlebitis	6 (60%)	1 (14%)	0.067
Obliterative phlebitis (surgical cases)*	6/6 (100%)	1/4 (25%)	0.009

*Six IgG4-related cases and 4 non-IgG4-related cases.
hpf indicates high-power field; IgG, immunoglobulin G.

TABLE 3. Clinical Characteristics of Patients With Retroperitoneal Fibrosis

Case	Age	Sex	Clinical Symptom*	Medical History	Extraretroperitoneal Sclerosing Lesions†	Serum IgG4 (mg/dL)
1	68	M	None	Bronchiectasis	Sialadenitis, dacryoadenitis	874
2	78	M	Edema in lower extremities	Bronchial asthma, duodenal ulcer		502
3	57	M	None	Bronchial asthma	Reticular lung lesion	2330
4	65	M	Backache	Tonsillitis	Autoimmune pancreatitis	491
5	65	M	Lower abdominal pain			173
6	67	M	None		Hypophysitis, thickening of falx cerebri	1270
7	52	M	Backache	Angina pectoris	Periaortitis in thoracic aorta, reticular lung lesion	392
8	77	M	Fever	Prostate cancer		526
9	58	M	Backache			235
10	78	M	None			154
11	70	F	Lumbar pain			10
12	69	F	Backache			35
13	45	F	Backache	Rheumatoid arthritis		53
14	70	F	Backache			12
15	30	F	Lower abdominal pain			NA
16	38	F	Edema in lower extremities			47
17	72	M	None			25

*Only symptoms related the retroperitoneal fibrosis.

†Suspected of having IgG4-related lesions; cases 1-10, IgG4-related; cases 11-17, non-IgG4-related.

F indicates female; IgG, immunoglobulin G; M, male; NA, not available.

None of the cases examined in this study involved malignant lesions around the retroperitoneum.

DISCUSSION

Clinically, cases of IgG4-related retroperitoneal fibrosis differed from non-IgG4-related cases in sex and serological findings. It is no wonder that assaying serum IgG4 concentrations is the most useful noninvasive examination for the diagnosis of IgG4-related disease.

Indeed, in this study, the patients with IgG4-related retroperitoneal fibrosis all had high-serum IgG4 levels. Interestingly, they were all adult males as well, consistent with the male predominance in other IgG4-related diseases such as autoimmune pancreatitis.¹¹ In contrast, most of the non-IgG4-related cases involved females, and younger patients were identified in this group. Such differences might be important for the discrimination between IgG4-related cases and non-IgG4-related cases

FIGURE 1. Histologic features of retroperitoneal fibrosis. A, Numerous immunoglobulin G4 (IgG4) positive plasma cells are identified in IgG4-related retroperitoneal fibrosis (IgG4 immunostaining: $\times 200$). B Diffuse lymphoplasmacytic infiltration is associated with irregular fibrosis in IgG4-related lesion [hematoxylin and eosin (H&E) staining: $\times 100$]. C Mild mononuclear cell infiltration and fibrosis is observed in non-IgG4-related retroperitoneal fibrosis. Inflammation is less severe compared with IgG4-related lesions (H&E staining: $\times 200$). D Sclerosing inflammation is associated with formation of a lot of lymph follicles in an IgG4-related case (H&E staining: $\times 20$). E A lot of eosinophilic infiltration is identified in IgG4-related retroperitoneal fibrosis (H&E staining: $\times 400$). F Obliterative phlebitis is observed in IgG4-related retroperitoneal fibrosis (Elastica van Gieson staining: $\times 200$).

TABLE 4. Serum IgG4 or IgG4 Concentrations and Antinuclear Antibodies in Patients With Retroperitoneal Fibrosis

	IgG4-related	Non-IgG4-related	P
IgG (mg/dL)			
Average (range)	2408 (1125-2560)	1940 (1250-2560)	0.515
> 1600	8/10 (80%)	5/6 (83%)	0.873
IgG4 (mg/dL)			
Average (range)	695 (154-2330)	30 (10-53)	0.001
> 135	10/10 (100%)	0/6 (0%)	< 0.001
IgG4/IgG ratio (%)	26.8 (9.6-60.8)	1.4 (1.0-2.4)	0.001
ANA (≥ 40 titer)	4/9 (44%)	5/7 (71%)	0.296

ANA indicates antinuclear antibodies; IgG, immunoglobulin G.

in the clinical setting. It might be worth examining serum IgG4 concentrations in cases of retroperitoneal fibrosis, especially if the patient is an adult male.

Before starting this study, we expected there to be differences in location and shape between IgG4-related and non-IgG4-related retroperitoneal fibrosis. Because an inflammatory abdominal aortic aneurysm is partly an IgG4-related disease, we speculated that retroperitoneal fibrosis around aorta or arteries might be related to IgG4.⁹ However, no significant difference could be identified in this study. A periaortic or periarterial distribution was most common in both IgG4-related and unrelated lesions. In this study, we retrospectively referred to radiologic reports. Therefore, more detailed examinations using magnetic resonance imaging or nuclear medicine might reveal radiologic differences, because there were some histologic differences between the 2 groups.

Pathologically, the IgG4-related and non-IgG4-related lesions differed in the number of IgG4-positive plasma cells and the ratio of IgG4/IgG-positive plasma cells. As with other IgG4-related diseases, eosinophilic

infiltration and obliterative phlebitis were also important in the diagnosis of IgG4-related retroperitoneal fibrosis. However, it should be noted that obliterative phlebitis was not common in needle biopsy cases, probably because of the small size of specimens. The diagnosis in IgG4-related cases might be based only on H&E-stained specimens, because IgG4-related lesions were more inflammatory than non-IgG4-related lesions. In non-IgG4-related lesions, fibrosis was more pronounced. However, 1 non-IgG4-related case showed highly inflammatory lesions resembling IgG4-related retroperitoneal fibrosis on H&E-stained specimens.

It is an interesting and important issue whether non-IgG4-related retroperitoneal fibrosis might be burned out IgG4-related lesions. Some of non-IgG4-related retroperitoneal fibrosis might be burned out IgG4-related lesions. However, there has been no report clearly describing histopathology of burned out IgG4-related disorders. Therefore, it seems difficult to conclude this issue at this point. It is difficult to consider all non-IgG4-related cases in this study as burned out lesions, because their ages and sex were different compared with patients with IgG4-related retroperitoneal fibrosis.

All the patients treated with steroids responded well. Some might argue that distinguishing between IgG4-related and non-IgG4-related lesions is not so important if steroid therapy is effective in both cases. However, it is becoming more important to correctly classify retroperitoneal fibrosis because the characteristics of IgG4-related disease will be clarified further. Recently, a relationship between IgG4-related lesions and malignant lymphoma was reported.^{2,13} In this study, no patient developed a malignant lymphoma, although there might be a relationship between IgG4-related retroperitoneal fibrosis and malignant lymphoma occurring in the retroperitoneum.

There are no standard diagnostic criteria for retroperitoneal fibrosis. Computed tomography and magnetic

TABLE 5. Treatments and Recurrences in Patients With Retroperitoneal Fibrosis

Case	Follow-up Period (months)	First Therapy	Recurrence	Therapy for Recurrence
1	25	Surgery	Once	Steroid
2	168	Steroid	Twice	Steroid
3	8	Steroid		
4	25	Steroid		
5	20	Steroid		
6	60	Steroid		
7	48	Steroid		
8	5	Steroid and ureteral stent		
9	60	Steroid		
10	20	Ureteral stent		
11	16	Steroid	Once	Ureteral stent
12	86	Steroid		
13	9	Steroid		
14	51	Steroid		
15	27	Steroid		
16	23	Ureteral stent		
17	15	Surgery		

Cases 1-10, IgG4-related; cases 11-17, non-IgG4-related.

resonance imaging are considered the modalities of choice for the diagnosis of retroperitoneal fibrosis.^{14,15} The finding of a retroperitoneal soft tissue mass with involvement of ureters, arteries, and inferior vena cava can suggest a diagnosis of retroperitoneal fibrosis. Serological examination of inflammatory or autoimmune markers also supports the diagnosis. Usually, histologic diagnosis is not necessary if locations/shapes and clinical history are not atypical.^{14,15} However, histologic examination might be becoming important not only for excluding neoplastic or infectious nature, because the discrimination between IgG4-related and non-IgG4-related can help better characterize the biology or pathogenesis of both the groups and better predict the possibility of other IgG4-related processes at other anatomic sites.

Most reports on IgG4-related retroperitoneal fibrosis have been case reports, although in 1 brief letter, Yamashita et al¹⁶ concluded that retroperitoneal fibrosis with sclerosing lesions at other sites was an IgG4-related disease. Those particular cases correspond to cases 1, 3, 4, 6, and 7 in this study. In their study, retroperitoneal fibrosis without other sclerosing lesions could not be clearly classified as IgG4-related or not. In contrast, in this study, we could classify the lesions into 2 groups on the basis of histologic features using immunostaining. The reason for this difference is unclear, but the size of specimens might have had an influence. They did not examine serum IgG4 concentrations, which might be useful for borderline cases.

In conclusion, this study revealed that retroperitoneal fibrosis could be classified into IgG4-related and non-IgG4-related cases. This distinction seems important to help better characterize the biology or pathogenesis of both groups and better predict the possibility of other IgG4-related processes at other anatomic sites, and the possibly increased risk of lymphoma.

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