Original Article

Clinical and Pathological Characteristics of IgG4-Related Periaortitis/Periarteritis and Retroperitoneal Fibrosis Diagnosed Based on Experts' Diagnosis

Ichiro Mizushima, MD, PhD,[1] Satomi Kasashima, MD, PhD,[2] Yasunari Fujinaga, MD, PhD,[3] Kenji Notohara, MD, PhD,[4] Takako Saeki, MD, PhD,[5] Yoh Zen, MD, PhD,[6] Dai Inoue, MD, PhD,[7] Motohisa Yamamoto, MD, PhD,[8] Fuminari Kasashima, MD, PhD,[9] Yasushi Matsumoto, MD, PhD,[9] Eisuke Amiya, MD, PhD,[10] Yasuharu Sato, MD,[11] Kazunori Yamada, MD, PhD,[1] Yukako Domoto, MD, PhD,[12] Shigeyuki Kawa, MD, PhD,[13] Mitsuhiro Kawano, MD, PhD,[1] and Nobukazu Ishizaka, MD, PhD[14]

IgG4-related disease is a systemic disease, characterized by elevation of serum IgG4 and, histopathologically, massive infiltration of IgG4+ lymphocyte and plasma cell infiltration, storiform fibrosis, causing enlargement, nodules or thickening. It may affect various organs simultaneously or metachronously. Here we analyzed the clinical and pathological characteristics of 99 patients diagnosed with IgG4-related periaortitis/periarteritis and retroperitoneal fibrosis. Of 99 patients (women/men, 15/84; mean age 67.3±9.5 years), 33 were diagnosed based on the histopathological findings of perivascular/retroperitoneal lesions, 50 were diagnosed based on the characteristic imaging findings of perivascular/retroperitoneal lesions and the presence of definitive IgG4-related disease in other organ(s), and the remaining 16 patients were diagnosed by experts based on the characteristic imaging findings of perivascular/retroperitoneal legions, serological findings, response to glucocorticoid treatment, and/or the presence of suspected IgG4-related disease in other organ(s). According to the new organ-specific criteria proposed by experts, 73 (73.7%) diagnoses were categorized to be definitive, and 6 (6.1%) and 17 (17.2%) diagnoses were categorized to be probable and possible, respectively. Further analyses are needed to clarify the optimal diagnostic and therapeutic strategy of IgG4-related periaortitis/periarteritis and retroperitoneal fibrosis. (This is a translation of J Jpn Coll Angiol 2018; 58: 117–129.)

Introduction

IgG4-related disease (IgG4-RD) is an inflammatory sclerosing disease of an unknown etiology, which was first

[1] *Division of Rheumatology, Department of Cardiovascular and Internal Medicine, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan*
[2] *Department of Clinical Laboratory Science, Kanazawa University, Kanazawa, Ishikawa, Japan*
[3] *Department of Radiology, Shinshu University School of Medicine, Matsumoto, Nagano, Japan*
[4] *Department of Anatomic Pathology, Kurashiki Central Hospital, Kurashiki, Okayama, Japan*
[5] *Department of Internal Medicine, Nagaoka Red Cross Hospital, Niigata, Niigata, Japan*
[6] *Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan*
[7] *Department of Radiology, Kanazawa University Graduate School of Medicine, Kanazawa, Ishikawa, Japan*
[8] *Department of Rheumatology and Clinical Immunology, Sapporo Medical University, Sapporo, Hokkaido, Japan*
[9] *Department of Cardiovascular Surgery, National Hospital Organization, Kanazawa Medical Center, Kanazawa, Ishikawa, Japan*
[10] *Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*
[11] *Faculty of Health Sciences, Okayama University Medical School, Okayama, Okayama, Japan*
[12] *Department of Pathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*
[13] *Department of Internal Medicine, Matsumoto Dental University, Matsumoto, Nagano, Japan*
[14] *Department of Cardiology, Osaka Medical College, Takatsuki, Osaka, Japan*

reported in 2001 by Hamano et al. who noted elevated serum IgG4 levels in patients with autoimmune pancreatitis.[1] Since then, reports have revealed the serologic characteristics of and distinguishing lesions with common pathological features in the organs throughout the entire body.[2] IgG4-RD is typically characterized by localized or diffuse swelling in, the hypertrophy of, and the presence of nodular lesions in the affected organ, although similar lesions have been found surrounding arteries, the renal pelvis, and the ureter, as well as in the soft tissue in the pelvis.[3,4] As a result, these lesions in IgG4-RD are now referred to as IgG4-related periarteritis/retroperitoneal fibrosis.

Previous reports that analyzed many patients with IgG4-RD revealed that the incidence of periarterial/retroperitoneal lesions in such patients was relatively high[5–7]; however, the clinical features of IgG4-related periarteritis/retroperitoneal fibrosis have not yet been fully clarified. This is attributed to the fact that for this disease, although some organs have specific diagnostic criteria, a comprehensive criteria requiring tissue sampling is required for definite diagnosis.[8] Moreover, performing the biopsy of periarterial/retroperitoneal lesions is difficult as it is highly invasive and accompanies a risk of complications, making it difficult to accumulate and analyze cases that correspond to any diagnostic criteria. Conversely, reports on IgG4-related periarteritis diagnosed on the basis of serologic findings, the presence of extravascular lesions, and the imaging results of periarterial/retroperitoneal lesions indicate that this disease presents distinguishing clinical characteristics shared with IgG4-RD, such as elderly male-predominance, the complications of allergic disorders, elevated serum IgG4 levels, elevated serum IgE levels, and eosinophilia.[9]

For the pancreas and bile duct, for which sampling by biopsy cannot be easily achieved in the same way as the periarterial/retroperitoneal lesions, organ-specific diagnostic criteria have been established.[10,11] These include serological, imaging, and pathological findings regarding the target organ as well as the identification of lesions in other organs, all of which are combined to establish one of the following diagnostic grades: definite, probable, or possible. In clinical practice, if several typical pathological findings are observed, "definite" grade is determined based on the pathological findings of the target organ alone. Conversely, if the other diagnostic items are adequately satisfied, the same diagnosis can be established even without obtaining any pathological findings regarding the target organ.[10,11]

To clarify the clinical features of IgG4-related periarteritis/retroperitonitis, we accumulated and analyzed medical data on 99 patients, including those diagnosed based on the pathological findings and on other organ lesions and imaging findings by specialists with abundant experience in treating IgG4-RD at 10 institutions throughout Japan. After considering the present state of diagnosis at these specialist institutions, we propose an organ-specific diagnostic criterion, which is considered appropriate for periarterial/retroperitoneal lesions.

Subjects and Methods

Subjects

The study population included 99 patients with IgG4-related periarteritis/retroperitoneal fibrosis who were diagnosed from January 1, 1995 to November 30, 2015 at the following hospitals in Japan: the Kanazawa Medical Center, Kanazawa University Hospital, Sapporo Medical University Hospital, Kobe University Hospital, Shinshu University Hospital, Nagaoka Red Cross Hospital, Okayama University Hospital, Kurashiki Central Hospital, The University of Tokyo Hospital, and Osaka Medical College Hospital. All subjects were diagnosed with this disease according to the final decisions of experts based on the presence of periarterial/retroperitoneal imaging findings consistent with those of this disease, the histological findings of periarterial/retroperitoneal lesions from whom tissues were obtained, clinical progress consistent with that of IgG4-RD (such as steroid responsive), and the exclusion of other diseases. The diagnosis of lesions other than those associated with periarterial/retroperitoneal ones was achieved based on the exclusion of other conditions as well as pathological, imaging, and/or histological findings. Including organ lesions other than periarterial/retroperitoneal ones, we examined in particular detail whether the comprehensive diagnostic criterion or organ-specific diagnostic criterion was satisfied, which served as a ground for diagnosing IgG4-related periarteritis/retroperitoneal fibrosis. Among patients included in the present study, we also included those who underwent resection of periarterial/retroperitoneal lesions before the disease concept of IgG4-related periarteritis/retroperitoneal fibrosis was established. These cases were diagnosed with the disease upon subsequent re-evaluation of the resected specimens, including IgG4 immunostaining, and the consideration of image findings and clinical progress.

Of the 99 patients examined in the present study, IgG4-RD diagnosis, according to the comprehensive diagnostic criteria, was definite in 61 patients, probable in 9, possible in 28, and denied in 1. Among the 28 patients with possible IgG4-RD, 7 satisfied the revised diagnostic criteria for type 1 autoimmune pancreatitis[10] and 2 satisfied the diagnostic criteria for IgG4-related sialadenitis/dacryoadenitis.[8] The remaining 19 patients were diagnosed with IgG4-RD on the basis of clinical features such as elevated serum IgG4 levels consistent with those of IgG4-RD, good

response to steroids, and the exclusion of other diseases. In the one patient in whom IgG4-RD was denied, based on the comprehensive diagnostic criteria, insufficient IgG4-positive plasma cell infiltration was observed in the retroperitoneal tissue obtained via biopsy. However, histological findings including storiform fibrosis and obliterating phlebitis were identified, and a subsequent IgG4-RD diagnosis was made based on clinical features consistent with those of IgG4-RD, including good responsiveness to steroids, and the exclusion of other diseases.

Sampling of periarterial/retroperitoneal lesions was performed in 33 patients, with samples obtained from 35 lesions. These specimens were collected from 17 lesions by surgical resection of the affected artery in 16 patients, from 8 lesions by surgical thoracolaparotomy of periarterial/retroperitoneal lesions in 8 patients, from 6 lesions by needle biopsy of the periarterial, retroperitoneal, or renal pelvic and ureteral lesions in 6 patients, and from 4 lesions by autopsy in 3 patients.

We retrospectively analyzed the clinical characteristics, including subjective symptoms, laboratory data, image findings, and histopathological findings, of 99 patients at the time of diagnosing IgG4-related periarteritis/retroperitoneal fibrosis.

Approval for the present study was obtained from the ethical review boards of the Kanazawa Medical Center, Kanazawa University Hospital, Sapporo Medical University Hospital, Kobe University Hospital, Shinshu University Hospital, Nagaoka Red Cross Hospital, Okayama University, Kurashiki Central Hospital, and The University of Tokyo Hospital, and Osaka Medical College. Informed consent for the use of all data and specimens was obtained from each patient. The present study was conducted in accordance with the Declaration of Helsinki.

Image evaluation

All patients had undergone whole-body computed tomography (CT) at the time of diagnosis, and all the resulting image data was interpreted by a radiologist with extensive experience in IgG4-RD at each institution. Based on these CT images, the site affected by periarterial/retroperitoneal lesions and extra-periarterial/retroperitoneal lesions were recorded. A periarterial diagnosis was determined when a soft tissue shadow was seen surrounding the aorta and arteries. Retroperitoneal fibrosis was diagnosed when a soft tissue shadow was seen on the renal pelvis and ureter or when placoid tumorous lesions were observed in the retroperitoneal region. Adjacent non-lesion sites were compared, and if luminal dilatation was observed in blood vessels at the affected site, this was defined as "with liminal dilatation of the affected site." In contrast, if a reduction in the luminal diameter was observed in the blood vessels of the affected site, this was defined as "with luminal reduc-

tion of the affected site." We also evaluated the presence or absence of hydronephrosis caused by periarterial/retroperitoneal lesions of the affected site.

Histological evaluation

In 33 patients (33.3%), we performed tissue sampling of the periarterial/retroperitoneal lesions. Using 35 specimens of these lesions that were formalin-fixed and embedded in paraffin after sampling, we evaluated the presence or absence of optical microscopy findings, which are commonly considered to be observed in IgG4-RD lesions. These included lymphocyte and plasma cell infiltrations, storiform fibrosis, and obliterating phlebitis[12] as well as the previously reported characteristics of periarterial/retroperitoneal lesions such as lymphoid follicles, eosinophilic infiltration, and perineural inflammatory cell infiltration.[3] In addition, neutrophil-predominant cell infiltration and epithelioid granuloma formation,[12] which are considered difficult to observe in IgG4-RD lesion tissues, were also evaluated. To evaluate IgG4-positive cell infiltration, we conducted immunostaining using anti-human IgG4 antibodies (clone HP6025; Invitrogen, Carlsbad, CA, USA) and using anti-human IgG (clone RP023; Diagnostic BioSystems, Pleasanton, CA, USA) or anti-human CD138 antibodies (clone MI15; DakoCytomation, Glostrup, Denmark) to evaluate IgG-positive cell infiltration. The number of positive cells per high power field (HPF) was measured, and the mean value from three different HPFs was used for the specimen. These histopathological evaluations and diagnoses were performed by a pathologist who was well-experienced in diagnosing IgG4-RD at each of our participating institutions.

Comparison of clinical features between patients with different diagnostic approaches

The 99 patients included in our study, who were diagnosed as mentioned above, were classified into three groups according to the different diagnostic approaches used. Group A included patients (n=33) who were diagnosed based on the histological evaluation of periarterial/retroperiarterial lesions. Group B included patients (n=50) with definite diagnoses of other organs according to existing diagnostic criteria, who were diagnosed based on the imaging findings of periarterial/retroperitoneal lesions and did not correspond to those of group A. Group C included patients (n=16) who were diagnosed considering serologic findings, the imaging results of periarterial/retroperitoneal lesions, the findings suggestive of the presence of lesions in other organs, and the general clinical course such as steroid responsiveness in patients who did not correspond to those of groups A and B. To examine the difference in the clinical features of patients diagnosed by different diagnostic approaches, we compared clinical

characteristics, such as subjective observations, laboratory data, and image findings across the three groups.

Statistical analysis

Statistical analyses were performed using SPSS version 22. Data was presented as means ± standard deviations or medians/interquartile ranges. A significant difference in mean values between groups was determined using the Mann–Whitney U test, the Kruskal–Wallis test, or analysis of variance. A significant difference in incidence was determined using the Fisher's exact test and Chi-square test. A p value of <0.05 was considered statistically significant.

Suggested diagnostic criteria

With reference to the existing diagnostic criteria,[10,11] data obtained from analyzing the characteristic findings of 99 patients was collated, and a tentative plan was proposed for an organ-specific diagnostic criterion for IgG4-related periarteritis/retroperitoneal fibrosis by the Ministry of Health, Labour, and Welfare study group. The validity of the proposed diagnostic criterion was discussed and examined in a joint working group consisting of members from the Japanese Circulation Society and the Ministry of Health, Labour and Welfare study group. After reaching a consensus, a diagnostic criterion for IgG4-related periarteritis/retroperitoneal fibrosis is presented here.

Results

Clinical features of patients at diagnosis

The characteristics of 99 patients at the time of diagnosis are presented in **Table 1**. There were 84 males (84.8%) and 15 females (15.1%), with a combined mean age of 67.3 ± 9.5 (39–85) years. Two patients were receiving treatment of a small amount of prednisolone for IgG4-related other organ lesions. No other patients were receiving immunosuppressive therapy, including steroids, at the time of diagnosis. Some type of clinical symptoms were observed in 42 patients, with pain (abdominal, lateral region, back, and chest) in 23, fever in 8, edema (of the lower limbs in all patients) in 4, general fatigue in 3, and weight loss in 1. Other symptoms that were not early associated with periarterial/retroperitoneal lesions included mouth dryness in 5 patients, respiratory distress in 3, visual disturbance in 2, and coughing and diarrhea in 1. Subjective symptoms were not observed either in 20 of the 26 patients presenting the luminal dilatation of the affected vessel at the time of diagnosis or in 14 of the

Table 1 Baseline characteristics, laboratory examinations, and lesion localization among overall study patients

Variables	Overall (n=99)	Variables	Overall (n=99)
Patient characteristics		**Periarterial and retroperitoneal lesions**	
Male gender, n (%)	84 (84.8)	Any perivascular lesions, n (%)	96 (97.0)
Age, years	67.3±9.5	Abdominal aorta, n (%)	67 (67.7)
Smoking history, n (%) (n=82)	53 (64.6)	Thoracic aorta, n (%)	8 (8.1)
Presenting symptoms		Iliac artery, n (%)	50 (50.5)
Pain, n (%)	23 (23.2)	Coronary artery, n (%)	9 (9.1)
Fever, n (%)	8 (8.1)	Mesenteric artery, n (%)	8 (8.1)
Edema, n (%) (n=97)	4 (4.1)	Others, n (%)	10 (10.1)
General malaise, n (%)	3 (3.0)	Retroperitoneal fibrosis, n (%)	24 (24.2)
Shortness of breath, n (%)	3 (3.0)	**Other organ involvement**	
Laboratory examinations		Any coexisting lesions, n (%)	72 (72.7)
WBC, cells/μL (n=88)	6,400 (4,725–7,553)	Lacrimal gland/eye, n (%)	20 (20.2)
IgG, mg/dL (n=96)	2,183 (1,763–2,962)	Salivary gland, n (%)	36 (36.4)
IgG4, mg/dL (n=97)	551 (207–1,315)	Pituitary gland, n (%)	5 (5.1)
IgG4 ≥135 mg/dL (n=97)	90 (92.8)	Pericardium, n (%)	7 (7.1)
IgG4/IgG ratio (n=96)	28.8±17.2	Lung, n (%)	17 (17.2)
IgG4/IgG ratio ≥8% (n=96)	88 (91.7)	Pleura, n (%)	2 (2.0)
IgE, U/mL (n=83)	250 (95–565)	Bile duct, n (%)	4 (4.0)
Positive antinuclear antibody (n=88)	13 (14.8)	Pancreas, n (%)	28 (28.3)
C-reactive protein, mg/dL (n=89)	0.30 (0.09–0.96)	Kidney, n (%)	16 (16.2)
Soluble IL-2 receptor, U/mL (n=58)	894 (657–1,178)	Renal hilum, n (%)	13 (13.1)
Positive rheumatoid factor (n=66)	12 (18.2)	Prostate, n (%)	6 (6.1)
		Skin, n (%)	1 (1.0)
Associated conditions		Nerve, n (%)	1 (1.0)
Arterial dilatation, n (%)	26 (26.3)	Lymph nodes, n (%)	33 (33.3)
Hydronephrosis, n (%)	21 (21.2)	Others, n (%)	3 (3.0)

21 patients with hydronephrosis. Some types of allergic symptoms, such as bronchial asthma, and allergic rhinitis, were observed in 37 patients. At the time of diagnosis, 27 patients were smokers and 26 others were non-smokers, i.e., they did have a history of smoking.

Blood immunological finding

At the time of diagnosis, 92.8% of our patients (90/97) had elevated serum IgG4 levels exceeding 135 (median, 551; interquartile range, 207–1,315) mg/dL. Similarly, 81.3% of patients (78/96) had elevated serum IgG levels at diagnosis (median, 2,183 mg/dL; interquartile range, 1,763–2,962 mg/dL; reference value, 870–1,700 mg/dL). In addition, for 50.6% of patients (42/83), serum IgE levels were elevated at the time of diagnosis (median, 283 IU/mL; interquartile range, 114–575 IU/mL; reference value, <250 IU/mL). Hypocomplementemia was observed in 24.4% of patients (19/78). Positive test results were obtained for antinuclear antibodies and rheumatoid factors in 14.8% (13/88) and 18.2% (12/66) of patients, respectively. Elevated serum sIL-2R levels were observed in 87.9% of patients (51/58; median, 894 U/mL; interquartile range, 657–1,178 U/mL; reference value, 122–496 U/mL). We also found that 23.6% of patients (21/89) had serum CRP levels >1.0 mg/dL, while 48.3% (43/89) had serum CRP levels >0.3 mg/dL (median, 0.30 mg/dL; interquartile range, 0.09–0.96 mg/dL; reference value, 0.30 mg/dL) (**Table 1**).

Image findings

Of the 99 patients, 96 had hypertrophic, tumorous lesions surrounding the aorta and arteries as observed on CT. In the remaining three patients, no periarterial lesions were observed and only retroperitoneal fibrosis was observed. The affected vessel was the thoracic aorta in 8 patients, the abdominal aorta in 67, the iliac artery in 50, the mesenteric artery in 8, the coronary artery in 9, and the splenic artery in 2. We found only one patient in each case where the affected vessel was the celiac, hepatic, short gastric, colic, femoral, internal carotid, vertebral, and the meningeal arteries (**Fig. 1**). Two patients presented lesions of the portal vein. At the time of diagnosis, luminal dilatation of the affected vessel was observed in 26 patients (26.3%). Conversely, luminal reduction was observed in five patients (5.0%), among whom four had coronary artery stenosis and one had iliac artery stenosis.

With regard to retroperitoneal fibrosis, 24 patients (24.2%) presented with lesions of the retroperitoneum, those surrounding the ureter, and those of the renal pelvis. Hydronephrosis was observed in 21 patients and was bilateral in 6, left-sided only in 10, and right-sided only in 5.

Furthermore, 72 patients presented periarterial/retroperitoneal lesions primarily comprising the lesions of the salivary glands, lacrimal glands, pancreas, kidneys, and lungs (**Table 1**).

Histological findings

The 35 collected periarterial/retroperitoneal lesion specimens included 20 specimens from the aorta (abdominal aorta: 17, thoracic aorta: 2, and lesions extending the thoracoabdominal aorta: 1) as well as 10 specimens from the aorta branching vessel (coronary artery: 5, iliac artery: 4, and mesenteric artery: 1). We also found retroperitoneal lesions not surrounding arteries in five specimens. In all these specimens, lymphocyte and plasma cell infiltrations were observed, and in the periarterial lesions, infiltration was primarily found in the tunica adventitia of the arterial wall. Inflammatory cell infiltration in the tunica media was observed in two specimens, one of which showed a high degree of infiltration. Storiform fibrosis was found in 25 specimens (71.4%) and obliterating phlebitis in 25 (71.4%), with both observed in 22 (62.9%) and one or the other observed in 28 (80.0%; **Fig. 2**). Concerning the other optical microscopy findings, lymphoid follicles were observed in 17 specimens (48.6%), eosinophilic infiltration (>10/HPF) in 14 (40.0%), and perineural inflammatory cell infiltration in 13 (37.1%). Neutrophil infiltration (>10/HPF) was observed in only one specimen (2.9%), microgranuloma formation in one (2.9%), and multinucleated giant cells in two (5.7%).

The mean number of infiltrative IgG4-positive plasma cells was 90.0/HPF (approximately 12–200/HPF) and ex-

Fig. 1 Contrast-enhanced computed tomography (CT) findings of IgG4-related periaortic/periarterial lesions.
Thickened periaortic/periarterial lesions of infrarenal abdominal aorta (**A**), bilateral iliac arteries (**B**), and coronary artery (**C**) are observed.

ceeded 10/HPF in all specimens, two of which had IgG4-positive plasma cells <30/HPF and were both obtained by biopsy. The IgG4/IgG-positive cell ratio exceeded 40% in 32 specimens (91.4%). One samples with this ratio of <40% was obtained by surgery and two were obtained by biopsy (**Table 2, Figs. 2** and **3**).
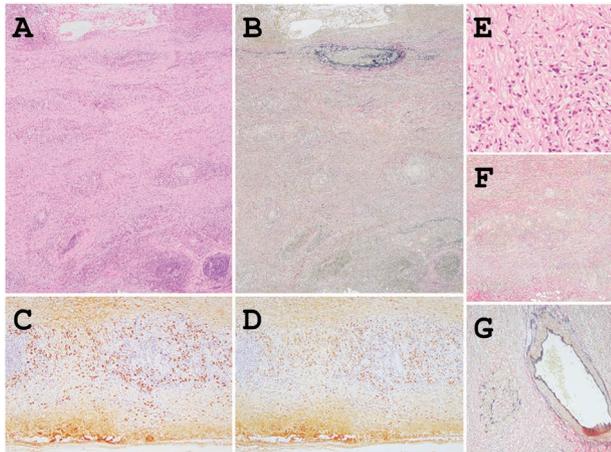
Fig. 2 Histopathological findings in surgical specimens of IgG4-related periarterial/retroperitoneal lesions.

(**A**, **B**, **C**, **D**) Samples from one patient. An 18-mm sample of tissue was obtained surgically. Serum IgG4 concentrations were 2,330 mg/dL in this patient. Hematoxylin-eosin (HE) staining (**A**), Elastica van Gieson (EVG) staining (**B**) and immunostaining for IgG (**C**) and IgG4 (**D**) are shown. The lesion consists of a dense inflammatory infiltrate, fibrosis (**A**), and obliterative phlebitis (**B**). In addition, many IgG-positive and IgG4-positive plasma cells are noted with the IgG4/IgG ration being >70%. (**E**, **F**, **G**) Samples from another patient. The sample of 10 mm in size was obtained surgically. Serum IgG4 concentrations were 491 mg/dL in this patient. HE staining (**E**) and EVG staining (**F**, **G**) are shown. Lymphoplasmacytic infiltration into the background of storiform fibrosis is observed (**E**, **F**). Obliterative phlebitis is also noted (**G**).

Non-periarterial/retroperitoneal lesions of other organs

One clinical characteristic of IgG4-RD is that lesions can appear in a simultaneous or heterochronic manner in organs throughout the entire body. In 72 of 99 patients (72.7%), non-periarterial/retroperitoneal lesions were observed using pathological and imaging methods (mean, 1.9 [0–8] organs). Organ lesions with a high incidence included salivary gland lesions in 36 patients, lacrimal gland/other eye socket lesions in 20, pancreatic lesions in 28, renal lesions in 29, pulmonary lesions in 17, and lymph node lesions in 33 (**Table 1**). Of all subjects, non-periarterial/retroperitoneal lesions were histologically evaluated in 52, of which 46 satisfied the conditions of pathological findings specified in the comprehensive diagnostic criteria.[8)] In 56 patients (56.6%), concurrent other organ lesions were diagnosed as definite based on the existing comprehensive diagnostic criteria or based on the organ-specific diagnostic criteria.

Differences in clinical features between patient groups with different diagnostic approaches

Across the A, B, and C groups, we noted a difference in the incidence of pain, serum IgG4 levels, serum IgG4/IgG ratios, serum CRP levels, the frequency of iliac artery lesions, the incidence of luminal dilatation and aneurysmal formation of the affected vessel, and the incidence of concurrent lesions in other organs. Many of these differences involved groups A and B, where group B had significantly higher serum IgG4 levels, a greater number of other organs affected with lesions, a lower incidence of luminal dilatation of the affected vessel, and lower serum CRP levels (**Tables 3** and **4**).

Diagnostic criteria for IgG4-related periarteritis/retroperitoneal fibrosis

With reference to the diagnostic criteria for type 1 autoimmune pancreatitis[10)] and for IgG4-related sclerosing
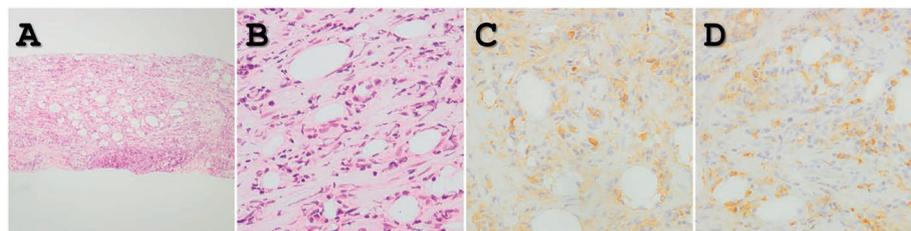
Fig. 3 Histopathological findings in biopsy samples of IgG4-related periarterial/retroperitoneal lesions. (**A**, **B**, **C**, **D**) Needle-biopsy samples from one patient. Serum IgG4 concentrations were 392 mg/dL in this patient. Hematoxylin-eosin staining (**A**, **B**) and immunostaining for IgG (**C**) and IgG4 (**D**) are shown. Retroperitoneal adipose tissue is involved in the fibroinflammatory process (**A**). Many lymphocytes and plasma cells are observed (**B**). Both IgG- and IgG4-positive plasma cells are present on immunostaining (**C**, **D**).

Table 2 Histopathological findings of samples from group A patients

	Autopsy (n=4)	Biopsy (n=14)	Surgery (n=17)	P value
IgG4-positive cell infiltration				
IgG4 ≥10/HPF (n=3*/14/16*)	3 (100)	14 (100)	16 (100)	>0.99
IgG4 ≥30/HPF (n=3*/14/16*)	3 (100)	12 (85.7)	16 (100)	0.219
IgG4/IgG >40%	4 (100)	12 (85.7)	16 (94.1)	0.573
Other characteristics				
Storiform fibrosis, n (%)	3 (75.0)	9 (64.3)	13 (76.5)	0.746
Obliterative phlebitis, n (%)	3 (75.0)	8 (57.1)	14 (82.4)	0.298

* Data of an IgG4-positive cell number in one sample was not available.

Table 3 Baseline characteristics and laboratory examinations by subgroups

Variables	Group A (n=33)	Group B (n=50)	Group C (n=16)	P value
Patient characteristics				
Male gender, n (%)	28 (84.8)	44 (88.0)	12 (75.0)	0.451
Age, years	69.2±8.2	66.3±9.8	66.7±11.1	0.379
Smoking history, n (%) (n=18/49/15)	12 (66.7)	32 (65.3)	9 (60.0)	0.913
Presenting symptoms				
Pain, n (%)	12[†] (36.4)	5 (10.0)	6[♀] (37.5)	0.007
Fever, n (%)	5 (15.2)	1 (2.0)	2 (12.5)	0.077
Edema, n (%) (n=32/50/15)	2 (6.3)	1 (2.0)	1 (6.7)	0.554
General malaise, n (%)	2 (6.1)	1 (2.0)	0 (0.0)	0.425
Shortness of breath, n (%)	0 (0.0)	2 (4.0)	1 (6.3)	0.416
Laboratory examinations				
WBC, cells/μL (n=23/50/15)	6,400 (4,500–9,100)	6,300 (4,800–7,250)	6,830 (4,700–7,870)	0.532
IgG, mg/dL (n=32/50/14)	1,979 (1,578–2,545)	2,336 (1,892–3,268)	1,980 (1,677–2,587)	0.064
IgG4, mg/dL (n=32/50/15)	424[†] (153–694)	877 (403–1,440)	280 (196–648)	0.005
IgG4 ≥135 mg/dL (n=32/50/15)	27 (84.4)	49 (98.0)	14 (93.3)	0.067
IgG4/IgG ratio (n=32/50/14)	21.4[†] (9.3–32.2)	32.6 (20.5–49.3)	14.2[♀] (11.9–30.2)	0.006
IgG4/IgG ratio ≥8% (n=32/50/14)	25[†] (78.1)	49 (98.0)	14 (100)	0.003
IgE, U/mL (n=22/47/14)	513 (133–930)	227 (51–452)	322 (62–507)	0.057
Positive antinuclear antibody (n=27/48/13)	2 (7.4)	8 (16.7)	3 (23.1)	0.366
C-reactive protein, mg/dL (n=23/50/16)	0.59[†] (0.16–3.10)	0.20 (0.09–0.66)	0.36 (0.12–1.87)	0.027
Soluble IL-2 receptor, U/mL (n=7/39/12)	662 (506–1,007)	903 (710–1,280)	944 (670–1,081)	0.365
Positive rheumatoid factor (n=6/46/14)	3 (50.0)	7 (15.2)	2 (14.3)	0.106

[†] p<0.017 in Group A vs Group B by Mann–Whitney's U test or Chi square test
[♀] p<0.017 in Group B vs Group C by Mann–Whitney's U test or Chi square test

cholangitis,[11)] we included four new diagnostic items: [1] the imaging findings of periarterial/retroperitoneal lesions, [2] serological results, [3] the pathological findings of periarterial/retroperitoneal lesions, and [4] the presence of lesions in other organs. Based on our analysis of 99 patients in this study, we determined the content of each diagnostic item and created new diagnostic criteria for IgG4-related periarteritis/retroperitoneal fibrosis (**Table 5**).

Regarding items derived from imaging efforts, those required for the diagnosis of periarterial lesions included "hypertrophic lesions of the arterial wall (tunica adventitia) (or circumferential) or soft density mass in the surrounding tissue." In addition, a reduction in luminal size, luminal dilatation, differential diseases/conditions, and the common sites of onset were also noted. With regard to

the renal pelvis and ureter, findings required for a diagnosis included "hypertrophic lesion extending from the renal pelvis to the ureter," and the common sites of onset were additionally noted. For other retroperitoneal lesions, the image findings required for diagnosis included "placoid soft tissue shadow of the retroperitoneum in the pelvis." In the present study, one of these characteristics was confirmed in all patients.

Of the serological findings, we considered the serum IgG4 level of >135 mg/dL, which is the common reference value in IgG4-RD. In the present study, approximately 90% of our patients exhibited elevated serum IgG4 levels.

From the pathology findings, we included four items from the existing diagnostic criteria[10,11]: [1] marked lymphocyte and plasma cell infiltrations with fibrosis, [2]

Table 4 Periarterial/retroperitoneal lesions and other organ involvement by subgroups

	Group A (n=33)	Group B (n=50)	Group C (n=16)	P value
Periarterial and retroperitoneal lesions				
Any perivascular lesions, n (%)	31 (93.9)	50 (100)	15 (93.8)	0.206
Abdominal aorta, n (%)	20 (60.6)	36 (72.0)	11 (68.8)	0.552
Thoracic aorta, n (%)	3 (9.1)	4 (8.0)	1 (6.3)	0.943
Iliac artery, n (%)	10[†,§] (30.3)	29 (58.0)	11 (68.8)	0.013
Coronary artery, n (%)	6 (18.2)	2 (4.0)	1 (6.3)	0.081
Mesenteric artery, n (%)	3 (9.1)	5 (10.0)	0 (0.0)	0.427
Others, n (%)	2 (6.1)	5 (10.0)	3 (18.8)	0.384
Retroperitoneal fibrosis, n (%)	8 (24.2)	12 (24.0)	4 (25.0)	0.997
Associated conditions				
Arterial dilatation n (%)	14[†] (42.4)	6 (12.0)	6 (37.5)	0.005
Hydronephrosis, n (%)	7 (21.2)	9 (18.0)	5 (31.3)	0.529
Other organ involvement				
Any coexisting lesions, n (%)	12[†] (36.4)	50 (100.0)	10[�] (62.5)	<0.001
Lacrimal gland/eye, n (%)	1[†] (3.0)	18 (36.0)	1 (6.3)	<0.001
Salivary gland, n (%)	4[†] (12.1)	31 (62.0)	1[ᵒ] (6.3)	<0.001
Pituitary gland, n (%)	2 (6.1)	3 (6.0)	0 (0.0)	0.602
Pericardium, n (%)	1 (3.0)	4 (8.0)	2 (12.5)	0.449
Lung, n (%)	3 (9.1)	11 (22.0)	3 (18.8)	0.307
Pleura, n (%)	1 (3.0)	0 (0.0)	1 (6.3)	0.266
Bile duct, n (%)	0 (0.0)	4 (8.0)	0 (0.0)	0.130
Pancreas, n (%)	3[†] (9.1)	25 (50.0)	0[ᵒ] (0.0)	<0.001
Kidney, n (%)	1[†] (3.0)	14 (28.0)	1 (6.3)	0.005
Renal hilum, n (%)	2 (6.1)	7 (14.0)	4 (25.0)	0.178
Prostate, n (%)	1 (3.0)	5 (10.0)	0 (0.0)	0.231
Skin, n (%)	1 (3.0)	0 (0.0)	0 (0.0)	0.364
Nerve, n (%)	1 (3.0)	0 (0.0)	0 (0.0)	0.364
Lymph nodes, n (%)	2[†,§] (6.1)	24 (48.0)	7 (43.8)	<0.001
Others, n (%)	1 (3.0)	2 (4.0)	0 (0.0)	0.719
Number of coexistent lesions [A]	0[†] (0–1)	3 (2–4)	1[ᵒ] (0–3)	<0.001
Number of coexistent lesions [B]	0[†] (0–1)	2 (1–3)	0[ᵒ] (0–2)	<0.001

"Any coexisting lesions" included lymph node lesions. For the calculation of "number of other organ involvement", the mean±standard deviation of the number of the sum of those organs/tissues listed in "Other organ involvement" in the table was calculated including (A) or not including (B) lymph node lesion.

[†] p<0.017 in Group A vs Group B by Mann–Whitney's U test or Chi square test
[§] p<0.017 in Group A vs Group C by Mann–Whitney's U test or Chi square test
[ᵒ] p<0.017 in Group B vs Group C by Mann–Whitney's U test or Chi square test

marked IgG4-positive plasma cell infiltration, [3] storiform fibrosis, and [4] obliterating phlebitis. With regard to item [2], we integrated the existing diagnostic criteria for IgG4-RD[12] with the analysis results of the present study, and adopted "the number of IgG4-positive plasma cells > 30/HPF and with an IgG4/IgG-positive cell ratio > 40% as well as a diffuse distribution of positive cells" as a criteria for resected specimens such as those obtained by surgery and autopsy. We also adopted "the number of IgG4-positive plasma cells > 10/HPF and with an IgG4/IgG-positive cell ratio > 40%" for biopsy specimens. In the present study, 80% of the patients exhibited [3] or [4]. However, patients exhibiting either of the findings were defined as "a" and none of the two findings were de-

fined as "b"; based on this, we observed a difference when the final diagnostic grade was allocated.

The criteria we employed regarding lesions in other organs included "the presence of lesions in other organs that satisfy the criteria for a definite diagnosis according to the comprehensive diagnostic criteria or the organ-specific diagnostic criteria." Furthermore, the target organs included those that are frequently affected by IgG4-RD (the lacrimal gland, eye lesions, salivary gland, pancreas, bile duct, kidneys, or lungs). Because imaging findings for the periarterial/retroperitoneal lesions are not necessarily disease-specific, and it is not easy to collect tissue samples of such lesions, this item was considered to be more strict than those of the current diagnostic criteria.

Table 5 Proposed clinical diagnostic criteria for IgG4-related periarteritis/retroperitoneal lesions

---

A. Diagnostic items

1. Abnormal radiologic findings
    a. Low-density hypertrophic thickening or soft tissue masses surrounding the aorta and its major branches[*1, 2, 3, 4]
    b. Soft tissue masses in renal pelvic wall and/or around the ureter[*5]
    c. Soft tissue masses in the pelvis and paravertebral area
    [*1] Stenosis of the vessel lumen is not present in the aorta; however, luminal narrowing may be observed in the medium-sized vessels.
    [*2] Occasionally accompanied by luminal dilatation or aneurysm formation.
    [*3] It is necessary to exclude atherosclerosis, arterial dissection, infectious diseases (bacteria, tuberculosis, syphilis, etc.), other forms of vasculitis, malignant diseases such as malignant lymphoma and cancers and Erdheim–Chester disease.
    [*4] The lesions may in general involve medium-to-large-sized vessels.
    [*5] It is common in the renal pelvis and upper ureter.

---

2. Elevated serum IgG4 level (IgG4135 mg/dL)

---

3. Histologic findings of the periaortic/periarterial and/or retroperitoneal regions
    a. (i), (ii), (iii)/(iv)
    b. (i), (ii)
        (i) Marked lymphocyte and plasmacyte infiltration and fibrosis[*1, 2, 3]
        (ii) IgG4-positive plasma cell infiltration:
            Surgical samples: IgG4-positive plasma cells/HPF >30/hpf, and ratio of IgG4/IgG positive cells >40%
            Biopsy samples: IgG4-positive plasma cells/HPF >10/hpf, and ratio of IgG4/IgG positive cells >40%
        (iii) Storiform fibrosis
        (iv) Obliterative phlebitis
    [*1] Infiltration of lymphocytes and plasma cells is observed in the periarterial regions. Vasculitis in the medial layer may be present in the thoracic aorta.
    [*2] Findings of obliterative phlebitis may be more easily assessed by Elastica van Gieson staining than hematoxylin eosin staining.
    [*3] Necrosis, granuloma, and neutrophil infiltration is not usually observed; when these findings are present, differential diagnosis should be carefully undertaken.

---

4. Other organs involvement
    When IgG4-related disease is definitively diagnosed in the ophthalmus, salivary glands, pancreas, bile duct, kidney or lung by comprehensive diagnostic criteria or organ-specific diagnostic criteria for the indicated organs.

B. Diagnosis

1. Definite: 1 (a/b/c)+3a or 1 (a/b/c)+2+4
2. Probable: 1 (a/b/c)+3b or 1 (a/b/c)+4 or 3a
3. Possible: 1 (a/b/c)+2 or 3b

Upon examining 99 patients using this new diagnostic criterion, 73 (73.7%) corresponded to the definite diagnosis group, 6 (6.1%) to the probable diagnosis group, and 17 (17.2%) to the possible group. The remaining three patients did not correspond to any of these three categories. In these three patients, two had serum IgG4 levels <135 mg/dL and one had missing data for serum IgG4 levels and thus could not be evaluated. Therefore, none of the three patients satisfied the serological findings. Furthermore, one patient did not meet the criteria for the number of infiltrating IgG4 positive plasma cells in the periarterial/retroperitoneal lesion tissue, and the remaining two patients exhibited sufficient histological findings to correspond to IgG4-RD in the concurrent renal pelvis lesion. However, based on the existing diagnostic criteria (the comprehensive diagnostic criteria and the diagnostic criteria for IgG4-related kidney disease), a definite diagnosis of other organ lesions was not reached; therefore, the present organ-specific diagnostic criteria were considered inapplicable to these three patients.

Conversely, when periarterial/retroperitoneal lesions were diagnosed in 99 patients in our study using the comprehensive diagnostic criteria, IgG4-related periarteritis/retroperitoneal fibrosis was diagnosed as definite in 24 patients (24.2%), probable in 5 (5.1%), and possible in 76 (76.8%); moreover, the possibility of periarteritis/retroperitoneal fibrosis was denied in 4 (4.0%).

Discussion

In the present multicenter, collaborative, cross-sectional observational study, we analyzed many patients with

IgG4-related periarteritis/retroperitoneal fibrosis who were diagnosed by physicians with abundant experience in treating IgG4-RD throughout Japan. We found that the clinical and serological characteristics of this disease were comparable with those of IgG4-RD in other organs. Conversely, although the patients were diagnosed by specialists, we confirmed several points that may pose as problems in diagnosis using only the standard comprehensive diagnostic criteria. These included the fact that patients without non-periarterial/retroperitoneal lesions have low serum IgG4 levels, whereas patients with lesions other than these are unlikely to undergo periarterial/retroperitoneal lesion biopsy, which shows a high level of invasion. Taking into account the findings of the present study, as well as the current state of treatment of these diseases, and the problems involved, we proposed a diagnostic criterion specific to this disease.

Recent studies assessing a large sample of patients with IgG4-RD,[5–7] have demonstrated an interesting, common set of clinical features of IgG4-RD. Specifically, onset is most common in middle-aged to elderly males; moreover, allergic disorders and elevated serum IgE levels are observed at a relatively high frequency. While some patients present lesions in a single organ, many have lesions affecting multiple organs in a simultaneous or heterochronic manner, and it appears as systemic disease. Furthermore, in patients with periarteritis/retroperitoneal fibrosis who were examined in the present study, we confirmed that the clinical features were consistent with those reported in the aforementioned reports. In patients with IgG4-RD, most generally presented with mild subjective symptoms; moreover, 30% of them were asymptomatic, and their condition was often fortuitously detected, such as by circumstantial image testing.[5] In the present study, more than half of patients had no subjective symptoms. Even among those with complications associated with serious turning points such as the luminal dilatation of the affected vessel and hydronephrosis, the majority did not exhibit subjective symptoms. Therefore, for the treatment of IgG4-RD, we believe that it is important to be fully conscious regarding the potential onset and progression of serious complications associated with the lesion and that systemic screening should be performed in an appropriate manner using methods that are highly effective.

For diagnosing IgG4-related periarteritis/retroperitoneal fibrosis, the observation of characteristic hypertrophic, tumorous lesions surrounding arteries, the renal pelvis and ureter, or in other regions of the retroperitoneum using image testing, specifically using CT, are important for diagnosis. Indeed, in our present study, abnormal imaging findings of the affected vessel and retroperitoneum were observed in all 99 patients. In a detailed study by Inoue et al.,[11] the following observations were considered characteristic regarding CT findings of periarterial lesions: circumferential or partial arterial wall hypertrophy reflecting a lesion centered in the vessel's tunica adventitia, a uniform contrast effect in the lesion area in the late phase of contrast enhancement, various arteriosclerotic changes such as mural thrombosis and atheroma formation of the tunica media, and the calcification of the tunica media of the affected vessel, as well as branching vessels penetrating the lesion area without obstruction in cases involving aortic lesions. However, the disease specificity of these findings has not been fully examined, and similar imaging results have been reported in other diseases including infection (such as bacterial arthritis, tuberculosis, and syphilis), malignant diseases (such as lymphoma, solid cancer, and sarcoma), systemic vasculitis (Takayasu's arteritis, giant cell arteritis, and granulomatosis with polyangiitis), Erdheim–Chester disease, Rosai–Dorfman disease, and Castleman disease. Moreover, attention should be paid to distinguish changes in vascular wall caused by arteriosclerosis and arterial dissection. In the diagnostic criteria of the present disease, as items in the image findings, we additionally noted diseases and conditions that are important for an accurate differential diagnosis.

As hematoimmunological findings that are important for the diagnosis of IgG4-RD, we adopted elevated serum IgG4 levels from the existing diagnostic criteria and noted a similar result in approximately 90% of patients in the present study. Therefore, similar to that included in the existing diagnostic criteria, we included serum IgG4 level >135 mg/dL in the diagnostic criteria for IgG4-related periarteritis/retroperitoneal fibrosis. However, the frequency of elevated serum IgG4 differs depending on the affected organ, and even for the same organ, the frequency can vary as demonstrated in previous reports.[4,9,10] Furthermore, it has been observed that the higher the degree of fibrosis of the affected organ, the lower the number of infiltrating IgG4-producing plasma cells, and it is possible that in the organs such as retroperitoneal fibrosis that are determined to have been affected once symptoms have progressed, serum IgG4 levels are lower than those in other organs. In fact, Wallace et al. reported that serum IgG4 levels were significantly lower in patients with retroperitoneal fibrosis than in those without such lesions but with lesions in other organs.[6] Moreover, it is understood that serum IgG4 levels are correlated with the number of affected organs, and compared with patients with lesions in multiple organs, those with lesions in a single organ generally have lower serum IgG4 levels.[5,6] In the present study, group A comprised many patients with a single lesion, which may be attributed to the low serum IgG4 levels compared with those in group B. Taking this into consideration, the present diagnostic criteria is fortunately capable of making a definitive diagnosis in patients who

require a histological evaluation of periarterial/retro-peritoneal lesions, even if they do not have elevated serum IgG4 levels.

On the other hand, in the present study, it was observed that as a characteristic hematological finding apart from IgG4 in IgG4-related periarteritis/retroperitoneal fibrosis, serum CRP levels tended to be organ-specific. A cross-sectional study analyzing 334 patients with IgG4-RD reported that serum CRP levels ≥0.3 mg/dL were observed in only 27.4% of patients and ≥1.0 mg/dL were found in 9.8%,[7] which was approximately half of that found in the present study (48.3% and 23.6%, respectively). A positive correlation between aortic aneurysm diameter and serum CRP levels has been reported[14]; moreover, inflammatory cytokines expression has been observed in lesion tissues of IgG4-related inflammatory aortic aneurysms.[15] Such cytokines may explain the difference in inflammatory response depending on the specific conditions that accompany periarterial lesions such as aneurysm formation in the affected vessel. In fact, in the present study, compared with group B, group A had a significantly higher frequency of luminal dilatation of the affected vessel with higher serum CRP levels.

Histological findings are an important factor in the diagnosis of IgG4-RD, and it is recommended that a his-tological evaluation of the affected organ be performed whenever possible. In periarterial/retroperitoneal lesions, pathological analysis primarily using surgical specimens has revealed that histological findings comparable with those in the IgG4-RD lesions in other organs are pres-ent,[3,4] and this presence is now recognized. The common histological findings of IgG4-RD lesions, such as lympho-cyte and plasma cell infiltrations, storiform fibrosis, and obliterating phlebitis, were also observed at a high rate in the present multicenter collaborative study in periarterial/retroperitoneal lesions. Furthermore, neutrophil-predom-inant cell infiltration and epithelioid granuloma forma-tion, which are difficult to observe in IgG4-RD lesions, were rarely observed. Interestingly, in the present study, we noted a high IgG4-positive plasma cell infiltration in almost all specimens, which is one of the most important findings. Conversely, for these lesions, heterogeneous in-flammation and fibrosis depending on the site and staging have been identified. Moreover, in the present study, we found that in specimens obtained by biopsy, the frequency of storiform fibrosis and obliterating phlebitis tended to be lower than in those obtained by surgery and autopsy; moreover, some patients with biopsy had relatively few IgG4-positive plasma cell infiltration. Therefore, based on the current diagnostic criteria of IgG4-RD,[8,12] in our new diagnostic system for this disease we included the criterion of histological findings that differed between biopsy and resected specimens, such as those obtained by surgery and

autopsy.

The severe complications of IgG4-related periarteritis/retroperitoneal fibrosis include aneurysm formation, af-fected vessel rupture, and renal dysfunction caused by hydronephrosis. Reportedly, many of the former occurs in the absence of treatment, when patients with aneurysmal formation and rupture do not receive immunosuppressive therapy such as steroids[3]; however, the number of studies reporting affected vessel rupture after steroid therapy is also increasing.[16,17] It can be inferred that steroid therapy causes the thinning and weakening of periarterial lesions, which can increase the risk of rupture, in patients with luminal dilatation of the affected vessel prior to treatment; on the other hand, it was reported that in patients without luminal dilatation before therapy, no luminal dilatation was observed during the mean observation period of 33 months following steroid therapy.[9] As a result, the benefits and risks of steroid therapy for periarterial lesions remain controversial. Reportedly, in not only autoimmune disease attacking connective tissue but also other diseases, steroid therapy is associated with the exacerbation and rupture of aortic aneurysms.[18] Indeed, in a report on an animal ex-periment, it was suggested that steroid therapy promotes aortic rupture.[19] To examine the relationship between aneurysm formation or affected vessel rupture and steroid therapy, we believe that it is important to perform strict imaging follow-up when administering steroids to patients with IgG4-RD with periarterial lesions, irrespective of the presence or absence of luminal dilatation prior to treat-ment. Furthermore, the introduction of steroid therapy for patients with periarterial/retroperitoneal lesions should be determined after verifying that the treatment is highly needed, for example when symptoms such as fever and pain caused by the lesion are observed, when concurrent renal impairment caused by hydronephrosis is observed, and when treatment is needed for lesions in other organs. Furthermore, when luminal dilatation progresses and surgical treatment becomes necessary, it is important to have a system in place such that a vascular surgeon can be contacted without delay.

As hydronephrosis caused by periarterial/retroperito-neal lesions can also lead to irreversible renal impairment, this complication must be duly monitored for. According to a review of past reports on hydronephrosis caused by periarterial/retroperitoneal lesions in IgG4-RD, in 12 out of 22 patients whose renal functioning was evaluated, renal impairment was observed with serum creatinine levels exceeding 1.0 mg/dL[20]; moreover, some patients exhibited repeated recurrences that progressed to renal failure, even after treatment. Under such conditions, an international consensus statement regarding the manage-ment and treatment of IgR4-RD[21] recommended com-mencing early treatment. Although a standard protocol

has not yet been established, steroid therapy combined with urological surgical intervention such as stent placement and nephrostomy depending on the presence or absence of urinary tract infection and renal impairment are considered basic treatments.[20] The present study is a cross-sectional analysis involving patients assessed at the time of diagnosis; thus, we did not analyze treatment details nor the progress after treatment, but we recommend further examination to establish an evidence-based treatment policy for this condition.

We anticipate that the new organ-specific diagnostic criteria proposed here for periarterial/retroperitoneal lesions in IgG4-RD will significantly help in solving problems encountered while diagnosing these lesions using the earlier comprehensive diagnostic criteria. A definite diagnosis using the older comprehensive diagnostic criteria requires highly invasive tissue sampling as well as elevated serum IgG4 levels, which are considered difficult to observe in patients with a single periarterial/retroperitoneal lesion. Therefore, early diagnosis is difficult. In fact, in the present study, upon evaluating periarterial/retroperitoneal lesions using the older comprehensive diagnostic criteria in the 99 patients, a definite diagnosis of IgG4-related periarteritis/retroperitoneal fibrosis was achieved in only 24.2% patients. In addition, all patients with a definite diagnoses of IgG4-RD in other organs who did not undergo histological examination of the actual periarterial/retroperitoneal lesion were diagnosed only with possible disease or less, and patients in whom the periarterial/retroperitoneal lesion tissue adequately satisfied the criteria but who did not exhibit elevated IgG4 levels were diagnosed only with a probability of the disease. Conversely, upon evaluation using our new specific diagnostic criteria, these patients had a probability of definite diagnosis, and 73.7% of them were specifically diagnosed with definite IgG4-related periarteritis/retroperitoneal fibrosis. Therefore, we believe that using our proposed organ-specific diagnostic criteria substantially reduces invasiveness to the maximum possible limit and enables the determination of a considerably earlier diagnosis.

Furthermore, it is expected that such early diagnoses will help promote subsequent investigation on treatment options, clarify the disease cause and pathology by accumulating and analyzing patients, and lead to the establishment of an appropriate treatment policy. Conversely, with a single finding of elevated IgG4 levels, the infiltration of IgG4-positive plasma cells in affected tissue, or imaging findings characteristic to periarterial/retroperitoneal lesions, problems relating to disease specificity may arise.[22] Therefore, it is important to be fully conscious of the risks associated with combining and utilizing each item in a diagnosis. Furthermore, in the future, we need to explore imaging, hematological, and histological findings that are highly specific to this disease, while examining the diagnostic accuracy of the proposed new criteria and thereby still further possibly improve the diagnosis of this condition.

After the establishment of the clinical disease concept, new information regarding the etiology and pathophysiology of IgG4-RD has been successively elucidated. In addition to the pathological hypothesis of Zen et al. that involved T helper-2 cells, regulatory T cells, and related cytokines (IL-4, IL-5, IL-13, IL-10, and transforming growth factor-β),[23] it has been found that various cells such as follicular helper T cells, CD4-positive IL-1βI, TGF-β1, IFN-γ producing cytotoxic T cells, plasmablasts, and M2 macrophages are deeply involved in the etiology and pathology of IgG4-RD.[24,25] On the other hand, in IgG4-related inflammatory arterial aneurysms, the expression of IL-6 and inflammatory cytokines are reported to increase near the lesions.[15] We hope further elucidation of the pathophysiology specific to periarterial/retroperitoneal lesions.

Conclusion

Although the clinical features of IgG4-related periarteritis/retroperitoneal fibrosis are comparable with those of IgG4-RD of other organs, due care should be paid to serious complications that are specific to these lesions, such as aneurysm formation, affected vessel rupture, and hydronephrosis. We expect that the new organ-specific diagnostic criteria presented in this study, which freshly takes into account the clinical characteristics of this disease, will help in solving problems encountered while diagnosing this condition when using the earlier comprehensive diagnostic criteria. On the other hand, many points are unclear regarding the most appropriate treatment response and disease prognosis, and additional investigations are needed using a larger patient population to further examine the accuracy of the new specific diagnostic criteria and to determine an appropriate treatment plan.

Acknowledgments

Disclosure Statement

None of the authors and co-authors has any conflicts of interest to declare with regard to this report.

References

1) Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001; **344**: 732-8.

2) Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 2012; **366**: 539-51.

3) Kasashima S, Zen Y, Kawashima A, et al. A new clinico-pathological entity of IgG4-related inflammatory abdominal aortic aneurysm. J Vasc Surg 2009; **49**: 1264-71; discussion, 1271.

4) Zen Y, Onodera M, Inoue D, et al. Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. Am J Surg Pathol 2009; **33**: 1833-9.

5) Inoue D, Yoshida K, Yoneda N, et al. IgG4-related disease: dataset of 235 consecutive patients. Medicine (Baltimore) 2015; **94**: e680.

6) Wallace ZS, Deshpande V, Mattoo H, et al. IgG4-related disease: clinical and laboratory features in one hundred twenty-five patients. Arthritis Rheumatol 2015; **67**: 2466-75.

7) Yamada K, Yamamoto M, Saeki T, et al. New clues to the nature of immunoglobulin G4-related disease: a retrospective Japanese multicenter study of baseline clinical features of 334 cases. Arthritis Res Ther 2017; **19**: 262.

8) Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol 2012; **22**: 21-30.

9) Mizushima I, Inoue D, Yamamoto M, et al. Clinical course after corticosteroid therapy in IgG4-related aortitis/periaortitis and periarteritis: a retrospective multicenter study. Arthritis Res Ther 2014; **16**: R156.

10) Okazaki K, Kawa S, Kamisawa T, et al.; Working Committee of the Japan Pancreas Society and the Research Committee for Intractable Pancreatic Disease supported by the Ministry of Health, Labour and Welfare of Japan. Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013. I. Concept and diagnosis of autoimmune pancreatitis. J Gastroenterol 2014; **49**: 567-88.

11) Ohara H, Okazaki K, Tsubouchi H, et al.; Research Committee of IgG4-related Diseases; Research Committee of Intractable Diseases of Liver and Biliary Tract, Ministry of Health, Labor and Welfare, Japan, Japan Biliary Association. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci 2012; **19**: 536-42.

12) Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012; **25**: 1181-92.

13) Inoue D, Zen Y, Abo H, et al. Immunoglobulin G4-related periaortitis and periarteritis: CT findings in 17 patients. Radiology 2011; **261**: 625-33.

14) De Haro J, Acin F, Bleda S, et al. Prediction of asymptomatic abdominal aortic aneurysm expansion by means of rate of variation of C-reactive protein plasma levels. J Vasc Surg 2012; **56**: 45-52.

15) Kasashima S, Kawashima A, Zen Y, et al. Upregulated interleukins (IL-6, IL-10, and IL-13) in immunoglobulin G4-related aortic aneurysm patients. J Vasc Surg 2017; Apr 20. [Epub ahead of print]

16) Tajima M, Hiroi Y, Takazawa Y, et al. Immunoglobulin G4-related multiple systemic aneurysms and splenic aneurysm rupture during steroid therapy. Hum Pathol 2014; **45**: 175-9.

17) Kasashima S, Kawashima A, Kasashima F, et al. Immunoglobulin G4-related periaortitis complicated by aortic rupture and aortoduodenal fistula after endovascular AAA repair. J Endovasc Ther 2014; **21**: 589-97.

18) Tajima Y, Goto H, Ohara M, et al. Oral steroid use and abdominal aortic aneurysm expansion—positive association. Circ J 2017; **81**: 1774-82.

19) Reilly JM, Savage EB, Brophy CM, et al. Hydrocortisone rapidly induces aortic rupture in a genetically susceptible mouse. Arch Surg 1990; **125**: 707-9.

20) Mizushima I, Inoue D, Kawano M. Retroperitoneal fibrosis/periaortitis and hydronephrosis. In: Saito T, Stone JH, Nakashima H et al. eds. IgG4-Related Kidney Disease. Tokyo: Springer, 2016: 159-71.

21) Khosroshahi A, Wallace ZS, Crowe JL, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol 2015; **67**: 1688-99.

22) Strehl JD, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. J Clin Pathol 2011; **64**: 237-43.

23) Zen Y, Fujii T, Harada K, et al. Th2 and regulatory immune reactions are increased in immunoglobulin G4-related sclerosing pancreatitis and cholangitis. Hepatology 2007; **45**: 1538-46.

24) Della-Torre E, Lanzillotta M, Doglioni C. Immunology of IgG4-related disease. Clin Exp Immunol 2015; **181**: 191-206.

25) Mattoo H, Mahajan VS, Maehara T, et al. Clonal expansion of $CD4^+$ cytotoxic T lymphocytes in patients with IgG_4-related disease. J Allergy Clin Immunol 2016; **138**: 825-38.