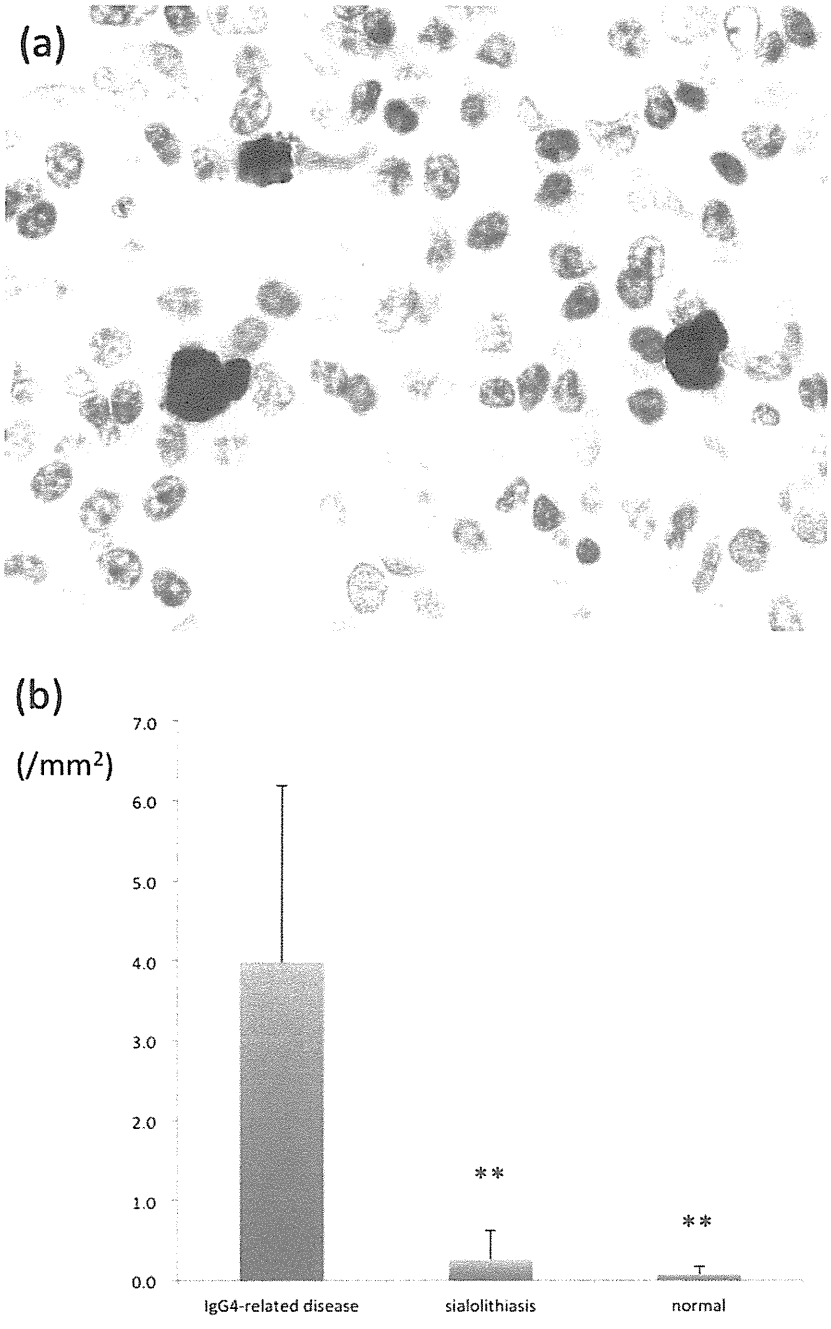

Figure 2 | Counts of IL-13-expressing cells by immunostaining. (a) Immunostaining for IL-13 revealed strong cytoplasmic positivity. Positive cells were morphologically similar to mast cells (IL-13, original magnification × 400). (b) Significantly greater numbers of IL-13-positive cells were observed in the IgG4-related disease group than in the control group ($p < 0.01$).

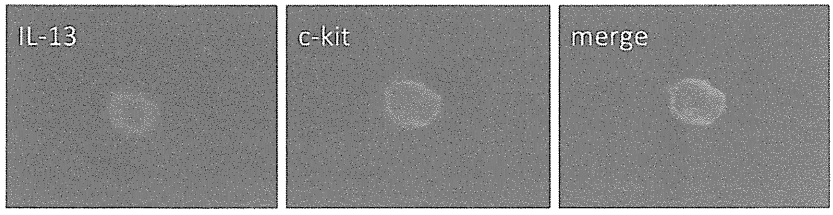

Figure 3 | Dual fluorescent immunostaining for IL-13 and c-kit. Dual fluorescent immunostaining detected positive cells for IL-13 and c-kit. The merged image demonstrates double positive-stained cells for IL-13 and c-kit.

IgG4-related disease also showed elevated IgE and peripheral blood eosinophila, which suggested that an enhanced Th2/Treg response is not related to allergic background but rather to IgG4-related disease itself[14].

On the other hand, some reports have suggested the importance of allergic reactions in the pathogenesis of IgG4-related disease. IgG4 is a unique antibody with a poor ability to activate complements and cells because of its low affinity for C1q and Fc receptors[15]. Unlike other IgG subclasses, IgG4 has anti-inflammatory activity and seems to inhibit IgE-mediated type I allergic responses by competing with IgE[15,16]. For example, some cases of autoimmune pancreatitis following bronchial asthma have been reported[17]. Recently, a case of IgG4-related disease was found to have regressed with only treatment of an anti-histamine agent and no systemic steroid therapy[18]. Based on these findings, IgG4-related disease may be related to an aberrant anti-inflammatory activity against to the allergic reaction.

Mast cells are well known to play important roles in the immediate immune response and release of histamine granules upon binding to IgE. However, previous studies have also shown that mast cells release various cytokines and chemokines and participate in multiple immune reactions[19,20]. We previously reported the possible role of mast cells in the production of Th2/Treg cytokines (IL-4, IL-10, and TGF-β1) in IgG4-related disease[7]. In this study, we found that mast cells might also produce IL-13, suggesting that it is a key factor in the elevation of serum IgE levels and number of eosinophils associated with IgG4-related disease. As mast cells are closely related to allergic reaction and IgE stimulation, these results indirectly suggest that a background of an allergic disorder and elevated serum IgE levels can be a trigger for the upregulation of mast cell-derived Th2/Treg cytokines. Further studies on the role of mast cells in IgG4-related disease and their interaction with Th2/Treg cells are required.

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Author contributions

Conceived and designed the experiments: Y.S. Performed the experiments: M.T. and Y.S. Analyzed the data: Y.S., M.T., K.O., K.T. and Y.G. Contributed materials: Y.O. and T.T. Wrote the paper: M.T., Y.S. and T.Y. All authors read and approved the final manuscript.

Additional information

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RESEARCH ARTICLE Open Access

Clinical course after corticosteroid therapy in IgG4-related aortitis/periaortitis and periarteritis: a retrospective multicenter study

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Abstract

Introduction: Immunoglobulin G4 (IgG4)–related aortitis/periaortitis and periarteritis are vascular manifestations of IgG4-related disease. In this disease, the affected aneurysmal lesion has been suspected to be at risk of rupture. In this study, we aimed to clarify the clinical course after corticosteroid therapy in IgG4-related aortitis/periaortitis and periarteritis.

Methods: We retrospectively evaluated clinical features, including laboratory data, imaging findings and the course after corticosteroid therapy, in 40 patients diagnosed with IgG4-related aortitis/periaortitis and periarteritis on the basis of periaortic/periarterial radiological findings, satisfaction of the comprehensive diagnostic criteria or each organ-specific diagnostic criteria, and exclusion of other diseases.

Results: The patients were mainly elderly, with an average age of 66.4 years and with a marked male predominance and extensive other organ involvement. Subjective symptoms were scanty, and only a small proportion had elevated serum C-reactive protein levels. The affected aorta/artery were the abdominal aortas or the iliac arteries in most cases. Thirty-six patients were treated with prednisolone, and the periaortic/periarterial lesions improved in most of them during the follow-up period. Two (50.0%) of four patients with luminal dilatation of the affected lesions before corticosteroid therapy had exacerbations of luminal dilatation after therapy, whereas none of the twenty-six patients without it had a new appearance of luminal dilatation after therapy.

Conclusions: The results of this retrospective multicenter study highlight three important points: (1) the possibility of latent existence and progression of periaortic/periarterial lesions, (2) the efficacy of corticosteroid therapy in preventing new aneurysm formation in patients without luminal dilatation of periaortic/periarterial lesions and (3) the possibility that a small proportion of patients may actually develop luminal dilatation of periaortic/periarterial lesions in IgG4-related aortitis/periaortitis and periarteritis. A larger-scale prospective study is required to confirm the efficacy and safety of corticosteroid therapy in patients with versus those without luminal dilatation and to devise a more useful and safe treatment strategy, including administration of other immunosuppressants.

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Introduction

Immunoglobulin G4 (IgG4)–related disease (IgG4-RD) is a recently recognized systemic inflammatory disease with multiorgan involvement [1-3]. IgG4-RD is characterized by tumefactive lesions, a dense lymphoplasmacytic infiltration with abundant IgG4-positive plasma cells, storiform fibrosis and elevated serum IgG4 levels. Writing from a pathological viewpoint, Stone *et al.* [4] and Kasashima *et al.* [5,6] described some patients with chronic aortitis/periaortitis or inflammatory aortic aneurysm as also having an IgG4-related condition. Microscopically, these lesions have a predilection for the adventitia and periaortic/periarterial tissue, although they also affect the media, indicating the disease have not just a periaortitis component but also an aortitis one [4-9]. In addition, Inoue *et al.* reported characteristic computed tomography (CT) findings of 17 Japanese patients with IgG4-related periaortitis and/or periarteritis. Macroscopically, this disease represents periaortic or periarterial, circumferential or partial, thickened or masslike lesions with or without aneurysmal change [10]. Presumably, IgG4-related periaortitis and periarteritis may have some overlap with IgG4-related retroperitoneal fibrosis. Inoue *et al.* proposed that this discrimination is dependent on the predominant location of the lesions. They deemed *periaortitis* appropriate to refer to lesions with predominant periaortic and concentric involvement, whereas periureteral or plaquelike lesions should be referred to as *retroperitoneal fibrosis* [10]. In this context, the concept of IgG4-related aortitis/periaortitis and periarteritis (PAo/PA) has been proposed [9]. However, the clinical characteristics and course after corticosteroid therapy in patients with IgG4-related PAo/PA have not been well-clarified. Moreover, although corticosteroid therapy has been suspected to increase the risk of aneurysm formation or rupture [5,8,10], the precise incidence of these complications and their timing in the clinical course have not been elucidated.

This state of affairs prompted us to undertake the present study to clarify the clinical characteristics and course after corticosteroid therapy in patients with IgG4-related PAo/PA.

Methods

Patients

From among 333 patients with IgG4-RD at Kanazawa University Hospital, Sapporo Medical University Hospital, Nagaoka Red Cross Hospital, Toranomon Hospital, Toyama University Hospital and Kanazawa Medical University Hospital between 1 January 1995 and 30 September 2013, we identified 40 with IgG4-related PAo/PA (Table 1). The diagnosis of this disease was made on the basis of the presence of consistent periaortic/periarterial radiological findings, the fulfillment of the published comprehensive diagnostic criteria (CDC) [11] or each organ-specific diagnostic criteria [12-14] and exclusion of other diseases. The diagnosis of extravascular lesions was made on the basis of physical examination, imaging findings and/or histopathological examination, in addition to exclusion of other conditions. According to the CDC, 25 patients (patients 2 through 5, 7, 8, 10, 11, 13 through 17, 19, 21 through 23, 26 through 28, 32, 34 through 36 and 38 in Table 1) were diagnosed with definite IgG4-RD, three (patients 1, 9 and 37) with probable IgG4-RD and 12 (patients 6, 12, 18, 20, 24, 25, 29 through 31, 33, 39 and 40) with possible IgG4-RD. Three (patients 6, 18 and 29) of these twelve patients fulfilled the revised diagnostic criteria for autoimmune pancreatitis (AIP) [13]. Well-experienced physicians of this disease diagnosed the remaining nine patients with IgG4-RD on the basis of a consistent clinical picture with elevated serum IgG4 concentrations and exclusion of other diseases. Twenty-nine (80.6%) of thirty-six patients who had extravascular IgG4-related organ involvement underwent biopsy of affected organs and showed histologically typical light microscopic findings [15] and copious IgG4-positive plasma cell infiltration. Histological evaluation of periaortic/periarterial lesions was performed in only one patient (patient 37) by means of incisional biopsy of the periaortic mass lesions, which did not show any vascular structures but histological findings compatible with IgG4-related retroperitoneal fibrosis. We retrospectively evaluated baseline clinical features, including subjective symptoms, laboratory data and imaging findings, in these 40 patients. Because follow-up data were absent or inadequate for seven patients (patients 1, 2, 21, 33, 37, 39 and 40), we limited the analysis of the clinical course to the remaining thirty-three patients (Figure 1). Two patients (patients 8 and 17) had been included in earlier studies ([16] and [17], respectively).

This study was approved by the Medical Ethics Committee of Kanazawa University, the institutional review board of Sapporo Medical University Hospital, the Ethics Committee of Nagaoka Red Cross Hospital, the institutional review board of Toranomon Hospital, the review board of the University of Toyama and the Research Ethics Committee of Kanazawa Medical University. Informed consent for publication of all data and samples was obtained from each patient. The research was conducted in compliance with the Declaration of Helsinki.

Imaging evaluation

All patients underwent whole-body CT examinations at the time of the initial diagnosis, and follow-up CT data were available for 33 patients, 31 of whom received corticosteroid therapy. All imaging data were reviewed by a single radiologist with extensive experience in IgG4-RD at Kanazawa University Hospital. Periaortic/periarterial lesions were described as circumferential or partial thickened wall

Table 1 Baseline characteristics of 40 patients with IgG4-related aortitis/periaortitis and periarteritis

Patient	Follow-up (mo)	IgG (mg/dl)	IgG4 (mg/dl)	IgE (IU/ml)	CRP (mg/dl)	Location of vascular lesion	Luminal dilatation before Tx	Extravascular lesions	Symptoms	Risk factor of arteriosclerosis	Initial PSL Tx (mg/day)
1	204	1,894	128	543	6.2	AA	(–)	La, Sa	abdo P, fever	(–)	30
2	120	2,840	693	468	0.1	AA	(–)	Sa	(–)	DM, Sm	30
3	96	5,970	3,100	259	1.56	AA	(–)	La, Sa, Hy, Pa	malaise	DM, HT	40
4	78	2,140	557	266	<0.10	AA, IA	(+)	La, Sa	(–)	DL, Sm	50
5	70	1,500	173	151	0.3	IA, SMA	(–)	Pa, RF	abdo P	DM, HT, DL, Sm	20
6	63	2,970	1,330	419	<0.10	AA	(–)	La, Sa, Pa, Ki, RF	malaise	DM, HT, DL, Sm	40
7	63	2,130	715	253	<0.10	IA	(–)	La, Sa	(–)	DM, DL, Sm	40
8	63	2,731	269	975	0.6	AA	(–)	Sa, RF	(–)	DM, HT, DL, Sm	30
9	57	1,790[b]	105[b]	212[b]	1.5[b]	AA, IA	(+)	Hy, Lu, Pa, Ly	(–)	DL	40
10	54	2,570	1,420	345	0.3	AA, IA	(+)	Pa	(–)	DM, HT	20
11	48	2,950	1,540	7.9	<0.1	AA	(–)	Sa, Bi, Pa, Pr	(–)	DM	30
12	43	1,487	196	447	0.6	AA, IA	(–)	RF	abdo P	DM, HT, DL, Sm	0
13	37	2,563	1,330	283	0.09	AA	(–)	Sa, Ki	pollakiuria	DL, Sm	45
14	35	2,319	734	542	1.19	TA, AA	(–)	Sa, Pa, Ki	(–)	DM, DL	40
15	34	1,458	158	452	0.22	AA	(–)	Sa, Ly	(–)	DM, HT, DL, Sm	30
16	27	2,081	870	1,285	0.0	AA, IA	(–)	Sa, RF, Pr	(–)	DM, HT	20
17	27	1,756	408	513	0.2	AA, IA	(–)	Sa, Pa, Ki	(–)	DM, HT, DL, Sm	20
18	27	1,762	144	24	0.32	AA, IA	(+)	Pa	(–)	DL, Sm	20
19	25	2,024	292	1,400	0.14	AA	(–)	Pa, RF	(–)	DM, HT, Sm	40
20	24	2,262	299	443	<0.05	AA	(–)	(–)	(–)	HT	0
21	24	2,184	236	365	0.3	AA	(+)	La, Sa	fever	DM, HT, DL	30
22	22	3,484	1,896	247	0.0	AA	(–)	La, Sa, Pa, Ki, Ly	(–)	Sm	35
23	15	4,171	2,120	<20	0.32	AA, IA	(–)	La, Sa, Ki	(–)	DM, HT, Sm	40
24	13	1,837	261	687	0.06	IA	(–)	RF	(–)	HT, DL	30
25	13	1,454	196	350	0.13	AA, IA	(–)	(–)	abdo P	Sm	15
26	10	2,213	455	NA	0.56	AA, IA	(–)	Sa, Ki	arthralgia	HT, DL, Sm	40
27	10	3,120	1,020	1,760	1.5	AA, IA, IMA	(–)	La, Sa	hoarseness, fever	Sm	30
28	9	2,936	1,070	17	0.0	TA, AA, IA	(–)	La, Sa, Pa, Ki	thirst	DM, DL, Sm	40
29	9	10,121	2,500	<20	0.37	IA	(+)	Pa, Ki, Ly	malaise	DM	50
30	9	1,200	147	NA	2.94	AA, IA	(–)	(–)	fever, malaise	DM, HT	30

Table 1 Baseline characteristics of 40 patients with IgG4-related aortitis/periaortitis and periarteritis *(Continued)*

31	8	1,475	210	111	0.3	IA	(–)	Sa	(–)	(–)	40
32	4	2,938	1,520	48	0.1	AA	(–)	La, Sa, Ki, RF	(–)	Sm	30
33	4	1,463	672	216	0.13	AA	(–)	Sa, Pl, Ca	(–)	Sm	0
34	3	2,439	782	703	0.2	AA, IA	(–)	La, Ki, RF	(–)	DM, DL, Sm	20
35	3	2,244	503	311	0.0	AA, IA	(–)	Ki	edema	(–)	30
36	2	1,950	711	737	0.0	AA	(–)	La, Sa, Lu, Ki	(–)	Sm	35
37	2	1,328	106	19	0.28	AA, IA	(+)	RF	(–)	DL	0
38	1	4,420	2,680	174	0.1	IA	(–)	La, Sa, Bi, Pa, Ki, Ne	diarrhea	Sm	50
39	1	2,276	835	<20	0.91	IA	(–)	Sa	(–)	HT	15
40	1	1,600	206	212	0.38	AA	(–)	(–)	abdo P, malaise	Sm	30

AA, Abdominal aorta; *abdo,* Abdominal; *Bi,* Bile tract; *Ca,* Pericarditis; *CRP,* C-reactive protein; *DL,* Dyslipidemia; *DM,* Diabetes mellitus; *F,* Female; *HT,* Hypertension; *Hy,* Hypophysitis; *IA,* Iliac artery; *IgE,* Serum immunoglobulin E at diagnosis; *IgG,* Serum immunoglobulin G at diagnosis; *IgG4,* Serum immunoglobulin G4 at diagnosis; *IMA,* Inferior mesenteric artery; *Ki,* IgG4-related kidney disease; *La,* Lacrimal gland, *Lu,* Lung; *Ly,* Lymph node; *M,* Male; Mo, month; *NA,* Not available; *Ne,* Nerve; *P,* Pain; *Pa,* Pancreas; *Pl,* Pleuritis; *Pr,* Prostate; *PSL,* Prednisolone; *RF,* Retroperitoneal fibrosis; *Sa,* Salivary gland; *Sm,* Past or current smoking; *SMA,* Superior mesenteric artery; TA, Thoracic aorta; *Tx,* Treatment. [b]Value under corticosteroid therapy.

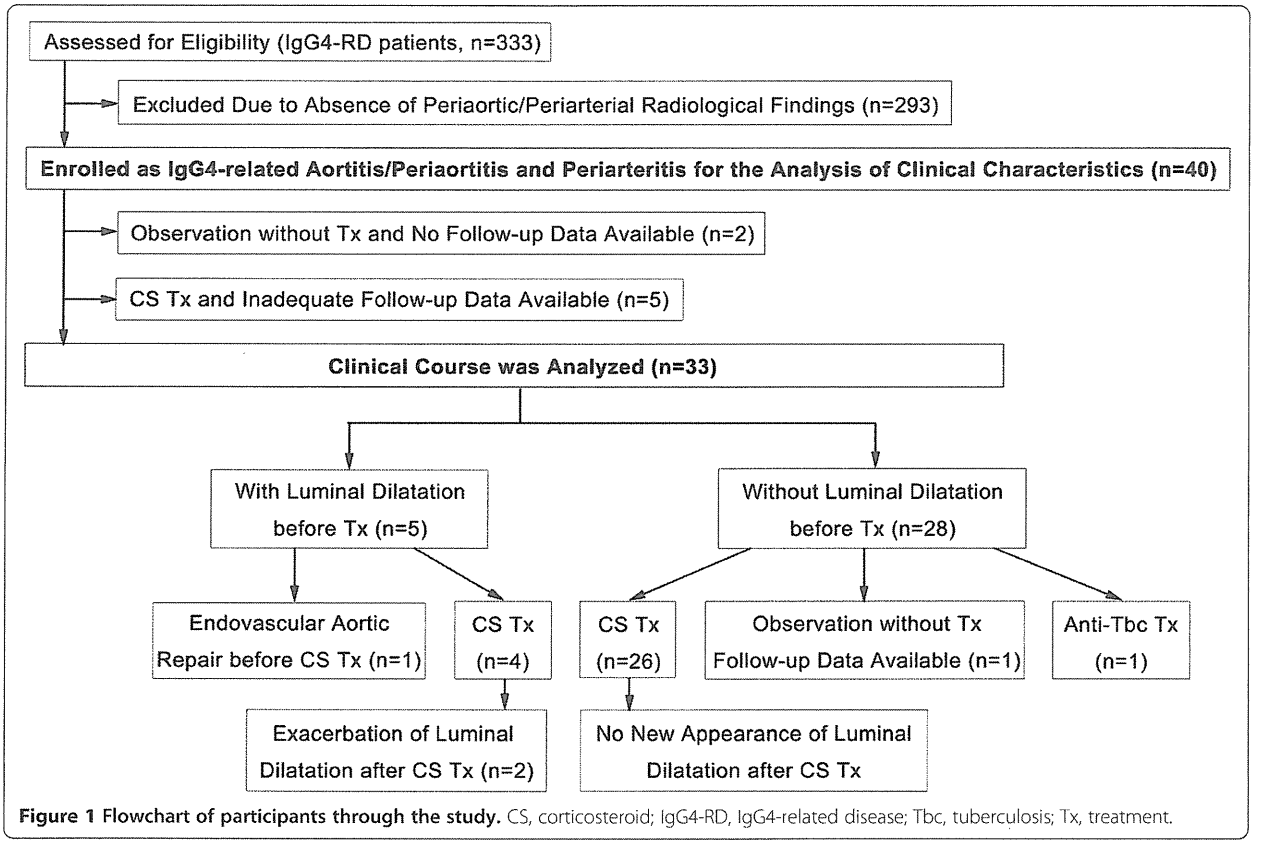

Figure 1 Flowchart of participants through the study. CS, corticosteroid; IgG4-RD, IgG4-related disease; Tbc, tuberculosis; Tx, treatment.

of the affected aortas/arteries with homogeneous enhancement visualized by contrast-enhanced CT. At the time of diagnosis, we also evaluated the findings of 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) for 20 patients and of gallium scintigraphy for 12 patients.

At the time of initial diagnostic CT imaging, after noting the affected site of aortas/arteries and extravascular lesions, we measured the maximum vascular wall thickness and diameter of the lumen in both affected and adjacent sites in each lesion. These two values were then longitudinally evaluated in the 33 patients whose follow-up imaging and clinical course information were available.

Improvement and relapse of periaortic/periarterial lesions during the clinical course were defined as decrease and reincrease of vascular wall thickness, respectively, at the same site as the maximum vascular wall thickness measured at the time of initial diagnosis. Luminal dilatation of periaortic/periarterial lesions was defined as being present when the luminal diameter of the affected site was more than 3 mm larger than that of adjacent normal sites. Exacerbation of luminal dilatation was defined as being present when more than 5-mm expansion of the luminal diameter was observed at the same site as the luminal dilatation detected at the time of initial diagnosis.

Statistical analysis

Statistical analysis was performed using SPSS version 19 software (IBM SPSS, Chicago, IL, USA). The significance of differences between groups was determined using Mann–Whitney *U* test or Wilcoxon signed-rank test, and the significance of differences in frequencies was analyzed with Fisher's exact probability test. Data are presented as means ± SD. Significant differences were defined as $P < 0.05$.

Results

Baseline characteristics

The baseline clinical characteristics of 40 patients are shown in Table 1. Our patient group was composed of 37 men and 3 women with an average age of 66.4 ± 7.1 years (age range, 44 to 75). One patient (patient 9 in Table 1) had been treated with prednisolone (PSL) at a dose of 5.0 mg/day for type 1 AIP. None of the other 39 patients had been treated with any immunosuppressants, including corticosteroids, before their diagnosis. Thirty-six patients (90.0%) had more than one IgG4-related extravascular lesion (average, 2.3 ± 1.5 organs; range, 0 to 6 organs). Involvement of the salivary gland was observed in 25 patients (62.5%), lacrimal gland in 14 (35.0%), pancreas in 14 (35.0%), kidney in 13 (32.5%), retroperitoneum in 13

(32.5%), prostate in 6 (15.0%), lung in 3 (7.5%) and hepatobiliary tract and hypophysis in 2 each (5.0%). The frequency of subjective symptoms was low (fever, 10.0%; abdominal pain, 12.5%; general malaise, 12.5%). Moreover, five of seven patients with luminal dilatation of the affected lesions at the time of diagnosis complained of no subjective symptoms. With regard to the major risk factors of atherosclerosis, diabetes mellitus (DM) was present at the time of diagnosis in 20 patients (50.0%), hypertension (HT) in 17 (42.5%), dyslipidemia (DL) in 18 (45.0%), current smoking in 9 (22.5%) and past smoking in 15 (37.5%). The mean follow-up period of all 40 patients after diagnosis was 33.9 ± 39.8 months (range, 1 to 204 months).

At diagnosis, 37 (92.5%) of 40 patients showed elevated serum IgG4 levels exceeding 135 mg/dl (average, 815 ± 771 mg/dl; range, 105 to 3,100 mg/dl). Thirty-one (77.5%) of forty patients showed elevated serum IgG levels (average, 2,551 ± 1,543 mg/dl; range, 1,200 to 10,121 mg/dl; normal range, 870 to 1,700 mg/dl). Twenty-three (60.5%) of thirty-eight evaluated patients showed elevated serum IgE levels (average, 403 ± 398 IU/ml; range, 7.9 to 1,760 IU/ml; normal range, <250 IU/ml). Although none of the patients had leukocytosis, 16 (41.0%) of 39 evaluated patients had eosinophilia (eosinophils >5%). Six (15.4%) of thirty-nine evaluated patients had hypocomplementemia. Antinuclear antibodies were positive in 16 (40.0%) of 40 patients and the rheumatoid factor in only 3 (8.1%) of 37 evaluated patients. Myeloperoxidase antineutrophil cytoplasmic antibodies (ANCAs) and proteinase 3 ANCAs were not observed in any of the evaluated patients (21 and 14 patients, respectively). Only six (15.0%) of forty patients had elevated serum C-reactive protein (CRP) level (CRP >1 mg/dl).

Treatment

The respective attending physicians decided the indications for treatment and the treatment regimen. Thirty-six of forty patients were treated with PSL at an average initial dose of 32.6 ± 9.7 mg/day (range, 15 to 50 mg/day) for the lesions associated with IgG4-RD. Only one patient (patient 1 in Table 1) received cyclophosphamide in addition to PSL. Endovascular aortic repair (EVAR) was performed for the periaortic lesions with marked luminal dilatation before corticosteroid therapy in one patient (patient 18) to prevent rupture. We excluded five patients (patients 1, 2, 21, 39 and 40) from the analysis of the clinical course because their follow-up imaging data were not available. During the clinical course of the other 31 patients, the initial PSL dose was generally continued until 2 to 4 weeks after the start of therapy and then gradually tapered. The PSL dose was tapered to 5 to 10 mg/day by 12 months in 18 (94.7%) of 19 patients whose follow-up period was more than 12 months. The average PSL dose at the last review was 10.0 ± 9.2 mg/day. Because one patient (patient 12) showed strong positivity in the tuberculin skin test and interferon γ release assays, he was treated with antituberculosis therapy only. The other three patients (patients 20, 33 and 37) were observed without any treatment (Figure 1).

Radiological findings at diagnosis

CT images revealed thickened lesions surrounding the aorta/artery in all patients. The affected aorta/artery data were for two thoracic aortas (Figure 2A), thirty-three abdominal aortas (Figure 2C), twenty-three iliac arteries (Figure 2E), one superior mesenteric artery (Figure 2G) and one inferior mesenteric artery. All 33 abdominal aortic lesions affected the infrarenal abdominal aorta, and only 6 lesions also affected the suprarenal abdominal aorta. CT also revealed typical extravascular lesions, mainly in the salivary glands, lacrimal glands, pancreas and kidney. Sixteen of twenty patients who underwent FDG-PET/CT, and only four of twelve patients who underwent gallium scintigraphy, showed significant uptake of the periaortic/periarterial lesions detected by CT.

Changes in radiological findings of periaortic/periarterial lesions after corticosteroid therapy

After corticosteroid therapy, reduction in the thickness of the periaortic/periarterial lesions was observed during an average follow-up period of 30.1 ± 26.2 months (range, 1 to 96 months) in 30 (96.8%) of 31 patients whose clinical course was analyzed (Figure 2), although 1 patient (patient 9 in Table 1) experienced relapse during PSL tapering at a dose of 7.0 mg/day. The average vascular wall thickness of the 34 periaortic/periarterial lesions of 31 patients at the time of diagnosis (7.1 ± 3.0 mm; range, 3 to 18 mm) significantly decreased after corticosteroid therapy (2.7 ± 2.0 mm; range, 1 to 9 mm) (Figure 2I). Generally, obvious radiographic improvement of more than 50% reduction in thickness was observed by 2 months after the start of therapy, after which point some patients showed further improvement and others showed almost no change (Figure 3). Eighteen of the thirty-four lesions had almost completely disappeared by the time of the last review. The rate of improvement, relapse or complete disappearance of the perivascular lesions did not differ significantly between the patients with multiple versus single vascular involvement, between those with versus without a specific other organ involvement such as AIP or between the presence or absence of any of the specific risk factors of atherosclerosis.

Luminal changes after corticosteroid therapy

Of the 31 patients whose clinical course was analyzed after corticosteroid therapy, 5 (patients 4, 9, 10, 18 and 29 in Table 1) had luminal dilatation of the periaortic/

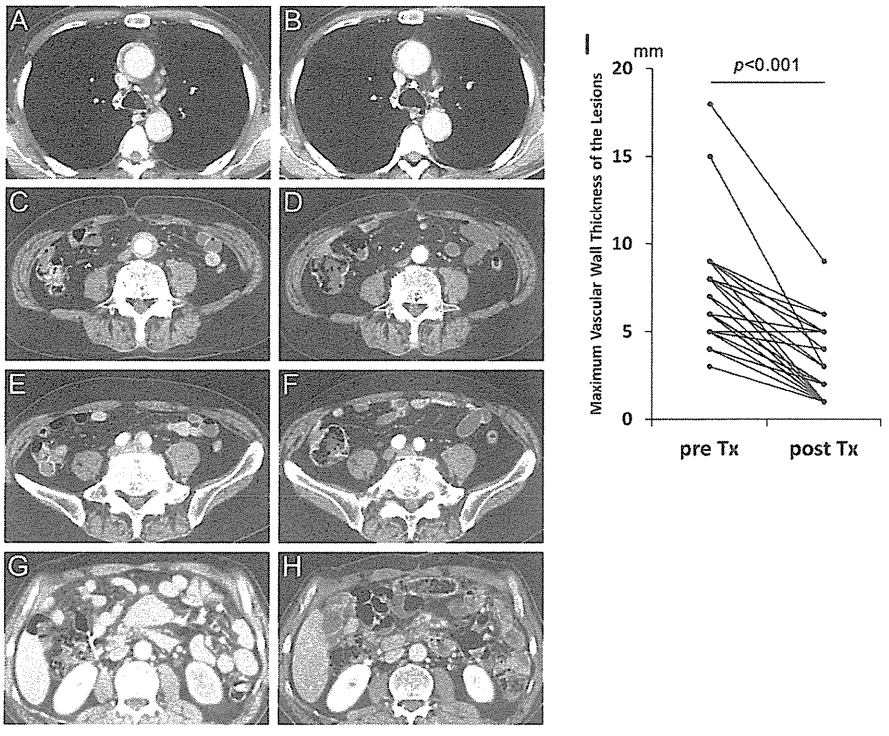

Figure 2 Contrast-enhanced computed tomography findings of periaortic/periarterial lesions and changes after corticosteroid therapy. A thoracic aortic lesion **(A)** had slightly improved 1 month after corticosteroid therapy **(B)**, an abdominal aortic lesion **(C)** and an iliac arterial lesion **(E)** had almost disappeared 10 months after therapy (**D** and **F**, respectively) and a superior mesenteric arterial lesion **(G)** showed fair improvement 2 months after therapy **(H)**. Significant pre- to posttherapy decreases in maximum wall thickness of periaortic/periarterial lesions were observed **(I)**. Tx, Treatment.

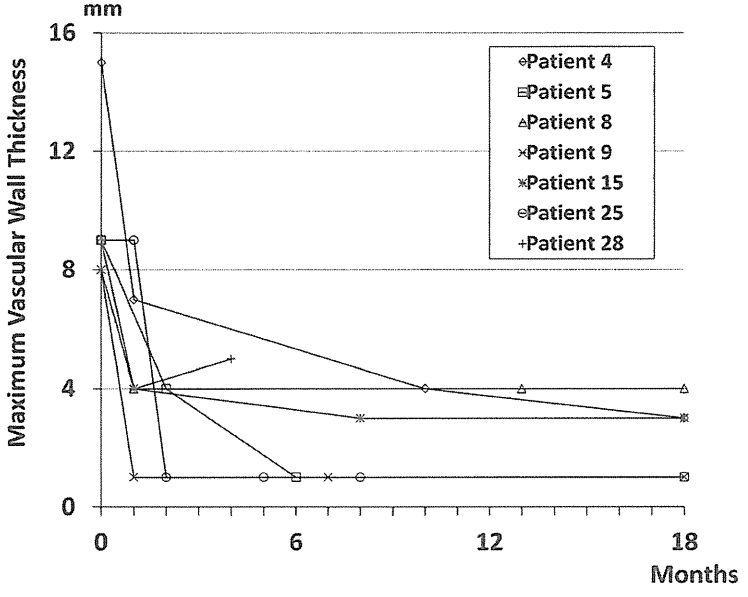

Figure 3 Changes in maximum vascular wall thickness of periaortic/periarterial lesions after the start of corticosteroid therapy. Data for patients who underwent follow-up computed tomography within 2 months after the start of therapy are shown.

periarterial lesions at the time of the initial CT (Figures 4A, 4C and 4E) and three (patients 10, 18 and 29) of them were diagnosed as having inflammatory aneurysm. One (patient 18) of them was treated with EVAR and PSL administration and did not have exacerbation of the luminal dilatation during the follow-up. The other four patients received PSL administration alone, in two (patients 9 and 10) of whom (50%) the luminal dilatation was exacerbated 28 and 46 months after the start of therapy, respectively (Figures 4B, 4D, 4F and 4G). Throughout the clinical course, patient 9 did not have hypertension and patient 10 received antihypertensive agents, which achieved good blood pressure control (below 140/90 mmHg). The luminal diameter was stable after corticosteroid therapy in the 26 patients without luminal dilatation at diagnosis (Figure 4H).

Outcome of patients without corticosteroid therapy

Four patients (patients 12, 20, 33 and 37 in Table 1) did not receive corticosteroid therapy. One patient (patient 12) treated with antituberculosis therapy had gradual improvement of serum IgG4 level, periaortic/periarterial lesions and retroperitoneal fibrosis. In another untreated patient (patient 20), periaortic/periarterial lesion showed no change during the 24-month follow-up period. No new appearance of luminal dilatation was observed in these two patients. Because follow-up imaging data of the other patients were lacking, we excluded them from the analysis of the clinical course.

Discussion

We analyzed the clinical course after corticosteroid therapy in patients with IgG4-related PAo/PA. To our knowledge, this study is the largest to evaluate corticosteroid safety and effectiveness in preventing new aneurysm formation in patients without luminal dilatation of periaortic/periarterial lesions, as well as the risk for exacerbation of luminal dilatation of such lesions in patients with it before therapy.

Biopsy of periaortic/periarterial lesions may cause massive hemorrhage. In our study, we could not perform histopathological examinations of these lesions, with the single exception of patient 37, whose specimens obtained by incisional biopsy of periaortic mass lesions showed only findings compatible with IgG4-related retroperitoneal fibrosis because of a lack of vasculature structures. To compensate for this difficulty, the presence of IgG4-related extravascular lesions, in addition to serological and typical radiological findings, was helpful in making a diagnosis of IgG4-related PAo/PA.

In contrast to our present study, the frequency of extravascular lesions was low in several previous studies. In those studies, periaortic/periarterial lesions were at an advanced stage with frequent aneurysmal formation, and the diagnosis was based mainly on the histopathological findings of the periaortic/periarterial lesions themselves because surgical treatment was selected [4,6,7,18,19]. In contrast, our cases seem to have been at an earlier stage, attributable to the fact that the identification of extravascular lesions

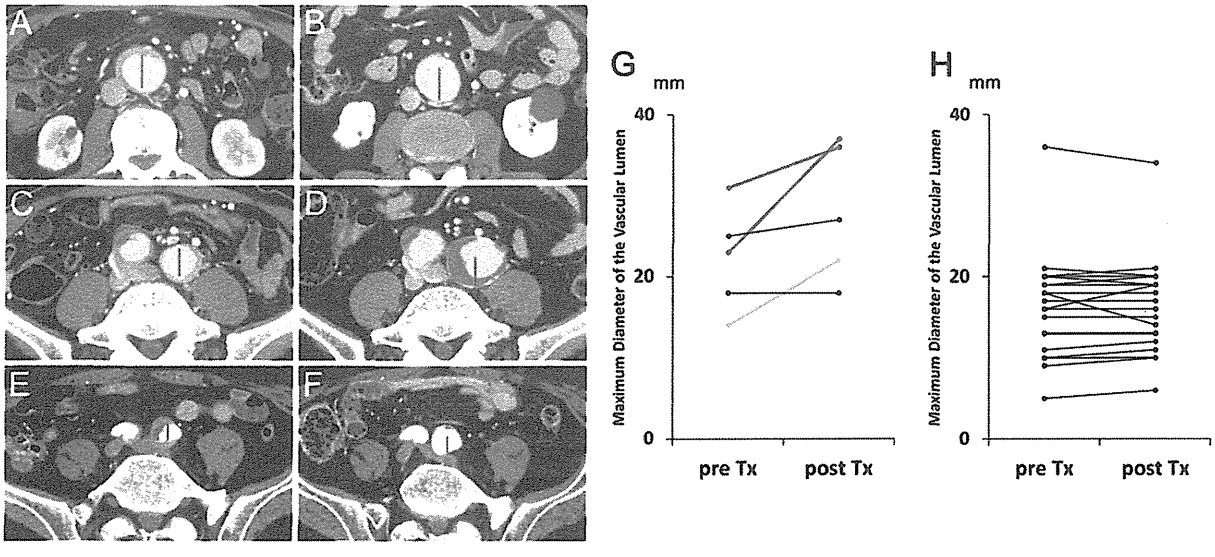

Figure 4 Exacerbation of luminal dilatation after corticosteroid therapy. Luminal dilatation (**A** and **C**, patient 10 in Table 1; **E**, patient 9) of the periaortic/periarterial lesions at the time of diagnosis was exacerbated after corticosteroid therapy (**B**, **D** and **F**, respectively). Red lines in each of the three paired images (**A** and **B**, **C** and **D**, and **E** and **F**, respectively) have the same length. Of five lesions from four patients with luminal dilatation, three lesions from two patients (red and yellow) in the maximum luminal diameter increased **(G)**, whereas no obvious increase was observed in the 28 lesions of the 26 patients without luminal dilatation **(H)**. Tx, Treatment.

and the recent greater awareness of these lesions facilitated the making of an early diagnosis.

Accordingly, in vasculature-restricted cases, the correct diagnosis of IgG4-RD is much more difficult to make. To diagnose such patients early, the indications and accuracy of CT-guided biopsy of periaortic/periarterial lesions should be investigated, the risks and benefits of a diagnostic trial of corticosteroid therapy should be evaluated and a search for other valuable and less-invasive diagnostic markers should be undertaken. In such cases, it is of great importance to exclude other differential diagnoses, such as malignancy, infections, autoimmune disease and drug reactions, which can mimic IgG4-related PAo/PA [20,21].

A definitive therapeutic strategy for IgG4-related PAo/PA has not been established, and to date indications for treatment and the type of treatment regimen have been decided by the respective attending physician. In type 1 AIP (IgG4-related pancreatitis), the pancreatic manifestation of IgG4-RD, consensus guidelines for treatment, which are based on copious clinical experience [22], have been available since 2010 [23]. In AIP patients, corticosteroid administration should be employed for patients with symptoms such as obstructive jaundice and abdominal and back pain. The initial oral PSL dose of 0.6 mg/kg/day, continuation of the initial dose for 2 to 4 weeks and tapering by 5 mg every 1 to 2 weeks to a maintenance dose (2.5 to 5 mg/day) over a period of 2 to 3 months are recommended. In our study, corticosteroid therapy was started at an initial PSL dose of less than 30 mg/day for eight patients, 30 to 40 mg/day for twenty-four patients and over 40 mg/day for four patients. In most of the patients whose follow-up period was more than 12 months, the PSL dose was tapered to 5 to 10 mg/day by 12 months. In this way, the initial therapy generally following the guidelines of AIP and maintenance therapy with relatively slow tapering were performed in our study, with good efficacy attained on the whole.

The results of this study suggest that luminal dilatation of affected lesions may actually occur during corticosteroid therapy in patients with IgG4-related PAo/PA. In past studies [5,8,10], it was speculated that corticosteroid and other immunosuppressive therapies might increase the risk of aneurysm rupture. Actually, an IgG4-RD patient with multiple aneurysms who died of aneurysm rupture after high-dose corticosteroid therapy has been reported [24]. In our present study, of 31 patients treated with corticosteroid, exacerbation of luminal dilatation were observed in only 2 who had already had it before therapy. Because blood pressure was maintained below 140/90 mmHg in these patients throughout their clinical course, hemodynamics seemed not to have influenced the exacerbation of luminal dilatation in any obvious fashion. In contrast, no patient without luminal dilatation showed a new appearance of it after therapy. These results suggest that more careful observation during corticosteroid therapy may be necessary to detect further luminal dilatation early in IgG4-related PAo/PA patients with preexisting luminal dilatation. However, because no patient with luminal dilatation and only one patient without luminal dilatation were observed without corticosteroid therapy, the natural course of the disease or of preexisting dilatation was not clarified. Moreover, the small number of patients with luminal dilatation precluded statistical analysis of the influence of independent risk factors on the luminal dilatation in IgG4-related PAo/PA. Therefore, whether preexisting luminal dilatation, corticosteroid therapy or some other factor is an independent risk factor for the aneurysm formation or exacerbation in IgG4-related PAo/PA patients will have to be clarified through multivariate analysis in a larger prospective study.

This study's results appear to support the contention that corticosteroid therapy can prevent new appearance of luminal dilatation in patients without it before therapy. In two case reports of IgG4-related aortitis/periaortitis patients with ruptured aortic aneurysms [25,26], immunosuppressive agents, including corticosteroids, had not been administered before aneurysm rupture. These case reports suggest that IgG4-related PAo/PA is itself a risk for aneurysm formation resulting in rupture when the lesions are left untreated. However, considering that no patient without luminal dilatation showed new appearance of it after therapy in our study, it is reasonable to surmise that corticosteroid therapy improves periaortic/periarterial lesions and prevents aneurysm formation at the affected site.

Therapeutic alternatives to corticosteroids have not been well-established in IgG4-RD. In some case reports and small case series, some oral immunosuppressive drugs, including azathioprine [27], methotrexate [28] and mycophenolate mofetil [29], have been reported to be effective. In addition, good effectiveness of rituximab, which eliminates B cells by binding the cell-surface marker CD20, has been described [30,31]. However, the efficacy of these drugs remains to be evaluated with regard to their effectiveness for periaortic/periarterial lesions and their influence on luminal dilatation in IgG4-related PAo/PA.

This study has a few limitations. First, the treatment regimen and follow-up protocols were inconsistent between patients because of its retrospective and multi-institutional nature. Second, although this study included more patients than past ones, the number of patients with luminal dilatation at the time of diagnosis was small. Third, the association between histopathological findings and clinical features could not be evaluated, because biopsy specimens for histopathological analysis of the periaortic/periarterial lesions could not be procured. Fourth, no patient with luminal dilatation at the time of diagnosis was observed without corticosteroid therapy.

Conclusions

The results of our study show the possibility of latent existence and progression of periaortic/periarterial lesions, the efficacy of corticosteroid therapy in preventing new aneurysm formation in patients without luminal dilatation of periaortic/periarterial lesions, and the possibility that a small proportion of patients may actually experience luminal dilatation of periaortic/periarterial lesions in IgG4-related PAo/PA. To confirm the efficacy and safety of corticosteroid therapy in patients with versus without luminal dilatation, and to devise a more useful and safe treatment strategy, including administration of other immunosuppressants, a larger-scale prospective study is required.

Abbreviations

AIP: Autoimmune pancreatitis; CDC: Comprehensive diagnostic criteria; CRP: C-reactive protein; CT: Computed tomography; EVAR: Endovascular aortic repair; FDG-PET/CT: 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography; IgG4: Immunoglobulin G4; IgG4-RD: Immunoglobulin G4 (IgG4)–related disease; IgG4-related PAo/PA: IgG4-related aortitis/periaortitis and periarteritis; PSL: Prednisolone.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IM and MK were responsible for study conception and design, data collection, data analysis and manuscript writing. DI, MoY, KY, TS, YU, SM, YM and TW were responsible for data collection, data analysis and critical revision of the manuscript SK, KH, KN and YN were responsible for study conception and design and critical revision of the manuscript. HT and HU were responsible for data collection, data analysis and critical revision of the manuscript. MaY was responsible for study conception and design, data collection, data analysis and critical revision of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Concise report

Identification of relapse predictors in IgG4-related disease using multivariate analysis of clinical data at the first visit and initial treatment

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Abstract

Objectives. Inducting clinical remission by glucocorticoid treatment is relatively easy in IgG4-related disease (IgG4-RD), but relapse also occurs easily with tapering of the steroid dose. The present study tried to analyse the cases to extract predictors of relapse present at the diagnosis of IgG4-RD.

Methods. Subjects comprised 79 patients with IgG4-related dacryoadenitis and sialadenitis, known as Mikulicz's disease, who were diagnosed between April 1997 and October 2013 and followed-up for >2 years from the initial induction treatment. They were applied to Cox proportional hazard modelling, based on the outcome of interval to relapse. We performed multivariate analysis for the clinical factors of these cases and identified predictors of relapse.

Results. Identified factors were male sex and younger onset in cases without organ involvement at diagnosis and low levels of serum IgG4 in cases with organ dysfunction at diagnosis. Complication with autoimmune pancreatitis and low steroid dose at initial treatment also tended to be associated with recurrence.

Conclusion. Follow-up is important in cases with recognized risk factors for relapse, including male sex and younger onset in cases without organ damage.

Key words: autoimmune pancreatitis, IgG4-related disease, Mikulicz's disease, multivariate analysis, relapse.

Introduction

IgG4-related disease (IgG4-RD) can cause irreversible damage to various organs through type 2 T helper (Th2) inflammation and progressive fibrosis [1, 2]. Induction of clinical remission is easily achieved using glucocorticoid treatment [3], but relapse also readily occurs when the steroid dose is tapered [4]. The annual rate of recurrence in 2012 was 19.0% in our facility, and half of relapsed cases reportedly present with new organ lesions [5]. On the other hand, many cases can continue in clinical remission with low-dose glucocorticoid, and steroid can even be discontinued in some cases. Because no markers can reflect disease activity and predict relapse in IgG4-RD, rheumatologists often encounter difficulties in clinical practice. Thus the present study tried to analyse cases followed for >2 years after initiating therapy to extract predictors of relapse present at the diagnosis of IgG4-RD.

Methods

Subjects comprised 79 patients with IgG4-related dacryoadenitis and sialadenitis, known as Mikulicz's

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disease, who were diagnosed between April 1997 and October 2013 and followed up for >2 years from the initial induction treatment. Cases were diagnosed with bilateral and continuous enlargement of the lacrimal and salivary glands, elevated levels of serum IgG4 and abundant infiltration of IgG4-bearing plasmacytes into involved organs. We analysed the following clinical factors: sex; age at onset; disease duration; eosinophil count; serum levels of IgG, IgG4 and IgE at diagnosis; presence of hypocomplementaemia and ANA and levels of RF at diagnosis; presence of organ involvement other than the lacrimal and salivary glands; numbers of organ lesions other than those of the lacrimal and salivary glands; complication with autoimmune pancreatitis, IgG4-related kidney disease or retroperitoneal fibrosis and the initial dose of steroid. Disease duration was defined as the interval between the appearance of subjective symptoms and the start of treatment. Autoimmune pancreatitis, IgG4-related kidney disease and retroperitoneal fibrosis were diagnosed based on imaging findings. As our treatment protocol, starting prednisolone at a dose of 0.6 mg/kg/day was appropriate with only lacrimal and salivary gland involvement, increasing to 1.0 mg/kg/day with multiple organ lesions. The initial dose of prednisolone was continued for 2–4 weeks, tapering the dose by 10% every 2 weeks. If the patient was >80 years of age or had existing complications, the amount of prednisolone was decreased up to 30% of the predetermined amount. Relapse was defined as re-enlargement of the lacrimal and/or salivary glands or appearance of other organ involvement.

First, all 79 cases were applied to Cox proportional hazard modelling, based on the outcome of interval to relapse. We performed uni- and multivariate analysis for each clinical factor and identified predictors of relapse. On multivariate analysis, we used the backward elimination method (Wald method, excluding factors presenting with $P > 0.1$) and extracted the factors offering high predictive power. The existence of organ involvement was considered to represent a strong risk factor for relapse. We stratified patients into groups with and without organ lesions at diagnosis and performed uni- and multivariate analysis for each group. In multivariate analysis, we applied those variables that showed $P < 0.2$ in univariate analysis and used the backward elimination method (Wald method, excluding factors presenting with $P > 0.1$). P-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS Statistics version 20.0.0 software (IBM, Armonk, NY, USA).

Written consent to use the information from these cases was obtained from all patients in accordance with the Declaration of Helsinki. This study proceeded under the approval of the Sapporo Medical University Hospital Institutional Review Board (SMU 22-57, 24-155).

Results

Table 1 shows the profiles of the patients. For the 79 cases, age at onset, presence of organ involvement and complication of autoimmune pancreatitis at diagnosis in univariate analysis and age at onset, levels of serum IgG and RF and presence of organ involvement at diagnosis in multivariate analysis were extracted.

The results from analyses by group with and without organ involvement, which was considered a strong predictor of relapse, showed that sex, age at onset and disease duration were significant on univariate analysis and sex and age at onset were extracted from multivariate analysis for the group without organ lesions at diagnosis. On the other hand, levels of serum IgG and IgG4 at diagnosis were significant on univariate analysis and the level of serum IgG at diagnosis was extracted by multivariate analysis for the group with organ dysfunction (Table 2).

Table 1 Characteristics of the patients

	Organ involvement at the first visit			
	Presence		Absence	
	No relapse during follow-up $n = 28$	Relapse during follow-up $n = 5$	No relapse during follow-up $n = 24$	Relapse during follow-up $n = 22$
Male:female, mean (S.D.)	8:20 (1:2.5)	3:2 (1:0.7)	16:8 (1:0.5)	10:12 (1:1.2)
Age at onset, mean (S.D.), years	62.6 (10.8)	45.8 (18.0)	60.3 (8.5)	55.2 (12.7)
Period of illness, mean (S.D.), years	1.39 (1.69)	4.00 (3.39)	1.29 (1.81)	2.45 (2.63)
Eosinophils, mean (S.D.), per ml	220.7 (252.8)	106.0 (60.7)	234.4 (195.5)	314.3 (287.8)
Serum IgG, mean (S.D.), mg/dl	2035.0 (1027.0)	1479.6 (160.2)	3326.3 (2338.5)	2264.5 (880.4)
Serum IgG4, mean (S.D.), mg/dl	556.5 (393.2)	221.8 (181.1)	1192.1 (1033.4)	716.7 (466.8)
Serum IgE, mean (S.D.), IU/ml	314.1 (439.4)	412.4 (395.5)	470.8 (391.9)	272.1 (241.3)
Hypocomplementaemia, %	14.3	20.0	29.2	18.2
ANA positive, %	17.9	40.0	25.0	18.2
RF positive, %	14.3	60.0	16.7	18.2

Table 2 Uni- and multivariate analysis for risk factors associated with relapse in IgG4-related disease

	Univariate analysis			Multivariate analysis		
	P-value	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI
Totals ($n = 79$)						
Male sex	0.120	1.869	0.850, 4.109			
Age at onset	**0.006**	**0.961**	0.935, 0.989	**0.004**	**0.955**	0.925, 0.985
Disease duration	0.062	1.119	0.994, 1.261			
Eosinophil count	0.641	1.000	0.998, 1.001			
Serum level of IgG before Tx	0.052	1.000	0.999, 1.000	**0.003**	**0.999**	0.999, 1.000
Serum level of IgG4 before Tx	0.111	0.999	0.999, 1.000			
Serum level of IgE before Tx	0.180	0.999	0.998, 1.000	0.051	0.999	0.997, 1.000
Hypocomplementaemia	0.312	0.602	0.225, 1.612			
ANA	0.707	0.839	0.337, 2.093			
RF	0.575	1.281	0.540, 3.042			
RF titre	0.743	0.998	0.989, 1.008	**0.010**	**1.018**	1.004, 1.033
Other organ involvement	**0.010**	**3.590**	1.355, 9.512	**<0.001**	**11.077**	3.028, 40.523
Number of other organ involvements	0.122	1.340	0.925, 1.940			
Autoimmune pancreatitis	**0.013**	**3.184**	1.280, 7.924			
IgG4-related kidney disease	0.953	0.968	0.333, 2.813			
Retroperitoneal fibrosis	0.447	1.379	0.603, 3.151			
Initial dose of glucocorticoid	0.595	1.009	0.977, 1.041	0.050	0.953	0.908, 1.000
Without organ involvement ($n = 33$)						
Male sex	0.078	7.842	0.796, 77.228	**0.015**	**342.461**	3.069, 38217.013
Age at onset	**0.022**	**0.938**	0.887, 0.991	**0.004**	**0.856**	0.769, 0.952
Disease duration	**0.008**	**1.554**	1.122, 2.152			
Eosinophil count	0.215	0.994	0.984, 1.004			
Serum level of IgG before Tx	0.115	0.996	0.992, 1.001			
Serum level of IgG4 before Tx	0.116	0.995	0.989, 1.001			
Serum level of IgE before Tx	0.996	1.000	0.998, 1.002			
Hypocomplementaemia	0.958	0.941	0.102, 8.715			
ANA	0.231	3.015	0.496, 18.334			
RF	0.108	4.397	0.724, 26.721			
RF titre	0.881	0.998	0.967, 1.029			
Initial dose of glucocorticoid	0.320	1.094	0.916, 1.306			
With organ involvement ($n = 46$)						
Male sex	0.928	1.041	0.441, 2.453			
Age at onset	0.152	0.974	0.939, 1.010			
Disease duration	0.882	1.011	0.875, 1.168			
Eosinophil count	0.978	1.000	0.998, 1.002			
Serum level of IgG before Tx	**0.012**	**0.999**	0.999, 1.000	**0.015**	**0.999**	(0.999, 1.000)
Serum level of IgG4 before Tx	**0.023**	**0.999**	0.999, 1.000			
Serum level of IgE before Tx	0.142	0.999	0.997, 1.000			
Hypocomplementaemia	0.204	0.491	0.164, 1.472			
ANA	0.148	0.438	0.144, 1.338			
RF	0.933	0.954	0.319, 2.851			
RF titre	0.800	0.999	0.990, 1.007			
Number of other organ involvements	0.375	0.732	0.367, 1.459			
Autoimmune pancreatitis	0.089	2.417	0.875, 6.673	0.054	2.828	(0.981, 8.157)
IgG4-related kidney disease	0.337	0.587	0.198, 1.741			
Retroperitoneal fibrosis	0.553	0.767	0.320, 1.842			
Initial dose of glucocorticoid	0.127	0.974	0.941, 1.008	0.055	0.960	0.921, 1.001

Tx: treatment. Significant values are indicated in bold. The upper section of the table shows total, the middle section shows without organ involvement other than lacrimal and salivary gland lesions and the lower section shows with organ involvement other than lacrimal and salivary gland lesions.

Male sex and younger onset in cases without organ involvement and a low level of serum IgG at diagnosis in cases with organ dysfunction were identified as predictors of relapse.

Discussion

The results of this analysis showed that extracted predictors of relapse differed between cases with

and without organ dysfunction at diagnosis in IgG4-related dacryoadenitis and sialadenitis. This might provide an opportunity to reconsider initial treatment in IgG4-RD.

First, we discuss cases without organ lesions other than of the lacrimal and salivary glands in IgG4-related dacryoadenitis and sialadenitis. Male sex and younger onset were predictors of relapse. IgG4-RD is a disorder based on Th2 inflammation [1]. With regard to the relationship between Th1/Th2 cytokine balance and sex hormones, oestrogen is known to promote the Th1 response [6], while progesterone promotes Th2 inflammation [7]. For this reason we have sometimes found that symptoms worsen when a female patient with IgG4-RD becomes pregnant. In addition, Th1 response is gradually suppressed in menopause due to the reduction in the production of oestrogen. In other words, Th2 immune response tends to be dominant in women after menopause. On the other hand, dihydrotestosterone, an active androgen, inhibits both Th1 and Th2 immune responses [8]. Th2 response is less likely to arise in males and younger patients due to the sex hormone environment. The occurrence of IgG4-RD in males and younger patients may thus suggest high disease activity. These results could also be confirmed using the SMART (Sapporo Medical University and related institutes database for investigation and best treatments of IgG4-RD) cohort database. We analysed 110 cases treated with maintenance therapy and overlapped them with the 79 subjects in the main analysis. The annual relapse rate in the male cases without organ involvement was 9.09% and in the female cases it was 3.85%. The amount of prednisolone at the maintenance treatment was 5.27 mg/day (S.D. 2.72) in males without organ involvement and 3.96 mg/day (S.D. 2.82) in females. Furthermore, there was no relapse in patients who were $\geqslant$70 years of age.

On the other hand, the low levels of serum IgG before treatment in cases with organ dysfunction are difficult to interpret. It was previously reported that expression levels of IL-6 mRNA at diagnosis of IgG4-RD were not significantly low [9]. The interpretation of this result is very difficult at present. In our analysis, complication with autoimmune pancreatitis and the use of low-dose glucocorticoid at initial induction therapy were not significant factors, but tended to be associated with relapse in cases with organ involvement. These factors might be identified as significant with increased numbers of cases for analysis.

The rate of complication with autoimmune pancreatitis was approximately 20% in these patients. Although this study could not suggest a precise interpretation, there was also a high rate of relapse in younger cases with autoimmune pancreatitis. This subject was not included in the cases with only autoimmune pancreatitis, and so was not statistically examined, but younger and male might be predictive risk factors in IgG4-RD.

There is currently no guideline on treatment in IgG4-RD as a whole. Japanese pancreatologists have developed a treatment guideline only for autoimmune pancreatitis. It recommends that the indication for steroid treatment is only symptomatic, starting at 0.6 mg/kg/day of prednisolone as initial dose [10]. This strategy can lead to clinical remission, but relapse often occurs. It is possible that the initial dose, which is required for the pathogenesis, is insufficient. Our analysis showed that the rate of recurrence was high in cases where we could not prescribe the predetermined amount and cases with multiple organ involvement.

We also have to follow up those cases with recognized risk factors for relapse, namely male sex and younger onset in the absence of organ damage. A sufficient dose of steroid at the initial induction treatment may inhibit recurrence in cases complicated with autoimmune pancreatitis.

Rheumatology key message

- Relapse predictors in IgG4-related disease without organ involvement at diagnosis were male sex and younger onset.

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Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist

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Abstract | Recognition of IgG4-related disease as an independent chronic inflammatory disorder is a relatively new concept; previously, the condition was thought to represent a subtype of Sjögren's syndrome. IgG4-related disease is characterized by elevated serum levels of IgG4 and inflammation of various organs, with abundant infiltration of IgG4-bearing plasma cells, storiform fibrosis and obliterative phlebitis representing the major histopathological features of the swollen organs. The aetiology and pathogenesis of this disorder remain unclear, but inflammation and subsequent fibrosis occur due to excess production of type 2 T-helper-cell and regulatory T-cell cytokines. The disease can comprise various organ manifestations, such as dacryoadenitis and sialadenitis (also called Mikulicz disease), type 1 autoimmune pancreatitis, kidney dysfunction and lung disease. Early intervention using glucocorticoids can improve IgG4-related organ dysfunction; however, patients often relapse when doses of these agents are tapered. The disease has also been associated with an increased incidence of certain malignancies. Increased awareness of IgG4-related disease might lead to consultation with rheumatologists owing to its clinical, and potentially pathogenetic, similarities with certain rheumatic disorders. With this in mind, we describe the pathogenic mechanisms of IgG4-related disease, and outline considerations for diagnosis and treatment of the condition.

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Introduction

IgG4-related disease is a new disease concept, established this century. As a chronic inflammatory disorder, IgG4-related disease is characterized by elevated serum levels of IgG4 and abundant infiltration of IgG4-bearing plasma cells into and fibrosis of the involved organs.[1] Whether the disorder is an autoimmune disease remains unclear; nevertheless, consultation with rheumatologists regarding patients with IgG4-related disease is increasing owing to the various organ dysfunctions involved (Figure 1) and the abnormal immune responses observed, which resemble those associated with certain rheumatic diseases, particularly Sjögren's syndrome.

To exemplify the major diagnostic clinical features of IgG4-related disease and highlight why patients with symptoms of this disease might be referred to rheumatologists, we present a typical case. The patient was a 65-year-old man, who had suffered from persistent swelling of both upper eyelids for 6 months before consulting an otolaryngologist after discovering bilateral painless tumours in the submandibular region (Figure 2a). The patient was referred to the rheumatology department on suspicion of Sjögren's syndrome (SS), although he demonstrated no sicca symptoms. Serological tests for both antinuclear antibodies (ANA) and anti-SSA/Ro antibodies were also found to be negative; however, elevated levels of serum IgG4 (786 mg/dl [7.86 g/l]; normal levels are <105 mg/dl [1.05 g/l]) were detected. Enhanced systemic CT imaging revealed bilateral enlargement of the lacrimal glands, submandibular glands and the pancreas, suggestive of inflammation of these organs (Figure 2b); multiple areas of poor contrast enhancement were also detected in the kidney, suggesting the kidneys were also inflamed. Abnormal signals were detected by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) at the hilar lymph nodes, as well as in the aforementioned organs. Subsequently, lymphoma was ruled out by open biopsy of the submandibular glands, whereas IgG4-related disease was confirmed based on the findings of severe IgG4$^+$ plasmacytic-cell infiltration and tissue fibrosis (Figure 2c).

As greater awareness of IgG4-related disease might lead to increased involvement of rheumatologists, this Review aims to provide a general overview of the disease with this audience in mind. In particular, we summarize our current understanding of the epidemiology, aetiology, pathogenesis, diagnostic features, treatment and prognosis of the disease. Increased knowledge of the aetiology and pathogenesis, in particular, might explain the similarities between IgG4-related disease and various rheumatic diseases, and could enable the development of novel treatments for these disorders.

A brief history of IgG4-related disease

IgG4-related dacryoadenitis and sialadenitis (also known as Mikulicz disease) and type 1 autoimmune pancreatitis (AIP) are representative of IgG4-related disease.[2,3] Mikulicz disease was first described in a case report by

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Competing interests
The authors declare no competing interests.

Key points

- IgG4-related disease represents a chronic inflammatory disorder characterized by various systemic organ dysfunctions, such as IgG4-associated dacryoadenitis and sialadenitis (also called Mikulicz disease) and type 1 autoimmune pancreatitis
- The disease is associated with elevated serum levels of IgG4 and specific histopathological features, including abundant IgG4$^+$ plasmacyte infiltration, and storiform fibrosis and obliterative phlebitis in the inflamed organs
- IgG4-related disease is also associated with a predominantly type 2 T-helper-cell cytokine profile, and infiltration of regulatory T cells is considered to be involved in the disease pathogenesis
- Comprehensive systemic and organ-specific diagnostic criteria have been defined for IgG4-related disease in Japanese populations, although criteria that classify the disease in other populations are not available at present
- Examination for systemic organ failure and screening for underlying malignancies is important during the diagnosis and follow-up of IgG4-related disease
- Glucocorticoids are effective in the treatment of IgG4-related disease, but the rate of relapse after tapering or discontinuing glucocorticosteroids is high

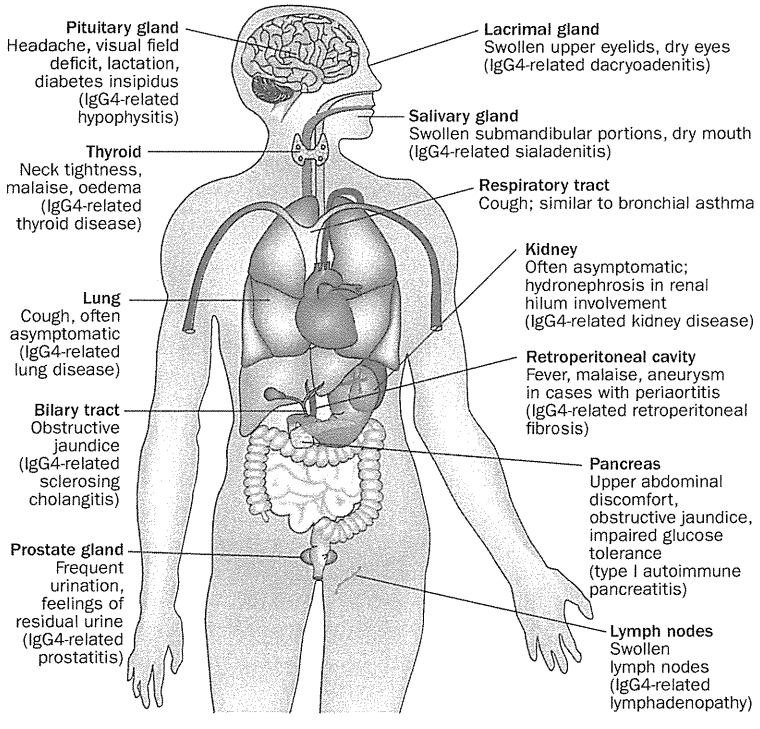

Figure 1 | Systemic organ involvement in IgG4-related disease. IgG4-related disease can present with various organ dysfunctions. This schematic shows the main organs affected and the clinical features of particular organ manifestations, and outlines the nomenclature used for each organ involvement.

Johann Freiherr von Mikulicz-Radecki (also known as Jan Mikulicz-Radecki), which was presented at a meeting of the Polish Medical Society in 1888 and published in 1892;[4] the patient presented with bilateral, symmetrical, painless swellings of the lacrimal, parotid and submandibular glands.[4,5] In 1927, Alexander Shaffer and Wilmot Jacobsen[6] classified idiopathic cases as Mikulicz disease, and secondary cases, associated with other diseases such as tuberculosis and sarcoidosis, which were known to exhibit similar symptoms, as Mikulicz syndrome. However, in the 1930s, Henrik Sjögren[7] investigated patients with keratoconjunctivitis sicca, noting the presence of swollen salivary glands, which led to the establishment of SS after he reported that this symptom reflected a systemic disorder. In the early 1950s,[8,9] Mikulicz disease was reported to be the same disease as SS, or a subtype of SS, based on histological findings. Consequently, from 1950s onwards, the term 'Mikulicz disease' disappeared from the literature for around 50 years; however, in Japan, otolaryngologists continued to discuss the differences between Mikulicz disease and SS. In the 1990s, we encountered cases of 'Mikulicz disease' (that is, idiopathic cases), and identified that the characteristic feature of Mikulicz disease is elevated serum levels of IgG4[10] and severe infiltration of IgG4$^+$ plasmacytes into the swollen lacrimal and submandibular glands.[11] Indeed, in the past decade, Mikulicz disease has been recognized as a disease quite distinct from SS.[12]

The history of AIP started with a case of chronic pancreatitis with hypergammaglobulinaemia, reported by Sarles and colleagues[13] in 1961. In 1982, a patient with 'AIP' attending the Massachusetts General Hospital, USA, was diagnosed with primary sclerosing cholangitis involving the pancreas.[14] During the 1990s, Kawaguchi *et al.*[15] and Toki *et al.*[16] focused on describing the pathology and imaging of AIP. Yoshida and co-workers[17] subsequently proposed the concept of AIP, which then became known worldwide. Moving into the 21st century, Hamano *et al.*[18,19] reported both elevated serum levels of IgG4 and infiltration of IgG4$^+$ plasmacytes into the pancreas in AIP, thus a relationship between AIP and IgG4 became apparent. At present, IgG4-related pancreatitis is defined as type 1 AIP, to distinguish the condition from type 2 AIP that presents with neutrophil-related pancreatitis.[20–22]

Mikulicz disease and type 1 AIP were, therefore, proposed as independent diseases; however, we encountered patients that demonstrated both disorders.[12,23] Furthermore, various other organ dysfunctions have been found to be associated with both Mikulicz disease and type 1 AIP. Consequently, the concept that both disorders are facets of a larger disease entity was established. IgG4-related autoimmune disease[24] and IgG4-related sclerosing disease[25] were proposed as descriptions of this disease concept from analyses in patients with type 1 AIP. Subsequently, systemic IgG4-related plasmacytic syndrome (SIPS)[12,26] and IgG4$^+$ multiorgan lymphoproliferative syndrome (IgG4$^+$ MOLPS)[27] were reported based on analyses in patients with Mikulicz disease. Such inconsistencies in the classification of IgG4-related disease created confusion. With the aim of moving toward unification of the nomenclature and establishing diagnostic criteria, the IgG4-related disease concept was discussed and examined,[28] and comprehensive diagnostic criteria for IgG4-related disease applicable to Japanese individuals were proposed in 2011.[29] At an international symposium held in the same year, recommendations regarding the nomenclature for IgG4-related disease and its individual organ system manifestations,[30] as well as consensus on the pathology of disease[31] were established. According to the resulting statement,[30] Mikulicz disease was positioned as IgG4-related dacryoadenitis