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Author Disclosure Statement

No competing financial interests exist.

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The clinical course of patients with IgG4-related kidney disease

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Long-term follow-up for IgG4-related kidney disease, including relapse information, is sparse. To gather data on this we retrospectively examined the clinical course of 43 patients with IgG4-related kidney disease, in which most patients were treated with, and maintained on, corticosteroids. One month after the start of treatment, most of the abnormal serology and radiology parameters had improved. In 34 of the steroid-treated patients whose follow-up period was more than 12 months (median 34 months), excluding one hemodialysis patient, the estimated glomerular filtration rate (eGFR) before treatment was over 60 ml/min in 14 patients (group A) and under 60 ml/min in 20 patients (group B). In group A, there was no difference between the eGFR before therapy and at the last review. In group B, the mean eGFR before treatment (34.1 ml/min) was significantly improved after 1 month (45.0 ml/min), and renal function was maintained at a similar level through last follow-up. Among 24 evaluated patients at the last review, however, renal atrophy had developed in 2 of 9 in group A and in 9 of 15 in group B. Relapse of IgG4-related lesions occurred in 8 of 40 treated patients. Thus, the response of IgG4-related kidney disease to corticosteroids is rapid, not total, and the recovery of renal function persists for a relatively long time under low-dose maintenance. A large-scale prospective study to formulate more useful treatment strategies is necessary.

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KEYWORDS: chronic kidney disease; corticosteroid therapy; follow-up; IgG4-related disease; tubulointerstitial nephritis

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IgG4-related disease (IgG4-RD) is a newly recognized fibroinflammatory condition characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and an elevated serum IgG4 concentration.[1–4] The most common feature of the renal involvement in IgG4-RD is tubulointerstitial nephritis (TIN) with abundant IgG4-positive plasma cells, but glomerular lesions such as membranous glomerulonephritis have also been described.[5–10] In addition, several radiologically evident lesions within the kidney, including the renal parenchyma and the renal pelvis, occur in association with other manifestations of IgG4-RD and often resolve with corticosteroid therapy. Therefore, the kidney lesion associated with IgG4-RD is referred to collectively as 'IgG4-related kidney disease' (IgG4-RKD), including radiologically identified renal lesions in the setting of some other form of organ involvement that has been confirmed histopathologically.[7,11] Recent studies have revealed several characteristic clinical features of IgG4-related TIN (IgG4-TIN), including predominance in middle-aged to elderly men, frequent association with IgG4-related conditions in other organs, high levels of serum IgG and IgG4, a high frequency of hypocomplementemia, a high serum IgE level, eosinophilia, characteristic radiologic findings in the kidney, and a good initial response to corticosteroids.[5–10,12] However, longer follow-up data for IgG4-RKD, including relapse information, are still sparse. In this study, we retrospectively analyzed the longer-term clinical course of IgG4-RKD in detail in a larger cohort, including the responses to corticosteroid therapy.

RESULTS

Baseline characteristics

A total of 43 patients diagnosed as having definite IgG4-RKD according to the published diagnostic criteria[7] were assessed in this study. The baseline clinicopathological characteristics

of the patients are shown in Table 1. All of them were Japanese (33 men and 10 women) with an average age of 63.5 ± 12.3 (27–83) years at the time of diagnosis of renal disease. The follow-up period after diagnosis was 3–189 months (mean 44.0 ± 40.1), and 37 (86%) of the 43 patients were followed up for more than 12 months (Figure 1). Of the patients, 42 (97.7%) had accompanying IgG4-related extrarenal lesions. Computed tomography (CT) examinations were performed in all of the 43 patients, and these revealed characteristic renal features of IgG4-RKD[7] in 31 (72.1%) of them (Table 1). The serum creatinine level was 0.4–7.26 mg/dl and the estimated glomerular filtration rate (eGFR) was 124.4–6.6 ml/min per 1.73 m^2. Renal pathology data were available for 30 patients, and all of them were found to have characteristic IgG4-related TIN.[7] Glomerular lesions other than global sclerosis were evident in 10 of the 30 patients: Henoch–Schönlein purpura nephritis in two,[13,14] membranous glomerulonephritis in two,[10,15] focal and segmental endocapillary proliferative glomerulonephritis in two, mesangioproliferative glomerulonephritis (with mild IgG and IgA deposition in the glomeruli) in two, IgA nephropathy in one, and membranoproliferative glomerulonephritis in one patient. Four patients had a history of malignancy at the time of IgG4-RKD diagnosis (rectal cancer, breast cancer, urinary bladder cancer, and gastric cancer in one each, respectively).

Treatment

Indications for treatment and the treatment regimen were decided according to the opinion of each attending physician. Among the 43 patients, 40 were treated with prednisolone (initial dose 20–60 mg/day; 0.35–1.0 mg/kg/day) for the lesions associated with IgG4-RD (Table 1 and Figure 1). The initial prednisolone dose had been reduced by ~10% at

Table 1 | Baseline characteristics of 43 patients with IgG4-related kidney disease

No.	Age	Sex	Follow-up (mo)	Extrarenal lesions	Renal radiology	Renal pathology	IgG4 (N < 105)	Low-C	Cr (mg/dl)	eGFR (ml/min)	U-Pr/U-B	PSL Tx (mg/day)
1	54	F	35	Sa, La	A	NA	785	(−)	0.4	124.4	(−)/(−)	40
2	79	M	32	Ly	E	TIN + endocap	409	(+)	0.54	108.6	(−)/(+)	20
3	58	F	32	La, Lu	D	NA	606	(−)	0.55	86.0	(−)/(+)	20
4	76	F	36	Sa, Lu	A, D	TIN	769	(−)	0.59	73.7	(−)/(−)	20
5	35	F	83	Sa, La, RF	D	TIN	191	(−)	0.6	90.3	(−)/(−)	50
6	51	F	66	Sa, Pa	A	TIN	744	(−)	0.6	81.1	NA/NA	40
7	46	F	33	Sa	A, B	NA	751	(−)	0.6	83.6	(−)/(−)	40
8	56	M	27	Sa, Pa, Lu	A	NA	2169	(+)	0.7	90.3	(−)/(−)	35
9	76	M	72 (dead)	Sa, Ly, Pa, Lu	A	TIN	1030	(+)	0.71	81.4	(−)/(−)	0
10	58	F	45	Sa, La, Ly, Ma	D	NA	2150	(−)	0.73	63.1	(−)/(−)	0
11	27	M	47	Sa, La, Ly, Pa	A	NA	1200	(+)	0.8	96.2	(−)/(−)	50
12	72	M	30	Ly	B (plain)	TIN + HSPN	1100	(+)	0.8	72.5	(2+)/(2+)	30
13	77	M	26	Sa	D	NA	438	(−)	0.86	65.8	(−)/(−)	20
14	68	M	58	Sa, La, Ly	B (plain)	NA	2940	(+)	0.9	64.8	NA/NA	60
15	56	M	55	Sa, La, Ly	A	TIN + MGN	1920	(+)	0.9	68.6	(2+)/(±)	50
16	45	M	34	Sa, La, RF	A	NA	671	(+)	0.9	73.0	(−)/(−)	40
17	70	M	6	Pa	E	TIN	623	(+)	0.9	64.3	(±)/(−)	30
18	62	M	7	Sa, La, Ly, Pa, Pro, Ao, Lu	A	NA	1920	(+)	0.92	62.8	(3+)/(+)	40
19	61	M	189	Sa, Ly, Pa, Thr	C	TIN	730[a]	(+)	1.09	54.3	(+)/(+)	60
20	59	M	18	Sa, Pa, Pro, RF	A	TIN	734	(−)	1.1	54.2	(−)/(−)	40
21	42	M	29	Sa, La, Pa, Lu	A	NA	948	(−)	1.1	59.8	(−)/(−)	40
22	58	M	47	He, Neu	A	TIN	1470	(−)	1.15	51.9	(−)/(−)	30
23	65	M	19	Sa, Ly, Lu, Pro, RF, Ao	D	NA	1330	(−)	1.18	48.9	(±)/(−)	45
24	58	M	48	Sa, Ly, Lu	E (plain)	TIN	1204	(+)	1.2	49.6	(+)/(−)	30
25	67	F	19	Ly, Lu	E	TIN	738	NA	1.23	34.2	(±)/(+)	40
26	75	M	6 (dead)	Sa, Ly, Lu	A,B	TIN	587	(+)	1.34	40.8	(+)/(−)	30
27	63	M	13	Sa, Pa, Lu, Ao	A	TIN	408	(−)	1.36	42.2	(+)/(−)	20
28	68	M	66	Sa	E	TIN	670	(+)	1.37	41.0	(−)/(−)	40
29	83	M	51		E (plain)	TIN + MN	924	(+)	1.48	35.5	(3+)/(3+)	40
30	80	M	3 (dead)	Pa	E (plain)	TIN + MPGN	660	(+)	1. 6	33.0	(2+)/(+)	0
31	60	M	156	Sa, Ly	B	TIN + MGN	305[a]	(+)	1.75	32.5	(+)/(±)	50
32	60	M	16	Sa, La	E (plain)	TIN	886	(−)	1.82	31.1	(+)/(−)	30
33	68	M	24	Sa, Ly	A	TIN + IgAGN	736	(+)	1.9	28.6	(−)/(−)	30
34	55	M	124	Sa, Pa	A	TIN	1780	(−)	2.1	27.3	(+)/(−)	40
35	61	F	23	Ly, Lu	A	NA	152	(−)	2.22	18.4	(+)/(−)	30
36	75	F	31	Sa, Ly, Lu	B (plain)	TIN + HSPN	486	(+)	2.25	17.1	(2+)/(2+)	30
37	75	M	14	Sa	E (plain)	TIN	890	(−)	2.34	22.2	(+)/(+)	35
38	69	M	10 (dead)	Pa	E (plain)	TIN	1340	(+)	2.36	22.5	(2+)/(±)	30
39	64	M	132	Sa, La	A	TIN	1360	(−)	2.9	18.4	NA / NA	20
40	74	M	6	Sa, La, Ly, RF, Ao	E (plain)	TIN	1370	(+)	4.65	10.5	(2+)/(2+)	30
41	76	M	39	Sa	E (plain)	TIN	1800	(−)	5.4	8.9	(+)/(+)	40
42	78	M	55 (HD)	Pa	A	TIN + MN	1860	(+)	6.17	7.6	(3+)/(+)	20
43	69	M	31	Sa, La, Pa, Ly, Lu, Pro	B (plain)	TIN + endocap	1120	(+)	7.26	6.6	(2+)/(2+)	30

Abbreviations: A, multiple low-density lesions on enhanced computed tomography; Ao, periaortitis; B, diffuse kidney enlargement; C, hypovascular solitary mass in the kidney; Cr, serum creatinine (mg/dl); D, hypertrophic lesion of renal pelvic wall without irregularity of the renal pelvic surface; E, normal; endocap, endocapillary hypercellularity; He, hepatopathy; HSPN, Henoch-Schonlein purpura nephritis; F, female; IgAGN, IgA nephropathy; IgG4, serum IgG4 (mg/dl); La, dacryoadenitis; Low C, low titer of serum complement; Lu, lung lesion; Ly, lymphadenitis; M, male; Ma, mastitis; MGN, mesangial proliferative glomerulonephritis; MN, membranous glomerulonephritis; Mo, month; MPGN, membranoproliferative glomerulonephritis; NA, not available; Neu, perineuritis; Pa, type 1 autoimmune pancreatitis; Pro, prostatitis; PSL Tx, initial dose of prednisolone; RF, retroperitoneal fibrosis; Sa, sialadenitis; Thr, thrombocytopenia; TIN, tubulointerstitial nephritis; U-B, hematuria; U-Pr, proteinuria.

[a]Value under steroid therapy.

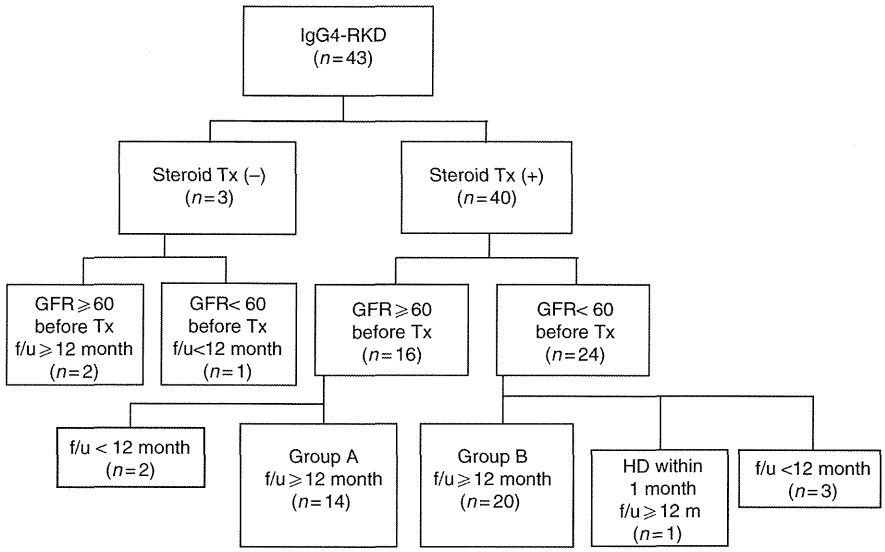

Figure 1 | Breakdown of the 43 patients with IgG4-related kidney disease (IgG4-RKD) according to treatment, estimated glomerular filtration rate (eGFR) before treatment, and follow-up period. f/u, follow-up period; GFR, glomerular filtration rate (ml/min); HD, hemodialysis; m, month; Tx, therapy.

1 month after the start of treatment, when most of the abnormalities of renal function, as well as serology and radiology parameters, had improved, and had been reduced to a maintenance dose by 12 months in most cases. Among the 35 patients who were treated and followed up for over 12 months, 33 (94.3%) were still being maintained on corticosteroids at the last review (mean prednisolone dose 5.8 ± 3.5 mg daily). Two patients (nos. 12 and 24) were weaned from corticosteroids 2 years after the start of treatment, and had been followed up without corticosteroids at the time of the last review. An immunosuppressant (azathioprine, cyclosporine A, or mizoribine) was added to the corticosteroids in four patients. Rituximab was used in one patient for frequent relapsing dacryoadenitis.

Table 2 | Characteristics of patients treated with corticosteroids and followed up for over 12 months

	Group A (eGFR before Tx ⩾60, *n* = 14)	Group B (eGFR before Tx <60, *n* = 20)	*P*-value
Age (year)	57.1 ± 15.9	64.4 ± 9.0	0.137
Male (%)	57.1 %	85.0 %	0.116
Follow-up (months)	42.4 ± 17.0	54.5 ± 52.4	0.381
Serum IgG4 before Tx (mg/dl)	1049.5 ± 774.7	969.2 ± 439.9	0.861
Hypocomplementemia (%)	50.0%	72.7 %	0.733
Renal imaging abnormality (%)	85.7 %	65.0 %	0.250
PSL dose (initial) (mg/day)	36.8 ± 13.2	36.0 ± 9.5	0.774
PSL dose (last) (mg/day)	5.5 ± 3.3	6.0 ± 3.7	0.482
eGFR before Tx (ml/min)	83.4 ± 16.0	32.5 ± 16.2	P<0.0001

Abbreviations: eGFR, estimated glomerular filtration rate; PSL, prednisolone; Tx, corticosteroid treatment.

Changes in eGFR after treatment

Before treatment, eGFR had decreased to <60 ml/min (31.8 ± 16.3 ml/min) in 24 of 40 treated patients (Figure 1), and the renal dysfunction was suggested to be caused by IgG4-TIN on the basis of the findings of renal biopsy. At 1 month after the start of treatment, it was significantly improved (43.5 ± 14.0 ml/min, $P<0.01$), although maintenance hemodialysis became necessary in one patient (no. 42) with renal failure.[15] Among the 34 patients who were treated with corticosteroids and followed up for over 12 months, excluding one hemodialysis patient, the eGFR before treatment was ⩾60 ml/min in 14 patients (group A) and <60 ml/min in 20 patients (group B) (Figure 1). There was no significant difference in baseline characteristics and corticosteroid treatment between the two groups, except for eGFR before therapy (Table 2). Immunosuppressive drugs were added in three patients (nos. 5, 11, and 15) in group A for steroid-dependent extrarenal lesions, and in one patient (no. 33) in group B because of fluctuation in the level of creatinine during maintenance steroid therapy. In group A, there was no difference between the eGFR before therapy and that at 1 month after the start of treatment, 12 months after the start of treatment, and at the last review (84.2 ± 17.0, 82.4 ± 16.1, 83.5 ± 14.0, and 82.9 ± 19.1 ml/min, respectively; Figure 2). In group B, eGFR before treatment (34.1 ± 15.8 ml/min) was significantly improved at 1 month after the start of treatment (45.0 ± 13.8 ml/min, $P<0.01$), and renal function was maintained at a similar level at both 12 months (46.8 ± 12.2 ml/min) and the last review (44.4 ± 11.0 ml/min; Figure 2). Except for one patient in whom maintenance hemodialysis became necessary within 1 month after the start of treatment (no. 42), no patient showed progression to end-stage renal disease during follow-up.

Changes in urinalysis parameters after treatment

Proteinuria and hematuria before treatment were absent or mild ('−' to '+' by qualitative analysis) in 28 of the 40 treated patients (Table 1), and none of them developed apparent proteinuria or hematuria (2+ to 3+ by qualitative analysis) during follow-up. Proteinuria or hematuria was

apparent before therapy in 9 of the 40 treated patients, and most of them had accompanying glomerular lesions. Among eight of nine patients (excluding the hemodialysis patient), protein excretion and hematuria remained unchanged in three (nos. 12, 18, and 40), improved (but persisted) in four (nos. 29, 36, 38, and 43), and disappeared in one (no. 15) at 1 month after the start of therapy, when renal dysfunction, radiological abnormalities, and hypocomplementemia had improved in all patients. In groups A and B, serial urinalysis data were available for five patients. In the patient with membranous glomerulonephritis (no. 29), protein excretion gradually decreased (2.3 g/g cr before treatment, 1.0 g/g cr at 1 month, 0.4 g/g cr at 12 months, and 0.3 g/g cr at the last review) (hematuria was transient because it had been caused by transurethral resection of the prostate for prostatic hypertrophy).[10] In the remaining patients, proteinuria and hematuria were absent or mild at 12 months after the start of treatment and at the last review.

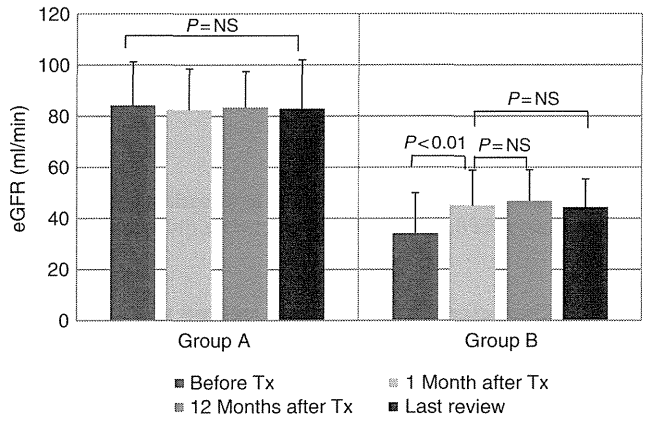

Figure 2 | Response to corticosteroid therapy (Tx) in terms of estimated glomerular filtration rate (GFR). In group A, there was no difference between the estimated GFR (eGFR) before therapy and that at 1 month after the start of treatment, 12 months after the start of treatment, and at the last review (84.2 ± 17.0, 82.4 ± 16.1, 83.5 ± 14.0, and 82.9 ± 19.1 ml/min, respectively). In group B, eGFR before treatment (34.1 ± 15.8 ml/min) was significantly improved at 1 month after the start of treatment (45.0 ± 13.8 ml/min, $P<0.01$), and renal function was maintained at a similar level at both 12 months (46.8 ± 12.2 ml/min) and the last review (44.4 ± 11.0 ml/min). NS, not significant.

Changes in renal CT findings after treatment

Among the 40 treated patients, renal radiologic features characteristic of IgG4-RKD that had been evident in 29 patients were improved at 1 month after the start of treatment in all of the 18 patients evaluated. Although, on the whole, contrast enhancement of the renal cortex demonstrated resolution of multiple low-density lesions on enhanced CT, scar-like focal cortical atrophy with decreased enhancement was found to have progressed in some patients a few months after the start of treatment.[12] The CT findings at the last review were evaluable for 24 patients (9 (64.3%) of 14 patients in group A and 15 (75.0%) of 20 patients in group B, $P=0.500$). There was no significant difference in age or follow-up period between the 9 patients in group A and the 15 patients in group B. Although renal atrophy was not evident in any of the patients before treatment, atrophy had developed in 2/9 (22.2%) in group A and 9/15 (60.0%) in group B ($P=0.084$) at the last review. Among 11 patients diagnosed as having renal atrophy at the last review, 8 showed bilateral focal atrophy (two in group A (nos. 6 and 11) and six in group B (nos. 19, 22, 28, 32, 35, and 36)), and 3 patients in group B (nos. 31, 33, and 41) showed bilateral global atrophy (Figure 3). There was no significant difference in pretreatment eGFR between the group with focal atrophy and the group without atrophy. In three patients who

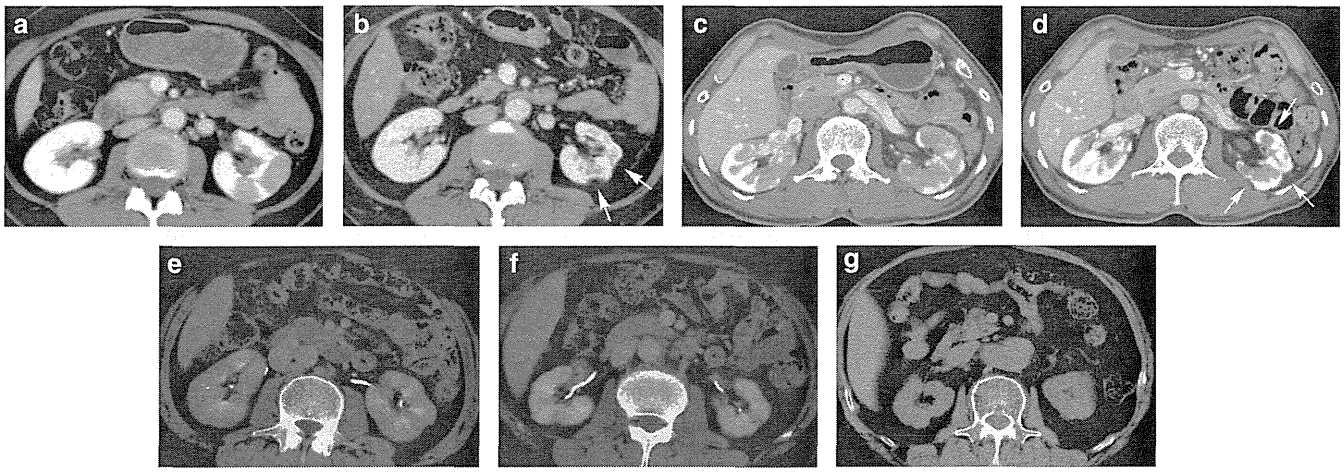

Figure 3 | Changes in computed tomography (CT) findings resulting from corticosteroid therapy. (**a**, **b**) CT findings in patient 6 (in group A) (**a**) before therapy (estimated glomerular filtration rate (eGFR) 81.1 ml/min) and (**b**) at the last review (eGFR 78.9 ml/min), and (**c**, **d**) those in patient 22 (in group B) (**c**) before therapy (eGFR 51.9 ml/min) and (**d**) at the last review (eGFR 63.1 ml/min). In both patients, multiple low-density lesions were evident on enhanced CT before therapy, and focal atrophy (arrows) had developed at the last review. (**e**–**g**) CT findings in patient 31 (in group B). (**e**) Before therapy, bilateral renal swelling with decreased contrast enhancement was observed (eGFR 32.5 ml/min). (**f**) At 1 month after the start of treatment, the bilateral renal swelling had improved, and contrast enhancement of the renal cortex had also ameliorated (eGFR 37.1 ml/min). (**g**) At the last review, bilateral global atrophy was shown by nonenhanced CT (eGFR 45.6 ml/min).

developed global atrophy, eGFR before treatment was <40 ml/min (32.5, 28.6, and 8.9 ml/min, respectively). In the hemodialysis patient (no. 42), CT at the last review demonstrated marked global atrophy of both kidneys.

Changes in serum IgG4 level and hypocomplementemia after treatment

The serum IgG4 level at 1 month after the start of treatment was decreased in all of 16 evaluated patients (842 ± 383 mg/dl before therapy and 325 ± 104 mg/dl at 1 month after treatment, $P<0.01$). Among the patients in groups A and B, data from serial examinations of the serum IgG4 level were available for 28 patients, of whom 13 (46.4%) showed re-elevation of the serum IgG4 level during follow-up. The serum IgG4 level at the last review of the 24 evaluated patients in groups A and B was 62–555 mg/dl (mean 208 ± 140 mg/dl), and it remained elevated (>135 mg/dl) in 17 (70.8%) of these patients. Hypocomplementemia was improved at 1 month after the start of treatment in all but 1 of the 11 patients evaluated. Although the complement level remained improved during follow-up in 11 of the 14 patients evaluated, 3 patients showed a decrease again, and all of them were diagnosed as having IgG4-RD relapse at that time (see section referring to relapse). In patients without hypocomplementemia before treatment, hypocomplementemia did not develop during follow-up.

Outcome of patients without treatment

Among the 43 patients, three were untreated, two patients (nos. 9 and 10) were followed up without treatment, and steroid treatment was avoided in 1 patient (no. 30) because of serious infection. In patient 9, swelling of the submandibular glands, and radiological abnormalities of the pancreas and the kidney had improved spontaneously by 6 months after the diagnosis of IgG4-TIN, and this condition was maintained during follow-up, although the lung lesions fluctuated. The serum IgG4 level was high (850–1050 mg/dl), and the serum CH50 level remained low (9–21 U/ml; normal 30–45 U/ml) during follow-up, despite fluctuation. Although the IgG4-RD status remained unchanged, this patient developed lung and colon cancers at 72 months after the diagnosis of IgG4-TIN, and these ultimately proved fatal. In patient 10, hypertrophy of the renal pelvic wall remained unchanged at 12 months after the diagnosis of IgG4-RKD, but had improved at the last review. The serum IgG4 level also decreased spontaneously (2150 mg/dl at diagnosis, 1160 mg/dl 12 months later, and 667 mg/dl at the last review). Patient 30 died of pneumonia 3 months after the diagnosis of IgG4-TIN.

Relapse of IgG4-RD after treatment

Among the 40 treated patients, 8 (20.0%) were diagnosed as having IgG4-RD relapse. Relapse occurred in the kidney ($n=3$) and also extrarenally ($n=5$: sialadenitis, dacryoadenitis, autoimmune pancreatitis, lymphadenopathy, and retroperitoneal fibrosis in one case each) during maintenance corticosteroid therapy (2.5–15 mg prednisolone daily, median 5 mg) at 12–66 (median 24.5) months after the start of treatment. There were no striking clinicopathological features at the time of diagnosis in the patients with relapse. In six of the eight relapsed patients, the dose of corticosteroids was increased and the increased corticosteroid dose was effective for all of the relapsed lesions. Two patients (one with sialadenitis and one with hypertrophy of the renal pelvic wall) were followed up without any increase in the dose of corticosteroids, and their condition remained unchanged. The levels of serum IgG and/or IgG4 at relapse were higher than those before relapse in six of the relapsed patients. The level of serum complement at relapse was examined in four patients, and a re-decrease was evident in three patients who had shown hypocomplementemia before therapy. In two of these three patients, relapses occurred in the kidney: TIN with infiltration of numerous mononuclear cells demonstrated by renal rebiopsy with re-elevation of the serum IgG4 level (no. 33) and a rapid rise in the serum creatinine level (1.25 to 1.84 mg/dl) with a re-increase of the serum IgG4 level (no. 43). At that time, a re-decrease of the serum CH50 level (38–14 U/ml, normal range 32–47 U/ml) was evident in patient 33, and a re-decrease of the serum C3 level (47 to 16 mg/dl, normal range 60–135 mg/dl) was evident in patient 43. Patient 31 showed re-enlargement of systemic lymph nodes, with a re-decrease of the serum CH50 level (53.9 to 25 IU/ml), although the kidney lesions were unchanged. In all patients, the re-decrease of the complement level improved as the dose of corticosteroids was increased. In one patient without hypocomplementemia before therapy, no decrease in the serum complement level was evident at relapse.

Adverse events after treatment

None of the patients required drug discontinuation because of adverse events. Although development or worsening of diabetes mellitus after corticosteroid therapy occurred in several patients, this was controlled by oral antidiabetic medication or insulin therapy. Avascular necrosis of the femoral head was evident in two patients. Two patients developed infection (diverticulitis in one and unknown origin in one), but were improved by antibiotic treatment. One patient developed steroid-induced psychosis, and one developed a compression fracture of a lumbar vertebra. Two patients were diagnosed as having gastric cancer within 1 month after the diagnosis of IgG4-RKD, and three patients were diagnosed as having cancer at over 12 months after the diagnosis of IgG4-RKD (gastric cancer, pharyngeal cancer, and rectal cancer in one patient each, respectively). Four of these five patients were still alive without relapse at the last review, but the other (no. 26) died of gastric cancer.

DISCUSSION

Responsiveness to corticosteroid therapy is a characteristic feature of IgG4-RD and consistently leads to improvement of most lesions, at least in the short term.[1,3,5–9,12,16,17] Type 1

autoimmune pancreatitis, the pancreatic manifestation of IgG4-RD, is the first recognized form of organ involvement,[18] and the long-term outcome of IgG4-RD has been most extensively examined in terms of the pancreatic lesions. Kamisawa *et al.*[19] retrospectively examined the outcome of 563 patients with autoimmune pancreatitis in Japan. In that study, the remission rate in steroid-treated patients (98%) was significantly higher than that in patients without steroid treatment (74%). The relapse rate in patients receiving steroid maintenance therapy (23%) was significantly lower than that in patients who stopped maintenance treatment (34%), and steroid re-treatment was effective in 97% of those who relapsed. Because tumefactive or hyperplastic lesions are characteristic, and many of the symptoms are caused by such morphologic changes in the affected organ, the effectiveness of corticosteroids in IgG4-RD is usually recorded in terms of the radiologic resolution and disappearance of clinical symptoms.[19,20] Chari and Murray[20] reported that remission (and also relapse) of IgG4-RD could refer to symptoms, serology, radiologic changes, or histology. On the other hand, treatment response and relapse in patients with renal disease is usually estimated in terms of improvement in renal function or urinary abnormalities.[21]

In IgG4-TIN, similar to autoimmune pancreatitis, a rapid response to steroid has been demonstrated.[5–9,12] In our earlier study, decreased renal function, hypocomplementemia, or abnormal renal radiologic findings were rapidly improved at 1 month after the start of corticosteroid therapy in 18 (94.7%) of 19 patients with IgG4-TIN.[5] The Japanese standard steroid treatment for autoimmune pancreatitis[22] involves oral administration of prednisolone (0.6 mg/kg/day) as induction therapy for 2–4 weeks, and then the dose is gradually tapered to a maintenance dose of 2.5–5 mg/day over a period of 2–3 months. Maintenance therapy with low-dose prednisolone is recommended to prevent relapse, but withdrawal of maintenance therapy within at least 3 years is also recommended for patients showing radiological and serological improvement. In the present retrospective study of IgG4-RKD, in which most of the renal dysfunction and renal parenchymal radiological abnormalities are responsible for IgG4-TIN, the induction regimen was similar to that for autoimmune pancreatitis, although the initial prednisolone dose varied somewhat in each case, and low-dose corticosteroid therapy had been maintained in most of the patients at the last review. Under these conditions, steroid therapy elicited rapid, but not total, improvement of renal function in patients whose eGFR had been <60 ml/min before therapy, and this effect persisted for a relatively long period. On the other hand, CT at the last review demonstrated that renal atrophy had developed in a considerable proportion of the patients, especially those in whom advanced renal damage had already been evident before therapy (22.2% in group A and 62.5% in group B, although the difference was not statistically significant). These results suggested that, although the response of IgG4-TIN to corticosteroids is certainly rapid, recovery may not be total and irreversible lesions may remain, especially in patients with advanced renal damage. In a study involving re-renal biopsy after treatment, Mizushima *et al.*[12] showed that regional fibrosis developed in the renal interstitium, even though the area of cell infiltration decreased, and suggested that these histologically evident fibrotic lesions might correspond to the focal atrophic lesions demonstrated by imaging. Accordingly, early treatment of IgG4-TIN appears to be necessary.

Spontaneous improvement or remission has been documented in IgG4-RD.[17] Indeed, in two of the present study patients, renal radiological abnormalities resolved spontaneously without renal dysfunction, suggesting that spontaneous improvement of radiologic parameters can also occur in IgG4-RKD. However, renal function did not recover completely in patients with advanced renal damage. Although the indications for corticosteroid therapy in IgG4-RKD have not been established, patients with renal dysfunction should receive it, and careful attention should be paid to renal function during follow-up without therapy.

In IgG4-RD, disease relapse is common and can occur in various organs irrespective of the clinical form evident at the first visit.[16,17,19,20,23] In this study, relapses occurred in 8 (20%) of 40 treated patients with IgG4-RKD including kidney lesions, similar to those in patients with autoimmune pancreatitis receiving maintenance treatment.[19] In autoimmune pancreatitis, withdrawal of maintenance therapy within at least 3 years is recommended for patients in remission to prevent steroid-related complications.[22] However, as relapse of renal disease probably leads to deterioration of renal function, which may irreversibly progress to end-stage renal disease, withdrawal of maintenance therapy for IgG4-TIN should be considered very carefully. In this study, renal atrophy had developed in a significant number of patients at the last review and relapse occurred in 20% of treated patients, suggesting that maintenance corticosteroid therapy under the present system may still be insufficient for treatment of IgG4-TIN. A large-scale prospective study is necessary to determine a more useful treatment strategy for IgG4-TIN, including a review of the need for maintenance corticosteroid therapy. Interestingly, a re-decrease of the serum complement level in three patients who had shown hypocomplementemia before therapy was associated with IgG4-RD relapse in all of them, suggesting that such a re-decrease of the serum complement level may be useful for prediction of relapse in IgG4-TIN patients. Kawa *et al.*[24] demonstrated that immune complexes appeared to be a useful marker of relapse of autoimmune pancreatitis. In IgG4-TIN, the frequency of hypocomplementemia is high and immune-complex deposition is a significant feature of renal histology.[5,6,25] Although the pathogenesis of immune-complex formation in IgG4-RD has not been elucidated,[3] changes in complement levels should be followed up carefully in patients with IgG4-TIN.

In contrast to the uniform rapid response in terms of renal function, radiology, and serology, the response in terms of

urinalysis parameters after therapy seemed to vary. In IgG4-RKD, TIN is the most common feature, and certain common pathologic features are shared between IgG4-TIN and extrarenal organs affected by IgG4-RD.[5,26] However, urinary abnormalities were usually associated with glomerular lesions, and the relationship between glomerular lesions and IgG4-RD has not been elucidated. Membranous glomerulonephritis is the most commonly observed glomerular lesion in IgG4-RKD and is thought to be associated with IgG4-RD.[9–11] However, even in membranous glomerulonephritis, the response of proteinuria to corticosteroid therapy varies from rapid[27] to gradual (patient 29 in this study), or almost none.[28] Changes in urinalysis parameters may not reflect the disease activity of IgG4-RKD precisely, and their significance should be considered carefully.

In patients with IgG4-RD, the risk of malignancies has been discussed.[16,29] In the present series of 43 patients with IgG4-RKD, 4 had a history of malignancy, and 7 malignancies were diagnosed in 6 patients after the diagnosis of IgG4-RKD; 2 patients died of their malignancies. Careful examination and long-term follow-up of IgG4-RKD patients for complications or the development of malignancies is therefore required.

In conclusion, IgG4-RKD shows rapid, but not total, improvement with corticosteroid therapy, and the recovery of renal function persists for a relatively long period under low-dose maintenance. However, a large-scale prospective study to formulate a more useful treatment strategy will be necessary.

MATERIALS AND METHODS

Patients

Among patients with suspected IgG4-RD seen at Nagaoka Red Cross Hospital, Kanazawa University Hospital, Sapporo Medical University Hospital, Niigata University Hospital, and Fukuoka University Hospital between January 2004 and March 2012, we identified 43 patients as having definite IgG4-RKD according to the published diagnostic criteria.[7] All of these patients showed elevation of the serum IgG4 level (>135 mg/dl). Renal pathology data were available for 30 patients, and all of them had the tubulointerstitial features characteristic of IgG4-RKD: dense lymphoplasmacytic infiltration with >10 infiltrating IgG4-positive plasma cells per high-power field and/or a IgG4 + /IgG + plasma cell ratio of $>40\%$ with fibrosis. In the other 13 patients, the diagnosis of IgG4-RKD was based on both the renal radiologic findings characteristic of IgG4-RKD (multiple low-density lesions on enhanced CT, diffuse kidney enlargement, a hypovascular solitary mass in the kidney, or a hypertrophic lesion in the renal pelvic wall without irregularity of the renal pelvic surface) and histologic findings in extrarenal organ(s) that were equivalent to those described above for the kidney. Among the 43 patients, 39 patients had been included in our earlier study (nos. 4, 9, 15, 17, 19, 22, 26, 28, 29, 31, 34, 38, 39, 41–43 were described in ref. 5).[5,7,10,12–15,30] Four of the 43 patients had been followed up for primary Sjögren's syndrome before 2004. The diagnosis of extrarenal lesions was made on the basis of physical findings and the results of imaging studies (CT and gallium citrate scintigraphy) and/or biopsy, in addition to exclusion of other diseases. Diagnosis of autoimmune pancreatitis was made in accordance with the 2006 Japan Pancreas Society revised criteria.[31] We retrospectively examined the treatment, renal function, urinalysis, and serological data, as well as renal CT findings, before therapy, 1 month after the start of treatment, 12 months after the start of treatment, at the last review, and at relapse. We also examined malignancies and adverse events during the treatment.

The study was approved by the review board of Nagaoka Red Cross Hospital and the boards of the collaborating institutions. All data and samples from patients were collected with their informed consent, and the study was conducted in compliance with the Declaration of Helsinki Principles.

Renal imaging and definition of renal atrophy

Whole-body CT imaging was evaluated in all patients before treatment, and follow-up CT data were available for 30 patients. The renal CT findings at the time of diagnosis of IgG4-RKD, changes during follow-up, and the presence of renal atrophy were based on information supplied by experienced radiologists at each of the institutions. Renal atrophy was classified as either focal or global.[32] Global renal atrophy was defined as an apparent reduction in renal length judged by each radiologist in consideration of the age and physique of each patient, and not simply as a decline in renal size before treatment. Focal renal atrophy was defined as loss of renal parenchyma with no apparent reduction in renal length. The renal length was measured on the long axis of the kidney on a CT workstation.

Definition of improvement and relapse

For extrarenal lesions, improvement of the organ involvement was decided according to changes in symptomatic, radiologic, serologic, or histologic features.[20] In IgG4-RKD, improvement of renal function (in terms of serum creatinine level or eGFR) was also considered.[21] Relapse of extrarenal lesions was decided on the basis of reappearance or worsening of symptomatic, radiologic, serologic, or histologic features.[20] In IgG4-TIN, a rapid rise in the serum creatinine level, after careful exclusion of other renal diseases, was also considered as relapse.[21] Re-elevation of the serum level of IgG or IgG4 alone was not considered to be relapse.[19] Because the relationship between IgG4-RD and glomerular lesions has not been fully clarified, and cases in which the glomerular lesion is the sole kidney lesion (without TIN) are not included in IgG4-RKD,[11] worsening of urinalysis parameters alone was not considered to be relapse of IgG4-RKD.

Statistics

Statistical analysis was performed using the paired Student's *t*-test, Wilcoxon signed rank test, Mann–Whitney *U*-test, and Fisher's exact probability test as appropriate. Data are presented as means ± s.d. A probability of $P<0.05$ was considered to indicate statistical significance.

DISCLOSURE

All the authors declared no competing interests.

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CLINICAL INVESTIGATION

A prevalence study of IgG4-related ophthalmic disease in Japan

Japanese study group of IgG4-related ophthalmic disease

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Abstract
Purpose Immunoglobulin (Ig)G4-related ophthalmic disease belongs to a category of ocular adnexal lymphoproliferative disorders, the most frequent group of orbital tumors and simulating lesions. The aim of this study was to elucidate the number of IgG4-related diseases of orbital lymphoproliferative disorders and correlate ages and sex of such patients from 18 centers in Japan.
Methods One thousand and fourteen patients with orbital lymphoproliferative disorders were enrolled in this study. All had pathologically diagnosed lymphoproliferative disorders with surgical samples of ocular adnexal tissue. Patients with conjunctival lesions and intraocular lymphoma were excluded.
Results Of the 1,014 cases of orbital lymphoproliferative disorders 404 (39.8 %) had extranodal mucosa-associated lymphoid tissue (MALT) lymphoma, 156 (15.4 %) had other malignant lymphomas, 191 (18.8 %) had non-IgG4 orbital inflammation, 219 (21.6 %) had IgG4-related orbital inflammation, and 44 (4.3 %) had IgG4-positive MALT lymphoma. Median age of the IgG4-related orbital inflammation group was 62 years, which is significantly lower than that of the MALT lymphoma group (median 66 years) and higher than the non-IgG4 orbital inflammation group (median 57 years). The male/female ratio was 105/114 in the IgG4-related orbital inflammation group.
Conclusions Nearly a quarter of orbital lymphoproliferative disorders in Japan are related to IgG4.

Keywords IgG4 · Orbital · Inflammation · MALT lymphoma · Lymphoproliferative

Introduction

A close relationship between immunoglobulin (Ig)G4 and Mikulicz's disease, characterized by symmetrical swelling of the lacrimal and salivary glands, was first elucidated by Yamamoto in 2004 [1]. Since then, many studies on IgG4-related disease (IgG4-RD) in the ophthalmic region have focused to a large extent on the lacrimal gland. Pathological features of IgG4-related dacryoadenitis are characterized as a prominent IgG4-positive lymphoplasmacytic infiltration accompanied by follicular (germinal center) formation and fibrosclerosis [2, 3]. In addition, a case series of clinical studies that includes IgG4-related Mikulicz's disease was established in Japan, with patients referred to as having systemic IgG4-related plasmacytic syndrome (SIPS) [4] and IgG4-positive multiorgan lymphoproliferative syndrome (IgG4-MOLPS) [5]. IgG4-related lesions in the ophthalmic region involve not only the lacrimal gland but also other ocular adnexa, such as extraocular muscles and branches of the trigeminal nerve [6–9]. Hence, a new classification seemed necessary, which resulted in the recently proposed comprehensive nomenclature of IgG4-related ophthalmic disease [10].

There is no doubt that IgG4-related ophthalmic diseases belong to a disease category of ocular adnexal lymphoproliferative disorders, which comprise the most frequent group of mass-forming diseases in the orbit [11, 12]. Orbital lymphoproliferative disorders also include lymphomas and non-IgG4 idiopathic orbital inflammation [7, 13], which are important differential diagnoses of IgG4-RD. The question is therefore raised as to what proportion

Members of the Japanese study group of IgG4-related ophthalmic disease are listed in the Appendix.

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of orbital lymphoproliferative disorders is related to IgG4. In this study, we collected a case series of patients with orbital lymphoproliferative disorders from multiple institutes in Japan and correlated diagnoses with ages and sex in patients with IgG4-related ophthalmic disease.

Patients and methods

This study reports on a case series of patients with orbital lymphoproliferative disorders from 18 institutes in Japan. This multicenter epidemiological study was approved by the ethics committee at the Graduate School of Medical Sciences, Kanazawa University, Japan (#1164). Cases were retrieved from a retrospective review of pathology specimens. All cases were Japanese and were pathologically diagnosed as lymphoproliferative disorders from surgical samples of ocular adnexal tissue (except conjunctiva and eyelids) during the period January 2003 to May 2012. The entry period was determined from the date when IgG4 immunostaining was used to diagnose IgG4-RD, and, therefore, varied among institutes. Lymphoproliferative disorder cases were divided into five main categories: (1) extranodal marginal-zone lymphoma of mucosa-associated lymphoid-tissue type without or with an unknown relationship to IgG4 mucosa-associated lymphoid tissue (MALT lymphoma), (2) malignant lymphomas other than MALT lymphoma (other lymphomas), (3) non-IgG4 orbital inflammation, (4) IgG4-related orbital inflammation, and (5) IgG4-positive MALT lymphoma. Patient numbers for each category were collected. Age and sex data were compared between groups, except the lymphoma group that included several distinct types of lymphomas. Diagnostic criteria were as follows: Malignant lymphomas were diagnosed on the basis of the World Health Organization (WHO) classification. Orbital inflammation included pathological diagnoses of reactive lymphoid hyperplasia, lymphoid infiltrative lesions, and historically so-called "inflammatory pseudotumor." It was sometimes difficult to determine whether a lesion was lymphoid hyperplasic or lymphoid infiltrative, and thus the latter was also included in the category of lymphoproliferative disorders. Cases with typical nonspecific idiopathic orbital inflammation, which led to steroid therapy without biopsy, were excluded from this study. Immunoglobulin heavy-chain gene rearrangement in surgical samples was often examined to support the differential diagnosis between MALT lymphoma and reactive lymphoid hyperplasia. IgG4-related orbital inflammation was determined by characteristic pathological findings: IgG4-positive lymphoplasmacytic infiltration accompanied by follicular formation (germinal center) and fibrosclerosis. Criteria for positive IgG4 immunostaining in orbital samples was either a ratio of IgG4-positive cells to IgG-positive cells ($IgG4^+/IgG^+$ cells) >40 % [14, 15] or when the number of IgG4-positive cells was >30 per high-power microscopy field [16, 17]. IgG4-positive MALT lymphoma was determined by a histopathologic and genetic diagnosis of MALT lymphoma accompanied by positive IgG4 immunostaining. Cases of conjunctival lesions were not included in this study because most conjunctival lesions are MALT lymphoma and IgG4-related conjunctivitis had not been experienced in previous reports [6, 7] or in any institution in this research group. Following the WHO classification, intraocular lymphoma is a category of central nervous system (CNS) lymphoma and thus such cases were also excluded from this study. Enrollment was irrespective of whether or not serum IgG4 was measured but which generally supported the pathological diagnosis of IgG4-RD. Kruskal–Wallis and Mann–Whitney tests with Bonferroni correction were performed to compare ages between disease category groups. Chi-square test was used to analyze sex differences; observed male and female numbers were compared to expected numerical values with a hypothesis that sex ratio would be 1.0 in each disease category.

Results

The breakdown of all histological types of the 1,014 cases of orbital lymphoproliferative disorders was 404 (39.8 %) with MALT lymphoma, 156 (15.4 %) with other malignant lymphomas, 191 (18.8 %) with non-IgG4 orbital inflammation, 219 (21.6 %) with IgG4-related orbital inflammation, and 44 (4.3 %) with IgG4-positive MALT lymphoma (Fig. 1). Diffuse, large B-cell lymphoma and follicular lymphoma were frequent within other malignant lymphoma groups. No lymphomas other than MALT lymphoma showed a relationship with IgG4 in this case series. Figure 2 depicts the age distribution and median ages of the four groups: MALT lymphoma, non-IgG4 orbital inflammation, IgG4-related orbital inflammation, and IgG4-positive MALT lymphoma. Most patients with IgG4-related orbital inflammation were >40 years, and median age was 62 years (63 for men and 60 for women). There were no patients younger than 20 years in the IgG4-related orbital inflammation group. Significant difference in ages among the four groups was detected by the Kruskal–Wallis test ($p < 0.001$). The age of the IgG4-related orbital inflammation group (median 62, range 23–90) was significantly lower ($p = 0.001$ by a Mann–Whitney test $< \alpha = 0.05/6 = 0.0083$, a level of significance determined by Bonferroni correction) than the MALT lymphoma group (median 66, range 25–93) and significantly higher ($p < 0.001$) than the non-IgG4 orbital inflammation group (median 57, range 13–88). There were no significant age

differences ($p = 0.239$) between MALT and IgG4-positive MALT lymphoma groups (median 67.5, range 38–92). Sex ratio (male/female) was 188/216 in the MALT lymphoma group, 68/123 in the non-IgG4 orbital inflammation group, 105/114 in IgG4-related orbital inflammation group, and 28/16 in the IgG4-positive MALT lymphoma group (Fig. 3); a chi-square test suggested there was no significant sex difference between the MALT lymphoma and IgG4-related orbital inflammation groups, whereas the sex ratio was significantly low in the non-IgG4 orbital inflammation group ($p < 0.001$) and high in the IgG4-positive MALT lymphoma group ($p = 0.043$).

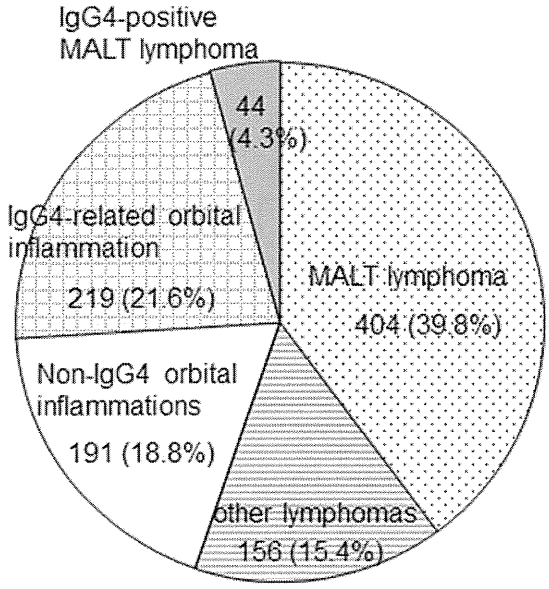

Fig. 1 Breakdown of diagnosis in a set of 1,014 cases of orbital lymphoproliferative disorders. Disease categories were extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), other lymphomas, idiopathic orbital inflammation showing no relationship with immunoglobulin (Ig)G4 (non-IgG4 orbital inflammation), IgG4-related orbital inflammation, and IgG4-positive MALT lymphoma

Discussion

The most characteristic pathological feature in IgG4-RD is dense lymphoplasmacytic cell infiltration [15, 18], the presence of which designates IgG4-related orbital lesions in groups of orbital lymphoproliferative disorders. Differential diagnoses among orbital lymphoproliferative disorders include malignant lymphomas, reactive lymphoid hyperplasia, lymphocyte infiltrative lesions, and lesions that were historically called orbital pseudotumors [7, 13, 17, 19]. Lymphoproliferative disorders comprise the most frequent group in mass-forming orbital diseases. In Japanese studies, the number of lymphoproliferative disorder diagnoses in cases with orbital tumors and simulating lesions was 43 % of 409 cases [20], 38 % of 1,334 cases [11], and 49 % of 213 cases [21]. Although the rate seems to be somewhat lower in the United States

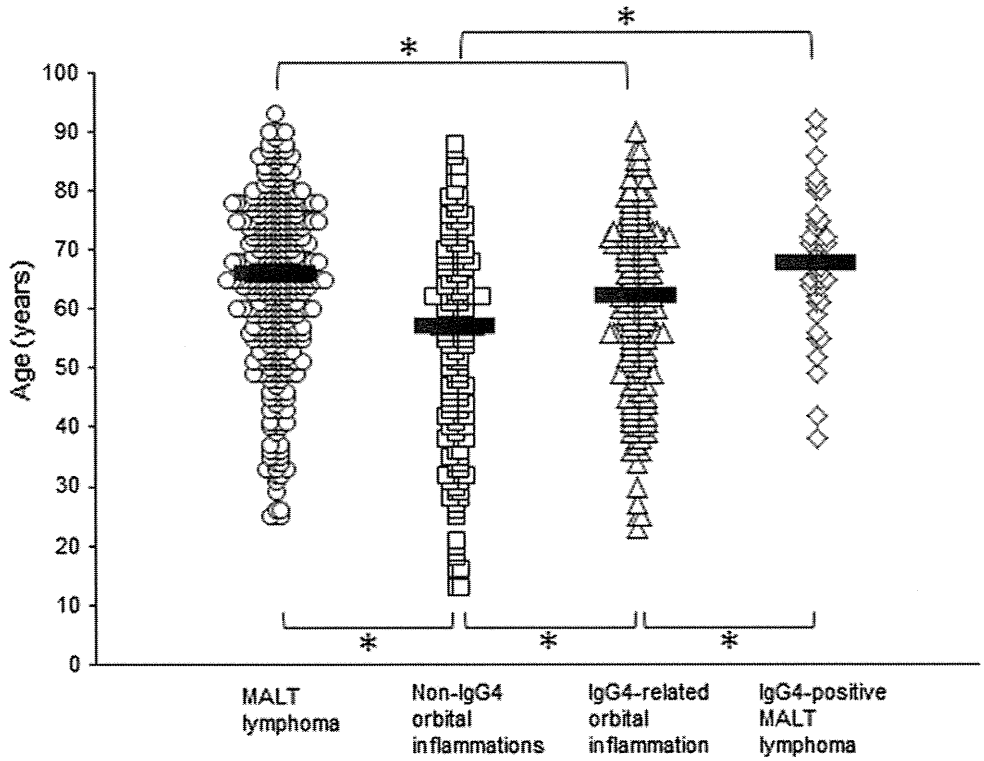

Fig. 2 Age distribution and median ages in disease groups of orbital lymphoproliferative disorders. Each plot depicts age at diagnosis in four groups: extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma, *circle*), idiopathic orbital inflammation showing no relationship with immunoglobulin (Ig)G4 (non-IgG4 orbital inflammation, *square*), IgG4-related orbital inflammation (*triangle*), and IgG4-positive MALT lymphoma (*diamond*). *Horizontal bars* median ages, *asterisks* significant difference by Mann–Whitney test ($p < \alpha = 0.05/6 = 0.0083$ determined by Bonferroni correction) between the two groups

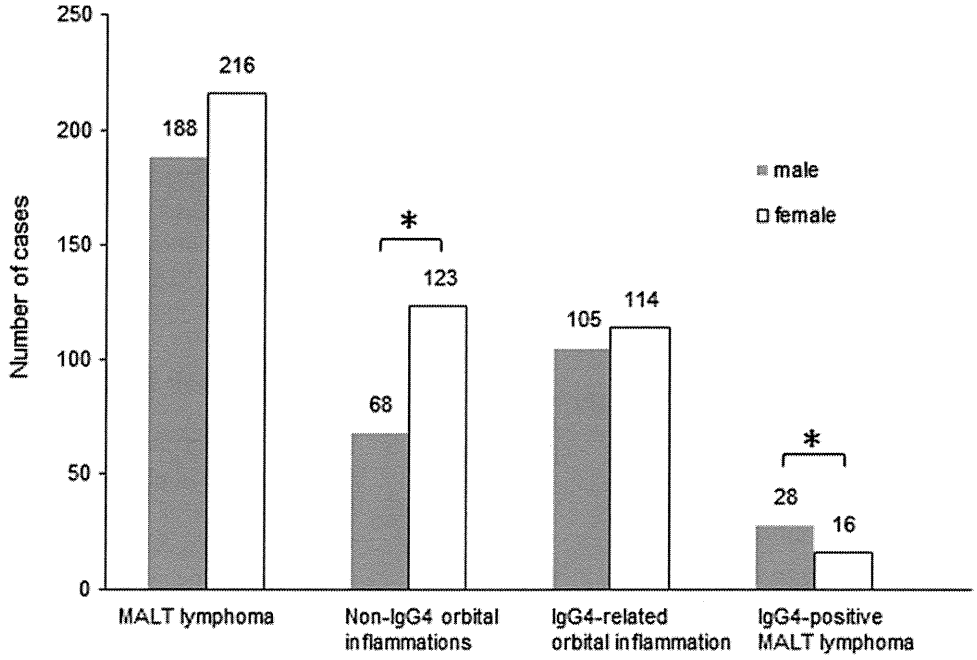

Fig. 3 Sex in orbital lymphoproliferative disorders. Each *bar* depicts the number of male (*gray bar*) and female (*white bar*) patients in the four groups of extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), idiopathic orbital inflammation showing no relation with immunoglobulin (Ig)G4 (non-IgG4 orbital inflammation), IgG4-related orbital inflammation, and IgG4-positive MALT lymphoma. *Asterisk* significant sex difference by chi-square test ($p < 0.05$)

Table 1 Summary of the ages and sex ratio in case series of immunoglobulin (Ig)G4-related disease from data in previous literature and in this study

Disease category of case series	Number	Mean age (years)	Age range (years)	Sex ratio male/female	References
SIPS, including Mikulicz's disease	40	58.9	25–88	11/29	Yamamoto et al. [4]
$IgG4^+$ MOLPS	64	57	17–77	31/34	Masaki et al. [5]
Ocular adnexal IgG4-related disorders	19	nd	nd	9/10	Ohshima [24]
IgG4-related orbital inflammation	16	56	41–76	8/8	Takahira et al. [17]
Ocular adnexal IgG4-related disease	21	59.3	39–86	10/11	Sato et al. [25]
Ocular adnexal IgG4-related lymphoplasmacytic infiltrative disorder	10	58	38–73	5/5	Kubota et al. [7]
IgG4-related lung and pleural disease	21	69	42–76	17/4	Zen et al. [29]
IgG4-related tubulointerstitial nephritis	23	65.2	40–83	20/3	Saeki et al. [30]
IgG4-related kidney disease	41	63.7	27–83	30/11	Kawano et al. [31]
Serum IgG4-positive autoimmune pancreatitis	45	63.7	27–83	36/9	Kamisawa et al. [32]
IgG4-related periaortitis and periarteritis	17	65	54–86	16/1	Inoue et al. [33]
IgG4-related perineural disease	7	58	44–74	7/0	Inoue et al. [34]
IgG4-related sclerosing sialadenitis	10	60	47–74	6/4	Ohta et al. [35]
IgG4-related orbital inflammation	219	61	23–90	105/114	This study

SIPS systemic IgG4-related plasmacytic syndrome, *MOLPS* multiorgan lymphoproliferative syndrome

(24 % lymphoproliferative disorders of 703 cases of orbital lesions [22] and 26 % lymphoproliferative disorders of 268 cases [23]), it appears certain that lymphoproliferative disorders form the most common pathology in the orbit [12].

The number of IgG4-RD diagnoses in cases of orbital lymphoproliferative disorders was previously reported in two Japanese institutes: 16 (25.8 %) of 62 orbital lymphoproliferative disorder cases [17] and 19 (32.8 %) of 58 orbital lymphoproliferative disorder cases [24]. Our multicenter study shows a similar rate: 263 (26.0 %) of 1,014 cases with orbital lymphoproliferative disorders were IgG4 positive. Together, these studies show that IgG4-related ophthalmic diseases account for approximately a quarter of orbital lymphoproliferative disorders in Japan. Orbital inflammation with mild clinical manifestation, regardless of a relationship with IgG4, would improve with low doses of steroids or even without medication and present no need

for lacrimal-gland biopsy or long-term follow-up. Such cases were not included in this study, and their incidence rate is uncertain.

It is noteworthy that in this study 44 (9.8 %) of 448 cases of MALT lymphoma were diagnosed as IgG4 immunopositive (Fig. 1). Previous studies also describe cases of ocular adnexal MALT lymphoma associated with IgG4-RD. Cheuk et al. [14] report three cases of ocular adnexal lymphoma arising in IgG4-related dacryoadenitis and determine that the rate of transformation of malignant lymphoma in the background of IgG4-related orbital inflammation was approximately 10 %, a value similar to that of this study. Sato et al. [6] first detected IgH (immunoglobulin heavy-chain) gene rearrangement in two cases of ocular adnexal IgG4-RD. In their later review, seven patients with ocular adnexal MALT lymphoma arising from IgG4-related orbital disease were reported [25] but the incidence was not stated. In addition, Kubota et al. [26] reported that ten cases of ocular adnexal MALT lymphoma had IgG4-positive plasma-cell infiltration, which comprised 9 % of 111 cases with ocular adnexal MALT lymphoma. These reports suggest that malignant lymphomas occur in the setting of IgG4-related orbital inflammation, whereas other reports indicate that IgG4-producing cells can also be neoplastic [14, 27]. Oyama et al. [28] reported a case of IgG4-expressing MALT lymphoma in the lacrimal gland and pelvis and suggest the possibility of de novo IgG4-positive orbital MALT lymphoma. To summarize, a few pathological states account for IgG4-positive MALT lymphoma: IgG4-negative lymphoma cells are coexistent with benign IgG4-producing plasma cells, and lymphoma cells have the ability to produce IgG4 either with or without benign IgG4-positive cells.

The age differences between IgG4-related orbital inflammation and IgG4-positive MALT lymphoma (Fig. 2) may support the idea that MALT lymphoma arises from pre-existing IgG4-related orbital inflammation. It is uncertain why the non-IgG4 orbital inflammation group in our study was younger than the IgG4-related orbital inflammation group, but one explanation may be that the former included young patients with orbital lymphocyte infiltrative lesions. Table 1 summarizes age and sex data compiled from various case series with IgG4-RD in the published literature [29–34]. Mean age of IgG4-related orbital inflammation in our study was 61 (median age 62) years, and values of other studies were also within the range of 55–65 years [4, 5, 7, 17, 25]. From these findings, it is obvious that patients with IgG4-related ophthalmic diseases who are younger than 20 years of age are extremely rare, which seems to be the key to the pathogenesis of this disease. In this study, there were no actual sex differences in the IgG4-related orbital inflammation group (Fig. 3). Following the data in Table 1, we propose that there is no sex difference in IgG4-related ophthalmic diseases, except for one report of female predominance in cases with Mikulicz's disease [4]. On the other hand, male dominancy has been demonstrated in some other categories of IgG4-RD, such as lung and pleural disease [29], kidney disease [30, 31], periaortitis and periarteritis [33], and perineural disease [34].

There is no doubt that the lacrimal gland is the tissue most frequently involved in IgG4-related orbital inflammation [17, 36]. Extraocular muscles [6, 10, 17, 36] and infraorbital and supraorbital nerve enlargements [8, 9, 17, 36–38] are also frequently diagnosed in cases of IgG4-related ophthalmic disease. Inflammatory lesions in adipose tissue [8] surrounding the optic nerve [17, 34], and even in the lacrimal drainage system [39, 40], occur less frequently. The nomenclature "IgG4-related ophthalmic disease" was proposed to cover all of these IgG4-related lesions occurring in the ophthalmic region [10].

In conclusion, nearly a quarter of orbital lymphoproliferative disorders are estimated to be related to IgG4 in Japan. Further studies are required to evaluate the incidence of each tissue involved in IgG4-related ophthalmic disease.

Appendix

Study group investigators in the Japanese study of IgG4-related ophthalmic disease.

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Clinical vignette

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IgG4-related orbital tumour with eye enucleation—infra-orbital nerve enlargement

A 40-year-old Japanese man presented with loss of vision and exophthalmos in the right eye. The MRI showed the lesion was around the optic nerve in the right orbit. Infra-orbital nerve enlargement (IONE) was apparent in the left orbit, but it was not recognized at that time (Fig. 1). The lesions were diagnosed as meningioma, and the right eye and orbital tumour were removed. Pathological analysis revealed abundant infiltration of IgG4-bearing plasmacytes and storiform fibrosis without meningioma cells. The lesion had developed around the optic nerve. Then the patient was introduced to us. Physical examination disclosed sensory nerve dysfunction around the bilateral cheeks, and serological testing revealed elevated levels of serum IgG4. IgG4-related ophthalmic disease was diagnosed and the patient was prescribed prednisolone at a dose of 40 mg/day, with gradual improvement of the IONE.

Perineuritis is a characteristic nerve lesion of IgG4-related disease, and often occurs at the optic nerve, trigeminal nerves (including supra- and infra-orbital nerves) and spinal nerves [1]. In particular, lesions of the infra-orbital nerve are recognized as IONE because the MRI finding is easily identifiable and useful for the diagnosis of patients with trigeminal nerve involvement [2]. When IONE is found, it is recommended to differentiate from IgG4-related disease and perform a biopsy before the ophthalmectomy.

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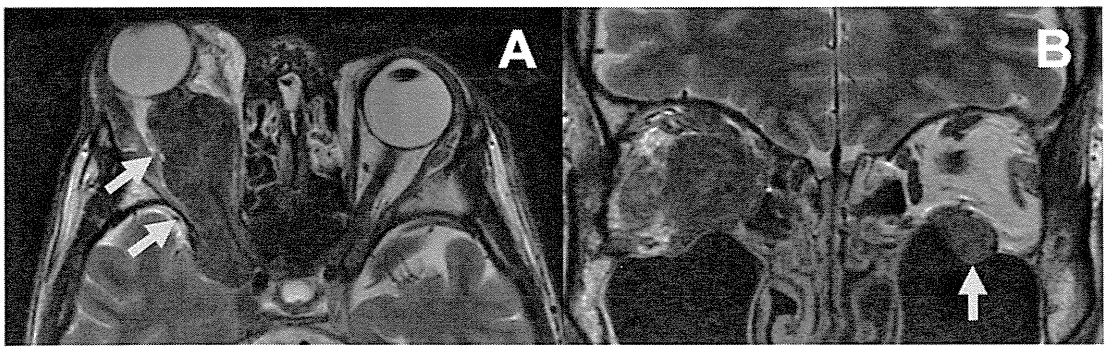
2 Ohshima K, Sogabe Y, Sato Y. The usefulness of infraorbital nerve enlargement on MRI imaging in clinical diagnosis of IgG4-related orbital disease. Jpn J Ophthalmol 2012;56:380–2.

Fig. 1 Preoperative brain MRI.



(**A**) T1-weighted axial imaging. The lesion is apparent around the optic nerve in the right orbit (arrow). The eyeball is extruded forward. (**B**) T1-weighted coronal imaging. Infra-orbital nerve enlargement (IONE) is apparent in the left orbit (arrow).