Clinical Features and Outcomes of Immunoglobulin G4-related Disease

Sua Lee
Seoul National University Hospital
Chul Woo Yang (yangch@catholic.ac.kr)
Seoul St. Mary's Hospital

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Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a newly recognized disease, and a few epidemiologic studies about this disorder have been published. This research aimed to describe the clinical, laboratory, and histopathological features and outcomes of IgG4-RD. Ninety-four patients who satisfied the comprehensive diagnostic criteria on IgG4-RD were included in this study. Fifty-eight (61.7%) were men. The mean age was 54.8 years, and the median follow-up duration was 32.9 months. The clinical feature between single and multiple organ involvement and with or without kidney involvement groups were evaluated based on symptoms and laboratory findings. The clinical outcome was assessed according to treatment strategies and response. Of 94 patients, 56 (59.6%) had multiple organs involvement. Patients with multiple organ involvement had higher serum IgG and IgG4 levels than those with single organ involvement. Those with IgG4-related kidney disease (IgG4-RKD) had worse renal function, and the incidence of peripheral blood eosinophilia and hypocomplementemia was higher in patients with renal involvement than in those without. Glucocorticoids-based therapy was most commonly used. (79.8%). Thirty-nine (41.5%) achieved complete remission. Eighteen (19.1%) relapsed after response to treatment. IgG4-RD had different clinical features and outcomes. The number of organ involvement and kidney involvement were not associated with clinical outcomes.

Introduction

Immunoglobulin G4-related disease (IgG4-RD) was first reported as Japanese patients with sclerosing pancreatitis in 2001.[1] Currently, IgG4-RD is considered a systemic disorders based on several reports. It is a unique immune-mediated disease that can occur in each organ.[2,3] Moreover, it is characterized by elevated serum IgG4 concentration, lymphoproliferative infiltration enriched with IgG4-positive plasma cells in affected tissues, and distinct storiform fibrosis in affected organs.[3-6] The global incidence of IgG4-RD remains unknown. To date, most studies include case reports, those with a small cohort, and epidemiological research. Most epidemiological studies have been reported in North America, Europe and Japan.[7-13] The current study aimed to evaluate the clinical features and outcomes of IgG4-RD.

Results

Basic demographic and clinical characteristics of patients with IgG4-RD

In total, 94 patients were diagnosed with IgG4-RD, and the number of newly diagnosed patients in our cohort increased annually (Figure 1). The basic demographic and clinical characteristics of all patients with IgG4-RD are presented in Table 1. The mean standard deviation (SD) age at diagnosis was 54.8 ± 14.2 years, and the median follow-up duration was 32.9 (interquartile range (IQR): 14.9, 55.4) months. In total, 58 (61.7%) of 94 patients were men. Three patients (3.2%) had autoimmune diseases prior to IgG4-RD. One patient had systemic lupus erythematosus, and two patients had Sjögren's syndrome. Five (5.2%) had malignant diseases such as thyroid cancer (n = 1), breast cancer (n = 1), prostate cancer (n = 1), gastric cancer (n = 1) and craniopharyngioma (n = 1). Among them, four had no malignant diseases at

the time of IgG4-RD diagnosis. Only one patient with prostate cancer was treated with hormone therapy. Fifty-six (59.6%) patients with IgG4-RD experienced involvement of two or more organs. Patients presented with various symptoms based on the organs involved. Flank pain (13.5%) was the most common symptom, followed by abdominal pain (12.5%) and eyelid swelling (12.5%). Five (5.2%) patients were incidentally found to have elevated serum creatinine level based on medical examinations. Four (4.2%) presented with fever alone. Further, 10 (10.6%) patients were incidentally diagnosed via imaging studies during health screenings. Imaging studies were performed to diagnose all patients, and computed tomography (CT) scan was the most commonly used method (78.4%).

Based on the laboratory findings, 12 (12.8%) patients presented with eosinophilia, and the median eosinophil count was 150.0/μL (IQR: 69.4, 282.1). Moreover, 10 of 12 patients with eosinophilia had multiple organ involvement. Approximately half of patients had an elevated serum erythrocytes sedimentation rate (ESR) or high-sensitivity C-reactive protein (hs-CRP). Of 69 patients who underwent the serum complement test, 10 (14.5%) had hypocomplementemia. Moreover, 62 (75.6%) of 82 patients who underwent the serum IgG4 level test had an elevated serum IgG4 concentration, which is part of the CDC. Eighteen (19.1%) patients had autoantibodies at the time of IgG4-RD diagnosis. Anti-nuclear antibody (ANA) was most commonly observed (n = 17 [18.1%]). One (1.1%), three (3.2%), three (3.2%), and one (1.1%) patient presented with anti-double stranded DNA antibody (anti-dsDNA Ab), Sjögren's syndrome-related antigen A antibody (anti-SSA/SSB Ab), anti-mitochondria antibody (AMA), and anti-centromere antibody (Ab), respectively. The median leukocyte count, lymphocyte count, hemoglobin, serum albumin, and albumin-to-globulin ratio were within normal range.

In total, 74 (78.7%) patients underwent biopsy of the involved organs. According to the comprehensive diagnostic criteria (CDC)[14], 44 (46.8%) patients were diagnosed with definite IgG4-RD.

The distributions of organ involvement are shown in Figure 2. In terms of clinical manifestations, the involved organs were extremely diverse. The lymph nodes (36.1%) were the most commonly involved organs. However, the retroperitoneum was the most frequently affected organ (26.6%) as an isolated organ. The incidence of retroperitoneum involvement was significantly higher in men than in women (35.6% vs 13.5%; P = 0.018). The commonly affected organs were the salivary gland (20.2%), lacrimal gland (18.1%), and kidney (13.8%). One patient had bone marrow (BM) involvement. Diffuse ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptakes in the spine, sternum, and both pelvic bones was confirmed, and the number of plasma cells increased by approximately 5% based on BM biopsy. The involvement of skull, tonsil, breast, pericardium, abdominal wall and bladder were found in each one patient.

Differences in clinical features between patients with single and those with multiple organ involvement

The differences of clinical features between patients with single and those with multiple organ involvement are presented in Table 2, and the distribution of organ involvement is shown in Figure 2. The mean age at diagnosis, male-to-female ratio, and prevalence of underlying diseases were similar between patients with single and those with multiple organ involvement. Eosinophilia and hypocomplementemia

were more commonly observed in patients with multiple than in those with single organ involvement. However, the results did not significantly differ. The serum IgG and IgG4 levels were significantly higher in patients with multiple organ involvement than in those with single organ involvement (P = 0.037 and P = 0.020, respectively). The retroperitoneum was the most commonly affected organ in patients with single and multiple organ involvement. The salivary gland was more frequently affected in patients with multiple than in those with single organ involvement (P = 0.014).

The proportion of patients with elevated ESR and CRP levels and those with autoimmune Ab did not differ between the single and multiple organ involvement groups.

Differences in clinical features based on the presence of IgG4-RKD

The differences in clinical features according to renal involvement are presented in Table 3. The patients with IgG4-related kidney disease (IgG4-RKD) were older than those without (P = 0.040). A high number of patients had hypertension prior to IgG4-RD diagnosis (P = 0.018). All patients with IgG4-RKD underwent biopsies of affected organs, and the characteristic pathologic findings were confirmed in all patients. Eleven patients with IgG4-RKD underwent kidney biopsies, and two biopsies of other affected organs, such as the lacrimal gland and bile duct. In terms of kidney biopsy findings, lymphoplasmacytic infiltration was observed in all tissues, and only one patient presented with obliterative phlebitis. The final diagnosis was tubulointerstitial nephritis (TIN). At the time of diagnosis, the renal function of patients with IgG4-RKD was worse than of those without. After treatment, eight (61.5%) patients with IgG4-RKD experienced improvement in Chronic Kidney Disease-Epidemiology collaboration eGFR (CKD-EPI-eGFR). Peripheral blood eosinophilia was more common in patients with IgG4-RKD (P = 0.011). The mean complement C3 and C4 levels were significantly lower in patients with IgG4-RKD than in those without (P = 0.026 and P = 0.031, respectively). Hypocomplementemia was more common in patients with IgG4-RKD (P = 0.007). The serum IgG and IgG4 levels did not significantly differ between patients with and without IgG4-RKD.

Treatment strategies and response

The treatment strategies and responses are shown in Figure 3 and 4. The most common treatment was glucocorticoids (GCs) monotherapy (n = 50 [53.2%]). GCs were administered in combination with other immunosuppressive agents or surgical resection. Hence, 75 (79.8%) patients received GCs-based therapy. Some patients did not respond to GCs monotherapy. Among them, 16 (17.0%) patients received GCs combined with other medications such as azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil. Nine (9.6%) patients who did not receive treatment were followed-up. Of them, three patients achieved complete remission. The median treatment duration was 14.7 (IQR: 4.2, 43.8) months. The median initial GCs (prednisolone) dose was 45 mg/day, and the median maintenance dose was 5 mg/day. The proportion of patients based on treatment strategies was similar between patients who presented with single and those with multiple organ involvement and those with or without IgG4-RKD.

Three patients were lost to follow-up after diagnosis. Therefore, 91 patients were evaluated for treatment response. The median interval from treatment initiation to follow-up imaging study was 3 months (IQR: 1.2, 6.5). In total, 43 (47.3%) and 34 (37.4%) patients had complete and partial response, respectively. Complete response was more common in patients treated with GCs combined with other immunosuppressive agents or surgical resection than in those who received other therapies (P = 0.044). The proportion of patients who responded to treatment was similar between the single and multiple organ involvement groups or with or without IgG4-RKD groups. In total, 39 (41.5%) of 91 patients achieved remission during the follow-up period, and 18 (19.1%) patients received additional treatments because of relapse. Remission was more common in patients with complete response during the first evaluation (P < 0.001). The remission and relapse rates did not significantly differ according to the presence of IgG4-RKD. Relapse was more frequent in patients with multiple than in those with single organ involvement (28.6% vs. 5.3%; P = 0.005). However, none of the patients died during the follow-up period.

Discussion

There were 94 cases of IgG4-RD in three medical college-affiliated hospitals during the 10.5- years study period. In our study, there were only 1-5 new cases per year within the first 6 years. However, it increased to more than 10 cases per year with the last 4 years. This finding showed that the diagnosis of IgG4-RD made by clinicians is increasing, and more cases of IgG4-RD may be reported in Korea, with consideration of the incidence of IgG4-RD (0.28 – 1.08 per 100,000) and the newly diagnosed patients each year of IgG4-RD (336 – 1300 patients) in Japan.[17]

The clinical features of IgG4-RD in our study were similar to those of previous studies in terms of sex, age, and organs involved.[10-13,15] Our study differed from previous studies. First, the initial clinical symptoms vary based on organ involvement. However, the most common symptoms in previous studies were salivary gland swelling, lacrimal gland swelling, and nonspecific abdominal pain.[10,12,16,17] By contrast, in our study, the most common symptom was flank pain, and all patients were initially diagnosed with retroperitoneal fibrosis (RPF) with hydronephrosis. RPF can occur due to several etiologies, and it is categorized as idiopathic and secondary based on the medications used, autoimmune disease, and malignancy. This study showed the role of IgG4-RD in the development RPF. Second, 10 (10.6%) patients were incidentally diagnosed via imaging studies during health screenings. If patients who incidentally found azotemia were included, 15 (16.0%) patients were not symptomatic at the time of IgG4-RD diagnosis. Third, in our cohort, unlike previous studies, pancreas involvement was significantly less common. The pancreas is frequently involved in IgG4-RD. The prevalence rate is approximately 25 ~ 60%, and that in our cohort is 8.5%.[12,13,16-18] Forth, in previous studies, allergic disease was commonly observed, and eosinophilia was frequently noted particularly among Japanese, Chinese and Caucasian.[10,12,16,17] However, in our cohort, only one patient had bronchial asthma, which was treated with steroid inhaler, prior to IgG4-RD diagnosis. The incidence of eosinophilia was relatively lower in this study than in previous studies.[11,12]

In our study, 38 and 56 patients presented with single and multiple organ involvement, respectively. Since IgG4-RD is a systemic disease, whether the clinical features and prognosis differed based on the number of organs involved was evaluated. Results showed no significant difference in clinical features and outcomes between patients with single and those with multiple organ involvement, except those with high serum IgG4 concentration and relapse in multiple organ involvement. These results were similar to those of previous studies.[11,16,17,19,20] Although patients had a higher serum IgG4 concentration and relapse rate in multiple organ involvement, the response to treatment and the rate of complete remission did not differ between patient with single and those with multiple organ involvement.

The kidney is one of the relatively common organs involved in IgG4-RD. However, only few studies have investigated the differences in clinical characteristics in patients with or without IgG4-RKD.[11,21] Thus, we compared the clinical features and outcomes between these patients. Results showed that patients with IgG4-RKD were older and had a higher incidence of hypertension. The association between renal and retroperitoneal involvement was not observed in our cohort. This finding may indicate that retroperitoneal involvement is not a secondary reaction to IgG4-RKD. In terms of renal histopathological findings, all patients had TIN. Glomerular changes were observed in one tissue. However, an accurate diagnosis could not be obtained due to 86% of global glomerular sclerosis. All glomerular and tubulointerstitial disease including TIN, membranous nephropathy, immunoglobulin A nephropathy, mesangial proliferative and membranous proliferative glomerulonephritis can be noted in histopathological findings, and TIN is known as the most common finding.[22,23] Lymphoplasmacytic infiltration with storiform fibrosis was the most common finding in our cohort. However, there were specific histological features that can be used to distinguish IgG4-RKD from other TIN in previous studies.[24,25] Hypocomplementemia was an important laboratory finding, particularly in IgG4-RKD, and this finding is in accordance with previous studies.[4,9,26] In general, serum IgG4 does not to bind to complement component 1q and does not activate the classical complement pathway.[5] Thus, the other IgG subtypes, such as IgG1 and IgG3, may be associated with the pathogenesis of IgG4-RD, with consideration of the incidence of hypocomplementemia.

GCs therapy is the gold standard for treatment. However, there is no the international standard guideline for treatment. IgG4-RD responds well to GCs therapy symptomatically, radiologically, and serologically.[5,6] The most common treatment was according to GCs-based therapy in our cohort. The rate of response to GCs-based therapy was 85.3%. However, the relapse rate was 21.3% when GCs therapy is discontinued or the minimal dose of GCs is maintained, and this is in accordance with a previous report.[27] In addition, approximately 10% of patients received the wait-and-see treatment. Among them, one-third had spontaneous remission based on a previous report.[27] In general, GCs therapy is the gold standard treatment. However, it is not curative. In addition, with consideration of spontaneous remission cases, further studies about the pathophysiology of IgG4-RD have to be conducted.

Our study had several limitations. First, this was a retrospective observational study. Second, the diagnosis and treatment strategy for IgG4-RD were inconsistent. Third, because the follow-up duration was short and there was a lack of standard tool for the assessment of disease outcome, some data

about treatment response and outcomes were missing. Despite these limitations, the biopsy rate was 78.7%. Moreover, the serum IgG4 concentration of most patients was measured, and all patients underwent imaging studies for IgG4-RD diagnosis.

In conclusion, kidney or other organ involvement is not significantly associated with clinical outcomes. Since IgG4-RD has different clinical features, it should be accurately diagnosed, and all physicians must actively diagnose and treat the condition. Hence, it is necessary to establish international diagnostic criteria and treatment guidelines.

Materials And Methods

Population

The current study was approved by the institutional review board of Seoul St. Mary's Hospital of the Catholic University of Korea (IRB No. KC20RASI6074), and it was performed in accordance with the Declaration of Helsinki. This retrospective observational study included patients diagnosed with IgG4-RD using the CDC from January 2009 to July 2020 at Seoul St. Mary's hospital, Yeouido St. Mary's hospital, and Uijeongbu St. Mary's hospital. Data were collected from the patient's electronic medical records.

Evaluation of clinical features

We extracted data on age at diagnosis, sex, follow-up duration, comorbidities (hypertension, diabetes, autoimmune disease, and malignancy), number of organs involved, type of imaging study, whether or not biopsy was required, IgG4-RD disease grade, and treatment strategies and duration. Information on clinical characteristics was collected from the patient's electronic medical records during the first hospital visit. Organ involvement was defined as the presence of lesions confirmed via imaging studies or characteristic pathological findings (e.g., dense lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells, storiform pattern of fibrosis, and obliteration of vein with lymphoplasmacytic infiltrate) of IgG4-RD on biopsy. Meanwhile, multiple organ involvement was defined as two or more affected organs.

We analyzed data regarding CBC, blood chemistry, ESR, and hs-CRP, serum complement component 3, complement component 4, serum IgG, IgG4, ANA, anti-dsDNA Ab, anti-SSA Ab, anti-SSB Ab, AMA, anti-centromere antibody, and urine protein-to-creatinine levels. Renal function was assessed using the CKD-EPI eGFR.

To confirm whether organs were affected, all patients underwent imaging studies, including CT scan, magnetic resonance imaging, and ^{18}F-FDG/CT scan at the time of diagnosis.

Diagnosis of IgG4-related disease

Patients were diagnosed with IgG4-RD according to the CDC and/or other specific criteria for each organ, such as the presence of type 1 autoimmune pancreatitis, IgG4-RKD, IgG4-related Mikulicz's disease (IgG4-related sialadenitis and dacryoadenitis), and IgG4-related sclerosing cholangitis.[14] The CDC comprises

three parts, which are as follows: (a) clinical or radiological features showing diffuse/localized swelling or masses in single or multiple organs; (b) serological examination showing elevated serum IgG4 concentrations (≥ 135 mg/dL); (c) histopathological findings including marked lymphoplasmacytic infiltrate with fibrosis and infiltrate of IgG4-positive plasma cells with an IgG4+/IgG+ plasma cell ratio of > 40% and IgG4+ plasma cell/high power field (HPF) of > 10. In addition, patients were classified into three based on the number of fulfilled criteria: (1) those who fulfilled all three criteria were diagnosed with definite IgG4-RD, (2) those who fulfilled the clinical and histopathological criteria but without elevated serum IgG4 concentrations were diagnosed with probable IgG4-RD, and (3) those who fulfilled the clinical and serological criteria but without histopathological features were diagnosed with possible IgG4-RD.

Evaluation of treatment response and outcomes

The standard guideline for the evaluation of treatment response has not yet been established. After treatment initiation, the clinical characteristics or follow-up radiologic findings were identified, and treatment responses were classified as follows:

(1) Complete response: there were no clinical symptoms, and complete disappearance of organ involvement was observed on follow-up imaging studies.

(2) Partial response: there was improvement in clinical symptoms, and > 50% of organ involvement was treated based on follow-up imaging studies.

(3) Stable disease: symptoms still remained and there was no change in organ involvement based on imaging studies, or there was less than 50% regression.

(4) Progression: new symptoms or organ involvement was found, or previous symptoms and organ involvement worsened.

The disease outcomes were complete remission and relapse after treatment completion or minimal maintenance treatment. Complete remission was defined as persistent state without symptoms and resolution of organ involvement after treatment within the follow-up period. Relapse was defined as reappearance of organ involvement or occurrence of new organ involvement after treatment completion.

Statistical analysis

Continuous variables (including demographic and clinical characteristics) with a normal distribution were presented as mean ± SD and those with a non-normal distribution as median (IQR). Categorical variables were expressed as frequency and percentage. The chi-square test was performed to compare different groups and categorical variables. Meanwhile, the Fisher's exact test was used if the assumptions required for parametric testing were not met. The student’s *t*-test and the Kolmogorov-Smirnov t-test were utilized to compare continuous variables with a normal distribution. The Mann-Whitney U-test was applied to compare variables with a non-normal distribution. A P value of < 0.05 was considered statistically

significant. All statistical analyses were performed using the Statistical Package for the Social Sciences software version 24 (IBM Inc., United States).

Declarations

AUTHOR CONTRIBUTIONS

Conceptualization, S.L.; data curation, S.L.; formal analysis, S.L.; methodology, C.W.Y., S.L.; project administration, C.W.Y.; supervision, C.W.Y.; writing-original draft, S.L.; writing-review and editing; S.L., C.W.Y.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

This study was approved by the institutional review board of Seoul St. Mary's Hospital of the Catholic University of Korea (IRB No. KC20RASI6074), and informed consent was waived from IRB due to the retrospective design.

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Tables

Table 1. Basic demographic and clinical features of IgG4-RD patients

Variables	Patients, n (%)
Sex, male	58 (61.7)
Underlying disease	36 (38.3)
DM	15 (16.0)
HTN	24 (25.5)
Autoimmune disease	3 (3.2)
Malignancy	5 (5.3)
Multiple (≥2 organs involved)	56 (59.6)
Presence of symptoms	84 (89.4)
Imaging study	
CT	74 (78.7)
MRI	15 (16.0)
^{18}F-FDG/CT	8 (8.5)
Laboratory findings	
Eosinophilia (> 500/μL)	12 (12.8)
Elevated ESR (> 20 mm/hr)	50/85 (58.8)
Elevated CRP (> 0.47 mg/dL)	42/91 (46.2)
Hypocomplementemia	10/69 (14.5)
Elevated serum IgG4 (≥ 135 mg/dL)	62/82 (75.6)
Positive autoantibodies	18 (19.1)
Biopsy	74 (78.7)
Disease grading	
Definite	44 (46.8)
Probable	23 (24.5)
Possible	27 (28.7)

DM, diabetes mellitus; HTN, hypertension; CT, computed tomography; MRI, magnetic resonance imaging; ^{18}F-FDG/CT, ^{18}F-fluorodeoxyglucose positron emission tomography; ESR, erythrocytes sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; IgG4, immunoglobulin G4.

Table 2. Differences in clinical features between patients with single and multiple organ involvement

Variable	Single organ (n=38)	Multiple organs (n=56)	*P*-value
Age at diagnosis (years), mean ± SD	55.4 ± 13.4	54.4 ± 14.8	0.473
Sex, male, n (%)	20 (52.6)	38 (67.9)	0.136
Follow-up duration (months), median (IQR)	25.5 (9.3, 43.5)	35.5 (23.2, 59.9)	***0.019***
Underlying disease, n (%)	16 (42.1)	20 (35.7)	0.532
DM	7 (18.4)	8 (14.3)	0.591
HTN	12 (31.6)	12 (21.4)	0.268
Autoimmune disease	1 (2.6)	2 (3.6)	1.000
Malignancy	3 (7.9)	2 (3.6)	0.391
Presence of symptoms	33 (86.8)	51 (91.1)	0.519
Eosinophilia (> 500/ μL), n (%)	2 (5.3)	10 (17.9)	0.114
Elevated ESR (> 20 mm/hr), n (%)	19 /35(54.3)	33/50 (62.0)	0.477
Elevated CRP (> 0.47 mg/dL), n (%)	18/37 (48.6)	24/54 (44.4)	0.693
Hypocomplementemia, n (%)	2 (7.4)	8 (19.0)	0.295
IgG (mg/dL), median (IQR) (normal range; 870 ~ 1700)	1417.5 (1060.8, 1698.5)	1671.0 (1274.0, 2354.0)	***0.037***
IgG4 (mg/dL), median (IQR) (normal range; 3.9 ~ 86.4)	277.5 (77.7, 470.5)	434.5 (164.5, 1197.5)	***0.020***
Elevated serum IgG4 (≥ 135 mg/dL), n (%)	21/32 (65.6)	43/50 (82.0)	0.092
Autoimmune Ab, n (%)	7 (18.4)	11 (19.6)	0.883
Biopsy, n (%)	25 (65.8)	49 (87.5)	***0.012***
Disease grading, n (%)			
Definite	12 (31.6)	32 (57.1)	***0.015***
Probable	10 (26.3)	13 (23.2)	0.731
Possible	16 (42.1)	11 (19.6)	***0.018***
Remission	15 (39.5)	24 (42.9)	0.744
Relapse	2 (5.3)	16 (28.6)	***0.005***

SD, standard deviation; IQR, interquartile range; DM, diabetes mellitus; HTN, hypertension; ESR, erythrocytes sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; IgG, immunoglobulin G; IgG4, immunoglobulin G4; Ab, antibody.

Table 3. Differences in clinical features according to the presence of IgG4-RKD

Variables	With IgG4-RKD (n=13)	Without IgG4-RKD (n=81)	*P*-value
Age at diagnosis (years), mean ± SD	62.2 ± 10.8	53.6 ± 14.3	***0.040***
Sex, male, n (%)	10 (76.9)	48 (59.3)	0.357
Follow-up duration (months), median (IQR)	32.9 (14.4, 56.2)	32.8 (14.7, 54.4)	0.980
Underlying disease, n (%)	8 (61.5)	28 (34.6)	0.074
DM	2 (15.4)	13 (16.0)	1.000
HTN	7 (53.8)	17 (21.0)	***0.018***
Autoimmune disease	0 (0.0)	3 (3.7)	1.000
Malignancy	2 (15.4)	3 (3.7)	0.139
Number of organ involvement, n (%)			0.445
Single	4 (30.8)	34 (42.0)	
Multiple (≥2 organs involved)	9 (69.2)	47 (58.0)	
Disease grading, n (%)			
Definite	9 (69.2)	35 (43.2)	0.081
Probable	4 (30.8)	19 (23.5)	0.729
Possible	0 (0.0)	27 (33.3)	***0.017***
Serum creatinine before treatment (mg/dL), mean ± SD	1.82 ± 1.49	1.14 ± 1.42	***0.005***
CKD-EPI eGFR before treatment (ml/min/1.73m^2), mean ± SD	56.8 ± 33.6	87.8 ± 28.5	***0.006***
Urine protein-to-creatinine ratio before treatment, median (IQR)	0.24 (0.18, 0.95)	0.12 (0.05, 0.47)	0.169
Eosinophilia (> 500/ μL), n (%)	5 (38.5)	7 (8.6)	***0.011***
Elevated ESR (> 20 mm/hr), n (%)	9/11 (81.8)	41/74 (55.4)	0.115
Elevated CRP (> 0.47 mg/dL), n (%)	8/13 (61.5)	34/78 (43.6)	0.229
Hypocomplementemia, n (%)	4/7 (57.1)	6/62 (9.7)	***0.007***
Elevated serum IgG4 (≥ 135 mg/dL), n (%)	9/12 (75.0)	53/70 (75.7)	1.000
Autoimmune Ab, n (%)	3 (23.1)	15 (18.5)	0.709

Remission	5 (38.5)	34 (42.0)	0.811
Relapse	4 (30.8)	14 (17.3)	0.265

IgG4-RKD, immunoglobulin G4-related kidney disease; SD, standard deviation; IQR, interquartile range; DM, diabetes mellitus; HTN, hypertension; CKD-EPI eGFR, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtrate rate; ESR, erythrocytes sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; IgG, immunoglobulin G; IgG4, immunoglobulin G4; Ab, antibody.

Figures

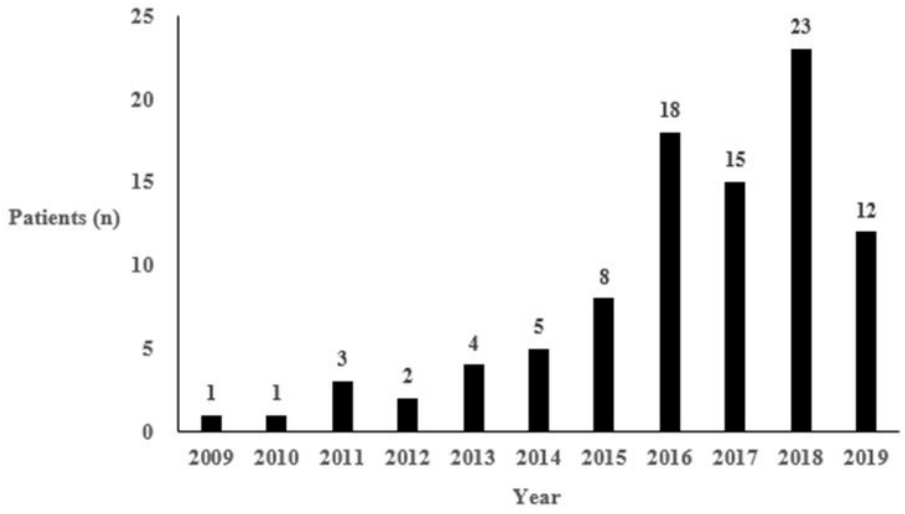

Figure 1

Number of newly diagnosed patients each year The number of patients newly diagnosed with IgG4-RD increased annually. IgG4-RD, immunoglobulin G4-related disease; n, number.

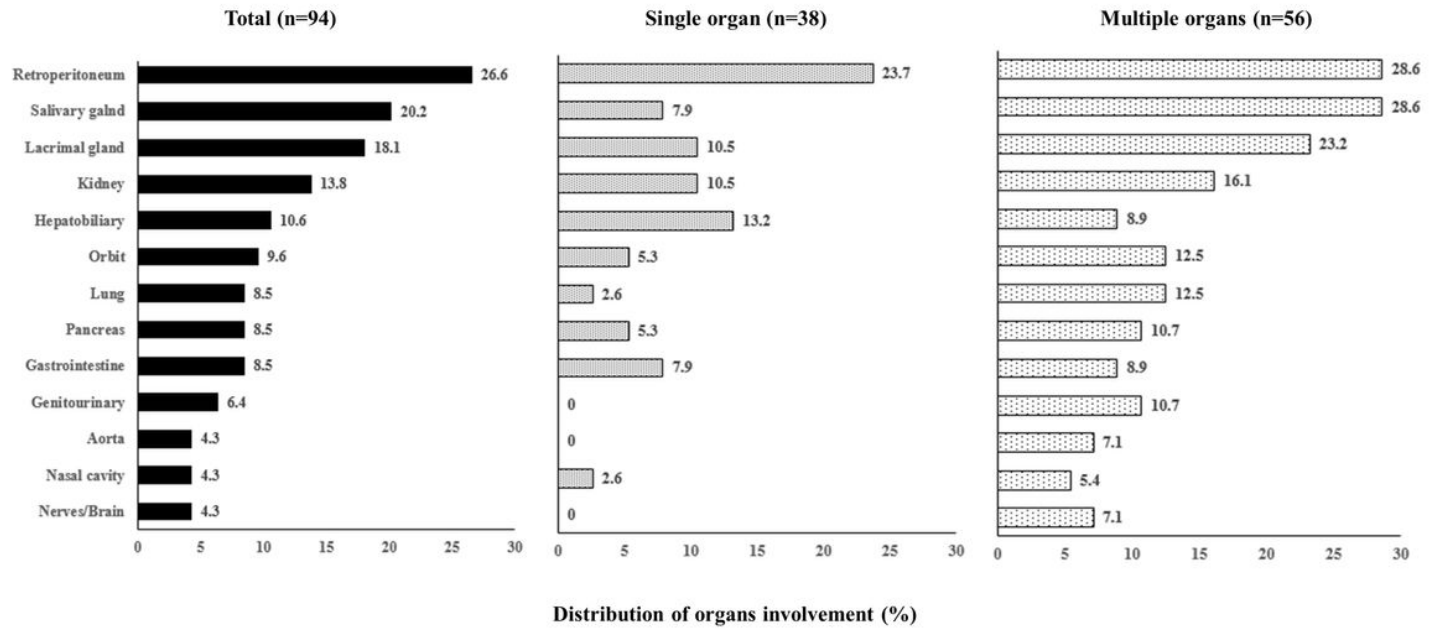

Figure 2

Distribution of organs involvement Distribution of organs involvement (%) in the total population, single organ involvement group, and multiple organs involvement group.

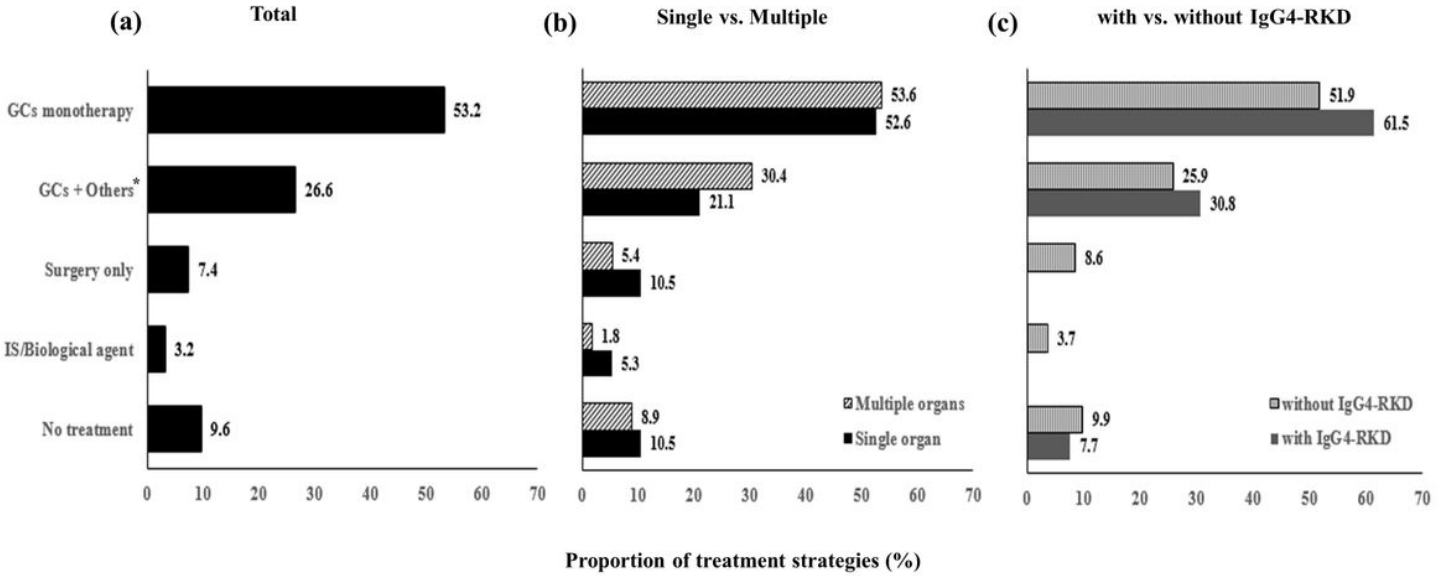

Figure 3

Treatment strategies (a) Proportion (%) of patients according to treatment strategies in the total population. (b) Differences in treatment strategies between the single and multiple organ involvement groups. (c) Differences in treatment strategies according to the presence of IgG4-RKD. GCs, glucocorticoids; IS, immunosuppressants; IgG4-RKD, immunoglobulin G4-related kidney disease. *azathioprine, methotrexate, cyclosporine, mycophenolate mofetil and surgery.

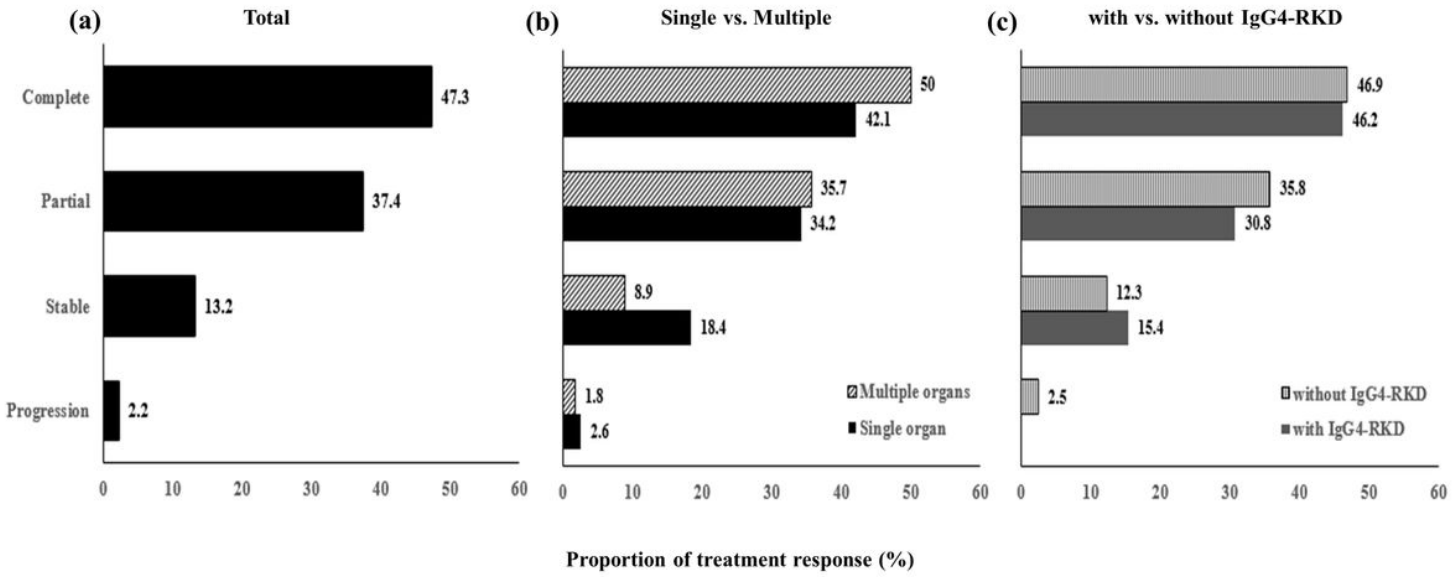

Figure 4

Treatment response (a) Proportion (%) of patients according to treatment response in the total population. (b) Differences in treatment response between the single and multiple organ involvement groups. (c) Differences in treatment response according to the presence of IgG4-RKD. IgG4-RKD, immunoglobulin G4-related kidney disease.