

**IgG4-Related Disease:
Clinical and laboratory features in 125 patients**

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Abstract

Purpose: IgG4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition that can affect nearly any organ. No detailed clinical and laboratory assessments have been reported in large numbers of patients with IgG4-RD diagnoses established by strict clinicopathological correlation.

Methods: We reviewed the baseline features of 125 patients with biopsy-proven disease. The diagnosis was confirmed by pathology review according to consensus diagnostic criteria and clinicopathologic correlation. Disease activity and damage were assessed by the IgG4-RD Responder Index (RI). Flow cytometry was used to assess levels of circulating plasmablasts.

Results: Of the 125 patients, 107 had active disease and 86 were on no treatment. Only 51% of the patients with active disease had elevated serum IgG4 concentrations. However, patients with active disease and elevated serum IgG4 concentrations were older, had a higher RI, a greater number of organs involved, lower complement levels, higher absolute eosinophil counts, and higher IgE levels compared to those with active disease but normal serum IgG4 ($P < 0.01$ for all comparisons). The correlation between IgG4+ plasmablast level and RI ($R = 0.45$, $P = 0.003$) was stronger than that of total plasmablasts and RI. Seventy-six (61%) of the patients were male, but no significant differences according to gender were observed with regard to disease severity, organ involvement, or serum IgG4 concentrations. Glucocorticoids failed to produce sustained remission in 77% of patients.

Conclusion: Nearly 50% of this patient cohort with biopsy-proven, clinically-active IgG4-RD had normal serum IgG4 concentrations. Serum IgG4 elevations identify a subset with more inflammatory features. IgG4+ plasmablasts correlate well with disease activity.

Introduction

IgG4-related disease (IgG4-RD) has emerged as a unique immune-mediated condition that links multiple fibro-inflammatory disorders previously regarded as separate entities (1). IgG4-RD, initially described in a cohort of Japanese patients with “sclerosing pancreatitis” (2, 3) has now been reported across an ethnically diverse spectrum in nearly every organ (4, 5). The disease has a predilection for middle-aged to elderly individuals and a tendency to affect males (5-9). The incidence and prevalence of IgG4-RD have not been established comprehensively because of the relative novelty of this diagnosis, but the burgeoning medical literature on this condition from all subspecialties within medicine, surgery, radiology, and pathology suggests that the disease remains under-recognized.

The gold-standard for the diagnosis of IgG4-RD, regardless of the organ(s) involved, is the identification of typical histopathology features (e.g., lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis) in the context of a significant IgG4+ plasma cell infiltrate (9). Serum IgG4 concentration elevations were once considered the *sine qua non* of the diagnosis, but normal serum IgG4 concentrations are now well-described even in the setting of active, biopsy-proven disease (1, 10, 11). The significance of the IgG4 antibody in disease pathogenesis remains unclear (12). Recent publications have described elevations in the levels of circulating plasmablasts, suggesting that the levels of such cells serve as both a diagnostic biomarker and a reliable indicator of disease activity (11, 13).

Most literature on IgG4-RD consists of case reports and small case series focused on individual organ manifestations, particularly the pancreas, kidney, biliary tree, and salivary glands (14-22).

We report here a detailed analysis of the clinical features of the first 125 patients diagnosed with IgG4-RD by strict clinicopathologic correlation at our center.

Methods

Cohort overview. This study was approved by the Partners Institutional Review Board. All patients signed written informed consent. The Massachusetts General Hospital Center for IgG4-Related Disease maintains a database of all patients with IgG4-RD evaluated in the Center. Data pertaining to demographics, prior treatment, and laboratory findings at baseline evaluations (between January 2, 2010 to September 30, 2014) were derived from the medical record. Forty-three of the patients included have been reported in some detail in other published studies(11, 13, 23, 24). Specifically, flow cytometry data were previously reported on 38 patients, 16 of whom were participants in a clinical trial (11, 13).

Age at onset refers to the age at which the patient first noticed the symptoms ultimately attributed to IgG4-RD or to the timepoint at which the disease was first recognized (whichever was earlier). Organ involvement was determined by a review of the patient's history, physical examination findings, imaging results, laboratory studies, and tissue biopsies. Multiorgan disease refers to the involvement of three or more organs. Damage (e.g., pancreatic insufficiency, chronic kidney disease, palate destruction) was determined through an organ-by-organ assessment of function, radiographic abnormalities (e.g., organ atrophy), damage related to surgical intervention (e.g., pancreatectomy), or chronic pain. Disease activity was assessed by the IgG4-RD Responder Index (IgG4-RD RI) (25). An IgG4-RD RI score ≥ 1 was classified as active disease such that all patients had clinical and/or radiographic evidence of active disease; in

three patients, disease was active but improving on treatment (RI score of 1 in each affected organ), while the remainder of patients with active disease had unchanged disease (RI score of 2), new/recurrent disease (RI score of 3), or worse disease despite treatment (score of 4). Each affected organ is scored separately in the RI, and all individual organ scores are summed to calculate the overall RI. Because of growing awareness that the serum IgG4 concentration has shortcomings as a disease biomarker (10) we report all RI scores without the inclusion of serum IgG4 concentrations.

IgG4-RD diagnosis and pathology methods. The diagnosis of IgG4-RD is predicated upon the careful clinicopathologic correlation because no single pathology feature is diagnostic and even a pathology picture highly consistent with IgG4-RD is seldom diagnostic without clinicopathologic correlation. All patients had biopsies from at least one organ that were reviewed and confirmed at our center. The pathology methods have been previously described (11, 13). Biopsies were evaluated for the presence of both specific histopathologic features and a significant infiltrate of IgG4+ plasma cells (9). The major histopathologic features include a dense lymphoplasmacytic infiltrate, fibrosis that has a storiform pattern in focal (or diffuse) areas, and obliterative phlebitis. At least two of these three features were present in all cases. We considered a significant IgG4+ plasma cell infiltrate to consist of more than 10 IgG4+ plasma cells/high power field (hpf) and an IgG4+:IgG+ ratio of at least 40% (9).

Serum IgG4 assays and other laboratory assessments. Serum IgG4 concentrations were measured by immunonephelometry using a Siemens BNII instrument and reagent sets obtained from either Siemens or The Binding Site. The prozone effect, known to occur with some

nephelometry assays in the setting of high antigen excess (26) was avoided by diluting all patients' samples until consistent measurements were obtained from one serial dilution to the next. The methods for measuring circulating plasmablasts by flow cytometry have been reported (13).

Statistical analysis. All statistical tests were performed using SPSS (Version 22, Chicago, IL, USA). Statistical differences for continuous, normally-distributed data were analyzed by Student t-tests; all continuous non-normally distributed data were analyzed by non-parametric testing. Categorical variables were assessed by Chi-square or Fisher's Exact Tests, as appropriate. Correlations were determined using the Pearson correlation coefficient (normally distributed) or the Spearman correlation coefficient (nonparametric data). A P-value <0.05 was considered significant for all statistical testing.

Results

Patient demographics. Of the 125 patients, 76 (61%) were men. The majority (76%) were non-Hispanic whites but other ethnicities were also represented (**Table 1**). The average age at evaluation was 55.2 years (+/- 13.9, range: 24-83). The average age at onset was 50.3 years (+/- 14.9, range: 12-82). The mean disease duration was 5.2 +/- 8.5 years and similar between newly- and previously-diagnosed patients. At their initial visit, 107 (86%) patients had active disease, 86 (69%) were on no treatment, and 39 (31%) were receiving immunosuppression for IgG4-RD (usually GCs).

Baseline disease activity. The mean IgG4-RD RI was 5.7 (+/- 4.9; range: 0-33). The RI correlated strongly with serum IgG4 concentrations ($r=0.5$; $P<0.001$) and with concentrations of total IgG and IgG subclasses 1, 2, and 3 ($r=0.3$, $r=0.2$, $r=0.3$, and $r=0.2$, respectively; $P<0.03$ for all correlations). The RI did not correlate with the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or levels of C3 or C4 (data not shown).

Organ involvement. The patient cohort included disease involvement at over 23 different known anatomic sites of disease, with a mean of 2.3 +/- 1.3 organs involved (range: 1-7, **Table 1**).

Table 2 displays the range of organs involved. The most commonly involved organs were the submandibular glands (35 cases, 28%), lymph nodes (34, 27%), orbits (28, 22%), pancreas (24, 19%), and retroperitoneum (23, 18%).

Damage at baseline evaluation. IgG4-RD was associated with damage caused by the disease (as opposed to treatment) in a total of 73 patients (58%) at the time of the initial evaluation (**Table 2**). These patients accumulated 89 items of damage at a total of 22 anatomic sites.

Surgery. Fifty patients (40%) had undergone surgery during evaluations of their illness. The surgical procedures were usually performed for the purpose of diagnosis or for erroneous diagnoses of cancer. The most common surgical procedures were pancreatic surgery (9 patients), followed by submandibular excision (8 patients) and ENT/sinus surgery (8 patients). Among 34 patients with lymphadenopathy, 21 had undergone a lymph node biopsy. The remaining diagnoses of lymphadenopathy were confirmed by imaging.

Previous treatment. Glucocorticoids (GC) were the most common therapy administered to patients prior to their evaluation (64 patients; 51.2%; **Table 3**). Eighty-six percent of patients improved with glucocorticoids but 77% did not achieve stable disease remissions following glucocorticoid treatment. Both conventional GC-sparing medications (e.g., methotrexate, azathioprine) and mechanical interventions (i.e., stents) had also been employed in these patients (**Table 3**). All patients treated with steroid-sparing agents (other than rituximab) had discontinued them prior to evaluation due to ineffective disease control. Two patients had been treated with radiation therapy for orbital disease; one was treated with radiation after surgery and did not have recurrence at the original site but the other experienced progressive disease despite the concomitant use of radiation and steroid-sparing agents. Sixteen patients (13%) had received either ureteral or biliary tract stents for complications related to IgG4-RD.

Laboratory findings. There was no significant difference in age at evaluation, age at disease onset, or number of organs involved among those with and without active disease at the time of their evaluation. Twenty-nine of the patients with active disease were on treatment at the time of evaluation. Among those with active disease, there was no significant difference in the serum IgG4 concentration between those on treatment (median 123mg/dL, IQR: 52-258; normal < 135 mg/dL) and those not on treatment (median 155mg/dL, IQR: 53-448, $P=0.66$). Among patients with active disease for whom erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) data were available – 98 and 92 patients, respectively – 53% had an elevated ESR (median 52mm/hr, IQR 35-78) and 40% had an elevated CRP (median 20.3mg/L, IQR 11.6-64.9). There was no difference in the distributions of ESR and CRP values ($P=0.76$).

Normal versus elevated serum IgG4 concentration patients. Among the 103 patients with active disease and serum IgG4 concentrations measured at the time of their evaluation, 53 (51.4%) had elevated serum IgG4 concentrations. Among those not on treatment but with active disease and serum IgG4 concentrations measured, 55.3% had elevated serum IgG4 concentrations (normal <135mg/dL, $P=0.26$ compared to those on treatment, **Table 4**). Patients with active disease and elevated serum IgG4 concentrations were older, had a higher RI score, a greater number of organs involved, lower complement levels, a higher absolute eosinophil count, and higher IgE levels compared to those with active disease but normal serum IgG4 levels ($P<0.01$ for all comparisons). Patients with pancreatic involvement were more likely to have an elevated serum IgG4 concentration than patients without pancreatic involvement (77% versus 47%, $P=0.03$).

Other IgG subclasses. Elevations of IgG subclasses other than IgG4 were common among patients with active disease, especially among those with an elevated serum IgG4 concentration (**Table 5**). Among the 48 patients with a normal serum IgG4 concentration but active disease and IgG subclass data available, IgG subclass elevations were infrequent: 2 (4%) had elevated IgG1, 5 (10%) had elevated IgG2, and 6 (13%) had elevated IgG3.

Plasmablasts among patients with active disease. Peripheral blood flow cytometry for plasmablasts was performed on 73 patients with active disease (**Table 4**). Twenty-nine patients had flow cytometry for IgG4+ plasmablasts. Patients with normal serum IgG4 concentrations had blood plasmablast and IgG4+ plasmablast levels equivalent to those of patients with elevated serum IgG4 levels. However, among the patients with IgG4+ plasmablasts measured, those with elevated serum IgG4 concentrations had a higher percentage of plasmablasts that were IgG4+

than did the patients with normal serum IgG4 concentrations (mean 66% +/- 16.5%, compared with 45% +/- 25.8%; $P=0.01$).

Serum complement levels. Among patients with active disease and complement levels measured ($N=81$), 20 (25%) had hypocomplementemia. Hypocomplementemia was common among IgG4-RD patients with kidney disease (7 of 10 patients; $P=0.002^1$). When considering those without kidney disease, hypocomplementemia was also common among those with pulmonary (6 of 12 patients, $P=0.006$), aorta (4 of 9 patients, $P=0.05$), and submandibular gland (6 of 26 patients, $P=0.06$) involvement. Patients with hypocomplementemia were more likely to have elevated serum IgG1, IgG2, IgG3, and IgG4 concentrations compared to those with normal complement concentrations ($P<0.02$ for all comparisons).

Correlations between clinical features, serum IgG4, and flow cytometry. Age at the time of evaluation correlated with the serum IgG4 concentration ($r=0.35$, $P<0.001$) and the number of organs involved ($r=0.25$, $P<0.01$). When controlling for age, the number of organs affected correlated moderately well with the serum IgG4 concentration ($r=0.39$, $P<0.001$) but not disease duration ($r=0.1$, $P=0.31$). Among all patients with peripheral blood plasmablast measurements ($n=94$), there were moderate correlations between the plasmablast levels and serum IgG4 concentration ($r=0.29$, $P<0.01$) as well as the RI ($r=0.22$, $P<0.03$). The correlation between IgG4+ plasmablast level ($n=42$) and RI ($R=0.45$, $P=0.003$) was stronger than that of total plasmablasts and RI.

¹ For all statistical comparisons in this section (unless noted otherwise), a Fisher's exact test was performed to investigate the significance of differences in the proportion of patients with hypocomplementemia and specific organ involvement (e.g., kidney) compared to those without involvement of that organ.

Clinical differences according to gender. The IgG4-RD patients in our cohort were more likely to be male than female, but we detected no differences with regard to age of onset, disease severity, or organ involvement. A higher percentage of male patients had IgG4-related autoimmune pancreatitis (25% versus 10%), but this comparison fell short of statistical significance ($P=0.06$). Among the patients with active disease at the time of evaluation, the males ($n = 61$) and females ($n = 42$) had similar IgG4 concentrations, circulating total and IgG4+ plasmablast levels, proportions of patients with an elevated IgG4 concentration, hypocomplementemia, multiorgan disease, and elevated inflammatory markers (data not shown).

Disease patterns according to organ involvement. We detected certain patterns of laboratory abnormalities according to some types of organ involvement. Patients with renal disease, lymphadenopathy, and retroperitoneal fibrosis, for example, comprised distinctive disease subsets. Comparisons are shown in **Table 6**. Whereas 7 of 10 patients with active IgG4-related kidney disease were hypocomplementemic at baseline, none of the 13 patients with active, untreated RPF had hypocomplementemia ($P < 0.001$). Among the 23 patients with RPF, only one also had kidney disease and only one had lymphadenopathy beyond the retroperitoneum. Serum IgG4 concentrations varied significantly across the subgroups, with medians of 406 mg/dL, 228 mg/dL, and 58 mg/dL, respectively ($P < 0.03$ for all comparisons).

Discussion

We describe the baseline clinical and laboratory features in 125 patients with IgG4-RD diagnosed by strict clinicopathologic correlation. Our study is unique in comparison to other IgG4-RD publications to date, most of which have been multi-center efforts focusing on

autoimmune pancreatitis or small case series. Only three studies have described cohorts of IgG4-RD patients with a variety of organ manifestations. The largest of these studies to date described 114 Japanese patients identified by a review of 20 years of pathology records (7). The focus of that study was the pathology of IgG4-RD in different organs rather than the clinical characteristics or laboratory features of disease. Chen et al. described 28 Chinese patients at a single center (8) and Ebbo et al. reported 25 patients from a multi-center registry comprised of reports by French physicians (6). Both of those series required an elevated serum IgG4 concentration as a criterion for entry.

Only 51% of patients in our cohort with active, untreated IgG4-RD had elevated serum IgG4 concentrations at their initial evaluation in our Center. This figure contrasts sharply with previous reports of patient series collected according to different criteria (1, 7, 8, 14, 18). Because serum elevations of IgG4 were the basis upon which IgG4-RD was first identified (2, 3) early studies and proposed diagnostic criteria have generally attached crucial importance to serum IgG4 concentrations (27). However, the use of serum IgG4 concentration elevations as a principal means of identifying patients inevitably skews study populations toward those with high serum levels. In our study, in contrast, the diagnosis was based on clinicopathologic correlation regardless of the serum IgG4 concentration. However, this observation must be interpreted cautiously as a variety of other explanations, including differences in patient demographics (e.g., ethnic background), previous treatment, organ involvement, and referral bias at our tertiary care center toward patients without elevated serum IgG4 concentrations may also contribute to the lower rate in our cohort.

Our study included 23 patients with RPF (18% of the overall cohort), 85% of whom had normal serum IgG4 concentrations. In contrast, nearly 80% of those patients with pancreatic involvement (n=24) had an elevated serum IgG4 concentration. The enrichment of our study population with RPF patients may partly explain the lower frequency of IgG4 serum elevations in our cohort. When the RPF patients were excluded, 67% of the remaining patients on no treatment at baseline had elevated serum IgG4 concentrations, more closely approximating prior estimates.

Although our data highlight potential shortcomings of serum IgG4 concentrations in the diagnosis and serial assessment of IgG4-RD, they also suggest that elevated serum IgG4 concentrations identify a subtype of IgG4-RD that is more “inflammatory” compared to patients with normal serum IgG4. That is, serum elevations in IgG4 concentration denote a large subset of IgG4-RD that is characterized by a greater likelihood of multiple organ involvement, high inflammatory markers, and low complement levels. Future studies might investigate whether this subgroup is less likely to respond to treatment or more likely to relapse following successful treatment (11, 14, 28, 29).

Findings from this study confirm our previous observations that IgG4-RD patients have elevated levels of circulating plasmablasts that are independent of serum IgG4 concentrations (11, 13). Moreover, the levels of circulating plasmablasts – especially IgG4+ plasmablasts – correlate well with disease activity as assessed by the IgG4-RD RI. Longitudinal studies of the utility of peripheral blood flow cytometry for gauging the need for re-treatment are an important agenda for future study.

Our study provides additional information about the utility of GC in IgG4-RD. GC were commonly employed as a treatment modality in our patients and 86% of the patients treated with GC responded at least initially to this therapy, a finding consistent with prior reports (7, 30, 31). However, it is clear that a large subset of patients fail to achieve stable, steroid-free remissions following the discontinuation of GC (32). This observation may be biased by the nature of our referral practice, which is more likely to see patients with severe, disease complicated by frequent relapses (7, 14, 30, 33). Although GC are regarded as the initial treatment of choice, our data highlight the need for studies investigating steroid-sparing agents as maintenance therapy in IgG4-RD (17, 30-32, 34-37).

IgG4-RD is widely acknowledged to affect men more commonly than women, as observed in our cohort (7, 16, 18, 38). The gender disparity in this cohort, however, was less prominent than often reported in the literature (male:female 1.6:1). Previous reports have described higher serum IgG4 concentrations among healthy males compared to healthy females (39) but in this study we observed no difference in the serum IgG4 concentrations between male and female patients. We also found no differences in organ involvement or disease severity as measured by the extent of organ involvement through the IgG4-RD RI.

The concept of permanent “damage” resulting from IgG4-RD has not been addressed in a large cohort of patients with diverse organ involvement. More than half (58%) of the patients in our cohort had sustained organ damage from IgG4-RD at the time of their evaluation in our center. The organs particularly susceptible to damage in our cohort were the pancreas, lungs, kidneys,

and major salivary glands. Particularly concerning is the large number of patients (40%) who had undergone surgical procedures (excluding fine-needle aspiration) before the diagnosis of IgG4-RD could be established. The most frequent surgical procedures were pancreatic resections and submandibular gland excision; in most cases, the diagnosis of IgG4-RD was based on findings related to the procedure. Broader education and greater awareness of IgG4-RD as a mimicker of malignancy may obviate the need for many surgical procedures.

Our data may provide insights into the mechanism of the hypocomplementemia observed in many patients with IgG4-RD. The IgG4 molecule is believed to bind complement poorly under most circumstances. Activation of the classical complement pathway by IgG4 is therefore an improbable explanation for the marked hypocomplementemia sometimes observed (17, 38, 40). In our cohort, patients with hypocomplementemia and elevated serum IgG4 concentrations also tended to have higher concentrations of other serum IgG subclasses, suggesting that one of the other IgG subtypes (e.g., IgG1 or 2) is responsible for low complement levels (41). Future studies might evaluate the presence of anti-hinge antibody (targeted against the IgG4 hinge) among IgG4-RD patients with an elevated serum IgG4 concentration and hypocomplementemia. Such antibodies were identified recently in rheumatoid arthritis patients with complement activation (40). In addition, a study evaluating complement deposition in biopsy specimens from patients with and without hypocomplementemia may illuminate differences in the mechanisms of damage.

Our findings highlight the variations in disease expression that exist in IgG4-RD. Major differences can be observed, for example, in comparisons across organ systems. This variability

of disease expression according to organ involvement is one likely explanation for the failure to recognize IgG4-RD as a unified, multi-organ disease until this century. As an example, patients with IgG4-related RPF and IgG4-related kidney disease differ substantially in terms of the number of organs involved, complement levels, and serum IgG4 concentrations (28). The rarity with which these two conditions occur together makes them particularly suitable for future studies investigating differences in disease phenotype. Differences in disease pathogenesis and mechanisms of damage may explain some of these observed phenotypic differences. Future studies might explore this hypothesis by studying gene expression in biopsy samples representative of distinct disease phenotypes (42). Moreover, optimal treatment strategies may differ by disease phenotype and future clinical trials might consider stratifying patients accordingly. Despite the multiple differences between the subset of patients with IgG4-related kidney disease and that with IgG4-related RPF, both subsets had blood plasmablast concentrations that were lower than those of patients without those types of disease involvement. The reason for this is not clear, but deserves further study.

Our study has a number of important strengths. First, it is the largest study of IgG4-RD affecting a broad array of organs reported to date, as well as the first pathology-based study to emphasize the clinical manifestations of disease. Second, we had the opportunity to evaluate many patients at a time when they were on no treatment. A particular strength of this work is that 107 patients had active disease and most were on no treatment at the time of their evaluation. We were therefore able to comment in detail on the clinical appearance and laboratory characteristics of active IgG4-RD. Third, we were able to expand upon the significance of circulating plasmablasts in IgG4-RD.

Our study also has a number of limitations. Our center is located within a Rheumatology Unit and therefore our patient population is skewed toward patients with multi-organ disease or at least the types of organ manifestations most likely to be evaluated by rheumatologists.

Pancreatic and other gastrointestinal manifestations of IgG4-RD may be under-represented in our study because patients with disease isolated to those sites are often managed primarily by gastroenterologists. Nevertheless, patients with type 1 (IgG4-related) autoimmune pancreatitis and IgG4-related sclerosing cholangitis contributed significantly to our study population. It is also possible that the clinical and laboratory features of our cohort of Western patients differs in some important ways from those of patients from other parts of the world. This hypothesis needs to be addressed through comparison studies of patient cohorts collected at different sites across the world. Finally, because of the retrospective nature of some aspects of our data collection, some elements of the data set (e.g., age at onset and organ involvement) may be affected by recall bias.

In conclusion, we have reported a large cohort of patients with IgG4-RD and diagnoses supported by histopathology. These data substantially augment our understanding of IgG4-RD, now more than a decade after its initial description. Serum IgG4 concentrations appear to be less important than originally believed for the purposes of diagnosis, and this point should be considered in discussions of diagnostic criteria. Damage is common in IgG4-RD but might be prevented with earlier diagnosis using minimally invasive approaches. Our observation of disease phenotypes distinguished by specific patterns of organ involvement, serum IgG4 concentrations, and hypocomplementemia deserve further investigation. These findings have

important implications for the diagnosis and management of IgG4-RD and will help guide the design of future studies.

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Table 1: Baseline Features of 125 Patients with Biopsy-Proven IgG4-Related Disease

Age at Evaluation (mean +/-SD, range, years)	55.2 +/- 13.9 (24-83)
Age of Onset (mean +/-SD, range, years)	50.3 +/- 14.9 (12-82)
Disease Duration (mean +/-SD, range, years)	5.2 +/- 8.5 (0-60)
Number of Organs (mean +/-SD, range)	2.29 +/- 1.3 (1-7)
% 1 organ involved	38%
% 2 organs involved	24%
% ≥3 organs involved	38%
% Organ Damage	58%
% Male	60.8%
Ethnicity	
% Caucasian	76%
% African-American	5.6%
% Hispanic	6.4%
% Asian	6.4%
% South Asian	2.4%
% Arab	2.4%
% Active Disease	82.4%
% with New Diagnosis of IgG4-RD at Initial Visit	74%
% on Treatment	31.2%
Responder Index (without IgG4 concentration) among active disease (mean +/- SD, range)	6.6 +/- 4.6 (1-33)
% Elevated IgG4 among active disease	51%
% Elevated IgG4 among active disease but off of treatment	55.3% [†]

[†] There was no significant difference in the proportion of patients with an elevated serum IgG4 concentration when comparing those with active disease on treatment to those off treatment (P=0.263).

Table 2: Sites of Organ Involvement and Damage in 125 Patients with IgG4-RD

Organ Involvement			
	# of cases (% of all cases)		# of Cases (% of all cases)
Submandibular	35 (28%)	Sinusitis	5 (4%)
Lymph nodes	34 (27.2%)	Prostate	4 (3.2%)
Orbit	28 (22.4%)	Meninges	3 (2.4%)
Pancreas	24 (19.2%)	Liver	3 (2.4%)
Retroperitoneal fibrosis	23 (18.4%)	Nasal Cavity	3 (2.4%)
Lung	22 (17.6%)	Sclerosing mediastinitis	2 (1.6%)
Parotid	21 (16.8%)	Sclerosing mesenteritis	2 (1.6%)
Other*	18 (14.4%)	Heart	2 (1.6%)
Kidney	15 (12%)	Gallbladder	2 (1.6%)
Aorta	14 (11.2%)	Skin	2 (1.6%)
Bile duct	12 (9.6%)	Mastoid	2 (1.6%)
Other ENT	10 (8%)	Tonsillitis	1 (0.8%)
Thyroid	7 (5.6%)		
Damage			
Submandibular Gland	10 (8%)	Thyroid	5 (4%)
Pancreas	10 (8%)	Orbit	4 (3.2%)
Surgical	9 (7.2%)	Chronic Pain	4 (3.2%)
Diabetes Mellitus	5 (4%)	Aorta/Valve	4 (3.2%)
Pancreatic Exocrine Insufficiency	4 (3.2%)	Sinus	3 (2.4%)
Kidney [†]	10 (8%)	Biliary	3 (2.4%)
Lung	10 (8%)	Palate	2 (1.6%)
Other**	9 (7.2%)	Nasal Septum	2 (1.6%)
Non-Aorta Vascular	6 (4.8%)	Total # Patients with Damage	73 (58%)
Genitourinary	5 (4%)		

* Other Organ Involvement (#1 patient, ^2 patients): Peripheral nerves[#], Appendix[#], Spleen[#], Cervical Fibrosis[#], Paraspinal mass[#], Palate[^], Pulmonary Artery[#], Coronary Arteries[#], Bone[^], Gum[#], Omentum[#], Testicle[#], Vocal Cords[#]. There was no breast or pituitary involvement.

** Other Damage: Hearing loss[#], Jaw[^], Parotid[#], Cosmetic[#], Ear[#], Cranial Nerve[#], Small Intestine[#], Pericardium[#]

[†] Damage to the kidneys included both the sequelae of tubulointerstitial nephritis and the development of hydronephrosis caused by retroperitoneal fibrosis.

Table 3: Prior Treatment and Response to Glucocorticoids (GC)

Treatment	Number of Patients
Glucocorticoids (% of cohort)	64 (51.2%)
No response	9 (14%)
Achieved remission but relapsed off of GC	26 (40%)
Achieved remission but relapsed during taper of GC	15 (23%)
Responded and on GC at evaluation	11 (17%)
Previously stabilized on GC and off GC	2 (3%)
Treated with GC and steroid-sparing agent	1 (1.5%)
Overall % Responding to GC	86%
GC-Sparing Agents	
Methotrexate	7 (5.6%)
Mycophenolate mofetil	3 (2.4%)
Tamoxifen	3 (2.4%)
Azathioprine	5 (4%)
Cyclophosphamide	2 (1.6%)
Intravenous immune globulin	1 (0.8%)
Rituximab	7 (5.6%)
Biliary Stents	8 (6.4%)
Ureteral Stents	8 (6.4%)
Radiation Therapy	2 (1.6%)

Table 4: Clinical and Laboratory Features in Patients with Active IgG4-RD and Elevated versus Normal Serum IgG4 Concentrations

	Normal Values	Elevated Serum IgG4 Concentration (≥ 135 mg/dL), N=53	Normal Serum IgG4 Concentration (<135 mg/dL) N=50	P-Value*
Age at Evaluation (mean, yrs)		60.3 (+/- 11.8)	51.4 (+/- 14.7)	0.001
Age of Onset (mean, yrs)		54.3 (+/- 15.1)	46.8 (+/- 15)	0.014
Gender (% Male)		58.5%	60%	1.0
Multi-Organ (%)		50.9%	28%	0.03
Single Organ (%)		28.3%	44%	0.11
Number of Organs, mean +/- SD		2.7 (+/- 1.5)	1.9 (+/- 1)	0.001
Damage		58.5%	54%	0.69
Responder Index without Serum IgG4, mean +/- SD		8.4 (+/- 5.3)	4.8 (+/- 2.9)	<0.001
Serum total IgG, median (IQR) mg/dL	767-1590	1573 (1240-2114) N=44	1130 (868-1310) N=49	<0.001
Serum IgG1, median (IQR) mg/dL	341-894	868 (650-1090) N=47	596 (499-724) N=49	<0.001
Serum IgG2, median (IQR) mg/dL	171-632	519 (381-750) N=47	366 (271-446) N=49	<0.001
Serum IgG3, median (IQR) mg/dL	18.4-106	76 (43-136) N=47	71 (41-90) N=49	0.04
Serum IgG4, median (IQR) mg/dL	2.4-135	379 (207-817) N=53	51 (28-96) N=52	<0.001
C3, median (IQR) mg/dL	86-184	96 (73-129) N=42	122 (106-155) N=37	0.001
C4, median (IQR) mg/dL	16-38	20 (11-27) N=42	28 (22-30) N=37	0.001
Hypocomplementemia (C3 or C4) %		42%	5.4%	<0.001
ESR, median (IQR) mm/hr	<20	34 (11-71) N=49	16 (9-52) N=46	0.07
CRP, median (IQR) mg/L	<8.0	5.5 (1.8-17.6) N=47	6.5 (1.8-13.0) N=44	0.9
Elevated ESR and/or CRP (%)		67%	46%	0.04
Absolute Eosinophil, median (IQR) /mm ³	0.0-900	290 (110-595) N=48	160 (60-250) N=47	0.005
Serum IgE, median (IQR) /mL	0-100	128 (36-462) N=45	46 (16-117) N=35	0.01
Plasmablast, median (IQR) /mL		3246 (1290-5525) N=43	3325 (1089-4712) N=27	0.36

IgG4+ Plasmablast, median (IQR) /mL		2425 (781-4961) N=19	1192 (397-3190) N=10	0.17
%IgG4+/Total Plasmablast, mean +/- SD		66% +/- 16.5%	45% +/- 25.8%;	0.01

* By Fisher’s Exact Test (Categorical), Unpaired T-Test (Parametric), Mann-Whitney U Test (Non-Parametric)

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Table 5: IgG Subclass Elevations Among Patients with Active IgG4-RD

	All Active Disease	Elevated IgG4	Normal IgG4
Total Serum IgG	28%	50%	10%
Serum IgG1	26%	49%	4%
Serum IgG2	23%	36%	10%
Serum IgG3	26%	38%	13%
Serum IgG4	51%	100%	0%

Table 6. Characteristics of Selected Disease Subsets: Patients with IgG4-Related Kidney Disease, IgG4-Related Lymphadenopathy, and IgG4-Related Retroperitoneal Fibrosis.**

Characteristic	Kidney Disease versus No Kidney Disease (n = 15)	Lymphadenopathy (LAD) versus No LAD (n = 34)	Retroperitoneal Fibrosis (RPF) versus No RPF (n = 23)
Organs involved (mean, S.D.)	3.1 +/- 1.8 vs 2.2 +/- 1.3 P = 0.02	3.3 +/- 1.5 vs 1.9 +/- 1.1 P<0.001	1.8 +/- 1.04 vs 2.4 +/- 1.4 P=0.045
Serum IgG4 (mg/dL) (median, [IQR])	406 [137-1102] vs 132 [49-353] P=0.02	228 [74-828] vs 131 [47-287] P=0.03	58 [20-131] vs 193 [74-493] P=0.001
Elevated Serum IgG4 Concentration (%)	75% vs 48.4 % P=0.12	63.3% vs 46.6% P=0.14	19% vs 59.8% P=0.001
C3 (mg/dL) (median [IQR])	68 [57-96] vs 119 [93-150] P<0.01	No difference	No difference
C4 (mg/dL) (median [IQR])	12 [7-19] vs 25 [17-30] P<0.01	No difference	28 [23-31] vs. 23 [13-28] P=0.052
Hypo- complementemia (%)	70% vs. 18% P=0.002	No difference	0% vs. 29% P=0.03
ESR (mm/hr) (median [IQR])	67 [53-84] vs. 18 [8-53] P= 0.001	No difference	No difference
C-reactive protein (mg/L) (median [IQR])	No difference	No difference	No difference
Plasmablast (/mL) (median [IQR])	1387 [975-3786] vs. 3784 [1529-5720] P=0.03	No difference	1038 [861-2810] vs. 3953 [1579-5720] P=0.002
IgG4+ Plasmablast (/mL) (median [IQR])	No difference (N=3)	No difference (N=6)	535 [230.35-781.07] vs. 3061 [969.25-5979.6] P=0.001 (N=7)
IgG4+ Plasmablast / Total Plasmablast (%)	No difference (N=3)	No difference (N=6)	No difference (N=7)

* By Fisher's Exact Test (Categorical), Unpaired T-Test (Parametric), Mann-Whitney U Test (Non-Parametric), **Except for number of organs involved, all other comparisons include only those patients with active disease