

Serum Immunoglobulin G4 Level Is a Poor Predictor of Immunoglobulin G4–Related Disease

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Objectives: Immunoglobulin G4–related disease (IgG4-RD) is characterized by elevation in serum IgG4 levels, typical multiorgan involvement and dramatic response to steroid therapy. We determined the predictive value of an elevated serum IgG4 for the diagnosis of IgG4-RD. We also sought to identify novel conditions, which have characteristic features of IgG4-RD.

Methods: We identified all Mayo Clinic Rochester patients with serum IgG4 levels measured between January 2008 and December 2011 ($n = 6014$). Those with elevated serum IgG4 levels (reference range, 121–140 mg/dL) were included in the analysis and were classified as “definite,” “probable,” or “no” IgG4-RD.

Results: Serum IgG4 levels were elevated in 390 subjects (6.5%) of whom only 39 (10%) had IgG4-RD (29 “definite,” 10 “probable”). The positive predictive value of an elevated serum IgG4 for IgG4-RD was poor (10%). Subjects with IgG4-RD differed from those without IgG4-RD in mean age (59.6 ± 15.2 vs 54.4 ± 18.3 years, $P < 0.05$), % males (90% vs 58%, $P < 0.05$), mean serum IgG4 level (437 ± 471 vs 223 ± 194 mg/dL, $P < 0.05$), and presence of chronic rhinosinusitis (7/39 vs 29/351, $P = 0.05$).

Conclusions: Elevated serum IgG4 levels are not specific for IgG4-RD and are likely to be a false-positive. Chronic rhinosinusitis is likely an as yet underrecognized manifestation of IgG4-RD.

Key Words: IgG4-related disease, multi-organ, serum IgG4, positive predictive value, rhinosinusitis, steroids

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Immunoglobulin G4–related disease (IgG4-RD) is a newly described chronic fibroinflammatory condition that derives its name from its frequent association with elevations in serum IgG4 levels and tissue infiltration with abundant IgG4⁺ plasma cells.¹ Additional characteristic features of IgG4-RD include the tendency to involve multiple organs and a dramatic response of the inflammatory infiltrate to steroid therapy.² A unique histopathologic pattern is seen in IgG4-RD afflicting certain organs such as the pancreas³; however, in other organs (such as lymph nodes and mucosal involvement of hollow organs), the diagnosis is not obvious by simply looking at the tissue.³ Similarly, characteristic imaging features are observed in the pancreas during an acute presentation, but not in all affected organs.

Pancreatic involvement in IgG4-RD is called type 1 autoimmune pancreatitis (AIP).¹ It is the discovery of serum IgG4

elevation as a characteristic marker of AIP⁴ and the study of other-organ involvement in AIP that lead to the concept of IgG4-RD.⁵ However, this entity is now known to involve virtually every organ system with or without pancreatic involvement, most commonly the biliary tree, salivary glands, lymph nodes, and orbital tissues.² Elevated serum IgG4 levels are typically present in patients with known manifestations of IgG4-RD and were once thought to be the most sensitive and specific serum test for this disorder. This finding has now been identified in several other diseases including pancreatic cancer,⁶ cholangiocarcinoma, primary sclerosing cholangitis,⁷ and other respiratory diseases.⁸

A recent study from our institution by Ryu et al⁹ highlighted the spectrum of disorders associated with elevated serum IgG4 levels and concluded that a majority of patients with serum IgG4 elevations do not have IgG4-RD. However, the study used an arbitrary cutoff for elevated serum IgG4 level of more than 140 mg/dL, despite the upper limit of normal (ULN) ranging from 121 to 140 mg/dL during their study period; thus, many patients with elevated serum IgG4 levels were likely missed. They also did not determine the value of 2-fold elevations of serum IgG4 as a predictor of IgG4-RD. Using this large cohort, we have also tried to identify possible novel entities that might be included in the spectrum of IgG4-RD.

From a large cohort of subjects who had serum IgG4 levels measured in clinical practice, the current study aims to further elucidate the diseases associated with serum IgG4 elevations and determine the predictive value for IgG4-RD. Multiple respiratory manifestations have been associated with IgG4-RD, including involvement of the lung parenchyma, lymph nodes, pleura, bronchial tree, and paranasal sinuses.^{8,10} Interstitial pneumonia, pleural-based lesions, central airway stenosis, asthma, and chronic rhinosinusitis are some of the findings described in the literature and shown to respond to steroid treatment initiated for IgG4-RD.^{11,12} We aimed to also clarify the relationship between IgG4-RD and certain sinopulmonary disorders.

MATERIALS AND METHODS

The study was approved by the institutional review board at Mayo Clinic. From Mayo Clinic Rochester’s electronic laboratory database, we identified all patients who had serum IgG4 levels measured at Mayo Clinic Rochester during a 3-year period from January 2008 to December 2011. Serum IgG4 levels were determined by first measuring the concentrations of IgG subclass proteins (IgG1, IgG2, IgG3, IgG4, and total IgG) using automated nephelometry.¹³ Human IgG4 latex reagent (Binding Site Group Ltd, Birmingham, UK) was used to quantify the serum IgG4 concentration. The ULN for IgG4 levels varied from 121 to 140 mg/dL during this period. Patients with a serum IgG4 concentration greater than the ULN were included in the analysis.¹⁴ The electronic medical record was reviewed to obtain basic demographic information and relevant clinical data. Specifically, we were interested in obtaining the ULN for serum IgG4, the clinical indication for measuring the serum IgG4

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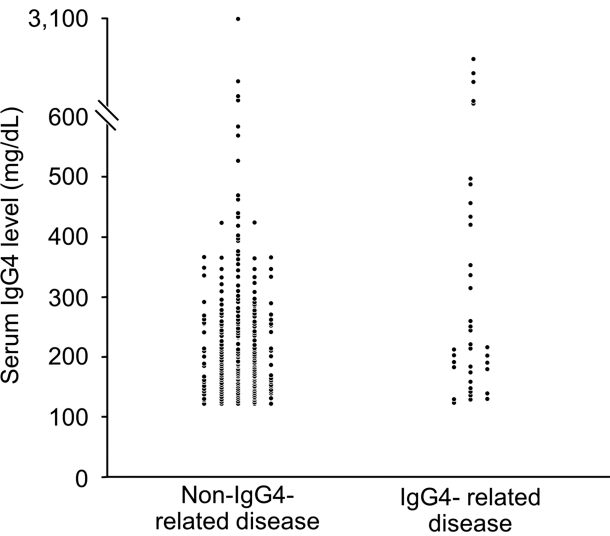


FIGURE 1. Scatterplot of serum IgG4 levels in IgG4-RD and non-IgG4-RD groups.

level, potential organ manifestations of IgG4-related disease, the presence of potentially related pulmonary diseases, and associated tissue biopsy results. The final diagnosis after clinical evaluation was also identified, and their response to treatment noted.

Patients who met the organ-specific criteria for known manifestations of IgG4-RD (AIP, IgG4-related sclerosing cholangitis, IgG4-related retroperitoneal fibrosis, IgG4-related sialadenitis, or IgG4-related orbital inflammatory pseudotumor) were classified as “definite” IgG4-RD.¹ In cases where a definitive diagnosis could not be made despite a strong suspicion of IgG4-RD, patients were classified as “probable” IgG4-RD. This terminology was based on suggestive clinical and imaging features, in conjunction with an elevated serum IgG4 level. Those patients designated as non-IgG4-RD had an elevated serum IgG4 level but did not meet any of the above criteria.

Statistical Analysis

Data are presented as number and percentage or mean ± SD. Demographic data were compared between patients with IgG4-RD (definite and probable) and non-IgG4-RD to determine the positive predictive value for diagnosis of IgG4-RD. A receiver operating characteristic curve was used to illustrate the predictability of IgG4-RD using serum IgG4 levels. Statistical comparisons were made using a 2-sample Student *t* test for

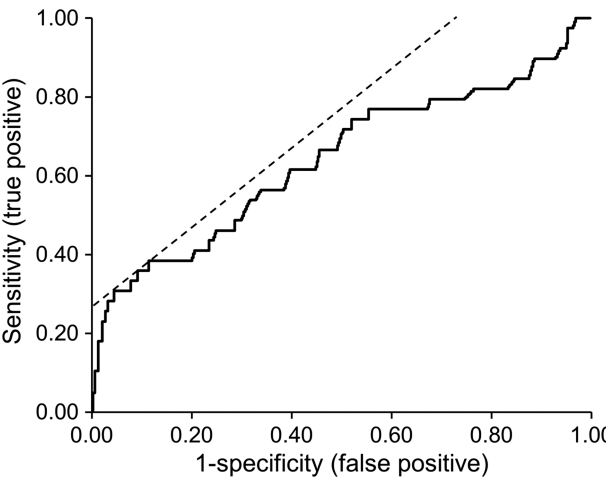


FIGURE 2. Receiver operating characteristic curve using any elevation of serum IgG4: x axis: the false positive rate for elevated serum IgG4; y axis: the sensitivity of elevated serum IgG4. Area under curve = 0.64.

continuous variables and χ^2 analysis for categorical variables. In all cases, $P \leq 0.05$ was considered statistically significant.

RESULTS

Among 6014 patients with a serum IgG4 measurement in the study period, 390 (6.5%) had a value greater than the ULN (>120–140 mg/dL). Elevations in serum IgG4 levels were further divided into mild elevations (1–2× ULN) and marked elevations (>2× ULN) (Fig. 1). Their demographics and IgG4 profile are outlined in Table 1.

Of the 390 patients with elevated serum IgG4, 39 (10%) had IgG4-RD (29 with “definite” IgG4-RD, 10 had “probable” IgG4-RD). Of the 29 patients with “definite” IgG4-RD, 20 (69%) were biopsy proven. Among those with an elevated serum IgG4 level, those with IgG4-RD were older and were more likely to be male compared with patients without IgG4-RD (Table 1). Mean serum total IgG levels, mean serum IgG4 levels, and proportion with serum IgG4 levels greater than 2 times the ULN were higher in those with IgG4-RD when compared with those without (Table 1). The positive predictive value of an elevated serum IgG4 for IgG4-RD was poor (Fig. 2).

Other common organ-specific diagnoses noted among the non-IgG4-RD group included pancreatic cancer, primary sclerosing cholangitis, and cholangiocarcinoma (Table 2). Respiratory diseases including asthma, rhinosinusitis, and bronchiectasis were

TABLE 1. Characteristics of the Study Patients

Characteristic	All Subjects With Elevated Serum IgG4	IgG4-RD: Definite + Probable	Non-IgG4-RD	P*
No. patients	390	39	351	
Age, mean (SD), y	54.9 (18.1)	59.6 (15.2)	54.4 (18.3)	<0.05
Male sex, n (%)	238 (61)	35 (90)	203 (58)	<0.05
Serum total IgG levels, mean (SD), mg/dL	1539 (600)	1677 (906)	1522 (557)	<0.05
Serum IgG4 levels, mean (SD), mg/dL	244.4 (245)	437 (471)	223 (194)	<0.05
Proportion with serum IgG4 1–2× ULN, n (%)	304 (78)	22 (56)	282 (80)	<0.05
Proportion with serum IgG4 2× ULN, n (%)	86 (22)	17 (43)	69 (20)	<0.05

*Comparison between IgG4-RD and non-IgG4-RD.

TABLE 2. Spectrum of Diseases Associated With Elevated Serum IgG4

	Diagnosis	No. Patients (%)
IgG4-RD	Definite IgG4-RD	29/390 (7.4)
	Probable IgG4-RD	10/390 (2.6)
	IgG4-related sclerosing cholangitis	7/39 (18)
	AIP	25/39 (64)
	IgG4-related retroperitoneal fibrosis	1/39 (3)
	IgG4-related sialadenitis	2/39 (5)
	IgG4-related orbital inflammatory pseudotumor	4/39 (10)
Pancreatic cancer		30/351 (8.5)
Cholangiocarcinoma		17/351 (5)
Primary sclerosing cholangitis		29/351 (8)

also noted in both the IgG4-RD and non-IgG4-RD groups. In 7 of 39 patients with IgG4-RD, rhinosinusitis was identified, compared with 29 of 351 patients with non-IgG4-RD. This difference was statistically significant, $P \leq 0.05$ (Table 3). Biopsy-proven IgG4-RD was found in 6 of 7 patients with rhinosinusitis. Moreover, in 5 patients, an improvement in rhinosinusitis symptoms and decreased IgG4 levels were documented following prednisone or rituximab therapy.

DISCUSSION

Previous studies on serum IgG4 measured in targeted populations with high probability of having 1 or other manifestation of IgG4-RD have reported high sensitivity and specificity (Fig. 2).^{4,15–17} In this large institution-wide study of all subjects who had serum IgG4 measured, in most of whom IgG4-RD was not clinically suspected or likely, we have shown that an elevated serum IgG4 is poorly predictive of IgG4-RD. Our data suggest that serum IgG4 elevations in patients without a strong suspicion for IgG4-RD are highly likely to be false positives.

Although elevated serum IgG4 levels are frequently associated with IgG4-RD (AIP, IgG4-related sclerosing cholangitis, IgG4-related retroperitoneal fibrosis, IgG4-related sialadenitis, or IgG4-related orbital inflammatory pseudotumor), elevations can be observed in a wide variety of other diseases. Elevated serum IgG4 levels have been demonstrated in approximately 7% of patients with pancreatic cancer.⁶ Similarly, serum IgG4 elevations have also been observed in 9% of patients with primary sclerosing cholangitis and 12% to 14% of patients with cholangiocarcinoma.^{7,18} In our cohort of patients, pancreatic cancer and primary sclerosing cholangitis were the most common diagnoses among our non-IgG4-RD cohort at 8.5% and 8%, respectively. In addition, 5% of the non-IgG4-RD cohort was diagnosed with cholangiocarcinoma.

Given its multiorgan nature, IgG4-RD with involvement of the sinopulmonary system has been proposed. The landmark article by Stone² highlighted several individual organ manifestations of IgG4-RD including involvement of the lung and

pleura; however, several studies since have also demonstrated involvement of the bronchial tree and paranasal sinuses. A study by Kamisawa et al⁵ demonstrated that up to 40% of patients with IgG4-RD had sinopulmonary manifestations such as bronchial asthma or chronic rhinosinusitis. Moteki et al¹⁹ revealed similar findings as approximately 32% of IgG4-RD patients had symptoms of chronic rhinosinusitis. Interestingly, many patients reported improvement in their sinus symptoms with initiation of corticosteroid therapy for IgG4-RD. Our study concurs with previous findings suggesting an association between IgG4-RD and rhinosinusitis (Table 3). In our cohort, 7 (35%) of 20 patients with biopsy-proven IgG4-RD had chronic rhinosinusitis, and 5 (71%) of these 7 patients who were not previously on steroids or rituximab noted improvement or resolution of their symptoms following initiation of prednisone or rituximab. There was also an associated improvement to the elevated serum IgG4 level after a few weeks of treatment. These findings provide further support to the concept of IgG4-related rhinosinusitis as a manifestation of IgG4-related disease.

Our study has limitations that bear mentioning. This was a retrospective study with the final analyses limited to the clinical data obtained from reviewing the electronic medical record. The diagnoses were determined by different clinicians at our institution based on their own clinical judgment. However, in most patients with elevated serum IgG4, there was no clinical clue of IgG4-RD, and they had another diagnosis to explain the presentation being investigated. And whenever there was suspicion, the clinicians did consider the diagnostic possibility of IgG4-RD. We have included those as probable IgG4-RD. It is still possible that some cases of IgG4-RD may have been missed especially in patients who did not have the classic presentation of IgG4-related disease.

In conclusion, elevated serum IgG4 levels can be seen in a wide spectrum of conditions, most of which are not IgG4-related diseases. In those patients without a strong suspicion for IgG4-RD, an elevated serum IgG4 level is highly likely to be a false positive. Sinopulmonary diseases can be seen in patients with IgG4-RD, and recent data suggest that chronic rhinosinusitis may be an unrecognized manifestation of IgG4-RD.

TABLE 3. Respiratory Diseases in Patients With IgG4-RD vs Non-IgG4-RD

Respiratory Disease	IgG4-RD, n (%)	Non-IgG4-RD, n (%)	P
Asthma	7/39 (18)	50/351 (14)	0.57
Rhinosinusitis	7/39 (18)	29/351 (8)	<0.05
Bronchiectasis	0/39 (0)	33/351 (9)	<0.05

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