

Salivary gland involvement disparities in clinical characteristics of IgG4-related disease: a retrospective study of 428 patients

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Abstract

Objectives. IgG4-related disease (IgG4-RD) has recently been recognized as a fibro-inflammatory condition featuring tumefactive lesions in multiple organs, and the salivary gland is one of the most commonly involved sites. We undertook this study to compare detailed demographic, clinical and laboratory characteristics of IgG4-RD patients with salivary gland lesions (IgG4-RD SG+) and salivary-gland-free IgG4-RD (IgG4-RD SG−) in a large cohort.

Methods. We carried out a retrospective review of the medical records of 428 cases of IgG4-RD diagnosed at Peking University People's Hospital between March 2006 and May 2018.

Results. Among 428 patients, 249 had salivary glands that were affected. IgG4-RD SG+ patients showed younger age at disease onset and diagnosis, and a longer interval between symptom onset and diagnosis. The IgG4-RD SG+ group involved more female patients, and allergic diseases were more common in this group. In terms of organ involvement, the IgG4-RD SG+ group were more frequently presented with lacrimal gland involvement, while lymph node, retroperitoneal fibrosis, pancreas, biliary system, kidney and aorta were more prominent in the IgG4-RD SG− group. In addition, the serum IgG4 level, IgG4/IgG ratio and IgE level were significantly higher in IgG4-RD SG+ patients. Patients with eosinophilia were more common in the IgG4-RD SG+ group, while elevated ESR, CRP and positive ANA were more common in the IgG4-RD SG− group.

Conclusion. We have revealed demographic, clinical and laboratory differences between IgG4-RD SG+ and SG− patients, which indicated potential differences in pathogenesis and important implications for the diagnosis and management of these two phenotypes.

Key words: IgG4-related disease, salivary gland, disparities, clinical characteristics

Rheumatology key messages

- IgG4-RD SG+ and IgG4-RD SG− patients are significantly different in clinical and laboratory features.
- Different pathogenesis may cause higher IgG4 and IgE level in IgG4-RD SG+ patients.
- Whole-body evaluation is more necessary in IgG4-RD SG+ patients.

Introduction

IgG4-related disease (IgG4-RD) has recently been recognized as a fibro-inflammatory condition featuring tumefactive lesions in multiple organs, which were previously regarded as isolated entities [1]. Such lesions are histologically characterized by numerous lymphocyte and

plasmacyte infiltration, fibrosclerosis, obliterative phlebitis and frequent elevated serum IgG4 levels [2–4].

IgG4-RD was initially recognized in a cohort of Japanese patients in 2001, after a link between elevated serum IgG4 levels and sclerosing pancreatitis was established [5]. And it was deemed as a systemic condition in 2003 [6]. Actually, cohort studies and case series have

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revealed that virtually all organ systems could be affected in this systemic disorder [7–11], and the salivary gland is one of the most commonly involved sites.

Moriyama *et al.* [12] and our previous researches have suggested that salivary gland involved IgG4-RD (IgG4-RD SG+) patients may present different features compared with IgG4-RD patients without salivary gland lesions (IgG4-RD SG–). By principal components analysis, we found that the whole transcriptome profile differed between the two groups, which indicated that different mechanisms may be involved in different phenotypes [13]. However, only dozens of patients were examined in these studies and the comparison has not been studied in detail.

In this study, we compared the demographic, clinical and laboratory characteristics of 249 IgG4-RD SG+ and 179 IgG4-RD SG– patients. To our knowledge, this is the first study focusing on comparison between these two phenotypes in a large cohort. Defining the characteristics of these two groups might facilitate advanced recognition of the condition, help to identify risk factors and develop a treatment strategy specific for each cluster.

Methods

Patients

A total of 428 patients who were diagnosed as IgG4-RD at Peking University People's Hospital between March 2006 and May 2018 were enrolled in this study. This study was approved by the Medical Ethics Committee of Peking University People's Hospital (Beijing, China). All patients provided written informed consent. According to the 2011 comprehensive IgG4-RD diagnostic criteria [14], 205 (47.9%), 50 (11.7%) and 173 (40.4%) cases were diagnosed as definite, probable and possible IgG4-RD, respectively. Definite patients and whole (definite, probable and possible) patients were well matched (Supplementary Table S1, available at *Rheumatology* online).

Patients' age, gender, disease duration, past or current allergy disease, and clinical manifestation were recorded. Allergic disease was particularly diagnosed according to the criteria from the European Academy of Allergy and Clinical Immunology (EAACI), and diagnosis was made by experienced specialists. This study was approved by the Medical Ethics Committee of Peking University People's Hospital (Beijing, China).

Laboratory tests, imaging studies and histological examination

Laboratory tests comprised complete blood count, ESR, CRP, serum Ig level, IgG subclasses, total IgE level, complement, liver and renal function profile and autoantibodies (including RF and ANAs).

All patients underwent image examinations, including ultrasonography, CT or MRI; and 18 F-fluorodeoxyglucose PET/CT was performed in some patients. According to previous research [15], the patients who did not show clinical symptoms but had obviously increased

fluorodeoxyglucose uptake in the salivary gland, were still considered as IgG4-RD SG+ patients.

Tissue biopsies were carried out on 255 patients, and all tissue biopsy samples were fixed in formalin and embedded in paraffin wax, then stained with haematoxylin and eosin. Antibodies against CD3, CD20, IgG, IgG4, CD138 and CD38 were used for immunohistochemical staining.

Statistical analysis

All statistical analyses were performed by SPSS 24.0. Data were analysed using descriptive methods, with standard summary statistics including mean (s.d.), median, interquartile range, and proportions. Differences for continuous, normally distributed data were performed using the Student's *t* test; continuous, non-normally distributed data were analysed by the Mann-Whitney test. Categorical variables were processed by χ^2 or Fisher's exact tests, as appropriate. The correlations of serum IgG4 levels and other parameters were determined using the Pearson's correlation coefficient for normally distributed data or the Spearman's rank correlation for nonparametric data. A *P*-value <0.05 was considered statistically significant.

Results

Patients' demographic characteristics

A total of 428 patients diagnosed with IgG4-RD were enrolled in this study. The demographic features are shown in Table 1. All 428 patients were divided into two groups according to the presence or absence of the salivary gland lesions: 249 cases (58.2%) had salivary gland lesions (IgG4-RD SG+), and 179 cases (41.8%) were without salivary gland lesions (IgG4-RD SG–). The mean age at disease onset of IgG4-RD SG+ group was 51.1 years, which was younger than that in the IgG4-RD SG– group (*P*=0.041). Mean ages at diagnosis were 53.5 years and

TABLE 1 Demographic and clinical characteristics of 428 IgG4-RD patients

Characteristics	Value
Number of cases, <i>n</i>	428
Definite diagnosis, <i>n</i> (%)	205 (47.9)
Probable diagnosis, <i>n</i> (%)	50 (11.7)
Possible diagnosis, <i>n</i> (%)	173 (40.4)
Mean age at disease onset, years (s.d.)	52.4 (14.1)
Mean age at diagnosis, years (s.d.)	54.5 (13.6)
Time from onset to diagnosis, months (s.d.)	24.6 (41.2)
Gender (Male : Female)	1.19 : 1
Complication of allergic disease, <i>n</i> (%)	172 (40.2)
Organ involvement, <i>n</i> (%)	
1 organ involved	91 (21.3)
2 organs involved	123 (28.7)
3 organs involved	122 (28.5)
≥ 4 organs involved	92 (21.5)

TABLE 2 Differences in demographic features and clinical characteristics between IgG4-RD SG+ and IgG4-RD SG− patients

Characteristics	IgG4-RD SG+	IgG4-RD SG−	P-value
Number of cases, <i>n</i>	249	179	
Follow up time (months), median (IQR)	28.0 (13.3–44.5)	29.5 (13.3–47.0)	0.92
Mean age at disease onset, years (s.d.)	51.1 (13.7)	54.2 (14.5)	0.041
Mean age at diagnosis, years (s.d.)	53.5 (12.7)	56.0 (14.5)	0.07
Time from onset to diagnosis, months (s.d.)	28.2 (45.0)	19.7 (34.9)	0.001
Gender (Male : Female)	0.96 : 1	1.78 : 1	0.001
Complication of allergic disease, <i>n</i> (%)	127 (51.0)	45 (25.1)	<0.001
Number of involved organs, median (IQR)	3 (2–4)	2 (1–3)	<0.001

IQR: interquartile range.

56.0 years, respectively. As a result, the time from onset to diagnosis was 19.7 months in the IgG4-RD SG− group, which was significantly shorter than that in the IgG4-RD SG+ group (28.2 months) ($P=0.001$). The gender ratio (Male : Female) of the IgG4-RD SG+ group and the IgG4-RD SG− group were 0.96 : 1 and 1.78 : 1, respectively ($P=0.001$) (Table 2).

Clinical features

The most common initial involved organ was the submandibular gland (51.4%) followed by the lacrimal gland in IgG4-RD SG+ patients, and pancreas (21.2%) followed by retroperitoneal fibrosis in IgG4-RD SG− patients. In terms of allergic disorders, IgG4-RD SG+ patients (51.0%) had a higher frequency of allergic diseases (allergic rhinitis, urticaria, asthma) than that in IgG4-RD SG− patients ($P<0.001$) (Table 2).

Organ involvement was evaluated by systematic standards including symptoms, signs, radiographic or other image examinations. In the total cohort, multi-organ involvement (range 2–10 organs) was found in 337 (78.7%) patients (Table 1). In IgG4-RD SG+ patients, the most commonly involved organs except for salivary glands were the lacrimal gland (51.8%) and lymph node (40.9%), followed by pancreas, of which the proportion of involvement dropped dramatically to 19.9%, while in IgG4-RD SG− patients the most commonly involved organs were lymph node (53.8%) and pancreas (38.3%), followed by retroperitoneal fibrosis (34.2%) (Table 3). The median number of affected organs in the IgG4-RD SG+ group was significantly higher than that in the IgG4-RD SG− group ($P<0.001$). Furthermore, it has been shown that patients with more than three organs affected were more common in the IgG4-RD SG+ group (Fig. 1). Specifically, the IgG4-RD SG+ group more often presented with lacrimal gland lesions while the IgG4-RD SG− group more often presented with lymph node, pancreas, retroperitoneal fibrosis, biliary system, kidney and aorta lesions.

Laboratory findings

We further compared the laboratory tests between these two groups (Table 4). The serum IgG4 level, IgG4/IgG ratio

and IgE level were significantly higher in IgG4-RD SG+ patients. We also found that the serum IgG4 value was positively correlated with IgG4/IgG ratio, total IgG and IgE level in both IgG4-RD SG+ patients and IgG4-RD SG− patients (Fig. 2). IgG4-RD SG+ patients were more commonly associated with elevated eosinophils counts (19.5% vs 9.5%, $P=0.007$), while the number of patients with elevated ESR and CRP was significantly higher in IgG4-RD SG− patients (32.0% vs 22.5% $P=0.028$ and 25.6% vs 9.6% $P<0.001$, respectively). Low titres of ANA were detected in 28 (21.2%) IgG4-RD SG− patients, which was significantly higher than that in IgG4-RD SG+ patients ($P=0.02$). Hypocomplementemia was a common finding in both IgG4-RD SG+ (32.1%) and IgG4-RD SG− (24.6%) ($P=0.09$), and the number of patients with low serum C4 was significantly higher in IgG4-RD SG+ patients ($P=0.024$).

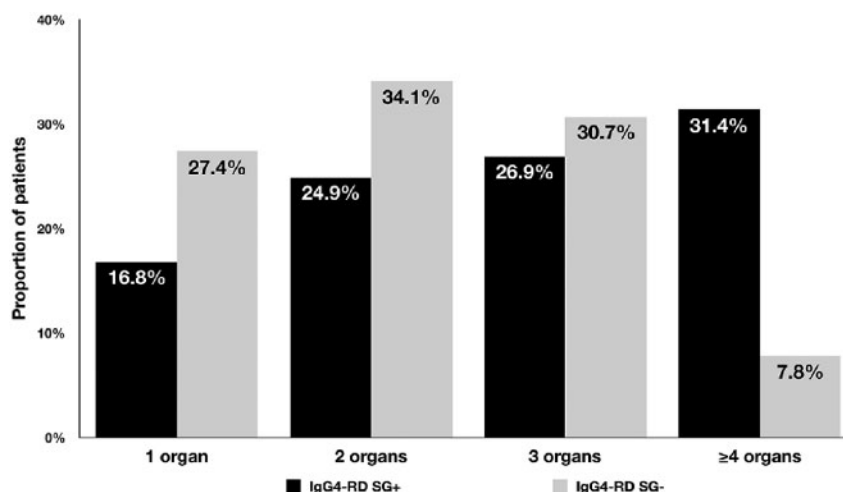
Discussion

We compared herein the demographic, clinical and laboratory features between 249 IgG4-RD SG+ patients and 179 IgG4-RD SG− patients, and we found many differences in the above aspects. To our knowledge, this is the first research focusing on these two phenotypes of IgG4-RD, and the sample size is large.

Our work suggests that IgG4-RD SG+ patients exhibit symptoms and get a diagnosis at an earlier age, although the latter comparison fell short of statistical significance. We consider that the most common initial complaint of IgG4-RD SG+ patients is enlargement of the salivary [16], which is easily noticed even in the absence of dysfunction and other symptoms. However, time from onset to diagnosis of IgG4-RD SG+ patients was longer than that in IgG4-RD SG− patients; in addition, some studies have shown that salivary secretion rate decreased with delayed management [17]. Therefore, clinicians are supposed to pay more attention to IgG4-RD, especially IgG4-RD SG+ patients, to counteract the trend of salivary glands damage. This study also reveals a higher percentage of female patients among the IgG4-RD SG+ patients, which is consistent with other studies [18]. It has been proposed that chronic antigen stimulation might lead to

TABLE 3 Comparison of organ involvement between IgG4-RD SG+ and IgG4-RD SG− patients

Organ involvement	IgG4-RD SG+, n (%)	IgG4-RD SG−, n (%)	P-value
Prostate	7 (2.8)	1 (0.5)	0.147
Lymph node	101 (40.9)	96 (53.8)	0.008
Retroperitoneal fibrosis	16 (6.8)	60 (33.5)	<0.001
Pancreas	44 (19.9)	65 (36.3)	<0.001
Biliary system	24 (10.7)	55 (31.6)	<0.001
Kidney	23 (9.7)	61 (33.7)	<0.001
Aorta	3 (1.4)	13 (7.3)	0.001
Lung	14 (5.9)	17 (10.5)	0.127
Lacrimal gland	129 (51.8)	19 (10.6)	<0.001
Pituitary gland	1 (0.4)	0 (0)	1

Fig. 1 Constituent ratio of organ involvement in IgG4-RD SG+ and IgG4-RD SG− patients

The proportion of patients with one, two, three and more than three organs lesion were 16.8%, 24.9%, 26.9% and 31.4% in IgG4-RD SG+ patients, while 27.4%, 34.1%, 30.7% and 7.8% in IgG4-RD SG− patients.

IgG4-RD [19]. We further speculate that female patients may be more easily exposed to some pathogenic factors from the oral cavity, and the cross-reaction between antibody and autoantigens is more easily established in salivary and lacrimal glands in female patients [20].

IgG4-RD is a systemic condition characterized by multiple organ involvement. We found that IgG4-RD SG+ patients have more organs affected. Therefore, it is necessary to perform an evaluation of the whole body to obtain a full view of the general condition of the patient in the clinical practice, especially for the IgG4-RD SG+ patients.

Elevated serum IgG4 level is one of the hallmarks of IgG4-RD. Furthermore, serum IgG4 level, IgE level, eosinophilia as well as anaphylactic disease were higher or more commonly observed in IgG4-RD SG+ patients. These findings indicate some different factors involved in the pathogenesis of these two phenotypes. Maehara *et al.* [21] described that dysregulated follicular T helper cells

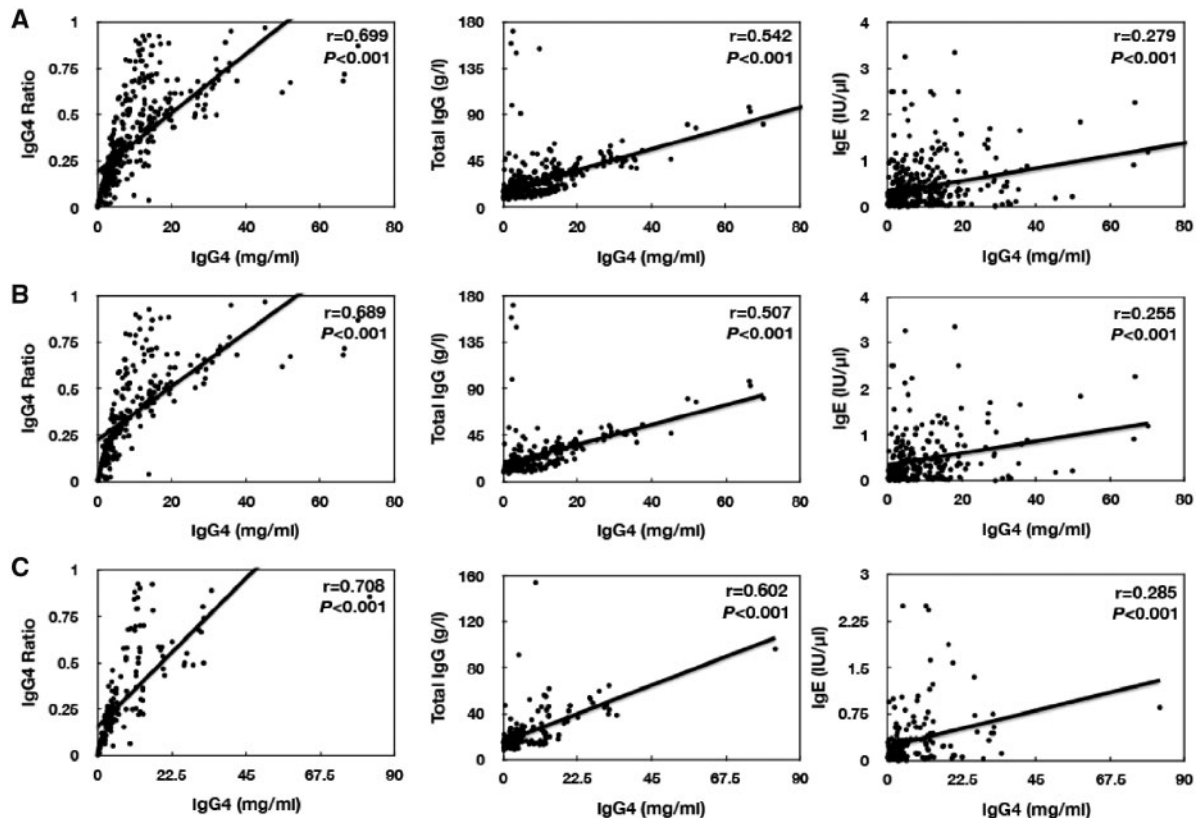
may participate in the lesion of salivary glands in IgG4-RD SG+ patients. Specifically, interleukin-21 secreted by these dysregulated follicular T helper cells is involved in the formation of ectopic germinal centres in salivary glands and class switching of IgG4 as well as IgE, which results in the higher IgG4 and IgE levels in IgG4-RD SG+ patients. Elevated IgE level is associated with allergic disease [22], and some allergic disease is thought to be involved in the pathogenesis of IgG4-related sialadenitis [23]. As a result, serum IgG4 level and IgE level of IgG4-RD SG+ patients are higher than that in IgG4-RD SG− patients. However, the mechanism of IgG4-RD remains unclear and deserves further study.

Our research may provide insights into the mechanism of the hypocomplementemia commonly observed in IgG4-RD patients. We found a higher percentage of hypocomplementemia in IgG4-RD SG+ patients, although the comparison is not statistically significant. The IgG4 molecule is believed to lose the ability to activate

TABLE 4 Laboratory findings in IgG4-RD SG+ and IgG4-RD SG− patients

Parameter	IgG4-RD SG+	IgG4-RD SG−	P-value
Serum IgG4 level (mg/dl), median (IQR)	666 (317–1405)	399 (209–1122)	<0.001
IgG4/Total IgG, median (IQR)	0.342 (0.181–0.528)	0.223 (0.109–0.428)	<0.001
Serum IgE (IU/ml), median (IQR)	294.4 (102.6–635.7)	182.4 (52.4–351.4)	<0.001
ESR (mm/h), median (IQR)	9 (4–14)	9 (5–23)	0.068
Elevated ESR, <i>n</i> (%)	56 (22.5)	57 (32.0)	0.028
Elevated CRP, <i>n</i> (%)	21 (9.6)	47 (25.6)	<0.001
Eosinophilia, <i>n</i> (%)	49 (19.5)	18 (9.5)	0.007
ANA (+), <i>n</i> (%)	32 (12.9)	28 (21.2)	0.021
RF (+), <i>n</i> (%)	34 (13.7)	24 (13.6)	1.00
Hypocomplementemia, <i>n</i> (%)	80 (32.1)	44 (24.6)	0.09
Reduced serum C4, <i>n</i> (%)	63 (25.3)	29 (16.2)	0.024
Reduced serum C3, <i>n</i> (%)	64 (25.7)	35 (19.6)	0.137

IQR: interquartile range.

FIG. 2 The relationship between serum IgG4 level and other laboratory findings

The serum IgG4 value was positively correlated with IgG4/IgG ratio, total IgG and IgE level in total IgG4-RD (A). The same correlation was found in IgG4-RD SG+ patients (B) and IgG4-RD SG− patients (C).

complementary systems through the Fab-arm exchange under most circumstances [24]. However, some researchers stated that a high concentration of IgG4 antibodies may retain mono-specificity and the potential to cross-link antigens, which would cause destructive

tissue inflammation and hypocomplementemia [25]. Hypocomplementemia is more commonly observed in IgG4-RD SG+ patients, and this may be because of the higher IgG4 levels they have. Besides, our data indicate that IgG4 level is positively correlated with total IgG level,

suggesting that other IgG subtypes may be responsible for the decrease of complement [26]. Moreover, van de Stadt *et al.* [27] found antibodies that targeted the IgG4 hinge in rheumatoid arthritis patients with complement activation, and these antibodies may cause the hypocomplementemia in IgG4-RD patients, particularly the IgG4-RD SG+ patients with higher IgG4 levels. Furthermore, patients in the IgG4-RD SG– group have much more retroperitoneal involvement, and the hypocomplementemia in patients with retroperitoneal lesions is rare [28], which is another reason for less hypocomplementemia in the IgG4-RD SG– group.

The limitations of this study include the fact that it was retrospective in nature, which means some affected organs might be ignored, although most patients underwent examinations of the whole body, even the FDG-PET. In addition, this is a single-centre study, and our centre is located within the rheumatology unit. Therefore, our patients may be skewed toward patients with multi-organ manifestations.

In conclusion, we have described demographic, clinical and laboratory differences between IgG4-RD SG+ and SG– patients. IgG4-RD SG+ patients were associated with younger age at disease onset, younger age at diagnosis and longer time from onset to diagnosis. Allergic diseases and multi-organ involvement were more commonly observed in the IgG4-RD SG+ group. IgG4-RD SG+ phenotype showed higher levels of IgG4 and IgE. These findings indicated potential differences in pathogenesis and important implications for the diagnosis and management of these two phenotypes.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1 Baseline characteristics of whole and definite IgG4-RD patients

Characteristics	Whole cases	Definite cases	P-value
Number of cases, n	428	205	
Mean age at disease onset (years±SD)	52.4±14.1	51.0±13.0	0.19
Mean age at diagnosis (years±SD)	54.5±13.6	53.4±12.4	0.25
Time from onset to diagnosis (months±SD)	24.6±41.2	27.9±43.9	0.72
Gender (Male:Female)	1.19:1	1.28:1	0.7
Complication of allergic disease, n (%)	172 (40.2)	98 (47.8)	0.07
Number of involved organs, median (IQR)	2 (2-3)	3 (2-4)	0.013*
Organ involvement, n (%)			
Prostate	8 (1.9)	6 (2.9)	0.58
Lymph node	197 (46.0)	96 (46.8)	0.85
Retroperitoneal fibrosis	76 (17.8)	30 (14.6)	0.33
Pancreas	109 (25.5)	44 (21.5)	0.27
Biliary system	79 (18.5)	32 (15.6)	0.37
Kidney	84 (19.6)	30 (14.6)	0.13
Aorta	16 (3.7)	6 (2.9)	0.6
Lung	31 (7.2)	19 (9.3)	0.38
Lacrimal gland	148 (37.3)	105 (51.2)	0.001*
Pituitary gland	1 (1.2)	1 (0.5)	1
Serum IgG4 level (mg/dL), median (IQR)	510 (266-1260)	666 (319-1395)	0.05*
IgG4/Total IgG, median (IQR)	0.271 (0.145-0.500)	0.324 (0.174-0.513)	0.19
Serum IgE(IU/ml), median (IQR)	243.5 (67.2-532.1)	275.0 (77.0-587.3)	0.23
ESR (mm/h), median (IQR)	9 (5-16)	8 (4-15)	0.55
Elevated ESR, n (%)	113 (26.4)	50 (24.4)	0.59
Elevated CRP, n (%)	68 (15.9)	32 (15.6)	0.93
Eosinophilia, n (%)	67 (15.7)	35 (17.1)	0.65
ANA (+), n (%)	60 (14.0)	35 (17.1)	0.31
RF (+), n (%)	58 (13.6)	29 (14.1)	0.84
Hypocomplementemia, n (%)	124 (29.0)	73 (35.6)	0.09
Reduced serum C4, n (%)	92 (21.5)	56 (27.3)	0.11
Reduced serum C3, n (%)	99 (23.1)	59 (28.8)	0.12