



Comparison of clinical and laboratory features of patients with and without allergic conditions in IgG4-related disease: A single-center experience in Japan

Takako Saeki, Daisuke Kobayashi, Tomoyuki Ito, Maasa Tamura, Seiichi Yoshikawa & Hajime Yamazaki

To cite this article: Takako Saeki, Daisuke Kobayashi, Tomoyuki Ito, Maasa Tamura, Seiichi Yoshikawa & Hajime Yamazaki (2018): Comparison of clinical and laboratory features of patients with and without allergic conditions in IgG4-related disease: A single-center experience in Japan, Modern Rheumatology, DOI: [10.1080/14397595.2017.1416891](https://doi.org/10.1080/14397595.2017.1416891)

To link to this article: <https://doi.org/10.1080/14397595.2017.1416891>



Accepted author version posted online: 18 Dec 2017.
Published online: 08 Jan 2018.



Submit your article to this journal [↗](#)



Article views: 31



View related articles [↗](#)



View Crossmark data [↗](#)

ORIGINAL ARTICLE



Comparison of clinical and laboratory features of patients with and without allergic conditions in IgG4-related disease: A single-center experience in Japan

Takako Saeki^a, Daisuke Kobayashi^{b,c}, Tomoyuki Ito^a, Maasa Tamura^a, Seiichi Yoshikawa^a and Hajime Yamazaki^a

^aDepartment of Internal Medicine, Nagaoka Red Cross Hospital, Nagaoka, Japan; ^bDepartment of Rheumatology, Niigata Rheumatic Center, Niigata, Japan; ^cDivision of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

ABSTRACT

Objective: The objective of this study is to compare the clinical and laboratory features of Japanese patients with IgG4-related disease, with and without allergic conditions.

Methods: We retrospectively examined the clinical and laboratory features and clinical courses of 51 patients with definitively diagnosed IgG4-RD, collected from Nagaoka Red Cross Hospital between January 2004 and August 2017, with reference to the presence of allergic conditions.

Results: Among these patients, 43% had allergic conditions. In the allergy group, the proportion of females was significantly higher, the age at diagnosis was significantly lower, and upper body organ involvement was predominant in comparison with the non-allergy group. There was no significant inter-group difference in the absolute number of peripheral blood eosinophils, the levels of serum IgG4 and IgE, the response to steroid, or the proportion of patients who relapsed.

Conclusion: The present findings suggest that there may be some differences in the clinical features of IgG4-RD patients according to the allergic conditions that are present, although eosinophilia and high serum levels of IgE and IgG4 are common features regardless of allergy.

ARTICLE HISTORY

Received 27 September 2017
Accepted 23 November 2017

KEYWORDS

Allergy; eosinophilia; IgE; IgG4; IgG4-related disease

Introduction

IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory condition characterized by infiltration of abundant IgG4-positive plasma cells with fibrosis, and usually an elevated serum IgG4 concentration [1,2]. In IgG4-RD, patients sometimes have accompanying allergic conditions, and often show peripheral blood eosinophilia and an elevated serum IgE level [3,4]. Therefore, allergic mechanisms have been considered to play a potentially key role in the pathogenesis of IgG4-RD, although the pathogenesis has not been elucidated. However, few data on the relationship between allergic conditions and IgG4-RD have been available. In the present study, we retrospectively examined the clinical and laboratory features of Japanese patients with IgG4-RD, with reference to the presence of allergic conditions.

Methods

Patients and samples

Between January 2004 and August 2017, 60 Japanese patients were sequentially diagnosed as having IgG4-RD in all departments of Nagaoka Red Cross Hospital. Among them, biopsy-proven 51 patients diagnosed as having definite IgG4-RD [5] were enrolled. Clinical information was collected from the medical records, including background characteristics, IgG4-RD manifestations, laboratory data

(serum concentrations of IgG4, IgE and peripheral blood eosinophils), details of any allergic condition at the time of IgG4-RD diagnosis, and the clinical course after diagnosis. Whole-body CT imaging was evaluated for all patients before therapy. The study was approved by the review board of Nagaoka Red Cross Hospital. All data from patients were collected with their informed consent, and the research was conducted in compliance with the principles of the Declaration of Helsinki.

Definition of improvement and relapse

For extra-renal lesions, improvement of the organ involvement was decided according to changes in symptomatic, radiologic, serologic or histologic features. In IgG4-related kidney disease, improvement of renal function (in terms of serum creatinine level or eGFR) was also considered. Relapse of extra-renal lesions was decided on the basis of re-appearance or worsening of symptomatic, radiologic, serologic, or histologic features. Worsening of allergic symptoms (coughing, wheezing, or rhinorrhea) alone without radiologic worsening or lesion re-growth in affected organs was not considered to be relapse. In IgG4-related kidney disease, a rapid rise in the serum creatinine level, after careful exclusion of other renal diseases, was also considered as relapse. Re-elevation of the serum level of IgG or IgG4 alone was not considered to be relapse.

Statistical analysis

The significance of differences between groups was determined using the paired Student's *t* test, Mann–Whitney *U* test or Wilcoxon signed-rank test, and the significance of differences in frequencies was analyzed with Fisher's exact probability test. Data are presented as means $\pm$ SD for continuous variables and as frequencies and percentages for categorical variables. The influences of allergic state (with or without) on involvement of each organ were determined by logistic regression analysis, and age- and sex-adjusted *p* were noted. Multiple regression analyses were performed to determine whether an allergic state influenced the ratio of the total number of affected organs in the upper body to that in the whole body after adjusting for the effects of age and sex. A probability of $p < .05$ was considered to indicate statistical significance. Statistical analysis was performed using SPSS version 19 software (IBM SPSS, Chicago, IL) or EZR [6].

Results

Clinical features

Of the 51 patients, 22 (43%) had allergic conditions [allergic rhinitis ($n = 15$), bronchial asthma ($n = 13$), and conjunctivitis ($n = 4$)] at the time of IgG4-RD diagnosis (Table 1). Six of the 13 patients with asthma also had allergic rhinitis, and all the patients with conjunctivitis had both allergic rhinitis and bronchial asthma. All patients in the allergy group had symptoms related to their allergies, and had been diagnosed as having allergic conditions by each attending physician at

the time of IgG4-RD diagnosis. None of the 51 patients were treated with steroid, their mean age was 67.0 ± 11.6 year, and 56.9% were male. In the allergy group, the proportion of males was significantly lower (36.4% versus 72.4%, $p = .010$), and the age at diagnosis of IgG4-RD was significantly lower [mean 61.0 year (42–85) versus 71.6 year (60–86), $p = .002$], in comparison with those of the non-allergy group. There was no significant inter-group difference in the total number of involved organs (3.3 ± 1.9 versus 3.1 ± 1.6 , $p = .690$). The organs most commonly involved were the submandibular glands (68%), lungs (50%), lymph nodes (50%), and lacrimal glands (46%) in the allergy group, and the submandibular glands (76%), kidneys (45%), pancreas (41%), and lymph nodes (41%) in the non-allergy group. Univariate analyses revealed no significant inter-group differences in the frequency of organs involvement. However, the ratio of the total number of affected organs in the upper body (head, neck, and thoracic area) to that in the whole body in each patient was significantly higher in the allergy group than in the non-allergy group ($80 \pm 24\%$ versus $56 \pm 32\%$, $p = .004$) (Table 1). Logistic regression analysis indicated that allergy was an important factor for lung involvement after adjustment for age and sex [odds ratio (OR) 5.64, partial 95% confidence interval (C.I.) 1.17–27.30, $p = .0316$] (Table 1). Multiple regression analysis indicated that the ratio of the total number of affected organs in the upper body to that in the whole body in each patient remained significantly higher in the patients with allergy after adjusting for the effects of age and sex [partial regression coefficient (95% CI) was 0.634 (0.0131–1.27), $p = .0456$].

Table 1. Clinical features of the IgG4-RD patients according to allergy.

	All ($n = 51$)	With allergy ($n = 22$)	Without allergy ($n = 29$)	<i>p</i>	Age-sex-matched <i>p</i>
Age at diagnosis of IgG4-RD, mean $\pm$ SD (years)	67.0 $\pm$ 11.6	61.0 $\pm$ 13.2	71.6 $\pm$ 8.1	.002	
Male, <i>n</i> (%)	27 (56.9)	8 (36.4)	21 (72.4)	.010	
Allergy, <i>n</i> (%)					
Rhinitis		15 (68.1)			
Asthma		13 (59.0)			
Conjunctivitis		4 (18.1)			
No. of involved organs, mean $\pm$ SD	3.2 $\pm$ 1.8	3.3 $\pm$ 1.9	3.1 $\pm$ 1.6	.690	
Organ involvement, <i>n</i> (%)					
Submandibular glands	37 (73)	15 (68)	22 (76)	.543	0.105
Lacrimal glands	17 (33)	10 (46)	7 (24)	.110	0.464
Lung	20 (39)	11 (50)	9 (31)	.169	0.032
Lymph nodes	23 (45)	11 (50)	12 (41)	.540	0.509
Pancreas	18 (35)	6 (27)	12 (41)	.296	0.583
RPF/periaortitis	12 (24)	3 (14)	9 (31)	.147	0.268
Kidney	17 (33)	5 (23)	12 (45)	.136	0.461
Others					
Orbit	4	3	1		
Skin (face)	1	1			
Nerve (cranial)	1	1			
Pituitary	1	1			
Pericardium	2	2			
Coronary artery	2	1	1		
Biliary tract	4		4		
Liver	1	1			
Peritoneum	1		1		
Prostate	1		1		
No. of upper affected organs/no. of total affected organs in a patient, mean $\pm$ SD (%)	66 $\pm$ 31	80 $\pm$ 24	56 $\pm$ 32	.004	

RPF: retroperitoneal fibrosis.

Table 2. Laboratory features of the IgG4-RD patients according to allergy.

	All (n = 51)	With allergy (n = 22)	Without allergy (n = 29)	p
Eosinophilia (Eo >5%), %	35	36	34	1.00
Elevated serum IgG4 (>135 mg/dl), %	100	100	100	1.00
Elevated serum IgE (>250 IU/ml), %	56	63	50	.52
Eosinophils (cells/ μ l), mean $\pm$ SD	327 $\pm$ 431	359 $\pm$ 367	302 $\pm$ 478	.65
Serum IgG4 (mg/dl), mean $\pm$ SD	836 $\pm$ 595	905 $\pm$ 685	780 $\pm$ 492	.46
Serum IgE (IU/ml), mean $\pm$ SD	691 $\pm$ 1082	536 $\pm$ 523	838 $\pm$ 1596	.44

Laboratory findings

Eosinophilia (eosinophils >5%) and elevation of the serum IgG4 (>135 mg/dl) and IgE (>250 IU/ml) levels were evident in 36%, 100%, and 63% of patients in the allergy group and 34%, 100%, and 50% of those in the non-allergy group, respectively; none of the inter-group differences were significant (Table 2). There were also no significant inter-group differences in the absolute peripheral blood eosinophil count or the levels of serum IgG4 and IgE before therapy (Table 2).

Clinical course after diagnosis

Indications for treatment and the treatment regimen were decided according to the opinion of each attending physician. The follow-up period after diagnosis was 3–99 months (mean 44.6 $\pm$ 29.9) in the allergy group and 4–228 months (mean 62.5 $\pm$ 58.4) in the non-allergy group ($p = .196$). Fifteen of the 22 patients (68.2%) with allergy and 21 of the 29 patients (72.4%) without allergy were treated with prednisolone ($p = .490$), and the others were followed up without therapy. The initial prednisolone dose was 0.5–0.6 mg/kg/d in all treated patients in both groups, excluding three patients who were diagnosed more than 10 years previously (prednisolone 0.8–1.0 mg/kg/d). All organ involvements associated with IgG4-RD were improved by steroid therapy in all patients in both groups. Among the treated patients, 12 with allergy and 19 without allergy were followed up for over 12 months, and nine of the 12 patients (75%) with allergy and all patients without allergy were still being maintained on corticosteroid at the last review (mean prednisolone dose 4.4 mg daily and 4.9 mg daily, respectively). There was no significant difference in the rate of IgG4-RD relapse [two of 15 treated patients (13.3%) with allergy and six of 21 patients (28.6%) without allergy ($p = .253$), during maintenance steroid therapy], although worsening of allergic symptoms alone was sometimes observed in the patients with allergy. Spontaneous improvement was observed in two of the seven untreated patients with allergy and two of the eight untreated patients without allergy (spontaneous regression of submandibular glands in all patients).

Discussion

In type 1 autoimmune pancreatitis, the prevalence of allergic disorders (15–40%) has been reported to be significantly higher than in patients with chronic pancreatitis or in age- and gender-matched controls [7,8]. In a retrospective multicenter study of 64 Japanese patients with IgG4-RD, the

prevalence of allergic rhinitis (26%) was significantly higher than that in patients with Sjögren's syndrome (2%, $p < .001$) [9]. Because peripheral eosinophilia, a high level of serum IgE and eosinophil infiltration in the affected organs have often been described in IgG4-RD, some researchers have speculated that the mechanism of allergy may be closely related to the pathogenesis of IgG4-RD, in view of reports indicating upregulation of Th2 and regulatory cytokines in IgG4-RD [10]. In 2013, Della Torre et al. [11] examined the prevalence of atopy, eosinophilia and IgE elevation in 70 patients with IgG4-RD at a single center, in whom a wide range of organs were affected. They found that the prevalence of atopy in IgG4-RD (22 of 70, 31%) was similar to that in the US general population, and that among patients who presented with either an elevated IgE level or peripheral blood eosinophilia the mean IgE concentrations and eosinophil counts were similar, regardless of whether atopy was present or absent. Accordingly, they suggested that eosinophilia and IgE elevation were probably induced by a process inherent to IgG4-RD itself (e.g. Th2 cytokines, such as IL-4 and IL-5) rather than atopy *per se*. In the present Japanese cohort study of IgG4-RD, in which the disease spectrum was also not limited to a specific compartment, the prevalence of allergy was 43%. Although the prevalence of allergic conditions in the general Japanese population has not been documented precisely, a nationwide study has indicated that the overall prevalence of rhinitis is 35.1% in men and 39.3% in women [12]. However, the prevalence appears to be higher in the younger than in the older population (18–25% of men and 20–30% of women in the 60–79-year age group) [12]. Because elderly men formed the dominant population in the present Japanese cohort study of IgG4-RD, allergic conditions might be relatively more prevalent in IgG4-RD patients than in the Japanese general population. Interestingly, however, there were no significant differences in the frequency of eosinophilia, serum levels of IgG4 and IgE, or mean IgE and IgG4 concentrations and peripheral blood cell counts between the allergy group and the non-allergy group. This parallels the results reported by Della-Torre et al. [11], and supports their suggestion that both elevation of the IgE concentration and eosinophilia are inherent characteristics of the IgG4-RD immune response itself, rather than being attributable to an underlying allergic condition.

On the contrary, the present study revealed some differences in the clinical features of the allergy group relative to those in the non-allergy group (female predominance, younger age, and predominant organ involvement in the upper body). Generally, the upper respiratory tract is likely to be exposed to allergens, and these allergens might be

more closely related to the development of upper organ involvement, than the lower organ involvement, in IgG4-RD. Among patients with IgG4-RD, elderly men are predominant in those with type 1 autoimmune pancreatitis [1], IgG4-related kidney disease [3] or IgG4-related retroperitoneal fibrosis [13], whereas the sex ratio was almost equal in those with IgG4-related dacryoadenitis and/or sialadenitis [14]. In the study by Della-Torre et al., the prevalence of retroperitoneal fibrosis was higher in the non-atopy group than in the atopy group (29% versus 5%) [11]. Although the causes of these clinical differences remain to be elucidated, allergic conditions might play a role in the differences of clinical features of IgG4-RD, even though allergy might not drive IgG4-RD directly. A larger-scale multi-center study that includes various IgG4-RD conditions will be necessary.

In conclusion, there may be some differences in the clinical features of IgG4-RD patients according to the allergic conditions that are present, although eosinophilia and high serum levels of IgE and IgG4 are common features regardless of allergy.

Acknowledgements

The authors thank Dr. Naohito Tanabe for his helpful comments.

Conflict of interest

None.

References

1. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. A novel clinical entity, IgG4-related disease (IgG4-RD): general concept and details. *Mod Rheumatol*. 2012;22:1–14.
2. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med*. 2012;366:539–51.
3. Saeki T, Nishi S, Imai N, Ito T, Yamazaki H, Kawano M, et al. Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. *Kidney Int*. 2010;78:1016–23.
4. Kawano M, Saeki T, Nakashima H, Nishi S, Yamaguchi Y, Hisano S, et al. Proposal for diagnostic criteria for IgG4-related kidney disease. *Clin Exp Nephrol*. 2011;25:810–19.
5. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol*. 2012;22:21–30.
6. Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant*. 2013;48:452–8.
7. Kamisawa T, Anjiki H, Egawa N, Kubota N. Allergic manifestations in autoimmune pancreatitis. *Eur J Gastroenterol Hepatol*. 2009;21:1136–9.
8. Sah RP, Pannala R, Zhang L, Graham RP, Sugumar A, Chari ST. Eosinophilia and allergic disorders in autoimmune pancreatitis. *Am J Gastroenterol*. 2010;105:2485–91.
9. Masaki Y, Dong L, Kurose N, Kitagawa K, Morikawa Kanda Y, Yamamoto M, et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis*. 2009;68:1310–15.
10. Zen Y, Fujii T, Harada K, Kawano M, Yamada K, Takahira M, et al. Th2 and regulatory immune reactions are increased in immunoglobulin G4-related sclerosing pancreatitis and cholangitis. *Hepatology*. 2007;45:1538–46.
11. Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. *Allergy*. 2014;69:269–72.
12. Konno S, Hizawa N, Fukutomi Y, Taniguchi M, Kawagishi Y, Okada C, et al. The prevalence of rhinitis and its association with smoking and obesity in a nationwide survey of Japanese adults. *Allergy*. 2012;67:653–60.
13. Mizushima I, Inoue D, Yamamoto M, Yamada K, Saeki T, Ubara Y, et al. Clinical course after corticosteroid therapy in IgG4-related aortitis/periaortitis and periarteritis: a retrospective multi-center study. *Arthritis Res Ther*. 2014;16(4):R156.
14. Yamamoto M, Yajima H, Takahashi H, Yokoyama Y, Ishigami K, Shimizu Y, et al. Everyday clinical practice in IgG4-related dacryoadenitis and/or sialadenitis: results from the SMART database. *Mod Rheumatol*. 2015;25:199–20.