Distinct impact of malignancy and allergy on the clinical and immunological features of IgG4-related disease

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Abstract

Objective

To clarify the clinical and immunological characteristics of IgG4-RD based on the underlying diseases.

Methods

Consecutive patients with IgG4-RD treated at Keio University Hospital between 2010 and 2021 were divided according to the presence of malignancy or allergy into three groups. The clinical characteristics and 56 immune cell subsets in the peripheral blood were compared between the groups.

Results

Among 123 patients, 18 (14.6%) had malignancy including 4 with allergy (malignancy group), 57 (46.3%) had allergy alone (allergy group), and 48 (39.0%) had neither (idiopathic group). In the malignancy group, the patients were older (70.1 vs. 54.4 vs. 64.9 years, p<0.001), male-dominant (83.3 vs. 42.1 vs. 54.2%, p=0.008), and had smoking habits (77.8 vs. 42.1 vs. 43.8%, p=0.02). They also had significant involvement of the aorta/large vessels (33.3 vs. 7.0 vs. 20.8%, p=0.02), while the patients in the allergy group tended to have orbital/lacrimal gland involvement. Remission and relapse rates were not different between the groups; however, overall survival was significantly poorer in the malignancy group (p=0.02). Comprehensive immunophenotyping of the peripheral blood revealed that the increase in CXCR5+CD2-double negative T cells and the decrease in naive CD8 T cells were characteristic of the malignancy group.

Conclusion

The clinical and immunological phenotypes of IgG4-RD differ among those with underlying diseases.

Key words

IgG4-related disease, allergy, atopic history, malignancy, cancer, immunophenotyping, double negative T cell, naïve CD8 T cell, prognosis

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Received on October 14, 2022; accepted in revised form on November 21, 2022.

Funding: this work was supported by JSPS KAKENHI grant no. JP 21K16292, and Keio University Medical Science Fund (Keio University Research Grants for Medicine and the Life Science) to M. Akiyama

Competing interests: none declared.

Introduction

IgG4-related disease (IgG4-RD) is a new entity of chronic fibro-inflammatory disease characterised by tumour-like mass lesions in various organs, pathological accumulation of IgG4+ lymphoplasmacytic cells, and elevated serum IgG4 levels (1, 2). Although IgG4-RD generally responds well to glucocorticoid therapy, disease relapse is frequent during glucocorticoid tapering, and some cases show a refractory disease course (3-5). Clarifying its pathogenesis and characteristics is important for establishing an optimal treatment strategy.

The aetiology of IgG4-RD remains unclear; however, allergic reactions are suspected to be involved in the context of IgG4 antibodies being produced by chronic allergen stimulation (6). Moreover, 40–70% of patients with IgG4-RD have an atopic history (7-10). In addition, the follicular helper T (Tfh) cells, which have been recently identified as critical players in the pathogenesis of IgG4-RD (11, 12), are also involved in allergen immunotherapy (13). However, some studies have also reported high complication rates of malignancy in patients with IgG4-RD compared to the general population (14-17). Indeed, IgG4 is produced in the process of immune tolerance not only in allergy but also in malignancy (18).

These multifactorial observations suggest that IgG4-RD is a heterogeneous syndrome that can be subdivided based on distinct pathophysiological mechanisms. This study aimed to elucidate the contribution of underlying allergy or malignancy to the clinical and immunological features of IgG4-RD.

Methods

Patients

Consecutive patients with IgG4-RD who visited the Keio University Hospital between 2010 and 2021 and fulfilled the 2011 comprehensive IgG4-RD diagnostic criteria (19) or the 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD (20-22) were enrolled in this study. All investigations were conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was waived in accordance with the Japanese regulations on gathering clinical information from their medical chart. The peripheral blood was collected for immunophenotyping. This study was approved by the ethics committee of Keio University School of Medicine (approval numbers 20130506 and 20130246).

Data collection

We collected the following clinical information from the patients' medical records at the time of IgG4-RD diagnosis and the subsequent visits: sex, age, atopic history, smoking history, presence of malignancy, involved organs, laboratory data, remission achievement, relapse, and treatment regimens. The patients were observed until April 2022.

Definition

We defined allergy as a history of allergic rhinitis, atopic asthma, or atopic dermatitis (8) and malignancy as a history of malignancy within three years before or after IgG4-RD diagnosis as a reference to cancer-associated myositis (23). A smoking history indicated current or past smoking habits. The disease activity of IgG4-RD was calculated based on the IgG4-RD responder index (IgG4-RD RI) (24). According to a previous report, the clinical types of IgG4-RD were divided into four groups (25): head and neck limited, Mikulicz and systemic, retroperitoneum and aorta, and pancreato-hepato-biliary. Remission was defined as an IgG4-RD RI score of 0 (26). Furthermore, relapse was defined as a new lesion appearance or return of abnormal findings on physical examination, laboratory tests, or imaging examinations that led to more intense treatment by the attending physicians. We did not consider the elevation of serum IgG4 alone as a relapse (3).

Flow cytometric analysis for blood immune cell subsets

We conducted comprehensive immunophenotyping of the peripheral blood mononuclear cells obtained from a subset of patients with IgG4-RD diagnosis, which was divided into 56 immune cell subsets by flow cytometry (27). The

Table I. Comparison of clinical characteristics of IgG4-RD stratified by malignancy and allergy.

	ALL n=123	Malignancy n=18	Allergy n=57	Idiopathic n=48	*p*-value
Age, years, mean (SD)	60.8 ± 14.5	**70.1 ± 8.6**	**54.4 ± 13.1.**	**64.9 ± 14.8**	**<0.001[ab]**
Male, n (%)	65 (52.8)	**15 (83.3)**	**24 (42.1)**	**26 (54.2)**	**0.008**
Smoking history, n (%)	59 (48.0)	**14 (77.8)**	**24 (42.1)**	**21 (43.8)**	**0.02[a]**
Malignancy, n (%)	18 (14.6)	18 (100)	0 (0)	0 (0)	-
Atopic history, n (%)	61 (49.6)	4 (22.2)	57 (100)	0 (0)	-
Organ involvement, n (%)					
Pachymeninges	3 (2.4)	0 (0)	2 (3.5)	1 (2.1)	1.00
Orbits and lacrimal glands	79 (64.2)	**8 (44.4)**	**45 (78.9)**	**26 (54.2)**	**0.004[ab]**
Salivary glands	73 (59.3)	7 (38.9)	39 (68.4)	27 (56.3)	0.08
Lymph nodes	64 (52.0)	10 (55.6)	29 (50.9)	25 (52.1)	0.97
Lungs	32 (26.0)	3 (16.7)	19 (33.3)	10 (20.8)	0.24
Aorta and large blood vessels	20 (16.2)	**6 (33.3)**	**4 (7.0)**	**10 (20.8)**	**0.01[a]**
Retroperitoneum	26 (21.1)	6 (33.3)	8 (14.0)	12 (25)	0.13
Pancreas	27 (22.0)	3 (16.7)	13 (22.8)	11 (22.9)	0.91
Bile duct and liver	3 (2.4)	0 (0)	0 (0)	3 (6.3)	0.11
Kidney	29 (23.6)	3 (16.7)	19 (33.3)	7 (14.6)	0.07
Skin	4 (3.3)	0 (0)	2 (3.5)	2 (4.2)	1.00
Number of organ involvements, mean (SD)	3.1 ± 1.6	2.7 ± 1.3	3.3 ± 1.7	2.9 ± 1.6	0.37
IgG4-RD RI, mean (SD)	12.0 ± 5.1	10.9 ± 4.3	12.6 ± 5.5	11.6 ±4.9	0.42
Clinical phenotype of IgG4-RD, n (%)					
Head and neck limited	41 (33.3)	6 (33.3)	21 (36.8)	14 (29.2)	0.73
Systemic and Mikulicz	68 (55.3)	7 (38.9)	34 (59.6)	27 (56.3)	0.33
Retroperitoneum and aorta	11 (8.9)	**4 (22.2)**	**2 (3.5)**	**5 (10.4)**	**0.04**
Pancreato-hepato-biliary	3 (2.4)	1 (5.6)	0 (0)	2 (4.2)	0.18
Serological findings, mean (SD)					
IgG, mg/dL	2023 ± 913	2015 ± 655	1934 ± 967	2134 ± 928	0.54
IgG4, mg/dL	645 ± 597	645 ± 572	656 ± 575	631 ± 642	0.98
IgG4/IgG ratio	0.28 ± 0.16	0.26 ± 0.16	0.31 ± 0.16	0.26 ± 0.15	0.27
IgE, IU/mL	899 ± 1288	1525 ± 2298	736 ± 797	829 ± 1143	0.10
sIL-2R, mg/dL	754 ± 801	613 ± 275	778 ± 702	779 ± 1028	0.75
CRP, mg/dL	0.34 ± 0.76	0.40 ± 0.67	0.22 ± 0.49	0.47 ± 1.00	0.22
Eosinophil count, /μL	347 ± 383	364 ± 344	409 ± 471	267 ± 249	0.17
Induction therapy, n (%)	n=88	n=10	n=44 n=34	0.56	
GC alone	82 (89.1)	10 (100)	42 (95.5)	30 (88.2)	
GC + IVCY	2 (2.2)	0 (0)	0 (0)	2 (5.9)	
GC + RTX	4 (4.3)	0 0)	2 (4.5)	2 (5.9)	
Initial dose of GC, mg/day	37.2 ± 12.9	43.8 ± 15.7	36.5 ± 9.4	35.9 ± 15.2	0.16
Maintenance therapy, n (%)				0.10	
GC alone	50 (54.3)	5 (50.0)	24 (54.5)	21 (61.8)	
GC + AZA	12 (13.0)	2 (20.0)	3 (6.8)	7 (20.6)	
GC + Tac	18 (19.6)	3 (30.0)	13 (29.5)	2 (5.9)	
GC + CyA	1 (1.1)	0 (0)	0 (0)	1 (2.9)	
GC + MTX	3 (3.3)	0 (0)	3 (6.8)	0 (0)	
GC + MMF	3 (3.3)	0 (0)	1 (2.3)	2 (5.9)	
GC + RTX	2 (2.2)	0 (0)	1 (2.3)	1 (2.9)	
Remission, n (%)	63 (71.6)	8 (80.0)	33 (75.0)	22 (64.7)	0.56

a: malignancy group *vs*. allergy group; **b**: allergy group *vs*. idiopathic group.
AZA: azathioprine; CyA: cyclosporin A; CRP: C-reactive protein; GC: glucocorticoid; Hb: haemoglobin; IgG4-RD: IgG4-related disease; IgG4-RD RI: IgG4-related disease-responder index; IVCY: intravenous cyclophosphamide; MMF: mycophenolate mofetil; PLT: platelet; sIL-2R: soluble interlukin-2 receptor; Tac: tacrolimus; RTX: rituximab; SD: standard deviation; WBC: white blood cell.

definitions of each immune cell subset are shown in Supplementary Table S1. Heparinised whole blood samples obtained from treatment-naive patients were immediately stained for 15 min with antibodies listed in Supplementary Table S2. The red blood cells were lysed with FACS Lysing Solution (BD Biosciences) based on the manufacturer's instructions. The cells were then washed two times and analysed using an LSRFortessa X-20 flow cytometer (BD Biosciences). The data were analysed using FlowJo v.10 software (Tree Star, Stanford University, CA, USA).

Statistical analyses

Data were presented as mean ± standard deviation (SD). Proportions between the two groups were compared using Fisher's exact test, and those with more than two groups were compared using one-way analysis of variance with Bonferroni *post-hoc* correction. Receiver operating characteristic (ROC) curve analysis was conducted to determine the cut-off values to discriminate between the two groups. Survival curves were depicted using Kaplan-Meier analysis and compared using the log-rank test.

Binomial multivariable logistic regression analysis was performed using the factors identified as significant in the previous monovariable analysis as covariates. The Cochran-Armitage test was used to detect significant trends. Statistical significance was set at p-value <0.05. All statistical analyses were performed using EZR (1.4) or GraphPad Prism software (v. 7 GraphPad Software, La Jolla, CA) (28).

Results

Patient demographic and clinical characteristics

In total, 140 patients with IgG4-RD were identified. After excluding 17 patients who lacked data on IgG4-RD diagnosis, 123 were enrolled in the study. The baseline clinical characteristics are summarised in Table I. The mean age was 60.8 years, in which 65 (52.8%) were male. The clinical types of IgG4-RD were head and neck limited (n=41, 33.3%), Mikulicz and systemic (n=68, 55.3%), retroperitoneum and aorta (n=11, 8.9%), and pancreato-hepatobiliary (n=3, 2.4%).

Presence of allergy and malignancy

Eighteen patients had malignancies and 61 patients had allergies, with four patients having both. The most frequent malignancy type was gastric cancer (n=3), followed by colon cancer, renal cell carcinoma, lung cancer, hepatic cell carcinoma, and malignant lymphoma (n=2 for each, Suppl. Table S3). Malignancy preceded IgG4-RD diagnosis in seven patients (38.9%). Malignancy was concurrently diagnosed with IgG4-RD in three (16.7%) patients. In addition, malignancy was diagnosed after IgG4-RD diagnosis in six (33.3%) patients. Two patients (11.1%) had more than one malignancy diagnosed at different times, before and after IgG4-RD diagnosis. Atopic history included allergic rhinitis (n=39), atopic asthma (n=9), and atopic dermatitis (n=1) with overlapping atopy in 12 patients.

We classified the four patients with both allergy and malignancy into the malignancy group and finally divided the patients into three groups as follows (Suppl. Fig. S1): malignancy group (n=18, 14.6%), allergy group

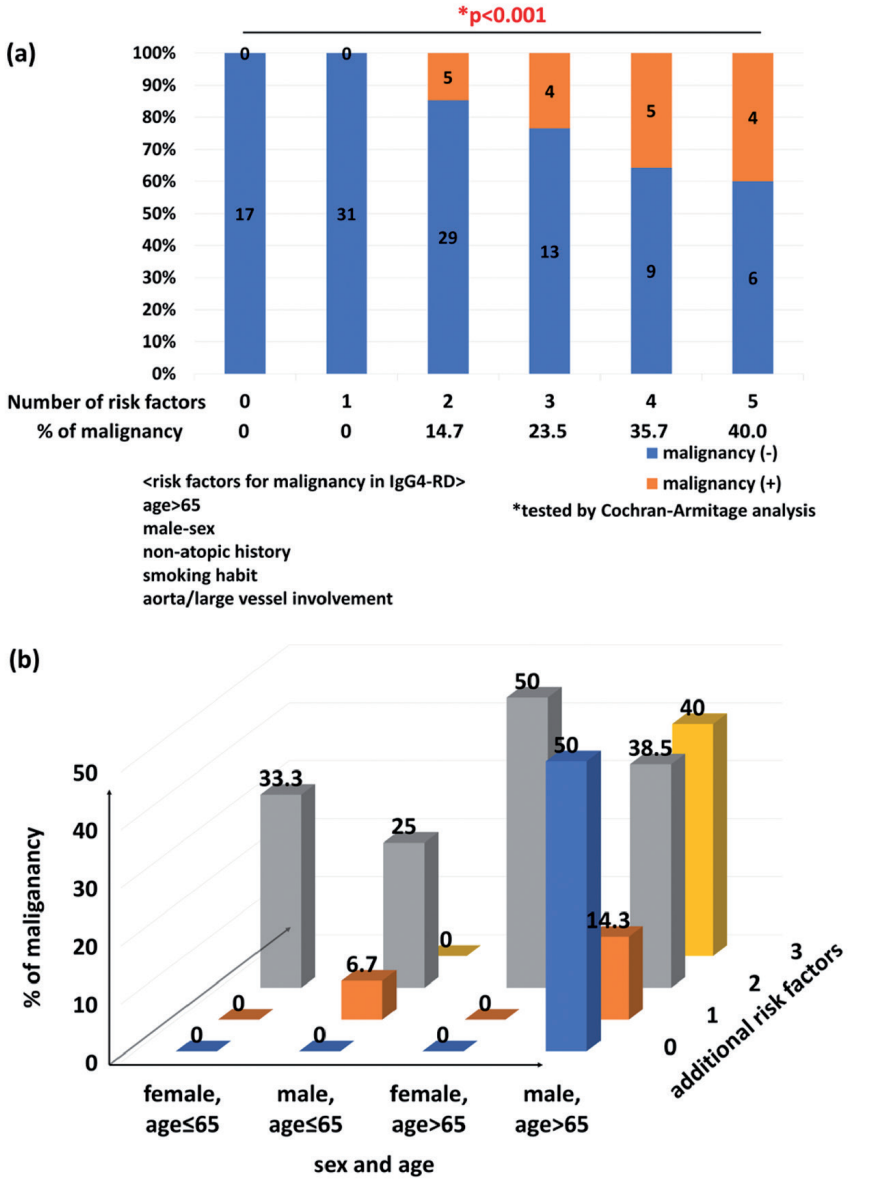

Fig. 1. Prevalence of malignancy depending on the score of risk factors.
(**a**) Prevalence of malignancy in patients with IgG4-RD was significantly increased up to 40% depending on the score of the total risk factors. (**b**) Prevalence of malignancy in patients with IgG4-RD stratified by sex, age and number of risk factors.

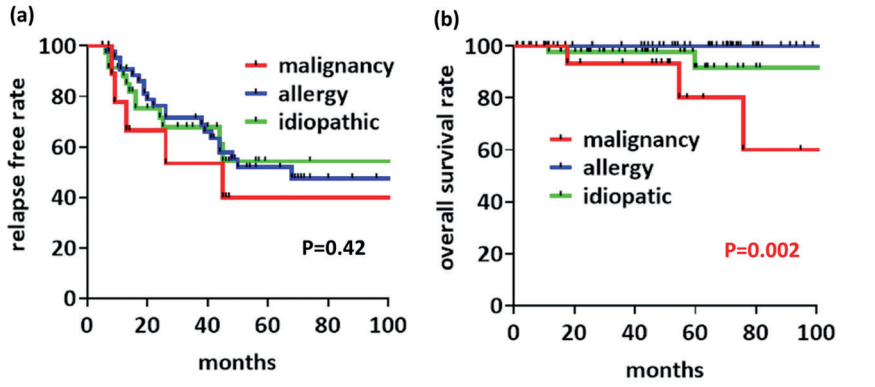

Fig. 2. Kaplan-Meier analysis for relapse and overall survival.
Relapse rates did not differ among the 3 groups (**a**), but overall survival was significantly worse in malignancy group (p=0.002) (**b**).

(n=57, 46.3%), and idiopathic group (n=48, 39.0%).

Comparison of clinical features between allergy and malignancy

We compared the clinical characteristics and laboratory data between the malignancy, allergy, and idiopathic groups and identified that age, sex, smoking habits, and type of organ involvement were significantly different (Table I). The patients in the malignancy group were significantly older than those in the allergy and idiopathic groups (70.1 *vs*. 54.4 *vs*. 64.9 years, $p<0.001$, respectively), were predominantly male (83.3 *vs*. 42.1 *vs*. 54.2%, $p=0.008$, respectively), and had smoking habits (77.8 *vs*. 42.1 *vs*. 43.8%, $p=0.02$, respectively). Regarding the involved organs, the aorta/large vessels were more frequently involved in the malignancy group (33.3 *vs*. 7.0 *vs*. 20.8%, $p=0.02$), while the patients in the allergy group tended to have orbital/lacrimal gland involvement. No significant differences were identified in the serum IgG4, IgG4/IgG ratio, IgE, and soluble interleukin-2 receptor levels among the three groups. When we divided the patients in the allergy group into patients with asthma and those with the other atopic history, we found that they shared common clinical features except for more lymph node involvement and higher eosinophil counts in the patients with asthma (Suppl. Table S4).

Risk factors for presence of malignancy

Binomial multivariable logistic regression analysis with explanatory variables identified by univariate intergroup comparison demonstrated that the age (odds ratio [OR] 1.07, 95% confidence interval [CI] 1.02–1.12, $p=0.005$), male sex (OR 5.30, 95% CI 1.50–20.1, $p=0.01$), non-atopic history (OR 4.16, 95% CI 1.28–13.5, $p=0.03$), smoking habit (OR 4.67, 95% CI 1.44–15.1, $p=0.01$), and aorta/large vessel involvement (OR 3.25, 95% CI 1.05–10.1, $p=0.04$) were independent risk factors for the presence of malignancy (Suppl. Table S5). The ROC curve identified the cut-off value for age of malignancy as 65 years (sensitivity 83.3%, specificity 59.0%, area under the curve 0.727). When we subcategorised all patients according to the number of risk factors (Fig. 1a), no patient with one or fewer risk factors had malignancy; however, the proportion of patients with malignancy increased with an increase in risk factors (two factors, 14.7%; three factors, 23.5%; four factors, 35.7%; five factors, 40.0%, $p<0.001$). We further stratified the patients by age, sex, and the number of additional risk factors. In addition, we identified that the presence of malignancy was most frequent in men aged ≥65 years, regardless of the other risk factors (Fig. 1b).

Clinical course of patients with IgG4-RD

We observed the patients for a mean duration of 61.8 months. Of 123 patients, 88 (71.5%) received immunosuppressive treatment. Glucocorticoid monotherapy was the treatment regimen for induction with no difference in the regimen among the groups, except for two (2.3%) and four (4.5%) patients who were treated with rituximab and intravenous cyclophosphamide with glucocorticoids, respectively. The overall remission rate was 71.4%, which was comparable between the groups (Table I). While the relapse rates did not differ among the three groups (Fig. 2a), overall survival was significantly poorer in the malignancy group (Fig. 2b). All three deaths in the malignancy group were malignancy-related, and one death in the idiopathic group was an accident unrelated to the IgG4-RD. In two patients with malignancy, IgG4-RD symptoms, including organ enlargement and serum IgG4 levels, improved with surgical resection of the cancer alone without any immunosuppressive treatment. The patients remained in drug-free remission for 4.5 years and for 1 year after surgery.

Immunological features of IgG4-RD with malignancy and allergy

We profiled a total of 56 peripheral blood immune cell subsets at IgG4-RD diagnosis in the patients that matched their age and sex in each group (5 patients in the malignancy group and 10 patients each in allergy and idiopathic group). The characteristics of the patients included in the immunophenotyping analysis are shown in Supplementary Table S6. This approach revealed that, compared to the idiopathic group, a decrease in the naive $CD8^+$ T cells and central memory $CD8^+$ T cells and an increase in the CXCR5+CD2- double-negative T cells were characteristics of the malignancy group. Furthermore, a decrease in the activated $CD4^+$ T cells, effector memory $CD4^+$ T cells, activated T helper 17 cells, and follicular helper type 1 T cells were characteristics of the allergy group (Fig. 3a). Notably, a dominant expansion of the CXCR5+CD2- double-negative T cells (Fig. 3a, b) and a decrease in the naïve $CD8^+$ T cells were uniquely observed in the malignancy group compared to both the allergy and idiopathic groups (Fig. 3a, c).

Discussion

This study focused on malignancy and allergy as the underlying diseases of IgG4-RD and revealed that clinical characteristics, like age, sex, and types of involved organs differed according to the presence of malignancy or allergy. Moreover, these clinical characteristics were as risk factors for the presence of malignancy. In addition, an increase in the CXCR5+CD2- double-negative T cells and a decrease in the naïve $CD8^+$ T cells are characteristic of malignancy in IgG4-RD.

A recent meta-analysis demonstrated that the patients with IgG4-RD had an increased risk of malignancy with a standardised incidence ratios of 2.57 (15). Particularly, the risk for malignant lymphoma and gastric, colon, lung, pancreatic and prostate cancers are increased in IgG4-RD (14-16). Recognising the risk of malignant complications at IgG4-RD diagnosis is important. Although IgG4-RD itself is a benign disease, our study showed that the patients with IgG4-RD complicated with a malignancy showed poorer survival outcomes. Moreover, our study implicated a possibility that surgical removement of malignancy improved IgG4-RD without any glucocorticoids or immunosuppressants. There are also similar case reports of

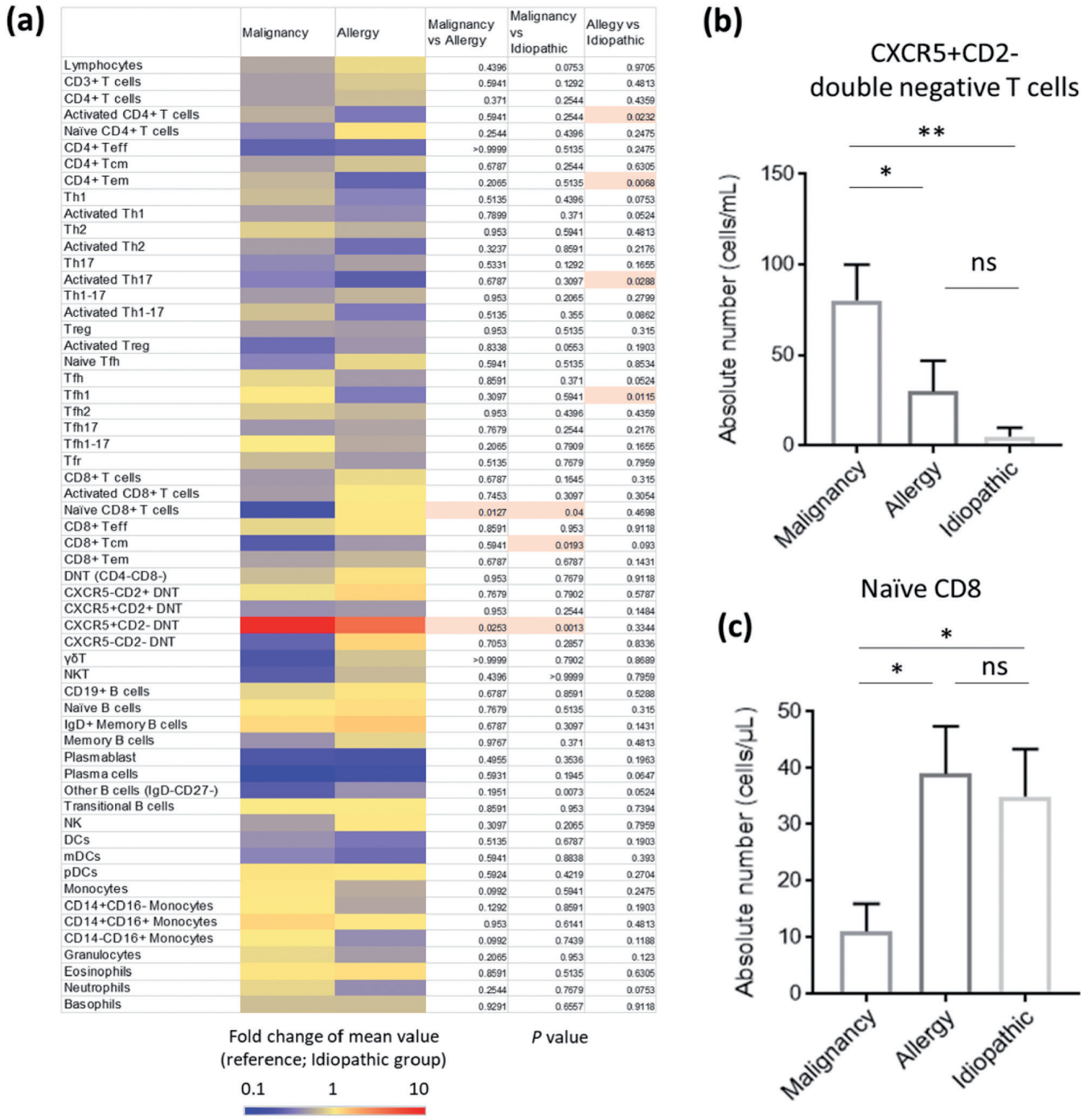

Fig. 3. Comprehensive analysis of blood immune cell subsets in patients with IgG4-RD based on the clinical subgroups.
Active, untreated patients with IgG4-RD were divided into three clinical subgroups (malignancy group; n=5, allergy group; n=10, or idiopathic group; n=10). (**a**) The mean absolute number of each immune cell subset was compared among three clinical subgroups. Fold change of mean value (the mean value in idiopathic group was referenced as 1) is shown by heatmap. The mean absolute number with SEM of CXCR5+CD2-double negative T cells (**b**) and naive CD8 T cells (**c**) are plotted as bars. Mann-Whitney test. *p<0.05, **p<0.01.

IgG4-RD that showed spontaneous improvement in swelling of the involved organs and serum IgG4 levels after surgical resection of concomitant cancers. This suggests that IgG4-RD is a paraneoplastic syndrome (29). Our present study identified the risk factors for malignancy as older age, male sex, smoking, non-atopic history, and large vessel involvement. These identified risk factors could help physicians conduct risk-based surveys for malignancy.

The association between allergy and IgG4-RD has been noted in several studies (7-10). Elevation of IgE, eosinophil counts, and serum cytokines, such as interleukin (IL)-4, IL-5, IL-13, and eotaxin-3 support the involvement of allergic reactions in IgG4-RD (2, 11, 12, 30-33). In contrast to the patients with malignancy, the patients with allergies were younger and tended to have lacrimal gland lesions in our study, which suggests that chronic transmu-

cosal exposure to allergens through the eyes and nasal mucosa may trigger the pathogenesis of IgG4-RD. Interestingly, we recently reported the elevation of allergen-specific IgE antibodies in locally affected lesions of IgG4-RD, suggesting the possible contribution of allergens to the development of this clinical phenotype (34). Further studies are needed to confirm this mechanism.

Our study also demonstrated that a significant expansion of CXCR5+CD2- double-negative T cells and a decrease in $CD8^+$ T cells are related to IgG4-RD complicated by malignancy. Double-negative T cells are classically characterised by the expression of the T cell receptor αβ; however, they lack CD4 and CD8 (35). Recent studies have reported that CXCR5 is critical for the migration of the double-negative T cells into the inflamed tissues or lymphoid follicles (36, 37). In addition, this immune cell subset is increased in autoimmune diseases, such as systemic lupus erythematosus and causes tissue damage in the inflamed lesions (3). Double-negative T cells are also known to exhibit cytotoxic effector functions against leukaemia and some malignancies (38, 39). While several studies have reported that the patients with IgG4-RD generally display characteristic immunophenotypes in the peripheral blood, which are dominated by the expansion of Tfh cells, cytotoxic T cells, and plasmablasts (11, 12, 40-42), we demonstrated that the CXCR5+CD2- double-negative T cells were uniquely increased in the patients with malignancy. In addition, the number of naïve $CD8^+$ T cells decreased in the malignant group. A decrease in $CD8^+$ T cells is considered a characteristic of immunosenescence, which can lead to the development of autoimmune diseases and malignancies (43). Our findings showed that the IgG4-RD patients with malignancy exhibited a characteristic immunophenotype that should be included in future studies to elucidate the pathological role of these immune cell subsets in IgG4-RD and malignancies.

This study had some limitations. First, an assertive survey for malignancy was not routinely performed in all patients, which could result in underestimated number of patients with malignancy. However, a systemic survey to search for organs involved by IgG4-RD could detect common malignant tumours. Second, the sample size, especially for immunophenotyping, was small. However, IgG4-RD is a rare, new disease entity, and our analysis of 123 patients with IgG4-RD warrants further studies to elucidate the mechanisms of IgG4-RD.

In conclusion, we identified the clinical and immunological similarities and differences between patients with IgG4-RD with malignancy and those with allergies. Further studies are needed to clarify the pathogenesis of IgG4-RD with malignancy and allergies.

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