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ORIGINAL ARTICLE

No overlap between IgG4-related disease and microscopic polyangiitis and granulomatosis with polyangiitis despite elevated serum IgG4 at diagnosis: a retrospective monocentric study

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Abstract

Objectives We investigated whether elevated serum IgG4 at the time of diagnosis of microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) may be associated with concurrent IgG4-related disease (IgG4-RD) in immunosuppressive drug-naïve patients.

Methods We retrospectively reviewed the medical records of 46 MPA and GPA patients with results on serum IgG4 and histology at diagnosis. Elevated serum IgG4 was defined as IgG4 > 135 mg/dL. We collected clinical and laboratory data at diagnosis including ANCA, white blood cell (WBC) count, haemoglobin, platelet, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum IgG4, and calculated Birmingham vasculitis activity score (BVAS) at diagnosis. We compared variables between patients with MPA and GPA and assessed the correlation of serum IgG4 and other continuous variables.

Results Twenty-eight patients (60.9%) were classified as MPA and 18 patients (39.1%) as GPA. The mean age at diagnosis was 61.0 years and 17 patients (37.0%) were men. The serum IgG4 at diagnosis was 1202.7 mg/dL and 37 patients (80.4%) had elevated serum IgG4 at diagnosis. We found no patients, who could be classified as IgG4-RD according to comprehensive diagnostic criteria for IgG4-RD among 46 patients. The mean serum IgG at diagnosis was not different between the two groups. Serum IgG4 was significantly correlated with inflammation-related variables at diagnosis including BVAS ($r = 0.367$), platelet ($r = 0.398$), ESR ($r = 0.327$), and CRP ($r = 0.373$).

Conclusions Elevated serum IgG4 is not associated with concurrent IgG4-RD, and it may reflect activity and inflammatory burden of vasculitis in patients with MPA and GPA at diagnosis.

Keywords Granulomatosis with polyangiitis · IgG4-related disease · Microscopic polyangiitis

Introduction

IgG4 is the least common of the four human IgG subclasses and its proportion is approximately 5% of total IgG. IgG4 exhibits bi-specific and functionally monovalent immunologic features through Fab-arm exchange, which could lead to the anti-inflammatory properties and restrict immune-complex formation [1]. IgG4-related disease (IgG4-RD) is characterised by two histological features of abundantly infiltrated IgG4+ cells and storiform fibrosis, resulting in organ dysfunctions [2]. Among several diagnostic approaches to IgG4-RD, comprehensive diagnostic criteria for IgG4-RD, which was proposed by the Umehara and Okazaki teams in 2011, are widely used for the classification of IgG4-RD. These criteria are composed of a cascade algorithm with three key items for definite IgG4-RD as follows: (i) organ involvement or damage, (ii) serum IgG4 > 135 mg/dL, and (iii) IgG4+/IgG+ cells > 40% and IgG4+ cells/high power field (HPF) > 10 on tissues from affected organs [3]. IgG4-RD may involve various organs and can provoke a mass in or enlargement of the affected organ. Because there are overlapped manifestations between IgG4-RD and other diseases, it has been recommended to exclude conditions that can clinically and histopathologically mimic IgG4-RD, such as

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antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) [4].

Antineutrophil cytoplasmic antibody-associated vasculitis is a group systemic vasculitides, which can affect small vessels ranging from capillaries to intraparenchymal arterioles and venules. AAV includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [5]. So far, there have been a few reports on overlapping IgG4-RD and AAV. A previous study reported the significant pathogenic association of IgG4-RD with GPA by assessing IgG4-expressing plasma cells in 43 GPA patients and 20 controls [6]. Another observational study provided the potential that IgG4-RD may overlap with AAV in 18 patients who fulfilled both criteria for IgG4-RD and AAV [7]. However, the clinical significance of elevated serum IgG4 in AAV patients, who have not been diagnosed as IgG4-RD previously, still remains unclear. On the other hand, enhanced IgG4 responses by upregulation of Th2 cytokines were occasionally observed in EGPA, thus IgG4-RD and EGPA could be considered to share similar clinical features [2]. Hence, in this study, we investigated whether elevated serum IgG4 at the time of diagnosis of MPA and GPA, not EGPA, may be associated with concurrent IgG4-RD in immunosuppressive drug-naïve patients.

Materials and methods

Patients

We retrospectively reviewed the medical records of 139 immunosuppressive drug-naïve patients with MPA and GPA, who fulfilled the inclusion criteria: (i) patients who had been first classified as MPA and GPA at the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, from October 2000 to December 2017; (ii) patients who met the 2007 European Medicines Agency algorithm modified by the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis [5, 8]; (iii) patients who had well-documented medical records with which to assess both clinical and laboratory data to calculate Birmingham vasculitis activity score (BVAS) at diagnosis [9]. Because BVAS for GPA has a different weight-system compared to BVAS, we evenly applied BVAS to both MPA and GPA patients to unify the scoring system; (iv) patients who had results on perinuclear (P)-ANCA and cytoplasmic (C)-ANCA or myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA levels at diagnosis; (v) patients who had results on serum IgG4 and histology at diagnosis; (vi) patients who had not been classified as IgG4-RD prior to diagnosis; (vii) patients who had no medical history including allergic diseases to affect either BVAS or serum IgG4 level [1, 2]; (viii) patients who had never received immunosuppressive drugs for AAV prior to diagnosis. Of 139 patients with MPA and GPA, 46 patients (33.1%) had results on serum IgG4 and histology at diagnosis. Elevated serum IgG4 was defined as IgG4 > 135 mg/dL [3]. Of 46 patients, 37 patients (80.4%) had serum IgG4 > 135 mg/dL and 9 patients (19.6%) had serum IgG4 ≤ 135 mg/dL. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0673), who waived the need for patient written informed consent, as this was a retrospective study.

Clinical and laboratory data

We obtained age at diagnosis and gender. Clinical and laboratory data at diagnosis including ANCA, white blood cell (WBC) count, haemoglobin, platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum IgG4 were collected. We calculated BVAS at diagnosis based on clinical and laboratory data. We also compared clinical and laboratory data between patient with MPA and GPA.

Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as a mean ± standard deviation, and categorical variables were expressed as a number (percentage). Differences in categorical variables between the two groups were analysed using the chi-square and Fisher's exact tests, whereas differences in continuous variables between the two groups were compared using the Mann-Whitney test. The correlation coefficient between serum IgG4 and other continuous variables was obtained using the Pearson correlation analysis. *P* values less than 0.05 were considered statistically significant.

Results

Baseline characteristics of 46 patients with MPA and GPA

The baseline characteristics were described in Table 1. Twenty-eight patients (60.9%) were classified as MPA and 18 patients (39.1%) as GPA. The mean age at diagnosis was 61.0 years and 17 patients (37.0%) were men. MPO-ANCA (or P-ANCA) was the most frequently detected ANCA (78.3%). One patient had both ANCAs and 5 patients had no ANCA. At diagnosis, renal involvement (69.6%) was the most common clinical manifestation, followed by pulmonary involvement (63.0%). The mean BVAS at diagnosis was 12.2. The mean WBC and platelet counts were 10,279.6/mm^3 and 337,500.0/mm^3,

Table 1 Baseline characteristics of 46 patients with AAV having the result of serum IgG4 at diagnosis

Variables	Values	MPA	GPA	*P* value
Variants of AAV				
MPA	28 (60.9)	28 (100)		N/A
GPA	18 (39.1)		18 (100)	N/A
Demographic data at diagnosis				
Age (years old)	61.0 ± 13.0	60.4 ± 14.0	62.1 ± 11.6	0.670
Male gender (*N*, (%))	17 (37.0)	9 (32.1)	8 (44.4)	0.399
ANCA at diagnosis (*N*, (%))				
MPO-ANCA (or P-ANCA)	36 (78.3)	25 (89.3)	11 (61.1)	0.024
PR3-ANCA (or C-ANCA)	6 (13.0)	0 (0)	6 (33.3)	0.001
MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA)	1 (2.2)	0 (0)	1 (5.6)	0.207
ANCA negative	5 (10.9)	3 (10.7)	2 (11.1)	0.966
Clinical manifestations at diagnosis (*N*, (%))				
General	19 (41.3)	12 (42.9)	7 (38.9)	0.790
Cutaneous	4 (8.7)	4 (14.3)	0 (0)	0.093
Mucous membranes/eyes	3 (6.5)	2 (7.1)	1 (5.6)	0.831
Ear nose throat (ENT)	14 (30.4)	5 (17.9)	9 (50.0)	0.021
Chest	29 (63.0)	16 (57.1)	13 (72.2)	0.301
Cardiovascular	5 (10.9)	3 (10.7)	2 (11.1)	0.966
Abdominal	0 (0)	0 (0)	0 (0)	N/A
Renal	32 (69.6)	23 (82.1)	9 (50.0)	0.021
Nervous system	8 (17.4)	4 (14.3)	4 (22.2)	0.488
Vasculitis activity and prognostic factors at diagnosis				
BVAS	12.2 ± 5.9	14.2 ± 5.7	9.1 ± 4.9	0.003
Laboratory results at diagnosis				
WBC (/mm^3)	10,279.6 ± 4627.4	9054.6 ± 3333.1	12,183.9 ± 5720.6	0.046
Eosinophil (/mm^3)	147.8 ± 179.7	184.3 ± 172.8	91.1 ± 180.1	0.086
Haemoglobin (g/dL)	11.1 ± 2.0	10.8 ± 2.1	11.4 ± 1.9	0.328
Platelet (× 1,000/mm^3)	337.5 ± 151.8	326.9 ± 141.1	354.0 ± 169.9	0.560
ESR (mm/h)	69.4 ± 36.8	70.1 ± 39.7	68.4 ± 32.9	0.886
CRP (mg/L)	47.8 ± 58.0	38.5 ± 53.4	62.2 ± 63.4	0.179
Serum IgG4 at diagnosis (mg/dL)	1202.7 ± 1886.7	1292.1 ± 2257.4	1063.8 ± 1138.4	0.693
Serum IgG4 at diagnosis > 135 mg/dL (*N*, (%))	37 (80.4)	21 (75.0)	16 (88.9)	0.247

Values are expressed as a mean and standard deviation or *N* (%)

AAV antineutrophil cytoplasmic antibody-associated vasculitis, *MPA* microscopic polyangiitis, *GPA* granulomatosis with polyangiitis, *MPO* myeloperoxidase, *ANCA* antineutrophil cytoplasmic antibody, *P-ANCA* perinuclear ANCA, *PR3* proteinase 3, *C-ANCA* cytoplasmic ANCA, *BVAS* Birmingham vasculitis activity score, *WBC* white blood cell, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *N/A* not applicable

respectively, and the mean haemoglobin was 11. 1 g/dL. The mean ESR and CRP were 69.4 mm/min and 47.8 mg/L. The mean serum IgG4 at diagnosis was 1202.7 mg/dL and its distribution was shown in Fig. 1. Thirty-seven patients (80.4%) had elevated serum IgG4 at diagnosis.

Comparison of variables between patients with MPA and those with GPA

There were no differences in age and gender between MPA and GPA patients. MPA patients exhibited the

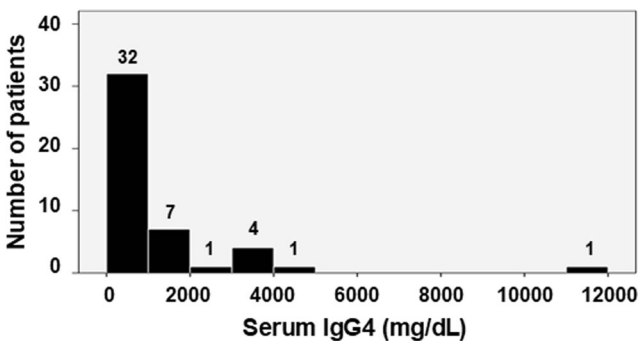

Fig. 1 The distribution of the concentration of serum IgG4 at diagnosis

higher rate of MPO-ANCA (or P-ANCA) positivity, whereas the lower rate of PR3-ANCA (or C-ANCA) positivity than GPA patients. Ear nose throat manifestation at diagnosis was more frequently documented in GPA patients than MPA patients (50.0% vs. 17.9%, $P = 0.021$), while renal vasculitis occurred more commonly in MPA patients than GPA patients (82.1% vs. 50.0%, $P = 0.021$). MPA patients exhibited the higher mean BVAS than GPA patients (14.2 vs. 9.1, $P = 0.003$). The mean serum IgG at diagnosis and the number of patients with serum IgG4 at diagnosis > 135 mg/dL were not different between the two groups (Table 1). Unlike EGPA, MPA and GPA might not affect serum IgG levels.

Biopsy sites and histological findings in 37 patients with serum IgG4 > 135 mg/dL at diagnosis

Among 37 patients, 21 patients (56.8%) had MPA. The mean age was 61.1 years and 14 patients (37.8%) men. The mean serum IgG4 was 1476.4 mg/dL. The most frequent biopsy site was kidneys (70.3%), followed by lungs (18.9%) and paranasal sinus (5.4%). One patient underwent biopsies on the kidney and lung and another patient underwent biopsies on the lung and nerve. No patient with serum IgG4 > 135 mg/dL at diagnosis fulfilled comprehensive diagnostic criteria for IgG4-RD proposed by the Umehara and Okazaki teams (Table 2).

Table 2 Biopsy sites and histological findings at diagnosis

Variables	Values
Patients with MPA and GPA with serum IgG4 > 135 mg/dL at diagnosis ($N = 37$)	
Variants of AAV	
MPA	21 (56.8)
GPA	16 (43.2)
Demographic data at diagnosis	
Age (years old)	61.1 ± 13.4
Male gender (N, (%))	14 (37.8)
Serum IgG4 at diagnosis (mg/dL)	1476.4 ± 2013.9
Biopsy sites at diagnosis (N, (%))*	
Kidneys	26 (70.3)
Lungs	7 (18.9)
Sinus	2 (5.4)
Nerve	1 (2.7)
Orbital mass	1 (2.7)
Subglottic mass	1 (2.7)
Histological findings compatible with IgG4-RD (N, (%))	0 (0)
Patients with MPA and GPA with serum IgG4 ≤ 135 mg/dL at diagnosis ($N = 9$)	
Variants of AAV	
MPA	7 (77.8)
GPA	2 (22.2)
Demographic data at diagnosis	
Age (years old)	60.4 ± 12.2
Male gender (N, (%))	3 (33.3)
Serum IgG4 at diagnosis (mg/dL)	77.8 ± 47.7
Biopsy sites at diagnosis (N, (%))**	
Kidneys	7 (77.8)
Lungs	1 (11.0)
Sinus	1 (11.1)
Nerve	1 (11.1)
Histological findings compatible with IgG4-RD (N, (%))	0 (0)

Values are expressed as a mean and standard deviation or N (%)

AAV antineutrophil associated vasculitis, *MPA* microscopic polyangiitis, *GPA* granulomatosis with polyangiitis, *IgG4-RD* IgG4-related disease

*One patient underwent biopsies on kidney and lung and another patient underwent biopsies on lung and nerve

**One patient underwent biopsies on lung and nerve

Biopsy sites and histological findings in 9 patients with serum IgG4 ≤ 135 mg/dL at diagnosis

Among 9 patients, 7 patients (77.8%) had MPA. The mean age was 60.4 years and 3 patients (33.3%) men. The mean serum IgG4 was 77.8 mg/dL. The most frequent biopsy site was kidneys (77.8%). One patient underwent biopsies on the lung and nerve. No patient with serum IgG4 ≤ 135 mg/dL at diagnosis fulfilled comprehensive diagnostic criteria for IgG4-RD proposed by the Umehara and Okazaki teams either (Table 2).

Correlation of serum IgG4 with activity and inflammatory burden of MPA and GPA in 46 patients

We conducted univariable linear regression analysis to assess the correlation between serum IgG4 and other continuous variables. Serum IgG4 was well correlated with BVAS ($r = 0.367$, $P = 0.012$), platelet count ($r = 0.398$, $P = 0.006$), ESR ($r = 0.327$, $P = 0.006$), and CRP ($r = 0.373$, $P = 0.011$) at diagnosis (Fig. 2). However, serum IgG was not correlated with eosinophil count at diagnosis ($r = 0.128$, $P = 0.395$).

Discussion

In this study, we investigated whether elevated serum IgG4 at the time of diagnosis of MPA and GPA may be associated with concurrent IgG4-RD in immunosuppressive drug-naïve patients. We found no patients, who could be classified as IgG4-RD according to comprehensive diagnostic criteria for IgG4-RD among 46 patients with MPA and GPA. Whereas, serum IgG4 was significantly correlated with inflammation-related variables at diagnosis including BVAS, platelet count, ESR, and CRP. Thus, we conclude that elevated serum IgG4 may not be linked to concurrent IgG4-RD, but it may be influenced by activity and inflammatory burden of MPA and GPA at the time of diagnosis. Furthermore, we reviewed the medical record for IgG4-RD development during follow-up in the same study population, but we could find no case of concurrent IgG-RD and MPA or GPA.

Nonetheless, in the real clinical settings, when serum IgG4 is 135 mg/dL or greater at diagnosis of MPA or GPA without evidence of IgG4-RD on histology, physicians may hesitate to perform an additional biopsy of other tissues or radiological tests to exclude IgG4-RD: for instance, renal histopathology reveals that pauci-immune necrotising vasculitis with granuloma suggesting GPA, but no evidence of IgG4-related tubulointerstitial nephritis or IgG4-induced membranous glomerulonephritis [2] or not. In this study, 37 patients had serum IgG4 > 135 mg/dL at diagnosis. Only one patient with an infiltrative lesion in orbital muscle exhibited IgG4+ plasma cells of 5/high power field and the IgG4+/IgG+ plasma cell ratio of 4.6% without eosinophil infiltration on the tissues. However, no patients fulfilled comprehensive diagnostic criteria for IgG4-RD proposed by the Umehara

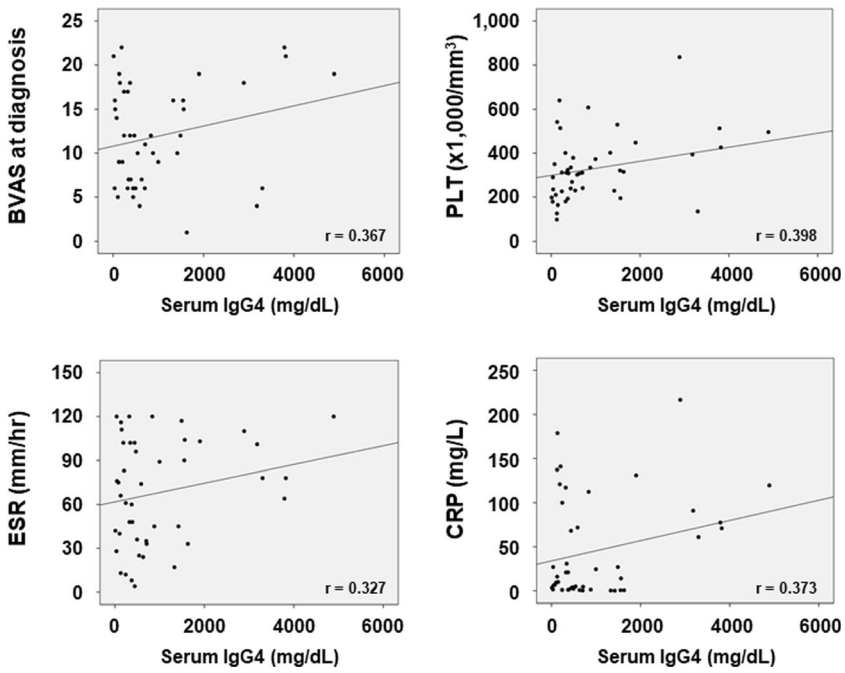

Fig. 2 The correlation of serum IgG4 with the inflammatory burdens of AAV. *BVAS* Birmingham vasculitis activity score, *PLT* platelet, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *AAV* antineutrophil cytoplasmic antibody-associated vasculitis

and Okazaki requiring IgG4+/IgG+ cells > 40% or IgG4+ cells/HPF > 10 on the tissues [3]. Furthermore, two patients underwent biopsies on two different tissues, which revealed MPA or GPA, but not IgG4-RD. Also, given that IgG4-RD develops in patients with MPA or GPA less frequently than those with EGPA [2, 10], these results may suggest that no additional interventions such as biopsy and positron emission tomography other than CT scans might be necessary to exclude IgG4-RD.

A recent review analysed 18 patients who met the 2012 Chapel Hill criteria for AAV and IgG4-RD comprehensive diagnostic criteria. They recommended that since AAV and IgG4-RD may overlap, physicians should consider whether atypical or refractory manifestations during AAV could be related to IgG4-RD [7]. If IgG4-RD is missed due to an overlapped diagnosis of MPA or GPA, will it cause significantly poor outcomes? Glucocorticoid and glucocorticoid-sparing agents including azathioprine, mycophenolate mofetil, and methotrexate are widely used drugs for IgG4-RD treatment. Rituximab could be considered as a therapeutic regimen for IgG4-RD, as it could deplete IgG4 producing plasma cells [4]. However, because IgG4-producing plasma cells are short-lived plasma cells, which leads to apoptosis within several weeks, the long-term therapeutic effect of rituximab on IgG4-RD could not be expected. Whereas in the treatment of MPA and GPA, induction therapeutic regimens include cyclophosphamide and rituximab [11, 12], and maintenance therapeutic regimens include various immunosuppressive drugs including rituximab [13]. Thus, although IgG4-RD is missed due to an overlapped diagnosis of MPA or GPA, because the potency of both induction and maintenance therapeutic regimens for MPA and GPA surpass that of those for IgG4-RD, poor outcome of IgG4-RD may not occur. However, in the opposite cases, misinterpreting MPA or GPA as concurrent IgG4-RD may lead to significantly poor outcome.

IgG4-RD could overlap with AAV concomitantly without the typical IgG4+ plasma cell infiltration on the affected tissues. A previous study reported, although comprehensive diagnostic criteria for IgG4-RD described IgG4+/IgG+ cells > 40% or IgG4+ cells/HPF > 10 on the tissues, histopathological features are currently considered primarily important, and tissue IgG4 counts and IgG4:IgG ratios are secondary in importance [14]. Another previous study regarding IgG4-related tubulointerstitial nephritis (TIN) was emphasised on the histopathological features. Storiform fibrosis and cell infiltration extending into the renal capsule were observed in most IgG4-TIN (92.3%), whereas neutrophil infiltration, severe tubulitis, severe peritubular capillaritis, granulomatous lesions, and necrotizing angiitis were observed in other types of TIN [15]. In addition to histopathological features and an elevated level of IgG4, low CRP was reported to be helpful to make a differential diagnosis between IgG4-RD and other diseases [16]. On the other hands, a previous study recommended urgent treatment in several IgG4-RD manifestations including aortitis, retroperitoneal fibrosis, proximal biliary strictures, tubulointerstitial nephritis, pachymeningitis, pancreatic enlargement, and pericarditis [4]. In these red-flag manifestation, no treatment may provoke irreversible organ-dysfunction. Thus, we suggest that physicians should perform additional evaluations for IgG4-RD in MPA and GPA patients under such conditions requiring a differential diagnosis or the urgent treatment of IgG4-RD.

The link between serum IgG4 and the inflammatory burdens in this study still remains unclear. We speculated the mechanism of the correlation of serum IgG4 with the inflammatory markers and activity of MPA and GPA in three ways. First, the study subjects were not classified as IgG4-RD in this study, and thus serum IgG4 might not be a pathologic antibody, which could enhance the inflammatory burdens based on the disease activity of IgG4-RD [17]. Second, despite no fully understood mechanism, IgG4 antibodies are considered to be produced by the dysregulation between Th1 and Th2 cells as well as Th2-related cytokines including interleukin (IL)-4 and IL-10 [18]. In terms of the pathophysiology of MPA and GPA, Th1 and Th17 cells are the key T cells rather than Th2, unlike EGPA [19]. Thus, this hypothesis could not explain the correlation between serum IgG4 and the inflammatory markers and activity of MPA and GPA. Third, the formation of immune response of IgG4 is limited due to the low affinity for Fc receptors and C1 complement [20]. However, a minority of IgG4 subclass, which could recognise ANCA-antigens, have been reported to bind Fc-gamma receptors and participate in the pathogenesis of AAV [21]. Therefore, it could be assumed that ANCA of IgG4 subclass might contribute to the correlation between serum IgG4 and the inflammatory markers and activity of MPA and GPA.

In this study, we first demonstrated that elevated serum IgG4 might not be associated with concurrent IgG4-RD at diagnosis of MPA and GPA in immunosuppressive drug-naïve patients. Whereas, we found that serum IgG4 was well correlated with activity and inflammatory burden of MPA and GPA. However, our study also has several issues. First, serum IgG4 was not measured in all 139 patients with MPA and GPA at diagnosis, as it has not been recommended as an obligatory item of the laboratory tests at diagnosis. Nevertheless, we believe that our study might provide the first answer to a question on the clinical implications of elevated serum IgG4 at diagnosis in patients with MPA and GPA, as a pilot study. Second, the number of this study was too small to represent all Korean patients with MPA and

GPA due to a single centre. Third, we could not show serial alterations in serum IgG4 in a patient due to a retrospective cross-sectional study. Future prospective and multi-centric studies with a larger number of patients will clarify the clinical implications of elevated serum IgG4 at diagnosis of MPA and GPA in patients.

Conclusions

Elevated serum IgG4 is not associated with concurrent IgG4-RD at diagnosis, and it may reflect activity and inflammatory burden of vasculitis in patients with MPA and GPA.

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Compliance with ethical standards This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0673), who waived the need for patient written informed consent, as this was a retrospective study.

Disclosures None.

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