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VASCULITIS (LR ESPINOZA, SECTION EDITOR)

IgG4-Associated Vasculitis

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Abstract Elevated IgG4 is characteristic of cases of IgG4-RD, a newly recognized systemic disease. However, several chronic inflammatory conditions, including rheumatic diseases, can also be associated with increased levels of IgG4. There have also recently been several reports describing an increased IgG4 immune response to some vasculitis syndromes, in particular Churg–Strauss syndrome and granulomatosis with polyangiitis. To avoid misdiagnosis, clinicians must be aware that the clinical manifestations of IgG4-RD and ANCA-associated vasculitis may overlap. The meaning of these observations is not yet understood, and more studies are needed to determine the true significance of the increased IgG4 response to vasculitis syndromes, especially anti-neutrophil cytoplasmatic antibodies (ANCA)-associated vasculitis.

Keywords Vasculitis · IgG4 · $IgG4^+$ plasma cells · IgG4-related disease · ANCA-associated vasculitis · Henoch–Schönlein purpura · Hypocomplementemic urticaria vasculitis syndrome

Introduction

Immunoglobulin G4 (IgG4) is the least common of the IgG subclasses identified in human serum, and is believed to be a unique antibody in terms of structure, function, and immunology regulation. The newly recognized IgG4-related disease (IgG4-RD) is characterized by elevated serum levels of IgG4 and by abundant infiltration of $IgG4^+$ plasma cells into affected organs. Currently regarded as a systemic disorder, IgG4-RD can resemble other illnesses. Although serum IgG4 level has been described as the most sensitive laboratory test, it lacks diagnostic specificity and its true value as a biomarker of the disease is therefore not well established. Several other pathological conditions associated with IgG4 elevation, including malignancies, allergic disorders, parasitic infections, and chronic inflammatory diseases, have been reported in the literature, usually as isolated findings. In recent years, several reports have described elevated serum IgG4 levels and increased $IgG4^+$ plasma cell infiltration of biopsy tissues for patients with systemic vasculitis. However, most data on this subject are from studies including patients with anti-neutrophil cytoplasmatic antibodies (ANCA)-associated vasculitis, especially Churg-Strauss syndrome (CSS). Because the morphological and clinical manifestations of ANCA-associated vasculitis and IgG4-RD may overlap, differential diagnosis could be a substantial challenge. Some studies have also suggested that ANCA of IgG4 specificity may affect the pathogenesis of ANCA-related vasculitis. In this review, we briefly describe some biological features of the IgG4 antibody, review data on serum IgG4 elevation in vasculitis syndromes, and discuss the possible effect of IgG4 on the pathogenesis of these entities.

Biological Features of IgG4 Antibody

IgG4 is believed to be a unique antibody, and is present in serum at levels in the range 0.35–0.51 mg mL^{-1} [1, 2•]. Its associations with several conditions, including involvement in allergen-specific immunotherapy [3] and protection from inflammatory manifestations during parasitosis, suggest it has a protective effect [4].

IgG4 production, like IgE production, is driven primarily by T-helper (Th) 2-cells. Overproduction of Th2-type cytokines, including interleukin (IL)-4, IL-5, IL-10, and IL-13, has been reported in association with increased IgG4 levels [5, 6]. These cytokines may contribute to the allergic manifestations,

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eosinophilia, and elevated serum levels of IgE and IgG4 reported to be associated with IgG4-RD [7]. IgG4 does not activate complement pathways, and its binding to Fcγ receptors is lower than that of other IgG subclasses. It therefore has less effector function than other IgG subclasses, raising questions about its pathogenic effect in human diseases [8–10]. Whether IgG4 is itself pathogenic or is simply an epiphenomenon related to other conditions remains to be determined.

Increased IgG4 Levels in Systemic Vasculitis

IgG4-RD has become an important unifying concept for several previously described fibroinflammatory multisystemic disorders. It is characterized by an increased serum level of IgG4, consisting mainly of $IgG4^+$ plasma cells, which is associated with a sclerosing lymphoplasmacytic inflammatory reaction [11, 12••, 13, 14]. However, increased serum IgG4 levels and $IgG4^+$ plasma cells have been revealed to be common to a variety of localized and non-specific chronic inflammatory conditions, including malignancies, infections, chronic skin lesions and rheumatic diseases [15, 16]. Care must therefore be taken to correctly interpret the plasma cell counts associated with these typical histopathology features.

Recently, several studies have reported increased serum levels of IgG4 and $IgG4^+$ cells in systemic vasculitis syndromes. Most clinical reports discuss small cohorts of patients with ANCA-associated vasculitis, especially CSS, although other vasculitis disorders have also been associated with an increased IgG4 immune response (Table 1).

IgG4 Immune Response in ANCA-Associated Vasculitis

The ANCA-associated vasculitis disorders comprise granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), CSS, and microscopic polyangiitis (MPA). They are characterized by necrotizing inflammation of the small vessels, in conjunction with ANCA directed to either proteinase 3 (PR3) or myeloperoxidase (MPO).

CSS, known as eosinophilic granulomatosis with polyangiitis, is a rare, systemic necrotizing vasculitis that affects the medium-sized small vessels (arterioles, capillaries, and venules) of patients with a history of bronchial asthma, allergic rhinitis, and sinusitis [17]. Its histology characteristics are an eosinophil-rich infiltrate, eosinophilic (extravascular) granulomas, and small and medium-sized vasculitis. CSS may present with systemic involvement, which often affects the upper and lower respiratory tract (pulmonary infiltrates) and peripheral nervous system (especially as mononeuritis multiplex), and less frequently affects the kidneys [18•].

A history of allergies, high serum IgE levels, peripheral eosinophilia, and eosinophilic infiltrates characteristic of CSS patients strongly suggest a Th-2 mediated disease, and elevated levels of Th-2 cytokines and chemokines (e.g. eotaxin-3, TARC/CCL17) during CSS pathogenesis have been reported [19, 20].

Although CSS and IgG4-RD have distinct histopathology characteristics, their clinical manifestations may overlap; patients with IgG4-RD also often have asthma and/or peripheral eosinophilia, with paranasal sinus, lung, and kidney involvement. The diseases also share the major characteristic of up-regulation of Th2 cytokines and IL-10, which may account for the enhanced IgG4 response observed for both syndromes (Table 2).

In recent years, some studies of CSS patients have revealed an association between increased serum IgG4 level and $IgG4^+$ cell tissue infiltration. Yamamoto et al. analyzed levels of IgG4 in the serum of five patients with CSS and MPO-ANCA positivity and 51 patients with Mikulicz's disease (MD), a condition recently categorized as an IgG4-RD. Remarkably, elevated IgG4 and increased IgG4/IgG ratios were found not only for MD, but also for CSS patients. In addition,

Table 1 Range of vasculitis syndromes associated with high serum-tissue IgG4 levels

Authors	Vasculitis	Number of cases	IgG4 elevation
Yamamoto et al. [21]	CSS	4/5 patients	Serum and tissue IgG4 and IgG4:IgG ratio
Yamamoto et al. [22]	CSS	5/5 patients	Serum IgG4
Vaglio et al. [23••]	CSS, GPA	18/24 (active) patients 24/24 patients	Serum IgG4 and $IgG4^+$:IgG ratio
Azuyawa et al. [24]	CSS	1 patient	Serum and tissue IgG4 and $IgG4^+$:IgG cell ratio
Ryu J et al. [25•]	CSS, GPA, PAN	3 patients 5 patients 1 patient	Serum IgG4
Chang et al. [29••]	GPA	8/26 patients	Tissue $IgG4^+$ and $IgG4^+$:IgG cell ratio
Ebbo et al. [30]	MPA Type II-MC	1 patient 1 patient	Serum IgG4
Wakamatsu et al. [34]	HUVS	1 patient	Serum and tissue IgG4 and $IgG4^+$:IgG cell ratio
Tamai et al. [35]	HSP	1 patient	Serum and tissue IgG4 and $IgG4^+$:IgG cell ratio

CSS, Churg–Strauss syndrome; GPA, granulomatosis with polyangiitis; PAN, polyarteritis nodosa; MPA, microscopic polyarteritis; MC, mixed cryoglobulinemia; HUVS, hypocomplementemic urticarial vasculitis syndrome; HSP, Henoch–Schönlein purpura

Table 2 Similarities of, and differences between, IgG4-RD, CSS, and GPA

Similarities	IgG4-RD and CSS	IgG4-RD and GPA	
Predominance of Th-response	Type 2 cytokines	–	
Respiratory symptoms	Bronchial asthma, sinusitis, allergic rhinitis	Chronic sinusitis	
Systemic involvement	Lung disease – kidney disease – peripheral neuropathy		
Serum findings	Peripheral eosinophilia, increased IgE and IgG4 levels	Increased IgG4 levels	
Histopathology findings	$IgG4^+$ plasma cells, rich eosinophil infiltration	$IgG4^+$ plasma cells	
Therapeutic approach	Good response to corticosteroids	Good response to corticosteroids	
Differences	IgG4-RD	CSS	GPA
Serum autoantibodies	–	ANCA positivity (P-ANCA)	ANCA positivity (C-ANCA)
Histopathology findings	Lymphoplasmacytic infiltrate, fibrosis in a storiform pattern, obliterative phlebitis	Small and medium-sized necrotizing vasculitis, extravascular eosinophilic granulomas	Small and medium-sized necrotizing vasculitis, palisading granuloma, neutrophilic microabscesses, fibrosis
Levels of $IgG4^+$ plasma cells infiltration	>50 per hpf	Variable (lower)	Variable (lower)
$IgG4^+$/IgG plasma cells ratio infiltration	>40 %	Variable (lower)	Variable (lower)

Th, T-helper; IgG4-RD, IgG4-related disease; CSS, Churg–Strauss syndrome; GPA, granulomatosis with polyangiitis; ANCA, antineutrophil cytoplasmatic antibodies; hpf, high-power field

tissue specimens from the kidneys of three patients with CSS revealed infiltration by numerous $IgG4^+$ plasma cells [21].

The same research team recently investigated the implications of high serum IgG4 levels found by rheumatology clinics. Using a cut-off value for serum IgG4 of 135 mg dL^{-1}, they found higher levels of serum IgG4 both for IgG4-RD patients and for patients with chronic inflammatory conditions, including autoimmune diseases. Elevated serum levels of IgG4 were found for CSS patients only (n=5) [22].

Vaglio et al. compared serum IgG4 levels and tissue infiltration by $IgG4^+$ plasma cells for patients with CSS (24 with active and 22 with quiescent disease), GPA (n=24), and atopic asthma (n=25), and for healthy controls. Approximately 75 % of patients with active CSS had higher serum IgG4 levels and IgG4/IgG ratios, and serum IgG4 levels were significantly higher for those with active CSS than for those with GPA or asthma. IgG4 levels were also higher for GPA patients than for healthy subjects. CSS patients' IgG4 levels correlated with disease activity and with the number of organs involved. Serum IgG4 levels dropped during remission, indicating that this IgG subclass may closely reflect disease activity in CSS patients [23••].

Azuyawa et al. reported the coexistence of two disorders (ANCA-negative CSS and IgG4-RD) in the same patient. High serum IgG4 levels and salivary gland swelling, with an eosinophil-rich tubulointerstitial nephropathy containing numerous $IgG4^+$ plasma cells, were observed in a patient with typical clinical features of CSS. The authors concluded that CSS patients may have a clinical condition similar to IgG4-related kidney disease [24].

A study conducted at the Mayo Clinic identified all patients with an elevated serum IgG4 concentration (>140 mg dL^{-1}), and medical records were reviewed to determine final diagnosis. The objective of the study was to determine the frequency of IgG4-RD and other disease associations for patients with elevated serum IgG4 levels. Of a large cohort of patients (n=3,300), 158 (4.8 %) had at least one high serum IgG4 level. Of this subset only 29 patients (18.4 %) met the criteria for definite or possible IgG4-RD. Remarkably, nine patients of the entire cohort (5.7 %), including five patients with GPA, three with CSS, and one with polyarteritis nodosa, had a final diagnosis of systemic vasculitis. Only a minority of patients with elevated serum IgG4 levels had IgG4-RD but, as revealed by previous studies, the serum IgG4 level was significantly higher for those patients than for patients with a non-IgG4-RD diagnosis [25•].

GPA is a systemic necrotizing vasculitis affecting medium-sized small vessels, and may present with limited (mainly upper respiratory tract, eyes and/or orbital) or systemic (lungs, kidneys, central and peripheral nervous system, skin, heart, joints, etc.) involvement [26].

GPA diagnosis is mostly on the basis of clinical findings, of ANCA positivity, and of characteristic histopathology findings in affected tissues. Necrotizing vasculitis and parenchymal necrosis with associated palisading granuloma, neutrophilic microabscesses, and fibrosis are the histology findings most characteristic of GPA [27]. GPA can strongly resemble IgG4-RD, especially histology test results.

Sensitivity and specificity are lower for biopsies from the orbit and upper respiratory tract, which may also lack the histopathology features commonly associated with GPA [28].

A study conducted at Mayo Clinic investigated the prevalence of $IgG4^+$ plasma cells for 26 patients with definitive clinical pathology diagnoses of GPA. An increased number of $IgG4^+$ cells was defined as an average number of $IgG4^+$-positive cells greater than 30 per high-power field (HPF), with an $IgG4^+$/IgG cell ratio greater than 40 %. Of 26 biopsies, eight (31 %) revealed increased $IgG4^+$ cell infiltration. These biopsies came from sinonasal (n=4) and orbital or periorbital tissues (n=4). All of these patients also had ANCA positivity (seven cases of C-ANCA, and one of P-ANCA) [29••]. To avoid misdiagnosis, clinicians should be aware that $IgG4^+$ cells can be greatly increased in GPA patient biopsies, especially for GPA patients with sinonasal and orbital/periorbital involvement. More studies are needed to confirm the possible effect of tissue-infiltrating $IgG4^+$ plasma cells on GPA pathogenesis.

A French group retrospectively studied a large cohort (n=646) of patients attending University Hospital, who had several diagnoses associated with serum IgG4 elevation. Fifty-nine patients had serum IgG4 levels over 135 mg-dL^{-1}, associated with a variety of diagnoses. It should be noted that 13.5 % of the patients with elevated IgG4 had a final diagnosis of autoimmune disease, and only 10 % presented with IgG4-RD. Among other rheumatic disease diagnoses, vasculitis was diagnosed in two patients (MPA in one case and hepatitis C-virus-associated type-II-mixed cryoglobulinemia in another). As reported after other studies, mean serum IgG4 levels and IgG4/IgG ratios were higher for IgG4-RD than for other diseases associated with IgG4 elevation [30].

Effect of ANCA-IgG4 Subclass in ANCA-Associated Vasculitis

The possible effect of the ANCA-IgG4 subclass on the pathogenesis of ANCA-related vasculitis has not been properly addressed. Some evidence supports the notion that immunology characteristics of MPO-ANCA might be associated with the disease mechanism of ANCA-related vasculitis.

ANCA are predominantly of the IgG isotype, especially the IgG1 and IgG3 subclasses. Brouwer et al. were the first to report that, for a cohort of patients with GPA, MPA, CSS, and other vasculitic syndromes, both PR3-ANCA and MPO-ANCA were predominantly of the IgG1 and IgG4 subclasses [31]. Later, Holland et al. found that, when isolated from ANCA-positive sera of GPA patients, the IgG4 subclass activated neutrophils in vitro by colligating PR3 with constitutively expressed Fc RIIa/IIIb receptors. This suggested a possible pathogenic effect of ANCA-IgG4 [32]. More recently, Liu et al. analyzed data from a Chinese cohort with GPA and MPA. In this study, titers of the anti-MPO IgG4 subclass for patients with GPA were significantly higher than for patients with MPA, again suggesting a possible effect of the MPO-ANCA IgG4 subclass on development of GPA. It has also been shown that higher titers of the MPO-IgG4 subclass for GPA patients could be indicative of underlying repeated, chronic, and intrinsic antigen stimulation of the immune system [33]. The precise effect of the IgG4-ANCA subclass on the pathophysiology of ANCA-related vasculitis needs further investigation.

IgG4 Immune Response in Other Vasculitis Syndromes

Evidence describing an increased IgG4 response to vasculitis syndromes other than ANCA-associated vasculitis is lacking. Wakamatsu et al. described a patient with clinical symptoms consistent with hypocomplementemic urticarial vasculitis syndrome (HUVS) who had very high serum IgG4 levels. A skin biopsy also revealed leukocytoclastic vasculitis with numerous $IgG4^+$ plasma cells and a high IgG4/IgG ratio. The authors discussed the probable coexistence of two diseases: HUVS and IgG4-RD [34].

High serum levels of IgG4 have been described concurrently in patients with Henoch–Schönlein purpura (HSP) nephritis. Direct immunofluorescence microscopy revealed positive staining with anti-human IgA and IgG, with C3 deposition in glomeruli, associated with many $IgG4^+$ plasma cells in the interstitium. In this study, HSP nephritis was complicated by IgG4-related tubulointerstitial nephritis (TIN). [35].

IgG4 production as a response to repeated exposure to environmental antigens has been described elsewhere [36], and may account for the increased IgG4 response observed to systemic vasculitis, and especially to CSS. Although the nature of the allergen is still unknown, it has been suggested that the higher levels of IgG and IgG4 observed in a subset of vasculitis patients may indicate immunological protection induced by allergen exposure.

Conclusions

The existence of a causal relationship between elevated IgG4 immune response and systemic vasculitis remains uncertain. An exception should be made for CSS, a condition that shares with IgG4-RD the up-regulation of Th2 cytokines and IL-10 which may be responsible for the increased IgG4 immune response reported for both diseases. The possibility that IgG4-RD and CSS have common immunopathogenetic mechanisms should be considered, and it should be determined whether the increased level of IgG4 associated with

vasculitis syndromes is relevant or should be regarded as an epiphenomenon.

IgG4 levels can be greatly increased by diverse chronic inflammatory diseases, in particular systemic vasculitis, and morphological and clinical manifestations of vasculitis and IgG4-RD may overlap. Awareness of these factors is needed to avoid misdiagnosis. More studies are necessary to determine whether the ANCA-IgG4 subclass has a pathogenic effect on the pathophysiology of ANCA-associated vasculitis.

Compliance with Ethics Guidelines

Conflict of Interest Rodolfo Perez Alamino declares that he has no conflict of interest.

Carlos Martínez declares that he has no conflict of interest.

Luis R. Espinoza declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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