IgG4 related disease: Current prospectives.

Aikaterini Sarantopoulou[1*], Alexandros Sarantopoulos[2], Evangelia Farmaki[1]

[1]Department of Pediatrics, Hippokration General Hospital, Aristotle University of Thessaloniki, Greece

[2]Department of Internal Medicine, Aristotle University of Thessaloniki, Hippokration General Hospital, Greece

Abstract

IgG4, a subclass of IgG, has been the subject of intense scientific research, resulting in the classification of heterogeneous clinical medical conditions, defined as IgG4 Related Disease (IgG4-RD). The ongoing investigation on refining the diagnosis, classification and pathophysiology of IgG4-RD, generated further questions on the role of IgG4 in inflammation, autoimmunty and induction of diseases and syndromes. On this regard, emerging reports indicate that this subclass of immunoglobulin G, may participate on the pathophysiology of autoimmune diseases, like Rheumatoid Arthritis. These reports provide new aspects of well-defined diseases of Internal Medicine, and support the fundamental knowledge immunologists rigorously support, that IgGs' role exceeds the boundaries of infections and actively participate in regulating the host's general homeostasis.

Keywords: IgG4-RD, Autoimmune diseases, B-cell depletion, Therapy.

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Clinical presentation and laboratory features of IgG4-RD

Several years have passed since the description of systemic diseases related to IgG4. Their clinical and pathophysiological heterogeneity constitutes a halt in adopting a specific nomenclature on the definition of these conditions. Even in widespread medical tools, IgG4-RD can be encountered by several names (Table 1). This difficulty is the result of the complexity and the vast questions raised by the so far research on the IgG4-RD.

Table 1. Current nomenclature referring to IgG4-RD.

Several names for IgG4-RD	IgG4-related disease
	IgG4-syndrome
	IgG4-associated disease
	IgG4-related systemic disease
	Hyper-IgG4 disease
	IgG4-positive multiorgan lymphoproliferative syndrome
	Systemic IgG4-related sclerosing syndrome

The first description of high IgG4 levels in a disease was reported in 2001 and regarded sclerosing pancreatitis, a condition that already had been described from the 60's but only in 1995 was described as immune-mediated disease [1-3]. Moreover association of autoimmune pancreatitis with fibrosclerosis added another piece in the puzzle of IgG4-RD.

Further investigation and pathology findings established some of the trademarks of the disease that include IgG4+plasmablast infiltration, spiral fibrosis, obstructive microvasculopathy and elevated IgG4 serum levels. On 2011, a Japanese study group established the first diagnostic criteria for IgG4-RD.

These criteria are currently applied and characterize a disease as definite, probable or possible, by assessing the presence of swelling or masses in a single or multiple organs, high levels of serum IgG4 and specific histopathological features [4].

Overtime, application of these criteria revealed that several diseases phenomenally unrelated between them, could be considered under the same spectrum. Orbital pseudotumor, prostatitis, interstitial pneumonitis, hypophysitis, inflammatory aneurysm, are some of the diseases that according to the above criteria could be defined as IgG4-RD [4].

Systemic application of the Japanese criteria revealed limitations in the diagnosis of IgG4-RD, due to unique organ-specific features. For this reason, the general diagnostic criteria, even though remain the system of reference, were adopted providing organ-specific diagnosis of IgG4-RD (kidney, eye, lachrymal and salivary glands). All these criteria adopt the core of the general criteria with a further application of local specific parameters that contribute to the diagnosis of the disease [5]. To note that those available for the diagnosis of kidney disease are the most complicated ones [6].

On daily clinical practice, a great proportion of diagnosed IgG4-RD concerns the gastrointestinal system [7]. IgG4-related sclerosing disease mainly refers to autoimmune pancreatitis and sclerosing cholangitis (SC).

Before the description of IgG4-RD, patients with IgG4-SC were diagnosed in the context of primary sclerosing cholangitis (PSC) [8]. Nevertheless, these two conditions have unique features that can help in their differential diagnosis.

These features involve clinic-pathological and radiographic findings (Table 2).

Table 2. Differential characteristics of IgG4-SC and PSC.

	IgG4-SC	PSC
	Clinico-pathological	
Gender	80% male	60% male
Age	>60 years old	40 years old
Elevated serum IgG4	70%	<10%
Response to steroids	Yes	No
Histology	IgG4+Plasmablast infiltration	"Onion-skin" fibrosis
	Radiographic	
Length of constriction	>10 mm (segmental strictures)	<5 mm (band-like strictures)
Margin	Faded (oedema)	Clear (fibrosis)
Peribilary oedema	Yes	No

The discrepancy of these two conditions regarding steroid efficacy, has encouraged the development of algorithms, which in some cases are rather complicated, in order to assess the differential diagnosis between IgG4-SC and PSC [9].

Today, the spectrum of IgG4-RD has been amplified, including cases that were earlier diagnosed in the context of other diseases [10-12] (Table 3). To note, that in contrast to liver disease, the retroperitoneal fibrosis imaging assessment cannot discriminate between IgG4-RD and other diseases [13].

Table 3. Medical conditions that in many cases can be diagnosed in the context of IgG4-RD.

Medical conditions that can be diagnosed in the context of IgG4-RD	Mikulicz's disease
	Reidel's thyroiditis
	Eosinophilic angiocentric fibrosis
	Autoimmune pancreatitis
	Inflammatory pseudotumor
	Cutaneous pseudolymphoma
	Membranous glomeronephritis
	Idiopathic hypertrophic pachymeningitis
	Retroperitoneal fibrosis
	Inflammatory aortic aneurysm

The predominant clinical presentation of an IgG4-RD patient consists of a middle-aged or older male, with edema and functional impairment of the target-organ or tissue, lack of general symptoms and record of 40% atopy when investigating on the medical history [14,15].

Note that even if the patient reports clinical findings from one organ or tissue, in fact, a clinical assessment will reveal multi-organ involvement in 60-90% of cases. As for the laboratory assessment, the majority of patients reveal a smooth increase of acute phase reactants (erythrocyte sedimentation rate-ESR, C-reactive protein-CRP), augmented IgE serum levels [16], low complement levels and organ-specific biochemical abnormalities. These last may be indicative of systemic complications of the disease that clinically remain silent.

Immunological aspects of IgG4-RD pathophysiology

The description of IgG4-RD has been accompanied by an intense investigation on defining the aspects of the immune response that are commonly involved in the pathophysiology of this novel cluster of diseases. One of the first findings was a common T-helper2-Type (Th2) mediation in the disease pathophysiology [17]. Th2 is an anti-inflammatory response accompanied by B-call and plasmablast activation with antibody formation. On a clinical level, predomination of this response explains the lack of systemic clinical findings (fever, malaise, etc.) in the context of these diseases.

On a pathophysiological level, a vast discussion has emerged, as for the oligoclonal or polyclonal expansion of B-cells in the disease. Several reports indicate an association of specific HLA class II molecules with IgG4-RD, indicating a specific B-cell class switch following exposure to a specific antigen [18]. Nevertheless, other reports support the theory of polyclonal activation of B-cells in the pathophysiology of the disease, implying a more general inflammatory condition as aetiopathogenetic insult [19]. More recent data support the oligoclonal B-cell expansion theory, since administration of B-cell depletion therapy (rituximab) is accompanied by oligoclonal expansion of IgG4+ plasmablasts with an auto-reactive signature [20].

IgG4-RD: An autoimmune disease?

From the first description of IgG4-RD, accumulating evidence indexed that a common autoimmune mechanism could rely in the core of the disease's pathophysiology. HLA-class II associations, oligoclonal B-cell implication, were some of the initial findings that strongly suggested that an organized immune response proceeds clinical manifestation of IgG4-RD. Despite the so far investigation, there are still unmet requisitions for a robust consideration of these diseases as autoimmune [21].

There are four criteria that have to be fulfilled for a disease to be considered as autoimmune. They are known as Witebsky and Rose criteria, were formulated in the late 50's and are valid up-to-date. According to these criteria, an autoimmune disease must be associated to a specific autoantigen against of which specific autoantibodies are produced. Investigation on this regard has not yet recorded a definite description of a specific autoantigen-autoantibody axis in the pathophysiology of IgG4-RD [22]. Nevertheless, there are other antibody-mediated syndromes in internal medicine, which are described as autoimmune and include a distinctive cluster of seronegative phenotype (Antiphospholipid Syndrome-APS) [23].

Therapy

Corticosteroids and B-cell depletion therapy (rituximab) constitute the milestone of IgG4-RD therapy [24]. Lower levels of serum IgG4 and absence of obstructive and systemic disease at the diagnosis predict a better clinical outcome following therapy [25]. In fact, a Japanese study has reported that 30% of patients with persistently elevated IgG4 relapsed after therapy, with the respective percentage being registered as low as 10% in patients with normal IgG4 levels [26]. Up-to-date therapeutic algorithms suggest a combined administration of steroids with rituximab in severe cases of relapsing disease. For an accurate follow up of these patients, clinical response indexes have been formulated, in order to detect any disease relapse the earliest possible [27]. With the so far applied therapeutic regimes, IgG4-RD retains a sustainable remission rate, even in aggressive forms of the disease.

Conclusion

A lot of research has still to be performed in order to better assess IgG4-RD's pathophysiology and reveal possible targets for further therapeutical interventions [28]. At this point it is useful to report that B-cell depletion therapy provides further considerations for IgG4 implication in other diseases [29]. It has been documented that in patients with rheumatoid arthritis who received rituximab therapy, IgG4 registered distinct variations among the four IgG subclasses [30]. Such findings will further clarify the role of IgG4 in systemic disease, and may evince further fields of IgG4 implication in internal medicine.

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*Correspondence to

Alexandros Sarantopoulos

Department of Internal Medicine,

Aristotle University of Thessaloniki,

Hippokration General Hospital, Greece