REVIEW

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

The role of IgG4 in cutaneous pathology

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Abstract

IgG4 is an immunoglobulin subtype that has many physiologic and morphologic peculiarities. In cutaneous pathology, IgG4 has been related to the pathogenesis of many diseases. Moreover, in the recent years, new IgG4-related diseases have been described. Since some involve the skin, either primarily or as part of their systemic manifestations, we have tried to briefly examine some of the cutaneous conditions related to IgG4.

Keywords: IgG4, IgG4-related sclerosing syndrome, bullous pemphigoid, Rosai–Dorfman.

Introduction

IgG4 is an immunoglobulin subtype that has many physiologic and morphologic peculiarities. In cutaneous pathology, IgG4 has been related to the pathogenesis of many diseases, many of which have been known and studied for decades. However, in the recent years, new systemic IgG4-related diseases have been described, and new concepts regarding the implication of IgG4 in many diseases (inflammatory and tumoral) have appeared. Some involve the skin, either primarily or as part of their systemic manifestations. In the current report, we briefly examine some of the cutaneous conditions related to IgG4.

Some peculiarities of IgG4

IgG is an immunoglobulin isotype with four subclasses. Although heavy chains of all these subclasses show more than 95% sequence homology, differences in the antigenicity of the heavy chains allow, however, four subtypes to be distinguished: IgG1, IgG2, IgG3 and IgG4 [1, 2]. IgG4 is the least common of all, counting for 0.7% to 5% of all IgGs [3]. IgG4 is also the most complex in structure and biology of all the IgG classes [4]. Similar to other IgG subclasses, IgG4 can cross the placenta into the fetal circulation [5], which has pathologic implications as explained below.

One of the most curious properties of IgG4 is its capacity for "half antibody exchange" *in vivo*, aka "Fab-arm exchange". This mechanism results in recombinant antibodies comprising two different binding specificities, with two different Fab arms and bi-specificity for a certain antigen [4] (Figure 1).

The result is that although IgG4 is able to act as a blocking antibody, it is practically unable to form large immune complexes [6, 7]. One consequence of this bispecificity is that significant amounts of bispecific antibodies will occur only when induced by two antigens that are present at the same time in the body. Such reduction in the capacity to form immune complexes significantly decreases the risk of auto-damage. This, together with the fact that IgG4 does not activate the complement via the classical pathway (although it may do, *via* the alternative pathway [8]) and to its low affinity for C1q and Fc receptors, results in IgG4 having a low theoretical potential for immune activation. Although the lack of affinity by Fc receptors is low, it is not non-existent: when acting in common with IgG1 and IgG3, IgG4 can bind FcγRIIIb on neutrophils, for instance [9].

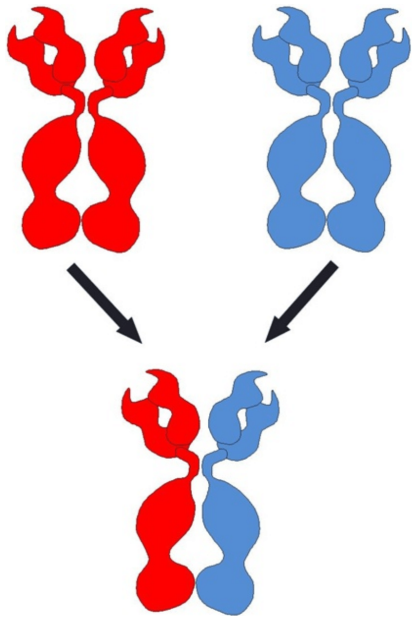

Figure 1 – ***Fab-arm exchange mechanism. This mechanism is not completely understood, but it seems to involve two intact four-chain IgG4 molecules, forming a bispecific IgG4 molecule.***

Researchers have also demonstrated that IgG4 autoantibodies are able to activate leukocytes, induce leukocyte-dependent tissue damage and induce Fc-dependent dermal–epidermal separation [10]. Basophils as well as mastocytes have membrane receptors that are able to bind IgG4 [11].

Another interesting aspect regarding IgG4 antibodies is that they commonly arise after long-term exposure to an antigen, therefore decreasing the degree of chronic inflammation to environmental stimuli. In addition, certain interleukins (IL), such as IL-10, stimulate the preferential production of IgG4 over IgE [12]. This is due to the increase in the number of allergen-specific IgG4-producing plasma cells [13] and not to switching from IgE to IgA, since the latter is physiologically impossible because of the sequence order in which the genes for the isotypes are arranged on the chromosome [14–16]. However, IgG4 and IgE are part of the T-helper 2 (Th2) response [17]. This does not mean that both types of immunoglobulins are simultaneously induced by the same stimuli, since, as has been demonstrated, the presence of IgG4 antibodies without IgE antibodies is not uncommon (aka the modified T-helper type 2 response). The latter seems to be "the typical 'healthy' response to an innocuous antigen" [17]. In fact, IgG4 seems to play a protective role in certain circumstances, such as in allergen-specific immunotherapy, in the tolerance of certain food [18] or in protection against allergic effects in parasitosis [19–21]. Such an effect could be due to several mechanisms. Some have already been described, such as IgG4's low affinity for C1q and the classical Fcγ-receptors and IgG4's preventive action against the formation of large immune complexes. In addition, IgG4 acts many times as a "blocking antibody", competing with IgE and therefore dumping IgE-mediated immune reactivity [22].

Although the shift from IgE to IgG4 is not possible, the shift from IgG1 to IgG4 is and would probably be a common mechanism after repeated exposure to an antigen [23]. This shift would be a natural defense to reduce the effects of complement-dependent antibodies [24].

IgG4 in cutaneous pathology

IgG4 has been related to many cutaneous diseases, some quite recently admitted in cutaneous pathology. Evidence of the existence of IgG4-related inflammation as well as neoplastic conditions is increasing significantly in the literature.

IgG4 in allergic symptoms and atopic dermatitis (IgE-negative allergies or modified T-helper type 2 response)

Many conditions related to a Th1 response generally induce follicles with germinal centers and suppression of the Th2 response and of IgG4 and IgE production [25]. In contrast, the response to certain allergens can sometimes induce IgG4 without IgE antibodies [26]: while exposure to low amounts of the antigen could induce either a low antibody response or no response [27] high exposure to an allergen can trigger a Th2 response with IgG4 cells without an accompanying IgE response [28].

Some studies from decades ago demonstrated that patients with atopic eczema have much higher serum IgG4 levels than healthy controls [29, 30]. However, although patients with atopic eczema have increased total IgG4 concentrations, the total IgG concentrations are usually unaffected [24]. This has been interpreted as a shift from another IgG subclass into IgG4, probably as a natural defense mechanism to decrease the level of complement-dependent antibodies [24]. Isotype switching occurs in mature B-lymphocytes in collaboration with helper CD4 T-cells and is cytokine dependent [31]. Such a mechanism has, for instance, been demonstrated in patients hyposensitized with pollen, dust mites and bee venom [23]. There is also a study in which patients with bee venom allergy were treated with Igs from pooled beekeeper plasma [32]. This treatment was shown to be protective against future bee stings. Unfortunately, the IgG4 antibody levels were not measured.

All these findings are in consonance with the fact that food-specific antibodies of the IgG4 subclass are frequently found in the normal population [33]. More recent studies also seem to corroborate that food-specific IgG4 does not indicate food allergy or intolerance but a physiological response of the immune system to some food components [34]. Some have recently remarked on the lack of solid evidence in relating IgG4 levels to chronic urticaria and other suspected allergy skin symptoms [35].

Although IgG4 has been related to the beneficial effects of allergen-specific immunotherapy, this aspect is also a matter of debate in the literature. Some claim that if no IgG4 antibody is induced by conventional immunotherapy, the therapy is likely to have been ineffective. While during the first phases of the immunotherapy the response is mainly IgG1, a switch of the IgG1/IgG4 ratio from <20% to >80% is generally accepted as a sign of successful allergen-specific immunotherapy [36].

IgG4 in parasitic infestations

While the immunologic response against intracellular protozoa is mainly Th1 dependent, the one against extracellular protozoa is mainly Th2. In addition, the parasite's success is not so much to damage the host but to avoid being recognized as foreign. In this sense, IgG4 could play a main role: in chronic parasitic infestations, a shift of Th2 with high levels of parasite-specific IgG4 has been demonstrated [19–21]. This shift would result in protection against allergic effects in parasitosis [19–21], which is beneficial for the host and, at the same time, one of the parasite's goals. IgG4 could therefore modulate the IgE immune response [37]. However, while for some IgG4 would block IgE [38], it would be a reaginic antibody for others [39]. Interestingly, several studies have demonstrated that IgG4 is associated with a higher susceptibility to reinfection in certain parasitosis, while IgE confers resistance [40]. Moreover, some have demonstrated that the presence of IgE and IgG4 responses shows a trend of compromising the resistance associated with IgE alone, which suggests that IgE response is attenuated by IgG4 [41].

A prominent IgG4 response has been reported in several parasitoses, including filariasis (Bancroftian or Brugian filariasis and onchocerciasis) [42, 43], schistosomiasis [44], cysticercosis [37] and echinococcosis [45, 46]. IgG4 also seems to play an important role in parasitic infestations more commonly seen in cutaneous pathology.

The plasma from subjects with ordinary scabies as well as crusted scabies shows significantly increased IgG4 levels to several antigens of the parasite, compared with naïve subjects [47]. Crusted scabies, however, showed extreme non-protective IgE and IgG4 scabies-specific antibody responses as well as eosinophila [47]. This might be related to an inappropriate Th2-polarized immune response in these patients [47].

In cutaneous leishmaniosis, the IgG4 response is also interesting. Some studies seem to suggest that while a Th1 response cures the lesions (either spontaneously or under the appropriate treatment) [48, 49]. The forms with a Th2 response are usually resistant to chemotherapy and disseminate through the cutaneous surface [49]. In the sera of patients with cutaneous disseminated leishmaniasis, the antibodies specific to leishmania are mainly IgG4 [50]. Lastly, patients with a mixed Th1 and Th2 pattern of response commonly have more destructive lesions in nasopharyngeal and oral mucosae, with a tendency to develop chronic lesions [49].

Regarding larva migrans, IgG4 has been the predominant reactive antibody found, for instance, in cases of gnathostomiasis [51].

In patients infected with *Wuchereria bancrofti* microfilariae, the IgG4 response against antigen extracts from *Wuchereria bancrofti* microfilariae or *Dirofilaria immitis* was significantly higher in early asymptomatic patients than in hydrocele or in chronic elephantiasis [52]. Moreover, the IgG4 response was slightly higher in microfilaremic than in amicrofilaremic subjects [52].

IgG4 and blistering diseases

Blister diseases of the skin are mainly mediated by antibodies. While diseases of the pemphigus group are mainly associated with antibodies to the epidermal components mediating cell–cell adhesion [53], subepidermal autoimmune bullous lesions are associated with antibodies against the dermal–epidermal junction [54]. IgG4 has been related to several such bullous diseases. In many, IgG4 deposits are also associated with C3 deposits. Since IgG4 does not fix the complement *via* the classical pathway, other IgG subclasses are probably responsible for these deposits [55].

IgG4 is related to pemphigus. The pathogenic mechanism is the binding of the antibody to certain proteins in the desmosome [56], causing the loss of cell–cell adhesion [57, 58] and the subsequent blister formation. In several types of pemphigus, the autoantibodies belong mainly to the IgG4 and IgG1 subclasses [56]. For instance, IgG4 is the IgG subclass that predominates in pemphigus vulgaris (anti-desmoglein 3) [59–61], vegentans (anti-desmoglein 3) [62], foliaceus (anti-desmoglein 1) [63], as well as in the endemic pemphigus foliaceus (fogo selvagem) [64]. In contrast, the autoantibodies in paraneoplastic pemphigus mainly belong to IgG1 and IgG2 subclasses [63].

In fogo selvagem, although initial autoimmune responses are mainly dominated by IgG1, the development of clinical disease (even if only prodromic) [65] seems to be characterized by an increase in IgG4 [66]. In addition, the transition from disease in remission to active disease seems to be associated with subclass switching from IgG1 to IgG4 [66]. Some have suggested that the presence of high levels of IgG4 anti-desmoglein 1 in clinically normal subjects could identify who may be at higher risk of developing clinical disease [66].

IgG4 has also been implicated in subepidermal blisters, such as bullous pemphigoid [55, 67]. Autoantibodies in bullous pemphigoid are directed against the hemidesmosomal antigens BP230 and BP180/type XVII collagen [54, 56]. IgG4 is the predominant subclass of autoantibodies in bullous pemphigoid, followed by IgG1, and occasionally by IgG2 and IgG3 [55, 68–72]. This latter fact has been recognized as one of the sources of false-negative direct immunofluorescence in studies of bullous pemphigoid [72], due to the limited reactivity of commercial antihuman IgG conjugates to the IgG4 subclass.

In bullous pemphigoid, IgG4 is detected not only in the sera from patients but also in skin biopsies by direct immunofluorescence [55].

A relationship between pemphigoid gestationis and IgG4 has also been documented. This condition is due to autoantibodies against the two hemidesmosomal proteins “bullous pemphigoid” (BP)180 and less frequently BP230 [73]. Some studies have demonstrated that IgG4 is less frequently found in the sera from patients with pemphigoid gestationis than IgG1 or IgG3 (80.95% IgG1; 66.66% IgG3; 33.33% IgG4; 28.57% IgG2) [74]. However, a study including 10 pregnant patients with pemphigoid gestationis, in which sandwich double antibody immunofluorescence and direct immunofluorescence was used, demonstrated that IgG4 was the predominant subtype (100% IgG4; 70% IgG2; 50% IgG1; 40% IgG3) [75].

Mucous membrane pemphigoid is another bullous disease related to IgG4. The autoantibodies found in this disease are mainly directed against laminin-332, BP180 (bullous pemphigoid antigen 2 or type XVII collagen) and the beta4 integrin [76, 77]. These antibodies mainly belong to the IgG4 and IgG1 subclasses [78]. Specifically, IgG4 anti-L-332 autoantibodies are a reliable marker for patients with cicatricial pemphigoid, when an appropriate technique is used in order to avoid false positives in bullous pemphigoid [79].

Epidermolysis bullosa acquisita is also related to IgG4 antibodies patients have against type VII collagen of the sublamina densa region of the epidermal basement membrane [80]. In this disease, the predominant antibodies belong to the subclasses IgG1 and IgG4 [81, 82].

In many of these diseases, since IgG4 crosses the placenta, the antibody can induce acantholytic skin disorders in neonates [83]. For instance, examples of neonatal pemphigus or gestational pemphigoid by transfer of maternal IgG autoantibodies to the neonate have been published [83, 84].

A similar mechanism of switching to the one described above for atopic dermatitis could be responsible for the poor correlation between disease activity and total IgG basement membrane zone antibody in bullous pemphigoid that has been observed in some studies

[85–87]. Some claim that the degree of inflammation depends on the IgG isotype rather than on the total IgG basement membrane zone autoantibody [88]. IgG4, for instance, has been demonstrated as the predominant subclass in bullous pemphigoid during remission but not in early disease [88]. In addition, in pemphigus, IgG4 is the most common subclass in patients in remission, whereas the IgG1 subclass is found in patients with active disease and less often when clinical remission is achieved [89].

Cutaneous IgG4-related disease

IgG4-related disease is a syndrome of unknown etiology that mainly appears in middle-aged and elderly patients, with a marked male predominance (although the involvement of certain organs, such as the salivary gland and the lachrymal gland, is as common in men as in women) [90]. The pathogenic mechanisms of the disease are not totally understood, although they are probably autoimmune [91]. Some autoantigens have been suggested as potential candidates, such as the 13.1 kDa protein that was isolated by Yamamoto M *et al.* in 2010 from patients with IgG4-related sclerosing syndrome but not from controls [92]. In addition, researchers have demonstrated that IgG4 from the sera of patients with the syndrome was able to bind epithelia from normal tissue of patients without the disease [93].

The most common clinical presentation is the involvement of one or more sites, usually in the form of a mass lesion. The organs most commonly involved are the exocrine glands (commonly the pancreas [94–97], hepatobiliary tree [98–101] or salivary gland [102]). The orbit and the lymph nodes are also often involved. However, virtually any organ could be involved [103] (Table 1) and cases affecting the retroperitoneum [104], aorta [105–107], mediastinum [108], lachrymal gland [109], soft tissue [110], pituitary gland [111], breast [112], kidney (always associated with extrarenal disease) [113], prostate [114], stomach [115], colon [116], lung [117], lymph node [118], central nervous system [119] and thyroid have been published [120].

The laboratory findings most commonly found are an increase in IgG4 and IgE [121] frequent presence of circulating autoantibodies and a favorable response to steroid therapy.

From a morphologic point of view, lympho-plasmacytic infiltrates are common, with occasional eosinophils, storiform fibrosis, obliterative phlebitis and sclerosis with increased IgG4+ plasma cells in tissues [122].

Cutaneous involvement has sometimes been reported [123, 124]. The lesions commonly manifest as plaques or nodules in the head and neck. In Sato Y *et al.* report [123], the authors describe skin lesions in two out of nine patients in whom "the skin lesions showed lymphoplasmacytic infiltration with abundant IgG4-positive cells and eosinophils". In the figure shown in the report, "plasma cells, small lymphocytes and eosinophils showed a nodular-forming infiltration in the intermediate to deep dermis".

Table 1 – *List of organs involved by IgG4-related disease*

Nervous system:
Meninges: pachymeningitis.
Pituitary: lymphocytic hypophysitis.
Digestive system:
Bile duct: sclerosing cholangitis.
Gallblader: sclerosing cholangitis; chronic cholecystitis.
Colon: chronic colitis.
Stomach: chronic gastritis.
Ampulla: active chronic duodenitis.
Pancreas: autoimmune pancreatitis.
Lachrymal gland: chronic sclerosing sialadenitis (Küttner tumor).
Mediastinum: mediastinal fibrosis.
Retroperitoneum: retroperitoneal fibrosis.
Kidney: tubulointerstitial nephritis.
Lung: interstitial pneumonia.
Prostate: chronic prostatitis and atrophy.
Lymph nodes: follicular hyperplasia.
Thyroid: thyroiditis.
Aorta: aortic aneurism.
Breast: chronic mastitis.
Skin: IgG4-related disease.

In Cheuk W *et al.* report [124], the morphologic features from the two reported cases were similar: the epidermis was spared, and the dermis and the hypodermis were involved. A perivascular and periadnexal lymphoid inflammatory infiltrate with plasma cells, histiocytes and eosinophils was evident. Immature plasma cells and lymphoid follicles were also found. Hyalinized collagen bundles within the lesions were obvious. The IgG4/IgG ratio varied from 68% to 100%. Cheuk W *et al.* also reported in the same paper two cases of pseudo-lymphoma in which "IgG4+ cells were markedly elevated" [124] but lacked more clinical information to confirm or to rule out an IgG4-related sclerosing disease. Even so, the authors concluded that "the existence of a 'solitary' cutaneous counterpart of the syndrome cannot be excluded" [124].

Others have demonstrated an increase of IgG4+ plasma cells in cutaneous plasmacytosis [125]. The patients had multiple red-brown papules and plaques over the trunk accompanied by polyclonal hypergamma-globulinemia and abundant infiltration of IgG4-bearing plasma cells [125]. However, such cases would not be related to IgG4-related sclerosing conditions diseases according to some [124] mainly due to the following: (1) Most times patients do not develop systemic disease. (2) While plasmacytosis is usually present as numerous skin lesions widely distributed over the body, cutaneous involvement by IgG4-related disease is commonly limited to regional skin lesions. (3) Plasmacytosis usually does not show any response to steroid therapy. (4) The infiltrate is mainly made of plasma cells, without large lymphoid aggregates, admixed small lymphocytes or lymphoid follicles. (5) There is usually no sclerosis in plasmacytosis. (6) The IgG4+ cells, although abundant, are on the low side of the cell count. According to these same authors [124], a high number of IgG4+ plasma cells, or a high IgG4+/IgG+ rate, is not enough to diagnose an IgG4+-related sclerosing disease. In fact,

some have demonstrated the ubiquitous occurrence of variably high numbers of IgG4-positive plasma cells under diverse non-specific inflammatory conditions [126].

Table 2 shows some published studies on cutaneous diseases in which the IgG4/total IgG ratio was evaluated. In most of the diseases other than IgG4-related syndrome, the IgG4/IgG ratio is below 50%, while in the two cases of cutaneous IgG4-related disease Cheuk W *et al.* reported, the ratio was more than 70% [124]. Even in Sato Y *et al.* cases of systemic IgG4-related lymphadenopathy with skin lesions, the ratio was more than 50% (albeit it was evaluated in the lymph nodes) [123]. From the three cases of cutaneous plasmacytosis presented by Miyagawa-Hayashino A *et al.*, the IgG4/IgG ratio was only (slightly) more than 50% in one case [125]. Therefore, according to some authors [124], cutaneous IgG4-related disease should be suspected when a lesion is rich in plasma cells or when it shows significant sclerosis, "especially if there accompanying mass lesions in sites commonly involved by IgG4-related sclerosing disease (such as orbit, salivary gland and pancreas)" [124] (Table 3). In such situations, one should be able to find a large number of IgG4+ plasma cells together with a high proportion of IgG4/IgG cells [124].

In addition, some have claimed that Rosai–Dorfman disease could belong to the group of IgG4-related disease [127]. However, some researchers have resisted this interpretation, [124] since Rosai–Dorfman disease shows specific clinical (mainly young patients) as well as morphologic (S100-positive histiocytes with large cytoplasm) features.

Table 2 – ***Published cases of cutaneous conditions with a an inflammatory infiltrate rich in plasma cells, in which the IgG4/IgG ratio has been investigated***

Published case	Reference No.	Diagnosis	IgG4+/IgG+ cell counts per high power field (skin biopsy)	Ratio IgG4/IgG [%]
Cheuk W *et al.* Case No. 1	[124]	Cutaneous IgG4-related sclerosing disease.	342/285	120
Cheuk W *et al.* Case No. 2	[124]	Cutaneous IgG4-related sclerosing disease.	425/630	76.46
Kuo TT *et al.* Case No. 1	[127]	Cutaneous Rosai–Dorfman disease.	137/267	51.31
Kuo TT *et al.* Case No. 2	[127]	Cutaneous Rosai–Dorfman disease.	128/348	36.78
Kuo TT *et al.* Case No. 3	[127]	Cutaneous Rosai–Dorfman disease.	107/290	36.89
Kuo TT *et al.* Case No. 4	[127]	Cutaneous Rosai–Dorfman disease.	121/356	33.98
Kuo TT *et al.* Case No. 5	[127]	Cutaneous Rosai–Dorfman disease.	192/402	47.76
Kuo TT *et al.* Case No. 6	[127]	Cutaneous Rosai–Dorfman disease.	113/296	38.17
Kuo TT *et al.* Case No. 7	[127]	Cutaneous Rosai–Dorfman disease.	204/422	48.34
Kuo TT *et al.* Case No. 8	[127]	Cutaneous Rosai–Dorfman disease.	55/239	23.01
Kuo TT *et al.* Case No. 9	[127]	Cutaneous Rosai–Dorfman disease.	49/298	16.44
Kuo TT *et al.* Case No. 10	[127]	Cutaneous Rosai–Dorfman disease.	21/114	18.42
Kuo TT *et al.* Case No. 11	[127]	Cutaneous Rosai–Dorfman disease.	190/759	25.03
Kuo TT *et al.* Case No. 12	[127]	Cutaneous Rosai–Dorfman disease.	82/402	20.39
Sato Y *et al.* Case No. 8	[123]	Systemic IgG4-related lymphadenopathy (intra-germinal center plasmacytosis type) with skin lesions.	–	58.7 (in the lymph node)
Sato Y *et al.* Case No. 9	[123]	Systemic IgG4-related lymphadenopathy (intra-germinal center plasmacytosis type) with skin lesions.	–	63 (in the lymph node)
Strehl JD *et al.*	[126]	Eight cases of plasma cell-rich dermatitis (four cases of lichen sclerosus et atrophicans, two cases of anus praeter associated inflammatory reaction, and one case each of posthitis and unguis incarnatus).	–	21 (mean ratio)
Miyagawa-Hayashino A *et al.* Case No. 1	[125]	Cutaneous plasmacytosis.	53/153	34.64
Miyagawa-Hayashino A *et al.* Case No. 2	[125]	Cutaneous plasmacytosis.	62/142	43.66
Miyagawa-Hayashino A *et al.* Case No. 3	[125]	Cutaneous plasmacytosis.	72/124	58.06

Table 3 – *Summary of cutaneous IgG4-related disease*

What is IgG4?

IgG4 is a T-helper cell 2-dependent immunoglobulin subtype with many physiologic and morphologic peculiarities.

What is IgG4's role in normal inflammation/host responses?

Due to its properties, IgG4 many times plays a "protective role" as in allergen-specific immunotherapy, in the tolerance of certain food, or in the protection against allergic effects in parasitosis.

IgG4 many times acts as a blocking antibody. It does not activate its complement via the classical pathway (although it may do so *via* the alternative pathway). IgG4 autoantibodies can activate leukocytes, induce leukocyte-dependent tissue damage, and induce Fc-dependent dermal-epidermal separation. Basophils and mastocytes have membrane receptors that can bind with IgG4. In addition, IgG4 many times competes with IgE and therefore dumping IgE-mediated immune reactivity.

What is an IgG4-related disease?

It is a lymphoproliferative disorder that shows hyper-IgG4-gammaglobulinemia and IgG4-producing plasma cell expansion of the organs involved.

What is the role of IgG4 in IgG4-related diseases?

The pathogenesis of an IgG4-related sclerosing disease is not totally understood. Many authors think that an allergic response is involved in such pathogenesis. Although arguments either for or against the autoimmune nature of the disease have been presented [124], it is generally believed that IgG4 probably represents a surrogate marker rather than playing a pathogenetic role.

What are the criteria for diagnosing a cutaneous IgG4-related disease?

The proposed diagnostic criteria vary among the different investigators, but some believe in the importance of strict and narrow criteria.

The following proposal, although not accepted by all, seems reasonable and complete [124]:

Criteria (of which *all* must be satisfied):

1) Compatible morphology (only extranodal site morphology is mentioned here):
   (a) Lymphoplasmacytic infiltration with or without lymphoid follicles;
   (b) Sclerosis;
   (c) Phlebitis can be evidenced or not. Arteries are always spared (unless in the lungs);
   (d) No significant population of proliferated myofibroblasts.
2) Absolute number of IgG4 positive cells over 50/high-power field (0.196 mm^2: ×40 objective, ×10 eyepiece, 20 mm field of view).
3) Percentage of IgG4+/IgG+ cells over 40% in areas with the highest density of positive cells.

Which organs can be involved in an IgG4-related sclerosing disease?

Practically any organ can be involved: Table 2 shows many of the diseases that are currently accepted as part of the IgG4-related spectrum. Skin involvement can be part of a systemic disease or appear as the only involved site.

Which cutaneous diseases are not an IgG4-related diseases despite presenting a high percentage of IgG4+ cells in the infiltrates evidenced in them?

- Cutaneous Destombes–Rosai–Dorfman disease.
- IgG4+-rich cutaneous conditions:
  → Some plasmacytosis;
  → Perforating collagenosis.

Is there a morphologic evolution in a cutaneous IgG4-related disease?

There is a spectrum of morphologic patterns, mainly represented by the pseudolymphomatous, the mixed, and the sclerosing patterns [124]. Although not totally agreed upon, there is a high suspicion that these patterns are nothing but snapshots of the evolution of the disease, which could evolve from the lymphomatous into the mixed pattern and then into the sclerotic one. This would explain why in the skin and in other sites where the disease is noted early, the pseudolymphomatous pattern is the one most commonly found.

What are the prognostic factors of an IgG4-related disease?

Some factors have been related to spontaneous remission or relapse of IgG4-related disease, especially of autoimmune pancreatitis. Factors predicting the relapse are, for instance, the presence of jaundice [147], diffuse pancreatic swelling [148, 149], duodenal papillitis [148] and presence of other organ involvement [148]. High serum IgG4 levels increase the risk of relapse, while low levels increase the possibility of spontaneous remission [150]. Adequate corticosteroid reduces the relapse rate [150].

Treatment considerations for IgG4-related diseases

Spontaneous regression without any treatment can sometimes happen [150].

The disease responds well to steroid therapy [151], although relapses can occur if the treatment is discontinued. Immunosuppressive and biologics are being introduced to manage recurrent disease. Recently, for instance, Rituximab has been successfully introduced as a therapeutic tool [152].

Cutaneous IgG4+ lymphoma?

IgG4+ lymphomas have already been described in several organs. In 2008, Cheuk W *et al.* published reports on three cases of ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis [128]. Two of the patients developed an extranodal marginal cell lymphoma, although these mucosa-associated lymphoid tissue (MALT) lymphoma cells were not derived from IgG4-producing cells. The third patient developed a follicular lymphoma.

In 2008, Sato Y *et al.* published a report on the first IgG4-producing lymphoma [129]. It was a marginal zone B-cell lymphoma with bilateral kidney masses and multiple enlarged retroperitoneal lymph nodes.

In 2009, Takahashi N *et al.* published reports on three cases of non-Hodgkin lymphoma that developed in patients with IgG4-associated systemic disease [130]. One developed a liver mass, one bilateral adrenal and liver masses with abdominal and mediastinal lymphadenopathies and the third a renal mass. The authors concluded that patients with IgG4-associated systemic disease might be at risk of developing non-Hodgkin lymphoma.

In 2010, Cheuk W *et al.* reported four cases of

idiopathic cervical IgG4-related disease [110]. Case No. 3 is especially interesting. In it, they found "several expansile foci comprising diffuse sheets of mature plasma cells mixed with small lymphocytes and occasional large lymphoid cells". "The plasma cells exhibited κ light chain restriction" and "IgG was expressed, but not IgA, IgM, or IgD". Cheuk W *et al.* even proved κ-light chain restriction in a large aggregate of plasma cells that surrounded a nerve. In conclusion, Cheuk W *et al.* interpreted such foci as extranodal marginal zone B-cell lymphoma (MZBCL) of mucosa-associated lymphoid tissue arising in the background of IgG4-related sclerosing disease [110].

Recently, Venkataraman G *et al.* published a report on a series of primary dural MZBCL, from which six showed numerous IgG4-positive plasma cells [131]. The IgG4/IgG ratio was evaluated in four cases and ranged from 69% to 104% (mean 85.25%). One of the cases showed colonized lymphoid follicles by IgG4+ plasma cells.

However, there are no publications yet on primary cutaneous IgG4+ lymphomas. It is probably just a matter of time before cases are published. Van Maldegem F *et al.* already suggested the existence of two types of primary cutaneous MZBCL. A small subgroup shows certain similarities with the non-cutaneous MZBCL, mainly expressing IgM. However, a second subgroup (the most common) shows switched Igs, mainly IgG, IgA and IgE [132]. In this series, the IgV_H-CDR3 sequence of the tumor clone was resolved in 21 cases of primary cutaneous MZBCL. Of them, 10 co-expressed IgG and IgA (14.28%) [132]. Moreover, this second subgroup has a cytokine profile more skewed toward the T-helper cell 2 (Th2) type [132]. In this context, IgG4 is a Th2-dependent isotype, and there is increasing evidence of the role of Th2 in the pathogenesis of IgG4-related disease in many organs [133, 134]. The Th2-dominant immune response is more activated in IgG4-related disease [135–138]. Furthermore, peripheral blood mononuclear cells collected from patients with IgG4-related disease produce predominantly Th2-type cytokines after T-cell stimulation [90]. In addition, Th2-dominant cytokine production has been shown in the salivary glands of patients with IgG4-related disease [135].

Role of IgG4 in the resistance to some dermatologic treatments

IgG4 has also been implicated in failures of the response to new therapeutic approaches. Infliximab (Remicade®), for instance, is a chimeric monoclonal antibody of the IgG1 class. Because of infliximab's TNF-alpha binding capacity, it has been approved for treating moderate-to-severe plaque psoriasis, as well as other inflammatory dermatoses and systemic disease involving the skin, such as severe atopic dermatitis, pityriasis rubra pilaris, pyoderma gangrenosum and cutaneous sarcoidosis [139].

Sometimes, a decrease in the therapeutic response can be related to neutralizing anti-infliximab antibodies [140]. IgG4 represents an important percentage of such antibodies, ranging from 8% to 89% in some studies on rheumatoid arthritis, for instance [140].

IgG4 vasculitis

Vasculitis (mainly lymphoplasmacytic aortitis) is a common manifestation of IgG4-related sclerosing syndrome [141]. In addition, cases of IgG4-related lymphocytic vasculitis have been described involving the lung [105, 142] and the heart [143].

Regarding skin, an exclusively cutaneous IgG4-related vasculitis has not yet been described, but skin can be affected in several vasculitic conditions related to IgG4. Such is the case of Wegener granulomatosis: in this disease, cutaneous inflammatory infiltrates that are plasma-cell rich can be found; in addition, anti-neutrophil cytoplasm antibodies (ANCA) to proteinase 3 (PR3) are predominantly of the IgG4 subclass [144].

Conclusions and future perspectives

IgG4 is clearly responsible for several diseases, many of which belong to the field of dermatology (Table 1). One of the most intriguing ones is the IgG4-related sclerosing disease in which the exact role played by IgG4 is not yet totally understood. It is not clear if IgG4 is involved in the pathogenesis of the disease or if it is a mere epiphenomenon. This will have to be clarified in the near future.

As briefly mentioned in Table 3, an IgG4-related sclerosing disease usually responds to steroid therapy, although relapses can occur if the treatment is discontinued. However, some recent studies suggest a potential therapeutic role for Rituximab, which probably acts by depleting the pool of B-lymphocytes that replenish the IgG4-secreting plasma cells (since the latter have a short life) [145].

IgG4+ cells usually account for approximately 5% of all IgG+ cells and they can therefore be found in a significant amount in many conditions with numerous plasma cells (most of which express IgG). Therefore, the criteria for diagnosing IgG4-related sclerosing disease should be precise (Table 3). Also, a cutaneous IgG4-related sclerosing disease has been diagnosed many times in the past as "pseudolymphoma." The dermatopathologist should suspect entities in those "pseudolymphomas" such as inflammatory fibrosclerosing lesions or inflammatory pseudotumors, with an abundance of plasma cells or showing significant sclerosis and no significant population of myofibroblasts, especially if there are accompanying mass lesions in sites commonly involved by IgG4-related sclerosing disease (such as pancreas, salivary gland, or orbit). In such cases, a search for appropriate criteria seems reasonable. IgG4 expression by plasma cells can be evaluated immunohistochemically. The antibodies are commercially available [146] and they perform very well in formalin-fixed, paraffin-embedded tissue [122].

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Received: January 15th, 2012 *Accepted: April 22nd, 2012*