IgG4-Related Skin Disease Successfully Treated by Thalidomide

A Report of 2 Cases With Emphasis on Pathological Aspects

Saskia Ingen-Housz-Oro, MD; Nicolas Ortonne, MD; Muriel Elhai, MD; Yannick Allanore, MD, PhD; Pierre Aucouturier, PhD; Olivier Chosidow, MD, PhD

Importance: In IgG4-related disease (IgG4-RD), skin involvement is rare and associated especially with systemic disease. We report 2 cases of isolated skin IgG4-RD successfully treated with thalidomide and investigated their phenotypic characteristics.

Observations: Two men had cephalic nodules. Skin biopsies revealed dense lymphocytic infiltrates with numerous plasma cells and fibrosis. IgG4-RD was confirmed by very high IgG4+ to IgG+ plasma cells ratios of 76% (patient 1) and 100% (patient 2). The serum IgG4 level was normal. There was no other organ involvement. Thalidomide therapy was introduced. After 6 months, lesions were in remission. Patient 1 required long-term, low-dose thalidomide, whereas patient 2 stopped treatment and showed no relapse. Immunostaining revealed numerous FoxP3+ cells in the interfollicular areas, which decreased with treatment in patient 2, and numerous follicular helper T lymphocytes (TFH) within the follicular germinal centers. There were numerous mast cells; some stained for interleukin (IL)-6, and expression of phospho-Smad2/3 was demonstrated.

Conclusions and Relevance: IgG4-RD may be skin limited. Cutaneous infiltrates comprise numerous FoxP3+ cells that may interact with mast cells to produce IL-6 and stimulate fibrosis synthesis via the transforming growth factor β/phospho-Smad2/3 pathway. The role of TFH cells remains to be studied. IgG4-RD should be added to the causes of cutaneous pseudolymphomas. Thalidomide could be considered as a therapeutic option in IgG4-RD.


IgG4-RELATED DISEASE (IgG4-RD), previously known as IgG4-related autoimmune disease, IgG4-associated multifocal systemic fibrosis, and IgG4-related sclerosing disease, is a rare systemic condition occurring in middle-aged adults and was first described in 2001 (first descriptions of IgG4-associated autoimmune pancreatitis) and 2003 (multiorgan involvement). It frequently presents as chronic pancreatitis associated with broad miscellaneous tumoral or nontumoral involvement of organs such as exocrine glands, orbit, kidney, retroperitoneum, aorta, liver, lungs, and lymph nodes. Single-organ localization has been reported, especially “autoimmune pancreatitis,” but with recent updated nomenclature, infiltration into the ocular adnexa and many other organs is also described. Elevated serum IgG4 level (>135 mg/dL) (to convert to grams per liter, multiply by 0.01) is the main biological feature. Histologically, IgG4-RD is characterized by 3 main features that may be variously associated: lymphoplasmacytic infiltrates, storiform fibrosis, and typically obliterator phlebitis. Plasma cells are numerous and polytypic with a high proportion of plasma cells positive for anti-IgG4 antibodies (IgG4+ to IgG+ plasma cell ratio, >40%), and >10 IgG4-positive plasma cells per high-power field). Corticosteroids are usually quickly effective and remain the drug of choice. Immunosuppressant agents (azathioprine and rituximab) have also been successful in cases of corticosteroid dependence or adverse effects.

Skin involvement is uncommon, although cephalic nodules with a clinical and histological aspect of cutaneous pseudolymphoma were found to be associated with systemic IgG4-RD. Recently, 2 more isolated cutaneous cases with noncephalic have been described, and the relationship between IgG4-RD and Rosai-Dorfman disease and angiolymphoid hyperplasia with eosinophilia is discussed. Herein, we describe 2 patients with skin-isolated IgG4-RD. Both patients received thalidomide, which resolved the le...
sessions. We investigated the immunological profile of the skin infiltrates in this cutaneous self-limited IgG4-RD and discuss the mechanism of action of thalidomide as possible treatment.

REPORT OF CASES

PATIENTS

Patient 1

A 36-year-old man was referred for 2 nodular lesions of the scalp that had appeared 4 years before. Findings from the first biopsy suggested chronic cutaneous lupus. However, treatment with hydroxychloroquine was ineffective, and the patient was lost to follow-up. He returned for consultation because of progressive enlargement of lesions, especially the frontal lesion. Skin examination revealed 2 nodular lesions, 2 to 5 cm, in the left frontal and vertex areas (Figure 1A). There were no other significant lesions or lymphadenopathy. The patient’s condition was in general normal; he had no fever or weight loss. Blood cell counts included the following: 6700 leukocytes/µL, 3600 neutrophils/µL, and 2300 lymphocytes/µL (to convert to 10³/µL, multiply by 0.001). The hemoglobin level was within the normal range (15.6 g/dL), as was platelet count (237 × 10³/µL). Renal function, liver transaminase and lactate dehydrogenase levels were normal; plasma electrophoresis did not reveal monoclonal gammopathy or polyclonal hyperglobulinemia.

Patient 2

A 45-year-old man presented a left frontal nodular lesion that had appeared 1 year before. Clinical examination revealed a 2.5-cm nodular lesion (Figure 1B) with no other dermatological lesions or lymphadenopathy. The patient’s condition was in general normal; he had no fever or weight loss. Blood cell counts included the following: 6600 leukocytes/µL, 3800 neutrophils/µL, and 2100 lymphocytes/µL. Hemoglobin level was within the normal range (15.5 g/dL), as was platelet count (296 × 10³/µL). Renal function, liver transaminase and lactate dehydrogenase levels were normal; plasma electrophoresis did not reveal monoclonal gammopathy or polyclonal hyperglobulinemia.

HISTOLOGICAL ASPECT

Both cases showed similar histological features: dense lymphocytic infiltrates occupying the whole dermis, extending into the hypodermis, with no atypical cells, no lichenoid changes, no eosinophils, and numerous reactive follicles containing germinal centers. Lymphocytic infiltrates were surrounded by areas of fibrosis, constantly showing a patterned arrangement with onion bulblike structures around vessels and storiform architecture (Figure 2). Using anti-CD138 antibody, we identified numerous plasma cells, mostly at the periphery of the follicles, without formation of plasma cell granuloma (Figure 3A). Plasma cells exhibited a polytypic expression of κ and λ light chains, with a κ to λ ratio of 1.6 (first patient) and 0.9 (second patient). Occlusive thrombophlebitis was never observed. Anti-CD20 antibody showed that most lymphocytes were B cells (Figure 3B). The CD4 to CD8 ratios were 3 in patient 1 and 5 in patient 2. Analyses of IgH and TCR-γ rearrangements by the standard protocol after DNA extraction from a fresh skin biopsy specimen revealed polyclonal aspects in both cases.

IMAGING

Thoracic, abdominal, and pelvic computed tomographic scanning did not reveal any lymph node, pancreatic, biliary, aortic, retroperitoneal, or renal abnor-
mality. Oculomotricity and visual acuity were normal; there was no eyelid swelling.

**TREATMENT**

Patients first received superpotent topical corticosteroids (ie, clobetasol propionate) for a few weeks, without efficacy. Because of clinical and histological similarities with cutaneous pseudolymphoma, the normal findings from all standard biological and radiological investigations, and the reported efficacy of thalidomide for cutaneous pseudolymphomas,15,16 both patients received thalidomide, 50 mg/d, for 1 month, and then 100 mg/d for 5 months. With thalidomide, both patients improved within a few weeks, with marked reduction of both cutaneous infiltration and erythema (Figure 4), with no adverse effects. After 6 months of treatment, thalidomide therapy was stopped. Patient 1 experienced a rapid relapse of disease, which led to a successful retreatment with thalidomide, 50 mg/d. After a follow-up of 21 months, the patient remained in complete remission with this dosage and experienced relapses whenever thalidomide dose was decreased to 50 mg every other day. In contrast, patient 2 did not experience any disease relapse, with a follow-up of 15 months.

In both cases, a follow-up biopsy, performed on residual lesions at 5 months to investigate the histological aspect and to confirm the nonmalignancy, revealed the same features as before treatment.

Because of the histological aspect of IgG4-RD, we decided to perform further investigations to confirm the diagnosis, investigate the immunological pattern of the cutaneous infiltrate, and follow its evolution with thalidomide therapy.

**CONFIRMATION AND INVESTIGATION OF IgG4-RD**

Skin biopsy specimens were formalin fixed and paraffin embedded by standard procedures; 3-μm-thick deparaffinized sections underwent hematoxylin-eosin staining and immunohistochemical analysis. The diagnosis of IgG4-RD was assessed by morphologic, immunohistochemical, and molecular parameters. We investigated the expression of human herpesvirus 8 (HHV-8) latency nuclear antigen (dilution 1:50 [A. Menarini Diagnostics]) and IgG4 (binding site; dilution 1:200). We evaluated the proportion of IgG4+ plasma cells by direct counting of plasma cells stained with anti-CD138 (dilution 1:100 [Dako]), antitotal IgG (dilution 1:5000 [ICN Biomedicals]), and anti-IgG4 monoclonal antibodies on 10 consecutive high-power fields. The staining procedure involved the Bond-Max device (Bond; Leica Microsystems).

![Figure 2](https://example.com/image2)

**Figure 2.** Histological aspects for both cases. Dense lymphocytic infiltrates in the dermis with many lymphoid follicles associated with fibrosis and numerous normal vessels (hematoxylin-eosin, original magnification ×50 [A] and ×200 [B]).

![Figure 3](https://example.com/image3)

**Figure 3.** Immunophenotypic studies. Representative sections from the pretreatment lesion biopsy of case 1. A, CD138 staining showing the plasma cells, mainly located in the vicinity of the lymphoid follicles (original magnification ×100). B, CD20 immunostaining showing that half of the infiltrate in this example correspond to B cells and highlighting the follicular architecture throughout the dermis and the hypodermis (original magnification ×50). C, Immunostaining for IgG4 highlights numerous IgG4+ plasma cells in the interfollicular area, but also in germinal centers (original magnification ×100). D, Immunostaining for Fox-P3 highlights numerous regulatory T cells with nuclear expression of FoxP3, representing 20% of the lymphocytic infiltrates in the present case (original magnification ×200). E, PD-1 staining showing numerous follicular helper T cells within the germinal centers of the follicles (original magnification ×100). F, ICOS (inducible T-cell costimulator) expression is broader than PD-1 (programmed death-1), highlighting numerous follicular helper T cells in the germinal centers, but also positive lymphocytes in the interfollicular areas (original magnification ×100). G, Immunostaining for CD117/c-Kit: numerous mast cells within the lymphocytic infiltrates (original magnification ×200). H, Immunostaining for interleukin 6: a proportion of mast cells, recognized morphologically by large granular, round, or spindle cytoplasm, show cytoplasmic expression of interleukin 6 (original magnification ×200).
tems and A. Menarini Diagnostics) with peroxidase and diaminobenzidine after antigen retrieval by heat with appropriate buffer. In both cases, HHV-8 staining was negative, ruling out multicentric Castleman disease.

In pretreated lesion biopsy specimens from patients 1 and 2, we observed that 40% of all plasma cells were IgG4⁺, with very high IgG4⁺ to IgG⁺ plasma cells ratios of 76% and 100%, respectively, sitting mostly in interfollicular areas but also sometimes within the germinal centers (Figure 3C). After 5 months of thalidomide therapy, the proportion of IgG4⁺ plasma cells decreased to 15% for patient 1 but remained high (56%) for patient 2, whereas IgG4⁺ to IgG⁺ plasma cells ratios remained similar as before treatment (100% in both patients).

All IgG subclasses, including IgG4, were investigated in the blood before treatment and showed normal ranges (patient 1: IgG4=0.26 mg/mL; patient 2: IgG4=0.4 mg/mL).

**IMMUNOCHEMICAL ANALYSIS**

To investigate the immunological profile of cutaneous infiltrates, immunostaining analyses were performed before treatment and after 5 months of thalidomide therapy.

Regulatory T cells were labeled with anti-FoxP3 antibody; mast cells and inflammation with c-Kit and anti–IL-6 antibodies, respectively; and activation of the transforming growth factor β (TGF-β) pathway with antiphosphorylated-Smad2/3 (antiphospho-Smad2/3) antibody. Smad3 is a fibroblastic intracellular protein involved in the TGF-β pathway and fibrotic diseases.17,18

Immunostaining for FoxP3 (clone 236/AE7, 1 hour, dilution 1:50 [Abcam]) involved a horseradish peroxidase–conjugated biotin/avidin system (Vectastain ABC–AP kit from Vector) after antigen retrieval by heat, and that for IL-6 (overnight, dilution 1:100 [Abcam]) involved rabbit antimouse immunoglobulins (Dako) as secondary antibodies. C-Kit (clone A4502, dilution 1:900 [Dako]), ICOS (inducible T-cell costimulator, dilution 1:200 [Euromedex]), and PD-1 (programmed death-1, dilution 1:100 [Abcam]) immunostaining involved the Bond-Max device.

The proportion of FoxP3⁺ and follicular helper T lymphocytes (TFH, defined by a PD-1⁺ and ICOS⁺ phenotype) was evaluated semiquantitatively (0%-10%, 10%-25%, 25%-50%, or >50%), and the density of dermal mast cells within infiltrates was evaluated quantitatively by direct counting of c-Kit–stained cells by microscopy in 10 consecutive high-power fields.

The expression of phospho-Smad2/3 was assessed in paraffin-embedded biopsy sections. After deparaffinization, antigen retrieval with Tris-EDTA-Tween and blocking with 10% horse serum, skin sections were incubated with polyclonal goat antihuman phospho-Smad2/3 (dilution 1:50 [Santa Cruz Biotechnology]) overnight at 4°C, then polyclonal donkey antigoat antibodies labeled with fluorescent dye Alexa Fluor 594 (Invitrogen) as secondary antibodies. Cell nuclei were stained with 4',6-diamidino-2-phenylindole (DAPI) (dilution 1:5000 [Sigma Aldrich]). Images were captured at 100-fold magnification.

Results of immunostaining (type and localization of positive cells, number or percentage of positive cells) for both patients are summarized in Table 1. Numerous regulatory T cells (FoxP3), TFH (PD-1 and ICOS) and mast cells (c-Kit) were identified within the infiltrates. The proportion of FoxP3⁺ regulatory T cells was the same before and after treatment. A nonquantified proportion of mast cells, but not lymphocytes, were IL-6⁺ and numerous fibroblasts showed phospho-Smad2/3 staining (Figure 3D-H and Figure 5).

**COMMENT**

In our 2 cases with cephalic nodules, several diagnoses could have been hypothesized: low-grade cutaneous B-cell lymphoma, pseudolymphoma, lupus tumidus, or
Kimura disease. The dense IgG4+ plasma cell infiltration, the absence of atypical and/or monotypic B-cell lymphocytes and clonal Ig rearrangement, and the polytypic light chain expression were arguments against a low-grade cutaneous lymphoma. In addition, the dense fibrosis seen in our cases is unusual in both cutaneous B-cell lymphomas and reactive lymphocytic hyperplasia. Thus, the diagnosis of skin-limited IgG4-RD was supported by cephalic nodules, as previously reported in IgG4-RD, suggesting histological data, normal general examination, and normal serum IgG4 level, contrasting with a high proportion of IgG4+ plasma cells in the lesions. In our cases, the proportion of IgG4+ plasma cells was very high (76% and 100%), in accordance with the definition of IgG4-RD. Consequently, these cases were considered a single-organ presentation of IgG4-RD, as previously described in the pancreas, in many other organs, and, recently, in the skin. However, IgG4+ plasma cells infiltration is not absolutely specific of IgG4-RD and may be found in other chronic inflammatory diseases.

In single-organ IgG4-RD, the IgG4 level may be elevated or within normal limits. If elevated serum IgG4 level is not an absolute criterion for IgG4-RD but seems more of a marker of systemic disease. In the Comprehensive diagnostic criteria for IgG4-RD, IgG4-RD may be considered without taking into account the serum level of IgG4 (Table 2).

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We found no obliterator phlebitis in our 2 cases, nor was phlebitis found in the previously published cutaneous cases. Obliterator phlebitis is not anymore a criterion for IgG4-RD in the recent comprehensive diagnostic criteria.

Treatment of systemic IgG4-RD is based on systemic corticosteroids and immunosuppressant agents (azathioprine and rituximab) in refractory or corticosteroid-dependent cases, but tumoral presentations may also be surgically treated. In our cases, surgery was not our first therapeutic choice because of the size and location of the nodules. Thalidomide was reported as effective for benign cutaneous lymphoid hyperplasia. Furthermore, it could be a good choice because of the fibrosis. Indeed, the anti-inflammatory and antifibrotic properties of thalidomide have been suggested. In both of our cases, thalidomide was effective, with quick deinfiltration of lesions (within <2 months). However, patient 1 needed long-term, low-dose (50 mg/d) therapy, without possibility of discontinuation.

The pathophysiologic features of IgG4-RD remain unknown. IgG4 may be a marker of the disease without being pathogenic. T-cell lymphocytes of the infiltrate comprise 20%-30% of germinal center cells. Infiltration of lesions (within <2 months). However, patient 1 needed long-term, low-dose (50 mg/d) therapy, without possibility of discontinuation.

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Table 1. Features and Comprehensive Diagnostic Criteria for IgG4-Related Disease

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2 lymphocytes, producing cytokines such as IL-4 and IL-10.14,23 The role of TFH, involved in B-cell compartment differentiation and immunoglobulin class switch, remains unclear but is supported by the presence of numerous follicles with germinal centers containing numerous TFFH, which we observed in our cases with ICOS and PD-1 stainings. In contrast, interfollicular PD-1–ICOS+ cells remain of uncertain origin.

Interestingly, we also found numerous mast cells. Of note, mast cell involvement in IgG4-RD has not been investigated. A proportion of the mast cells were shown to produce the proinflammatory cytokine IL-6. Because of the presence of both regulatory T cells and a high number of mast cells in our cases, we believe that these cells may interact in vivo and participate in the fibrosis, a usual feature of IgG4-RD. This hypothesis is supported by FoxP3+ regulatory T cells being able to stimuli IL-6 messenger RNA and protein expression in mast cells via TGF-β in response to various innate or adaptive stimuli, but involvement of the TGF-β/Smad pathway remains to be confirmed.20 Whether FoxP3+ cells in IgG4-RD could trigger both the fibrosis via the TGF-β/Smad pathway and a possible proinflammatory loop via activation of mast cells and secretion of IL-6 needs confirmation. Our 2 cases highlight the broad spectrum of IgG4-RD and show that skin should be added to the list of potential isolated involvements in the disease. Histological analysis with a complementary set of markers, especially IgG4+, remains essential for diagnosis. In addition, our data identify some pathways that could be critical for this uncommon condition and that may be targets. Finally, we suggest the effectiveness of thalidomide in the disease, which needs further evaluation in cutaneous IgG4-RD.

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Correspondence: Saskia Ingen-Housz-Oro, MD, Department of Dermatology, Henri Mondor Hospital, 51 avenue du Maréchal de Lattre de Tassigny, 94000 Créteil, France (saskia.oro@hmn.aphp.fr).

Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ingen-Housz-Oro and Ortonne contributed equally to the study. Study concept and design: Ingen-Housz-Oro, Ortonne, and Chosidow. Acquisition of data: Ingen-Housz-Oro, Ortonne, Elhai, Allanore, and Aucouturier. Analysis and interpretation of data: All authors. Drafting of the manuscript: Ingen-Housz-Oro, Ortonne, and Elhai. Critical revision of the manuscript for important intellectual content: Ingen-Housz-Oro, Ortonne, Allanore, Aucouturier, and Chosidow. Administrative, technical, and material support: Ortonne. Study supervision: Ortonne, Allanore, and Chosidow.

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REFERENCES