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Isolated Skin Involvement as Manifestation of Immunoglobulin G4-related Disease (IgG4-RD) Relapse

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors were involved in the diagnosis and treatment of the patient. Author SB had primary responsibility for drafting this manuscript. Author IM was actively involved in the evaluation of the findings and has revised this article. Both authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Immunoglobulin G4-related disease (IgG4-RD) is a very rare and little known sclerosing inflammatory disease of recent individualization.
Cutaneous manifestations during IgG4-RD are very rare. They are described as "infrequent" and "uncommon" by the majority of authors, and are often reported as sporadic clinical cases.
We report the original observation of isolated and polymorphic skin involvement of the head and neck as manifestation of IgG4-related disease relapse in 68-year-old man.
Our observation is distinguished by the polymorphism of skin lesions, the isolated nature of skin involvement (without associated involvement of other organs), and the association of lesions with different ethiopathogenic mechanisms.

Keywords: Immunoglobulin G4-related disease; IgG4-related disease; skin; relapse; immunoglobulin G4.

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1. INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a very rare and little known sclerosing inflammatory disease of recent individualization [1-3]. Indeed, its first description is attributed to Hamano H et al, who in 2003 noted the association of high levels of serum Immunoglobulin G4 (IgG4) with Lympho-plasmacytic sclerosing pancreatitis/ autoimmune pancreatitis [2].

The name IgG4-RD was subsequently proposed by Kamisawa T et al, to define the new clinicopathological entity associating: multiple organs fibroinflammatory sclerosis, tissue infiltration of IgG4 + plasma cells, and high levels of circulating IgG4 [4].

Recently, in 2011, Umehara clinical, laboratory, and histologic criteria were proposed to facilitate and harmonize the diagnosis of this disease [3]. These criteria include: Diffuse or localized swelling or masses in single or multiple organs, elevated serum IgG4 concentration (≥135 mg/dL), and histopathological examination showing marked lymphocyte and plasma cell infiltration, fibrosis, and infiltration of IgG4 + plasma cells (ratio of IgG4+ to IgG+ cells greater than 40% and greater than 10 IgG4+ plasma cells/high-power field). Definite cases of IgG4-RD must meet all 3 criteria [3].

The exact prevalence of this disease remains very difficult to estimate because of its extreme rarity; a Japanese epidemiological study suggested a prevalence of 0.28-1.08/100,000H [5].

Cutaneous manifestations during IgG4-RD are very rare [6-8]. They are described as “infrequent” and “uncommon” by the majority of authors [9,10], and are often reported as sporadic clinical cases [7,11-14].

We report the original observation of isolated and polymorphic skin involvement as manifestation of IgG4-related disease relapse in 68-year-old man, highlighting the importance of the dermatological examination in any patient followed for this disease.

2. CASE REPORT

68-year-old Tunisian man, with known IgG4-RD diagnosed for four years, was explored for cutaneous lesions of the head and neck evolving for two weeks and not improved by symptomatic treatment.

Initial diagnosis of IgG4-RD was made in front of localized retroperitoneal fibrosis, mesenteric panniculitis, fibrous thyroiditis, serum IgG4 concentration at 255 mg/dL, and histopathological examination of retroperitoneal fibrous biopsy showing compatible lesions: marked IgG4+ plasma cell infiltration, storiform fibrosis, and obliterative venulitis. He was treated with systemic steroid for two years with favorable outcome.

Three months after the patient inadvertently stopped his treatment; the skin lesions began to appear on the scalp and the neck, with annoying pruritus, and did not improve with symptomatic treatments.

The somatic examination showed multiple diffuse erythematous and infiltrated plaques on the scalp (Fig. 1) associated with some crusty lesions (Fig. 2), purplish nodular lesions on the nape of the neck (Fig. 3), and bilateral retroauricular ulcerative psoriasiform lesions (Fig. 4). The rest of the somatic examination was without abnormalities, in particular there were no visceromegalies, palpable masses, or peripheral lymphadenopathy.

Biology showed stigma of chronic inflammation with erythrocyte sedimentation rate at 88 mmH1, C-reactive protein at 10 mg/l, polyclonal hypergammaglobulinemia at 22 g/l, and normochrome normocytic anemia at 10.5g/dl.

The other basic laboratory tests were within normal limits: Leukocytes, neutrophils, lymphocytes, platelets, blood glucose, transaminases, creatinine, calcemia, serum ionogram, muscle enzymes, lipid parameters, and thyroid hormones.

The abdominopelvic ultrasound and thoracoabdominopelvian computed tomography were without significant abnormalities.

Anatomopathological examination of a biopsy of a nodular lesion of the nape confirmed the infiltration by IgG4+ plasma cells without signs of malignancy or granulomatosis.

The immunological assessment revealed high level of serum IgG4 at 185 mg/dL, negative anti-nuclear, anti-double-stranded DNA, and anti-thyroid antibodies.

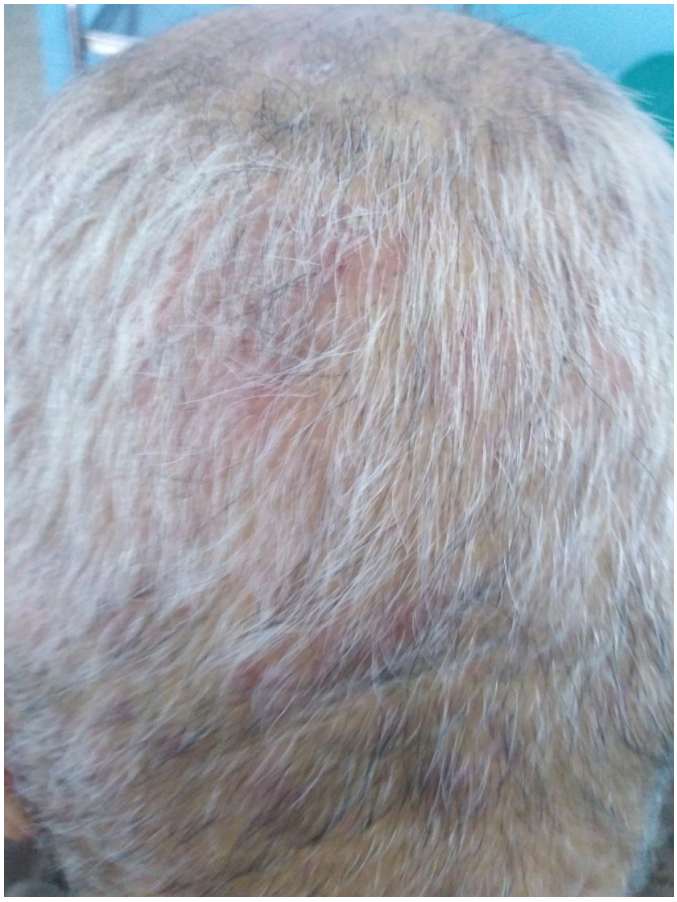

Fig. 1. Multiple erythematous scalp plaques

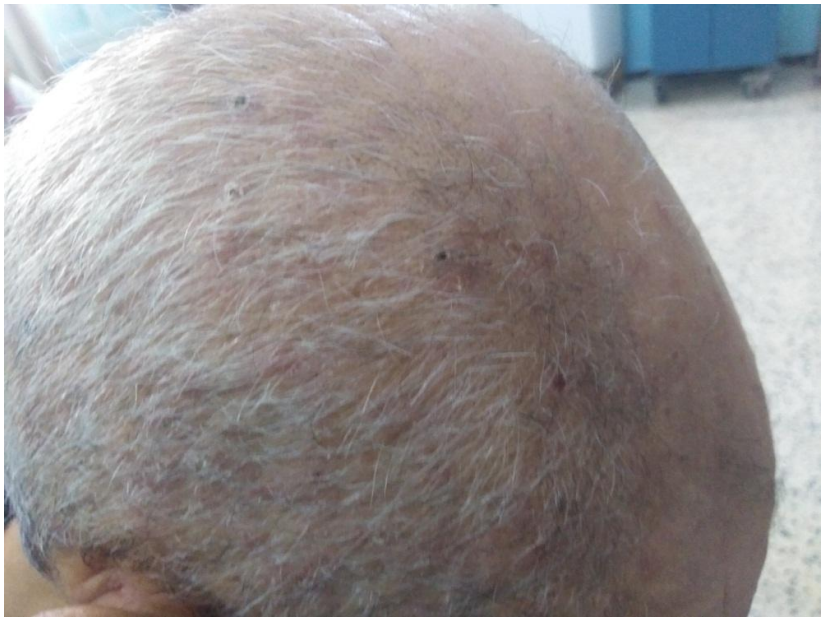

Fig. 2. Multiple nodular and crusted lesions of the scalp

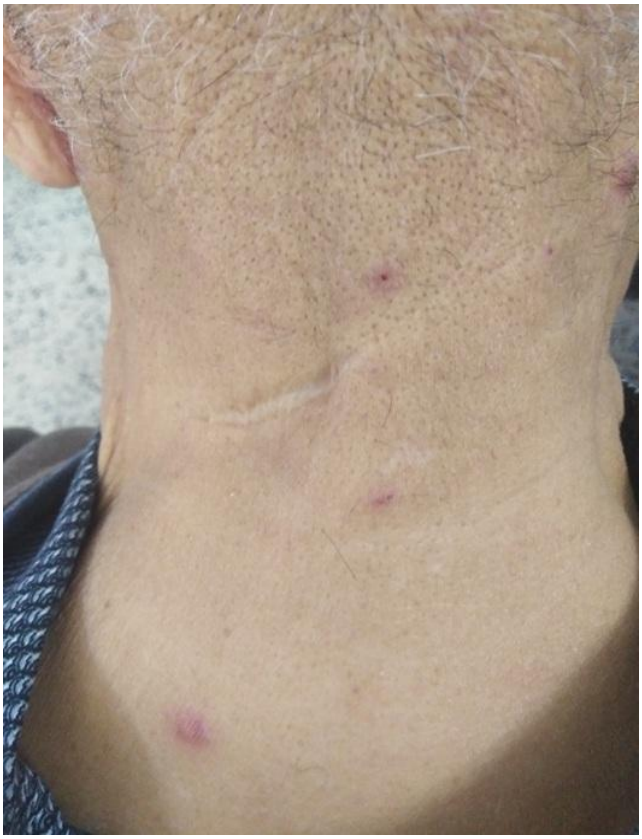

Fig. 3. Multiple nodular lesions of the neck

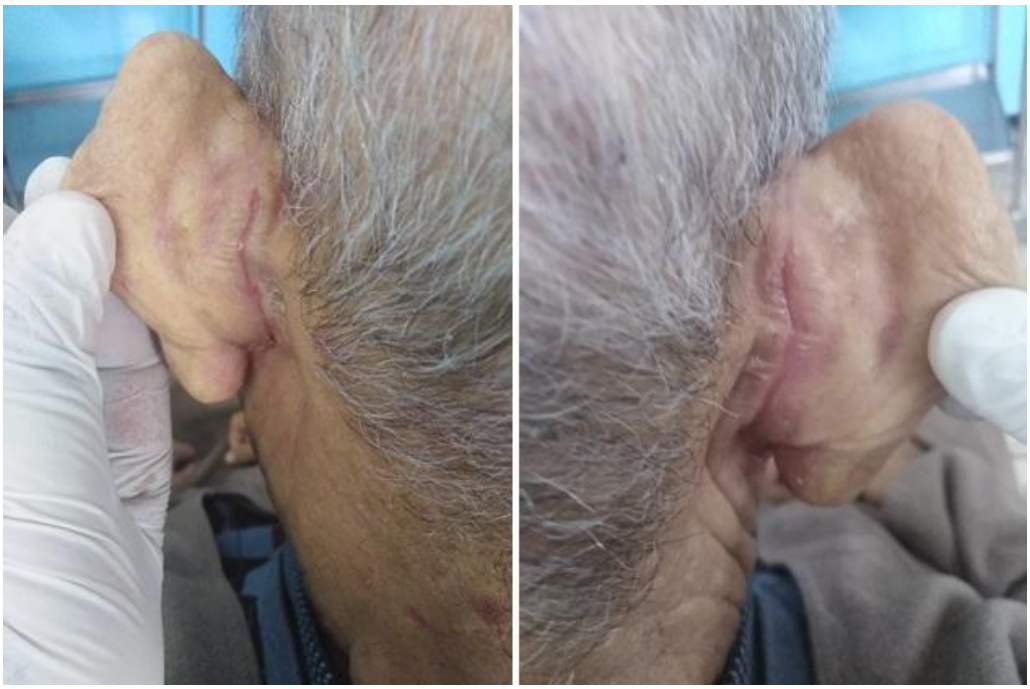

Fig. 4. Bilateral retroauricular psoriasiform lesions

Investigations for other specific visceral infiltration of IgG4-RD were negative. Thus, the diagnosis of a relapse of IgG4-RD with isolated cutaneous presentation was retained.

The patient was treated with systemic glucocorticoids at the dose of 1mg/kg/day for four weeks followed by progressive decrease with favorable evolution: rapid disappearance of pruritus and skin lesions, and normalization of biological parameters of inflammation. No recurrence has been noted for two years.

3. DISCUSSION

The cutaneous manifestations of IgG4-RD are of recent recognition; they therefore remain underdiagnosed and poorly defined [6-8]. Their frequency varies from 4.2 to 6.2% depending on the series and the ethnic groups [10,15]; the majority of observations are reported as sporadic clinical cases [7,11-14], and the last systematic literature review of 2019 identified only 52 cases of cutaneous involvement during IgG4-RD [6].

Exceptionally skin involvement may be the first manifestation revealing the disease [16,17]. Similarly, it may be the only clinical presentation of the disease (skin limited IgG4-RD) [18].

The cutaneous manifestations of IgG4-RD are very polymorphic and sometimes very difficult to diagnose. The recent work of Tokura Y et al, categorized seven subtypes of skin lesions associated to IgG4-RD: Cutaneous plasmacytosis, pseudolymphoma and angiolymphoid hyperplasia with eosinophilia, Mikulicz disease, psoriasis-like eruption, unspecified maculopapular or erythematous eruptions, hypergammaglobulinaemic purpura and urticarial vasculitis, and ischaemic digit [8].

The exact etiopathogenesis of these manifestations is not yet fully understood [6,8]. It appears to be multifactorial, involving, in addition to direct infiltration of the skin by the IgG4+ plasma cells characteristic of the disease, local inflammation mediated by the IgG4, and immune dysfunction [8,19,20]. According to Tokura's classification, the first three subtypes are induced by direct infiltration of the skin by IgG4+ plasma cells, while the other types are caused by inflammatory and immunological mechanisms [8].

The head and neck localizations are the most frequent and the most characteristic of the disease [7,11,21].

The prognosis for these skin disorders is usually favorable [11]. They respond quickly to systemic corticosteroid therapy [6,7,11]. In rare cases of corticosteroid resistance, thalidomide [18], azathioprine [6], and anti-CD20 antibodies (particularly rituximab) [22] may be successfully used.

4. CONCLUSION

Skin manifestations during IgG4-RD are rare, little known, and still largely underdiagnosed. They represent a real diagnostic challenge, particularly in cases where the cutaneous presentation remains isolated or initiates the disease. A better knowledge of these manifestations is necessary for health professionals to allow rapid diagnosis and appropriate management of the disease. Our observation is distinguished by the polymorphism of skin lesions, the isolated nature of skin involvement (without associated involvement of other organs), and the association of lesions with different ethiopathogenic mechanisms.

Likewise, dermatological examination is recommended in any patient previously diagnosed with IgG4-RD in front of any sign of relapse.

CONSENT

Oral and written Informed consent was obtained from the patient.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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