Portuguese Journal of Dermatology and Venereology

Permanyer

Check for updates

Port J Dermatol and Venereol.

CASE REPORT

Cutaneous IgG4-related disease treated with dupilumab

Doença cutânea relacionada com IgG4 tratada com dupilumab

Mafalda Pestana[1,2], Alexandre João[1,2], Susana Palma-Carlos[2,3], Paula Leiria-Pinto[2,3], and Ana L. João[1,2]*

[1]Department of Dermatology and Venereology, Unidade de Saúde Local de São José; [2]Centro Clínico Académico de Lisboa; [3]Department of Immunoallergology, Unidade de Saúde Local de São José. Lisbon, Portugal

Abstract

We present a 59-year-old male with a prolonged history of severe, treatment-resistant pruritic dermatosis and associated systemic symptoms, including fatigue and diarrhea. Dermatologic examination revealed widespread erythematous-brownish papules and nodules, prompting a skin biopsy that showed dense infiltration by immunoglobulin G4 (IgG4)-positive plasma cells, leading to a diagnosis of IgG4-related disease (IgG4-RD). The patient was treated with dupilumab, resulting in complete skin lesion resolution and significant improvement in quality of life. IgG4-RD, a rare inflammatory disease with potential multiorgan involvement, frequently challenges diagnosis due to diverse clinical presentations. This case highlights dupilumab effectiveness as a novel therapy for IgG4-RD with cutaneous involvement, offering a promising alternative for patients who do not respond well to corticosteroids.

Keywords: Immunoglobulin G4-related disease. Cutaneous. Dupilumab.

Resumo

Reportamos o caso de um homem de 59 anos, com dermatose intensamente pruriginosa desde há 7 anos, refratária à terapêutica, e associada a sintomatologia sistémica como astenia e diarreia. Ao exame objetivo dermatológico, o doente apresentava pápulo-nódulos eritemato-acastanhados disseminados, o que motivou a realização de biópsia cutânea cujo exame histopatológico revelou infiltrado rico em plasmócitos IgG4-positivo. Admitido o diagnóstico de doença relacionada com IgG4 (DR-IgG4), o doente iniciou tratamento com dupilumab, com consequente resolução da dermatose e melhoria franca da sua qualidade de vida. A DR-IgG4, uma patologia inflamatória rara com potencial envolvimento multiorgânico, representa frequentemente um desafio diagnóstico pela sua hetereogeneidade clínica. Este caso clínico enaltece a eficácia do dupilumab na DR-IgG4 com envolvimento cutâneo, surgindo como uma alternativa terapêutica promissora na doença não respondedora a corticoterapia.

Palavras-chave: Doença relacionada com IgG4-related. Cutânea. Dupilumab.

Correspondence:
Mafalda Pestana
E-mail: mafaldambp@gmail.com

Received: 30-10-2024
Accepted: 23-01-2025
DOI: 10.24875/PJDV.24000087

Available online: 27-03-2025
Port J Dermatol and Venereol. 2025;83(2):124-128
www.portuguesejournalofdermatology.com

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a rare systemic inflammatory condition characterized by tissue infiltration by IgG4-expressing plasma cells and progressive fibrosis, firstly identified in the 21st century. It occurs more frequently in middle-aged to elderly males and can synchronous or metachronously involve multiple organs[1,2]. Although the pathophysiology of IgG4-RD is not fully uncovered, studies suggest a predominance of the T helper (Th) type 2 immune response, with interleukin (IL)-4 playing a central role in the production of IgG4[3]. The disease clinical heterogeneity makes its diagnosis frequently challeging, with dermatologic manifestations appearing in a minority of cases[1]. Systemic corticosteroids are the first-line treatment; however, refractoriness and relapse on discontinuation are common[4,5]. Herein, we report a case illustrating the efficacy of dupilumab, a monoclonal antibody blocking IL-4 and IL-13 receptors, in treating cutaneous IgG4-RD, underscoring its potential role for patients who are resistant to corticosteroids.

Case report

A 59-year-old man was referred to our dermatology department due to a disseminated and extremely pruritic dermatosis with 7 years of evolution. In addition, he referred asthenia and frequent episodes of diarrhea. Fecal occult blood test was negative and thoracic, abdominal and pelvic computed tomoghrapy (CT) showed pulmonary emphysema, nodular thyroid, and prostatic calcifications. Systemic steroids provided relief, but the disease quickly relapsed on its tapering. Patient medical history was remarkable for allergic rhinitis, uncontrolled non-insulin dependent diabetes mellitus, dyslipidemia, and an episode of unilateral proptosis and diplopia 4 years before. At that time, as radiological examination demonstrated thickening of the left extraocular muscles, a diagnosis of inflammatory myositis was assumed, and the patient was treated with oral corticosteroids, resulting in clinical and imaging regression.

Dermatological examination showed a symmetric and extensive eruption affecting the face, trunk, buttocks, and upper and lower limbs, characterized by erythematous-brownish papules and papulonodules, some with crusts, amidst with excoriations and hyper- and hypopigmented macules and patches (Fig. 1). Bilateral mobile and painless cervical lymphadenopathies were palpable. Cutaneous lesions caused a debilitating pruritus (itch numeric rating scale 8/10) that markedly interfered with patient's quality of life (dermatology life quality index [DLQI] 11). The diagnoses of eczema and nodular prurigo were considered, and a skin biopsy was performed, revealing a dense perivascular and perifollicular lymphoplasmacytic infiltrate, rich in IgG4-positive cells (IgG4+/IgG+ > 40%) and eosinophils (Fig. 2). Laboratory tests showed IgG4 levels of 1570 mg/dL and immunoglobulin E (IgE) of 4563 KUI/L. The diagnosis of IgG4-RD was hence evoked, and complementary study revealed overlapping findings on body CT and colloid goiter on thyroid aspiration cytology. Treatment with dupilumab (300 mg sc every 2 weeks with a loading dose of 600 mg) was initiated as monotherapy. After 6 months, sparse cutaneous lesions were observerd and lower serum IgG4 and IgE levels (1450 mg/dL and 601 KUI/L, respectively) were noted. After 1 year of therapy, dermatosis resolution (Fig. 3), and a significant improvement of asthenia, gastrointestinal symptoms and quality of life (DLQI 0) were observed, accompanied by a noticeable decrease in serum IgG4 and IgE levels (724 mg/dL and 228 KUI/L, respectively).

Discussion

IgG4-RD is an immune mediated condition characterized by tumefactive lesions and progressive fibrosing of affected tissues[1,6]. Its true incidence is unknown and potentially underestimated, due to lack of awareness. Although the immunopathogenesis of IgG4-RD is not entirely understood, a Th2 immune reaction is proeminent, with IL-4, IL-5, and IL-10 playing a role in stimulating the expression of IgG4 and IgE and eosinophilia. IL-4 is the key cytokine, inducing IgG4 class-switch mediated by Th follicular cells. IL-13 promotes mitochondrial dysfunction, cellular senescence, and fibrosis, but its role in the fibrosis of IgG4-RD is still under debate[2,7]. Up to 31% of patients with IgG4-RD have an atopic background, suffering from allergic rhinitis, atopic dermatitis, or asthma[1,3].

IgG4-DR can virtually affect any organ and usually follows a subacute course with relatively mild symptoms[8]. Extracutaneous presentations include tumor-like enlargement, inflammation, and fibrosis of tissue such as lacrimal and salivary glands, orbits, gallbladder, pancreas, thyroid, lungs, kidneys, and lymph nodes[4]. Asthenia and weight loss are common unspecific symptoms, while organ-specific manifestations such as diarrhea, respiratory symptoms, or xeropthalmia vary widely. Erythematous and pruritic nodules, papules,

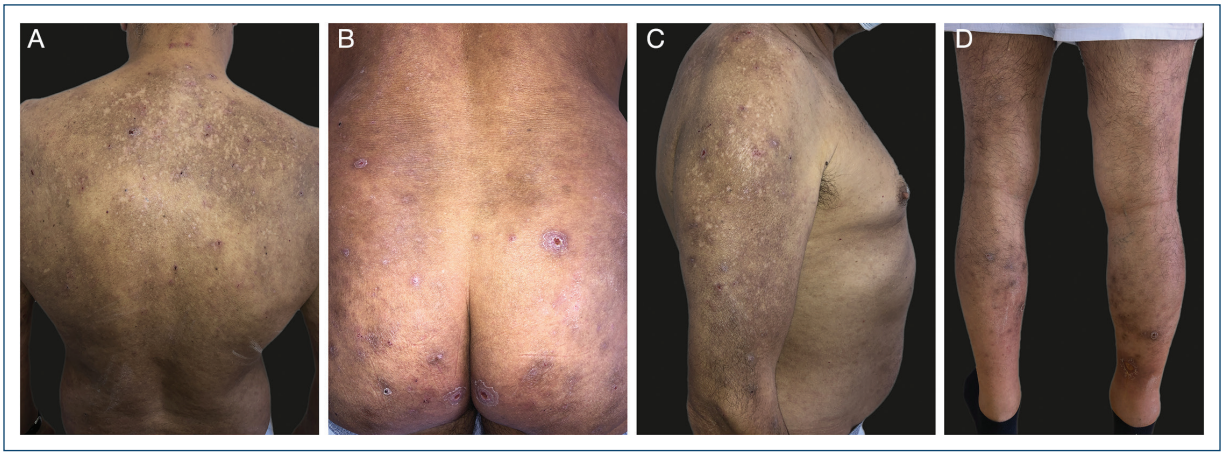

Figure 1. Baseline clinical presentation, with erythematous-brownish papules and papulonodules, excoriations and hyper- and hypopigmented macules and patches, mainly located on the **A:** trunk, **B:** buttocks and **C** and **D:** upper and lower limbs.

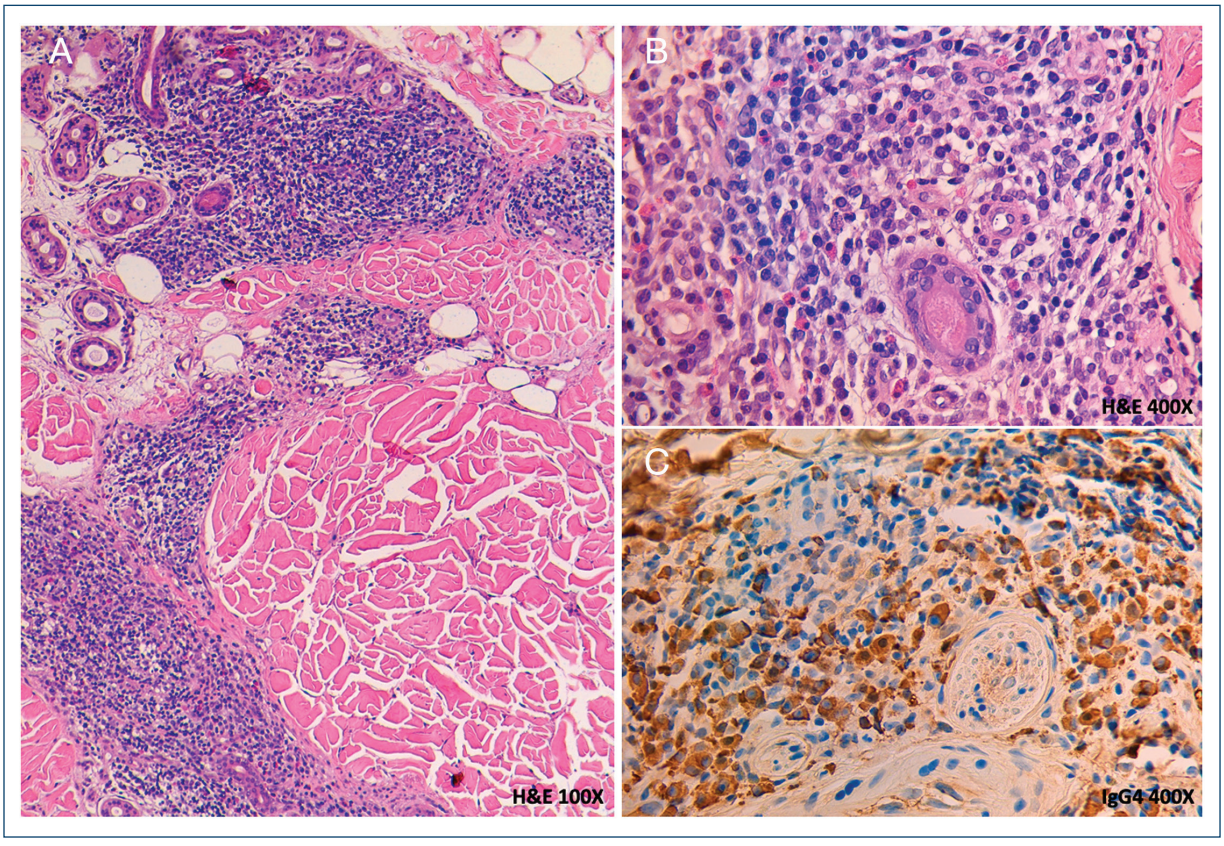

Figure 2. Histological findings on skin biopsy: dense lymphoplasmacytic infiltrate, rich in immunoglobulin G4-positive (IgG4+) cells and eosinophils.

and plaques are the most common cutaneous lesions, mainly appearing on the head-and-neck regions, but also on the trunk and extremities. Purpura and prurigo nodularis-like lesions have also been reported[9,10]. A Japanese study including 80 patients showed that skin lesions were identified in only 6.3% of IgG4-RD cases[11]. Cutaneous lesions are usually associated with systemic involvement, particularly of the orbit, lacrimal, and salivary glands[4]. Due to its clinical heterogeneity, the differential diagnosis of IgG4-RD is broad,

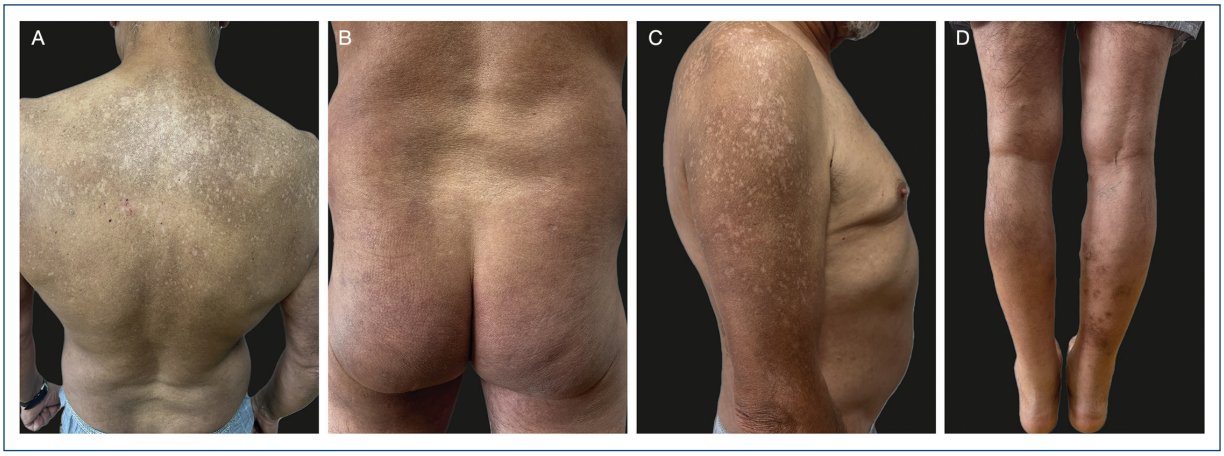

Figure 3. Significant improvement of cutaneous lesions at 1 year of therapy, with only post inflammatory hyper- and hypopigmented macules and patches remaining on the **A** and **B:** trunk, **C** and **D:** upper and lower limbs.

depending on the clinical presentation and specific sites of involvement[9].

Histopathology of affected organs shows dense lymphoplasmacytic infiltrates rich in IgG4+ plasma cells with frequent eosinophilic infiltration, storiform fibrosis, and obliterative phlebitis, the latter two seldom observed in skin biopsies[1,4,11]. Most patients present elevated serum IgG4 levels, which tends to correlate with the extent of organ involvement, hypergammaglobulinemia, elevated serum IgE (60%), and mild-to-moderate peripheral eosinophilia (34%)[1]. Comprehensive diagnostic criteria include clinically characteristic swelling or masses in single or multiple organs, serum IgG4 levels > 135 mg/dL, and histological features, namely, a ratio of IgG4+/IgG+ plasma cells > 40% on biopsy, that nevertheless is not specific as isolated and finding[1,4].

Prevention of irreversible fibrosis and organ function impairment is the major treatment goal. Systemic corticosteroids are the first-line therapy; however, relapses on discontinuation occur in up to 53% of cases[5].

Dupilumab, an IL-4 and IL-13 inhibitor, is approved for the treatment of type 2 inflammatory diseases such as atopic dermatitis, chronic prurigo, asthma, and chronic rhinosinusitis and nasal polyposis. Limited studies have demonstrated its safety and promising role in the treatment of IgG4-RD, mainly focusing on outcomes of asthma and rhinosinusitis[2,7,12,13]. Kanda M et al. reported a case series of four patients diagnosed with IgG4-related disease, predominantly affecting the submandibular and lingual glands, paranasal sinuses, and lungs, who were treated with dupilumab[2]. Similarly to our case, the two patients who underwent monotherapy with dupilumab took 3-6 months to experience a therapeutic effect.

Recent studies have focused on alternative therapies to corticosteroids, driven by a progressively deeper understanding of IgG4-RD pathophysiology. *In vitro* testing has shown that T cells from patients with IgG4-RD exhibit aberrant activation, associated with reduced expression of the inhibitory molecule CTLA4. However, in a case series of three patients diagnosed with IgG4-RD, the response to abatacept, a recombinant fusion protein of CTLA4, was inconsistent[14]. Considering the role of Janus kinases (JAK)/STAT pathway in the intracellular signaling of cytokines such as IL-4 and IL-13, JAK inhibitors may potentially mitigate chronic inflammation and tissue fibrosis in IgG4-RD. In fact, tofacitinib at 5 mg/day as monotherapy showed promising results in two patients with IgG4-RD, leading to partial or complete clinical response[15].

Studies focusing on the role of IL-13 inhibitors for the treatment of this disease are lacking. Current evidence points to a significant but problably not dominant role of IL-13 in the pathophysiology of IgG4-RD, which could justify the lack of studies with this biological agents.

Conclusion

This report highlights the efficacy of dupilumab in the treatment of cutaneous IgG4-RD, a debilitating and potentially difficult-to-treat rare condition. We further

underline the role of dermatologists in the diagnostic workup of this disease, to be considered in the presence of a persistent pruritic dermatosis with diverse systemic manifestations.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Takayama R, Ueno T, Saeki H. Immunoglobulin G_4-related disease and its skin manifestations. J Dermatol. 2017;44:288-96.
2. Kanda M, Kamekura R, Sugawara M, Nagahata K, Suzuki C, Takano K, et al. IgG4-related disease administered dupilumab: case series and review of the literature. RMD Open. 2023;9:e003026.
3. Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Prevalence of atopy, eosinophilia, and IGE elevation in igg4-related disease. Allergy. 2013;69:269-72.
4. Shenoy A, Mohandas N, Gottlieb A. Cutaneous and systemic igg4-related disease: a review for dermatologists. Dermatol Online J. 2019;25:1-10.
5. Yoshifuji H, Umehara H. Glucocorticoids in the treatment of igg4-related disease-prospects for new international treatment guidelines. Mod Rheumatol. 2022;33:252-7.
6. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol. 2012;22:1-14.
7. Yamamoto M, Yoshikawa N, Tanaka H. Efficacy of dupilumab reveals therapeutic target for igg4-related disease: simultaneous control of inflammation and fibrosis. Ann Rheum Dis. 2020;81:e50.
8. Charrow A, Imadojemu S, Stephen S, Ogunleye T, Takeshita J, Lipoff JB. Cutaneous manifestations of IgG4-related disease (RD): a systematic review. J Am Acad Dermatol. 2016;75:197-202.
9. Afra TP, Razmi TM, Bishurul Hafi NA. IgG4-related skin diseases: a brief review. J Skin Sex Transm Dis. 2020;2:94-8.
10. Hamaguchi Y, Yamada K, Kawano M, Fujimoto M, Takehara K. Prurigo nodularis-like skin eruptions in a patient with IgG4-related disease. Eur J Dermatol. 2013;23:541-2.
11. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for igg4-related disease (igg4-RD), 2011. Mod Rheumatol. 2012;22:21-30.
12. Simpson RS, Lau SK, Lee JK. Dupilumab as a novel steroid-sparing treatment for igg4-related disease. Ann Rheum Dis. 2019;79:549-50.
13. Nakajima I, Taniguchi Y, Tsuji H, Mizobuchi T, Fukuda K. Therapeutic potential of the interleukin-4/interleukin-13 inhibitor dupilumab for treating igg4-related disease. Rheumatology (Oxford). 2021;61:e151-3.
14. Mahajne J, Minici C, Lanzillotta M, Batani V, Dagna L, Della Torreet E. POS0352 genetic determinants of response to abatacept in patients with igg4-related disease. Ann Rheum Dis. 2023;82:425-6.
15. Khan S, Gordins P, Durairaj S. JAK Inhibition as a therapeutic strategy for IgG4-RD. J Investig Allergol Clin Immunol. 2021;31:280-1.