

# IgG4-related disease presenting with scarring alopecia of the scalp



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**Key words:** alopecia; IgG4-related disease; immunoglobulin G4.

## INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a recently described, systemic, fibroinflammatory disorder characterized by dense lymphoplasmacytic infiltrates that are abundant in plasma cells positive for IgG4. In many, but not all, cases, serum concentrations of IgG4 are increased.<sup>1</sup> Although IgG4-RD can affect virtually any organ, cutaneous involvement is rare, with fewer than 2% of affected patients having skin lesions.<sup>2</sup> Most of these cutaneous lesions are reported to occur on the mandible, cheek, and neck regions.<sup>3</sup> Here we describe a distinctive case of IgG4-RD presenting with scarring alopecia of the scalp, a finding that may mimic several other dermal-infiltrative processes.

## CASE REPORT

A 46-year-old man presented with a 10-year history of an asymptomatic enlarging nodule on the left mandible and progressive alopecia of the scalp. He previously received a diagnosis of cutaneous sarcoidosis based on histopathologic results from a prior scalp biopsy at a separate institution. The patient was treated with methotrexate, mycophenolate mofetil, and hydroxychloroquine without improvement.

On physical examination, a skin-colored, papulomatous, alopecic plaque was observed on the right temporal scalp (Fig 1) as well as a smooth, skin-colored, and mobile small nodule on the left mandible (Fig 2). Bilateral cervical lymphadenopathy was present. A thorough review of systems had normal findings.

A 4-mm punch biopsy of the scalp found a diffuse dermal histiocytic infiltrate admixed with intense lymphoplasmacytic inflammation and effacement of

### Abbreviations used:

HPF: high-power field  
IgG4-RD: immunoglobulin G4-related disease

the adnexal structures (Figs 3 and 4). Immunostains S100 and CD1a were negative; acid-fast bacillus, Fite, and Grocott-Gomori methenamine silver stains for microorganisms were also negative. Subsequent immunohistochemistry found an IgG4<sup>+</sup>/IgG<sup>+</sup> ratio of 80% (Fig 5). Clonality studies found a polytypic plasma cell infiltrate. Excisional biopsy of the left mandibular nodule showed similar histopathologic changes with a dense IgG4<sup>+</sup> plasma cell infiltrate, rendering a diagnosis of cutaneous IgG4-RD. Positron emission tomography/computed tomography to evaluate for systemic involvement was notable for generalized hypermetabolic lymphadenopathy, and bone marrow biopsy found mild  $\kappa$  restriction of plasma cells. The serum IgG4 level was 37.5 mg/dL (reference range, 2.4-121.0 mg/dL). The patient was treated with cyclophosphamide, bortezomib, and dexamethasone, resulting in regression of both the skin lesions and the lymphadenopathy. The affected scalp area continued to be alopecic at follow-up several months later.

## DISCUSSION

IgG4-RD is an increasingly recognized systemic inflammatory condition that may involve multiple organs, including lungs, kidneys, lymph nodes, meninges, and thyroid.<sup>4</sup> Cutaneous lesions are uncommon, and skin involvement that precedes other lesions as the first sign of disease is especially rare.<sup>5</sup> In this case, a plaque on the scalp associated with

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Funding sources: None.

Conflicts of interest: None disclosed.

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JAAD Case Reports 2018;4:555-7.

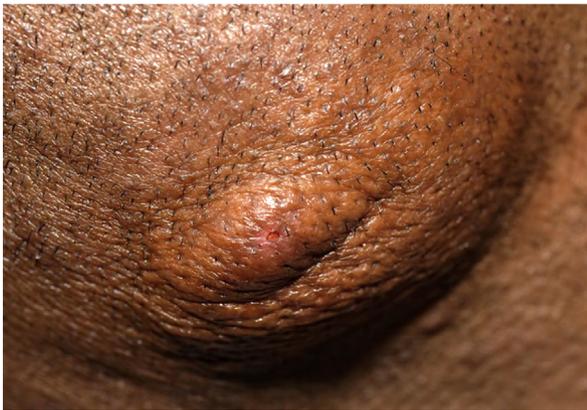
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<https://doi.org/10.1016/j.jidcr.2018.03.002>



**Fig 1.** Tumefactive alopecic plaque involving the right temporal scalp.



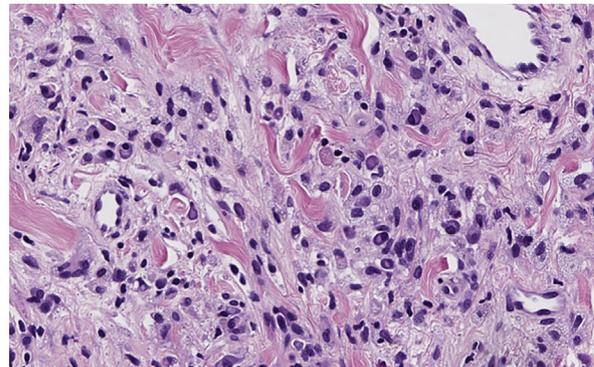
**Fig 2.** Smooth nodule on the left mandible.

progressive scarring alopecia was the initial manifestation of IgG4-RD.

The diagnosis of cutaneous IgG4-RD is challenging because of its clinical and histopathologic similarities to a number of other entities. Skin lesions generally present as tumefactive plaques or subcutaneous nodules in the head or neck regions.<sup>3</sup> These masses may clinically resemble lymphoma, pseudolymphoma, Langerhans or non-Langerhans cell histiocytoses, and sarcoidosis.<sup>4,6,7</sup> Histopathologically, the dense lymphoplasmacytic infiltrate of IgG4-RD often mimics the infiltrate found in several other inflammatory dermatoses, including Rosai-Dorfman disease, cutaneous multicentric Castleman disease, and B-cell lymphoma.<sup>5,8</sup> These conditions also may involve significant increases in IgG4<sup>+</sup> cell counts. In our case, negative S100 and CD1a stains excluded Rosai-Dorfman disease and Langerhans cell histiocytosis, respectively. Negative clonality studies further negated the possibility of B-cell lymphoma. Although a lymphoplasmacytic infiltrate predominates in IgG4-RD, variable degrees of histiocytic inflammation have been reported.<sup>6,9</sup> This result may



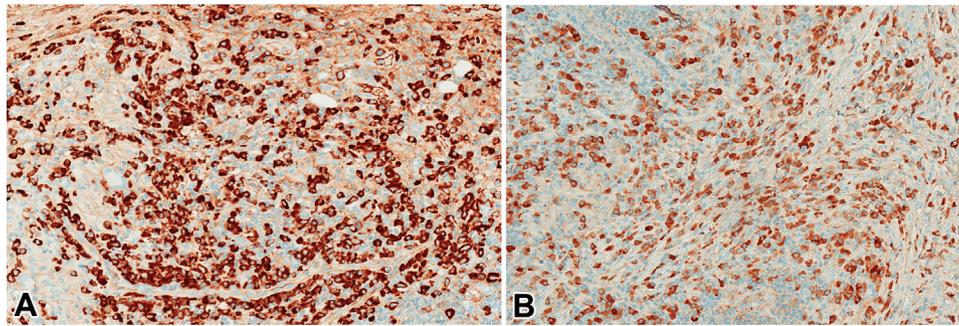
**Fig 3.** Punch biopsy specimen from the right temporal scalp. The 4-mm biopsy shows a diffuse dermal histiocytic infiltrate with dense lymphoplasmacytic inflammation, perifollicular fibrosis, and follicular effacement. (Hematoxylin-eosin stain; original magnification:  $\times 2$ .)



**Fig 4.** Tumefactive alopecic plaque. This view highlights numerous plasma cells. (Hematoxylin-eosin stain; original magnification:  $\times 40$ .)

further complicate the histopathologic interpretation of certain lesions and may lead to the misdiagnosis of granulomatous diseases such as sarcoidosis, which occurred initially in our case.<sup>6</sup>

The 2012 Consensus Statement on the Pathology of IgG4-RD proposed different diagnostic criteria for different organs.<sup>1</sup> The 3 most important pathologic findings across all organ systems are dense lymphoplasmacytic infiltrate, storiform pattern of fibrosis, and obliterative phlebitis.<sup>1</sup> According to the consensus statement, characteristics suggestive of cutaneous IgG4-RD include at least 1 of these pathologic findings, in conjunction with an IgG4<sup>+</sup>/IgG<sup>+</sup> cell ratio greater than 40% and more than 200 IgG4<sup>+</sup> cells per high-power field (HPF). However,



**Fig 5.** Immunostains of infiltrate. **A**, Immunostain shows an infiltrate rich in IgG4<sup>+</sup> plasma cells. The infiltrate had an IgG4<sup>+</sup> cell count of 80 per HPF and an IgG4<sup>+</sup>/IgG<sup>+</sup> ratio of 80%. **B**, IgG immunostain shown for comparison. (**A** and **B**, original magnifications: ×20.)

these criteria were based on the limited number of cases with skin disease reported in the literature.

In the largest case series of cutaneous IgG4-RD to date, the disease characteristics of 7 of 10 patients did not meet these diagnostic criteria.<sup>3</sup> Although all biopsies in that study showed dense lymphoplasmacytic inflammation, fibrosis was observed in only 4 patients, and only 1 patient had obliterative phlebitis. In this series, 1 case had an IgG4<sup>+</sup> cell count as low as 49 per HPF. On the basis of their results, the authors proposed new criteria for cutaneous IgG4-RD: an IgG4<sup>+</sup> cell count greater than 50 per HPF and an IgG4<sup>+</sup>/IgG<sup>+</sup> cell ratio greater than 60%. Importantly, serum IgG4 concentrations were normal in 30% of confirmed cases.<sup>10</sup>

Our patient had an IgG4<sup>+</sup> cell count of 80 per HPF and IgG4<sup>+</sup>/IgG<sup>+</sup> cell ratio of 80%. The serum IgG4 concentration was within the reference range. Although immunohistochemistry alone cannot establish a diagnosis of IgG4-RD, our patient's overall histopathologic findings in conjunction with tumefactive head and neck lesions and generalized lymphadenopathy were highly consistent with a diagnosis of IgG4-RD.

IgG4-RD often affects at least 2 organ systems, and chronic untreated disease typically leads to progressive fibrosis that may eventuate in organ dysfunction.<sup>6</sup> Associations with plasma cell dyscrasias and the development of certain malignancies have also been described.<sup>4</sup> Therefore, prompt diagnosis and treatment of IgG4-RD are essential. Systemic glucocorticoids are typically considered first-line therapy.<sup>4</sup> Our patient did not respond to an initial course of prednisone, but he did have substantial regression of cutaneous lesions and lymphadenopathy with cyclophosphamide, bortezomib, and dexamethasone combination therapy.

Of note, our patient did not have hair regrowth after involution of his scalp lesions at follow-up several months later, which is characteristic of a

scarring alopecia. This outcome correlates with the histopathologic findings of perifollicular fibrosis and follicular effacement at presentation.

We report a distinctive case of IgG4-RD presenting with cicatricial tumefactive scalp lesions as the initial manifestation of disease. Cutaneous IgG4-RD should be considered in the clinical differential diagnosis of chronic alopecia, especially in association with other nodular lesions of the head or neck, lymphadenopathy, and histologically diffuse dermal infiltrative processes.

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