

# T-Cell–Driven Fibroinflammation Inducing Follicular Dedifferentiation in Alopecia Areata and IgG4-Modified Disease

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**Abstract:** The definition of IgG4-related diseases incorporates a broad range of systemic diseases particularly a subset dominated by fibroinflammation. CD4+cytotoxic T cells have emerged as the major driving force for the fibroinflammation, and the pathogenetic role of IgG4 still remains to be determined. Cutaneous involvement is uncommon and is not well defined as elevated tissue IgG4 plasma cells are not a specific marker and prominent cutaneous fibroinflammation is often absent in cutaneous disease. We report the case of a patient with longstanding alopecia universalis and severe atopic dermatitis who presented with diffuse induration and mottled dyspigmentation of his scalp. Multiple scalp biopsies revealed diffuse interfollicular fibroinflammation and IgG4 plasma cells with induction of distinctive dedifferentiated follicles not seen in alopecia areata. This complex case may provide insight into the role of specific subsets of T cells not only in respect to the fibroinflammation linked to IgG4-related diseases but also the capacity to modify disease, follicular stem cell activation, immune privilege, cytotoxicity in alopecia areata, and the presence of atopy that may have contributed to the pathogenesis of this case.

**Key Words:** IgG4-related disease, alopecia areata, fibroinflammatory disease, follicular stem cells

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## INTRODUCTION

IgG4-related disease (IgG4-RD) links a broad group of tumefactive fibroinflammatory and lymphoplasmacytic conditions that are mainly systemic and can involve multiple organs.<sup>1–3</sup> Cutaneous involvement by IgG4-RD is not a major feature and at present is not clearly defined.<sup>4–9</sup> Elevated numbers of IgG4 dermal plasma cells may not necessarily define specific IgG4-RD cutaneous disease. Patients with defined systemic IgG4-RD and elevated circulating IgG4 plasma cells may have skin diseases such as psoriasis and vasculitis<sup>5</sup> that are not strictly IgG4-RD but reflect the egress of IgG4 plasma cells into the skin. In addition,

elevated numbers of IgG4 plasma cells can occur in lymphoproliferative processes such as IgG4 plasma cell myeloma<sup>10</sup> and marginal zone lymphoma<sup>11,12</sup> without clinical or histopathological distinct features and no association with other defined IgG4-RDs. Diffuse progressive fibroinflammation represents the most distinctive histopathological feature of IgG4-RDs. This clinical progressive tumefactive sclerosis links a distinct group of conditions that have been identified in multiple organs including autoimmune sclerosing pancreatitis, sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis. Although elevated IgG4 plasma cells form a consensus criterion to define IgG4-RD, their pathogenic role remains obscure and now the main driving force for fibroinflammation has been shown to be cytotoxic CD4+ T cells.<sup>13–15</sup> Whether defined numbers of IgG4 plasma cell are critical for the diagnosis of IgG4-RD in the setting of prominent fibroinflammation in comparison lymphoid and plasma cell hyperplasia related IgG4-RD with inherently increased plasma cells that more readily fulfill the quantitative criteria is unclear.

We report the case of a patient with longstanding alopecia universalis (AU) and severe atopic dermatitis (AD) who presented with diffuse induration and mottled dyspigmentation of his scalp. Multiple scalp biopsies revealed diffuse interfollicular fibroinflammation and elevated IgG4 plasma cells with induction of distinctive dedifferentiated follicles not seen in alopecia areata (AA). This complex case has provided an opportunity to explore the wider role of specific subsets of T cells that have been defined in respect to follicular stem cell activation, immune privilege, IgG plasma cell class switching, and alopecia areata that may have contributed pathogenically to this case presentation.

## CASE REPORT

A 59-year-old Sri Lankan man presented with a 20-year history of AA that was initially patchy but subsequently progressed to AU. The alopecia was initially treated with intralesional steroids with temporary response, but no treatment was pursued after the alopecia became more generalized. In addition, he had a 25-year history of recalcitrant AD with a recent generalized flare and erythroderma. Pruritus was generalized and included his scalp. Axillary and supraclavicular lymphadenopathy was noted on physical examination. There were no enlarged lacrimal or salivary glands. Over the last 4 years, dyspigmentation with both hypopigmented and hyperpigmented patches emerged over his bald scalp (Fig. 1A), neck, and upper chest. His current treatment for his AD includes clobetasol propionate cream, tacrolimus ointment to the face, and montelukast, 10 mg daily.

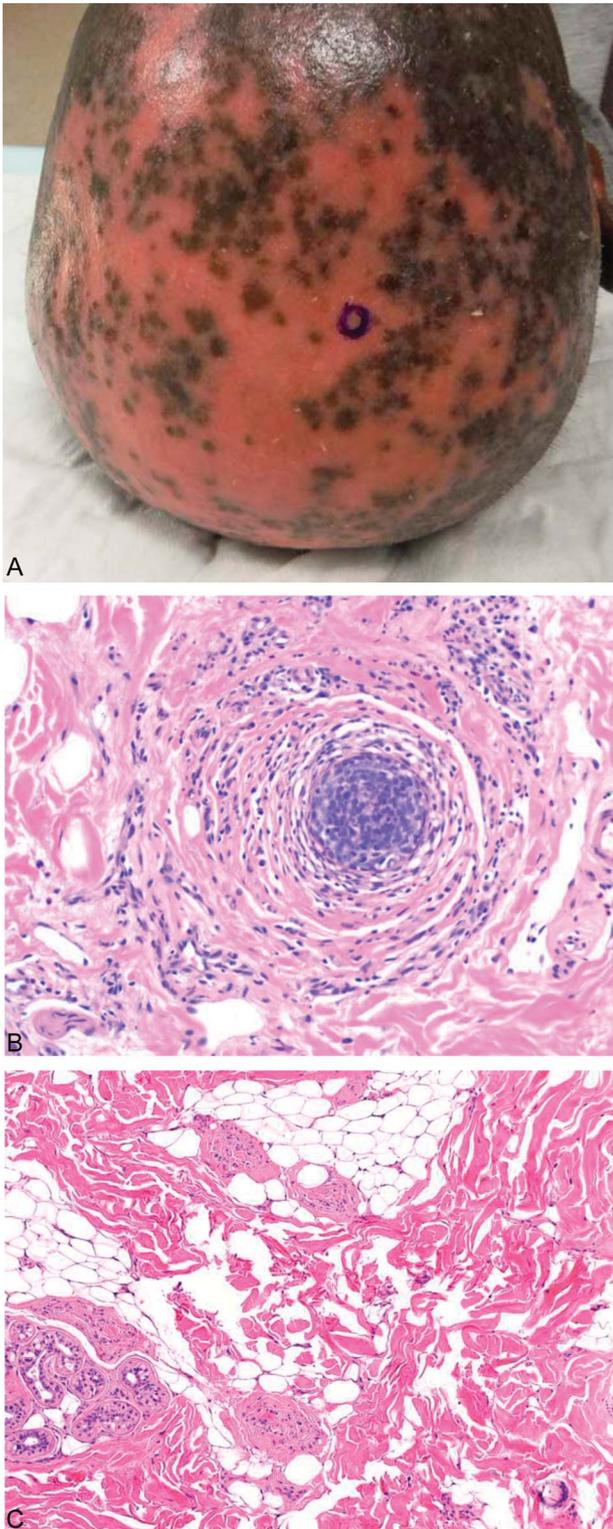
Laboratory investigations revealed elevated IgG4 1.341g/L (0.39–0.864 g/L), erythrocyte sedimentation rate 112 mm/h, and a

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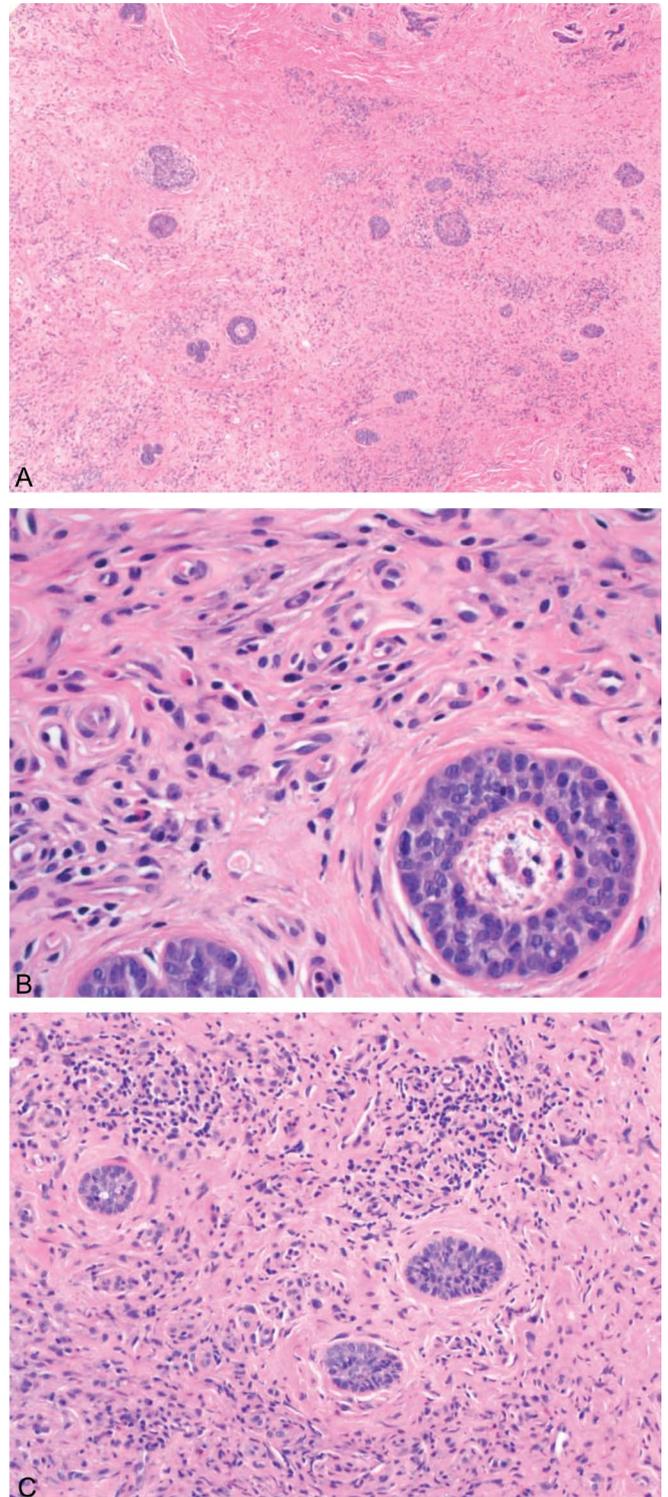
The authors declare no conflicts of interest.

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**FIGURE 1.** A, Clinical appearance of scalp with marked mottled dyspigmentation and alopecia universalis. B, Isolated differentiated follicular bulb with lymphocytic inflammation supporting alopecia areata (H&E,  $\times 100$ ). C, Transverse scalp section of the deep dermis and subcutis revealed lack of terminal follicles and presence of fibrous tracts reflecting follicular miniaturization seen in alopecia universalis (H&E,  $\times 50$ ).



**FIGURE 2.** A, Base of miniaturized follicles demonstrating gross dedifferentiation with irregular multilobated, asymmetrical linear, and annular follicular elements with reduced follicular density and diffuse interfollicular fibroinflammation (H&E  $\times 20$ ). B, Detail of ring-form follicular element outlined by prominent fibroinflammation (H&E,  $\times 400$ ). C, Small irregular dedifferentiated follicular elements without evident inflamed bulbs or telogen arrest follicular differentiation seen in alopecia areata (H&E, 200).

CD4/CD8 ratio of 5.95. Immunofixation, protein electrophoresis, ANA, ENA, dsDNA, liver, thyroid, and renal function were all normal. Whole-body noncontrast computed tomography confirmed the lymphadenopathy. Flow cytometry of an axillary lymph node showed no abnormalities and no elevation of IgG4 plasma cells and no abnormalities in the peripheral blood.

The clinical appearance of the alopecia was consistent with longstanding AA, but the basis for the scalp dyspigmentation was uncertain despite a family history of vitiligo. The presence of diffuse scalp induration and the striking dyspigmentation prompted scalp biopsies. The lichenified acral dermatitis was also biopsied. AA, eczema, vitiligo, and cutaneous T cell lymphoma were all included as differential diagnoses in the histopathological request form without further clinical details.

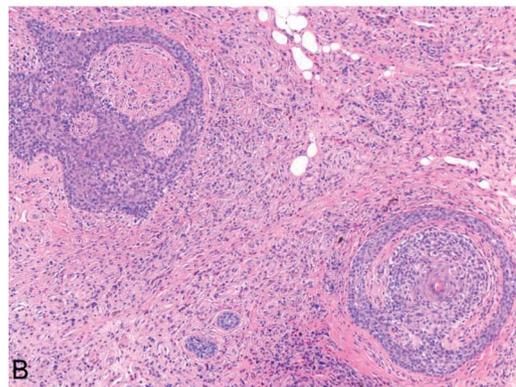
Three separate scalp biopsies showed similar findings. Initially features of AA were not apparent as the histopathology was obscured by striking changes with respect to follicular differentiation and interfollicular fibroinflammation. After obtaining a detailed clinical history of longstanding alopecia areata, the biopsies were reviewed for the histopathological presence of AA. Only solitary hair bulbs were found demonstrating peribulbar lymphocytes (Fig. 1B), and there was a loss of terminal follicles in the deeper dermis (Fig. 1C). Miniaturized follicles dominated the biopsies as expected in longstanding AU, but these were extensively dedifferentiated differing from the telogen germinal bulbs (TGUs) seen in AA and a factor that also obscured the diagnosis of AA. The miniaturized follicles resulted in asymmetrical dispersed small distorted, lobulated, and ring shaped epithelial structures lacking bulb differentiation or evidence of trichogenesis, embedded in a diffuse fibroinflammatory dermis (Fig. 2). Distorted and hypertrophic infundibular and pilar sheath epithelium with mantle-like arciform extensions was present in the upper dermis representing a distinctive pattern of follicular dedifferentiation separated by a fibroinflammation with plasma cells (Fig. 3). Only the superficial aspect of the infundibular canals was preserved, and the isthmus, follicular canals with their structured pilar sheaths and sebaceous glands were all no longer evident in the dedifferentiated follicles. The epidermis was irregularly acanthotic with lymphocytic inflammation and spongiosis reflecting this background AD (Fig. 4A). Within the fibroinflammatory tissue demonstrating a focal storiform pattern and angioplasia, there were prominent plasma cells and lymphocytes with scattered eosinophils and histiocytes (Fig. 4B). The lymphocytes were predominantly T cells positive with CD3 (Fig. 5A) and dominated by CD4<sup>+</sup>T cells with a preserved ratio to CD8<sup>+</sup> cells. CD5 labeling was retained, and CD20 was positive in 15% of lymphocytes and CD138 labeled 15% as plasma cells. IgG4<sup>+</sup>plasma cells were focally increased within the fibroinflammatory tissue with up to 20 cells in a high-power field (Fig. 5B). Prominent dermal melanin pigment was not confined to the subepidermal zone but was dispersed throughout the fibroinflammatory dermis separating the follicles. Patchy retention of epidermal melanin and the presence of SOX10 positive melanocytes excluded vitiligo as a central factor for the dyspigmentation. The stromal cells were positive for factor 13a, CD163, and CD10 but negative for CD34, and there was a loss of elastic fibers on specific staining. The biopsies from the lower limbs showed a lichenified dermatitis but no evident plasmacytic fibroinflammation or follicular pathology including dedifferentiation or lymphocyte folliculotropism.

## DISCUSSION

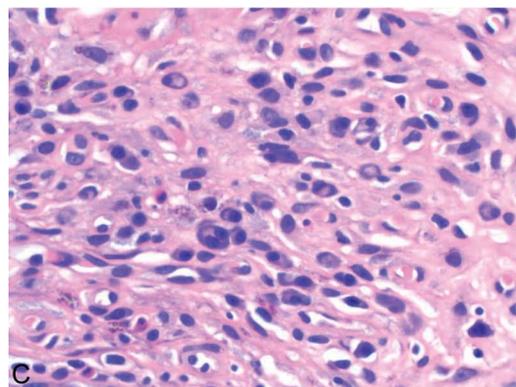
The histopathology of this case was immediately distinctive because of the presence of unusual dedifferentiated follicles separated by a diffuse inflammatory storiform



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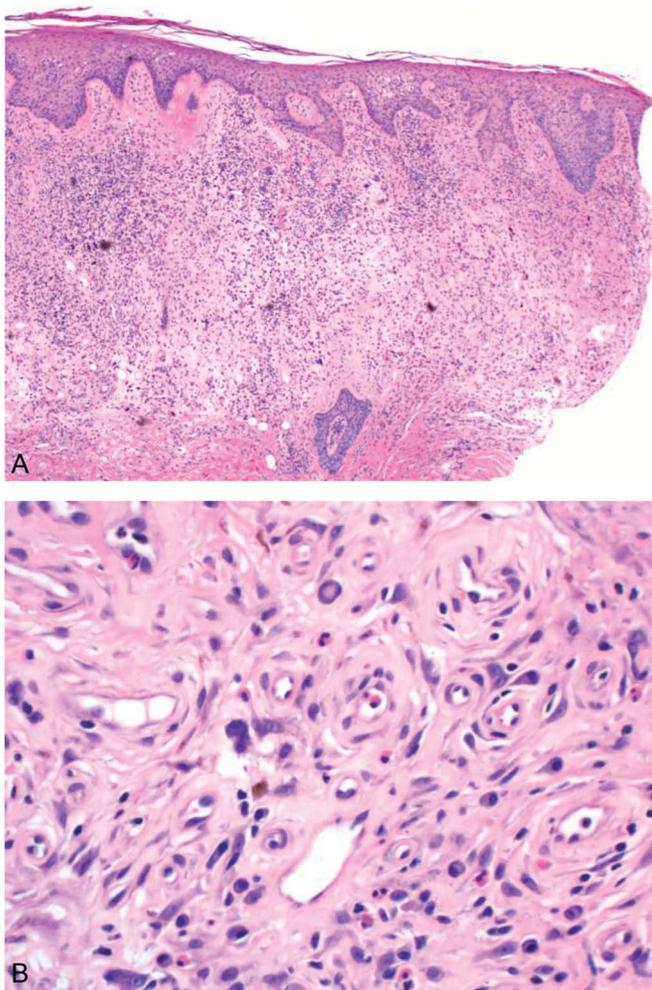


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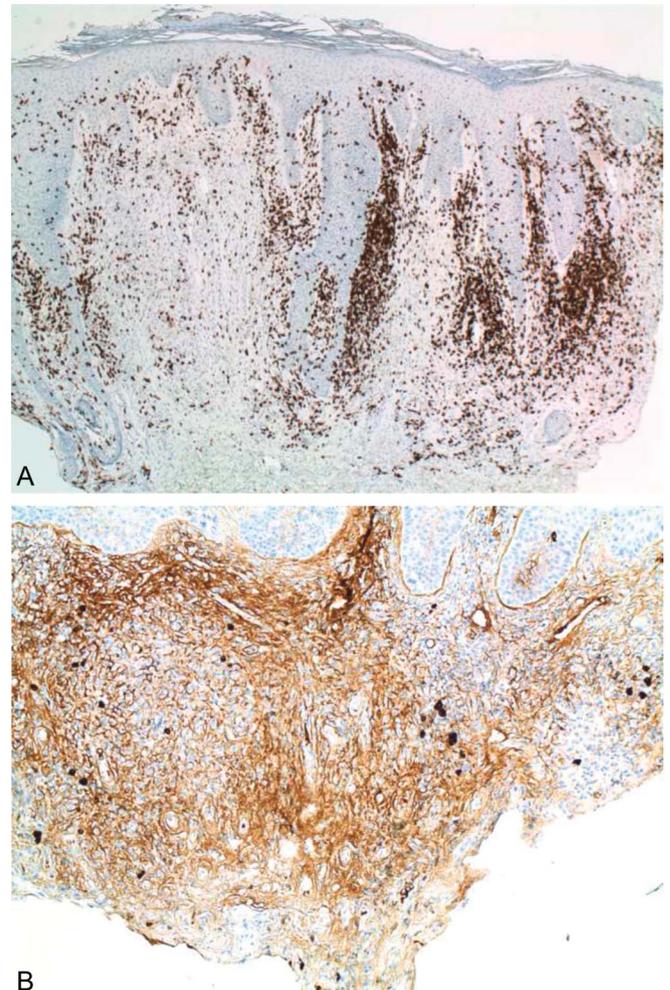
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**FIGURE 3.** A, Scanning magnification with grossly dedifferentiated follicles with hyperplastic pilar epithelial and arciform mantle-like cords embedded in fibroinflammation with melanin pigment. Loss of follicular canals, structured pilar sheaths, trichogenesis, or sebaceous follicles (H&E,  $\times 12.5$ ). B, Detail of dedifferentiated arciform follicles (H&E,  $\times 100$ ). C, Fibroinflammation with prominent plasma cells (H&E,  $\times 400$ ).



**FIGURE 4.** A, Scalp biopsy demonstrating epidermal acanthosis with spongiosis and underlying dermal edema and fibroinflammation (H&E,  $\times 100$ ). B, Detail of fibroinflammation with angioplasia, melanin pigment, and storiform pattern with mixed inflammation of lymphocytes, plasma cells, eosinophils, and histiocytes (H&E  $\times 400$ ).

fibroplasia replacing the dermis. Although plasma cells were present, lymphocytes dominated the inflammatory infiltrate. The lymphocytes were also admixed with scattered histiocytes, eosinophils, and neutrophils. The distinctive fibroinflammation combined with plasma cells prompted our review for IgG4-RD in this case. Although the ratio of IgG4 plasma cells was focally increased in the biopsies, the increase did not meet the consensus level designated for establishing IgG4-RD.<sup>2</sup> This however may be influenced by the stage of fibroinflammation and biopsy site. Only one scalp biopsy was available for the immunoperoxidase study. The serum IgG4 was elevated, but neither AA or AD are considered to be IgG4-RDs. Atopy is increased in individuals with IgG4-RD but is not an integral component, and elevated serum IgG4 levels can be found in atopic individuals without IgG4-RD.<sup>16</sup> Despite this, the possibility that the presence of atopy and elevated IgG4 levels was a necessary element in the fibroinflammation in our patient cannot be discounted.



**FIGURE 5.** A, Prominent perifollicular CD3-positive T lymphocytes ( $\times 100$ ). B, IgG4-positive plasma cells in fibroinflammation ( $\times 100$ ).

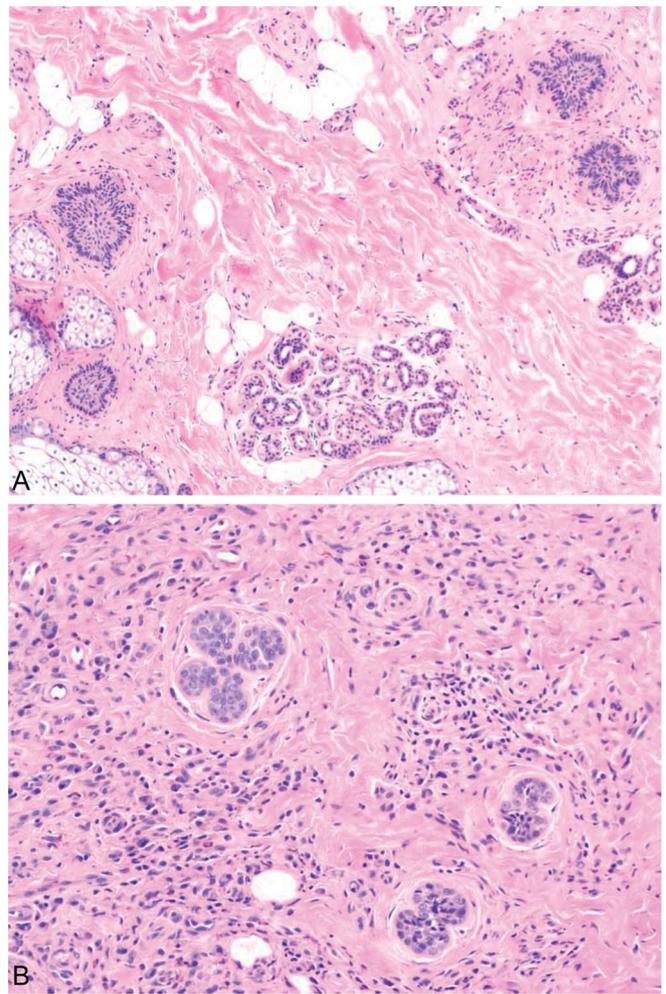
Since defining the initial diagnostic criteria of IgG4-RD,<sup>2</sup> a central issue is the actual role of IgG4 plasma cells in the pathogenesis of IgG4-RDs.<sup>1</sup> Currently quantitating IgG4 serum levels and tissue IgG4 plasma cells represent useful sentinel markers for IgG4-RD but are not a specific feature restricted to IgG4-RDs, and the current evidence is that IgG4 is not the principal driver of IgG4-RDs. This is understandable as the main function for plasma cells is essentially to produce variously classed antibodies that specifically bind to a wide spectrum of distinct antigens including autoantigens. This antigen binding leads to subsequent immunological presentation and processing. Antibody-related diseases from a dermatopathological perspective have been highlighted by immunofluorescence as complement binding antibody-antigen complexes producing distinctive patterns seen in vasculitis, immunobullous, and connective tissue diseases. This is clearly distinct from the situation with IgG4-RDs where such pathogenic deposition of antibodies has not been demonstrated although IgG4 may still play an undetermined role.<sup>17</sup>

In contrast to the restricted repertoire of plasma cells, the last decade has been associated with major advances particularly in reference to T cells. This includes defining distinct T-follicular helper cell responsible for IgG4 plasma cell class switching<sup>18</sup> and regulatory T cells (Treg) in the skin that facilitate epithelial stem cell differentiation<sup>19</sup> including hair follicles and maintaining follicular immune privilege. Regulatory T cells have been demonstrated to be particularly pertinent to the pathogenesis of AA.<sup>20–22</sup> Investigations on subsets of T cells, particularly CD4<sup>+</sup> cells, have been driven by the quest of expanding the range of biological treatments of a wide range of inflammatory diseases particularly in reference to inflammatory skin diseases. In the case of IgG4-RDs, the identification CD4<sup>+</sup> cytotoxic T cells has emerged as a major advance because this distinct subset produces interleukin 1, transforming growth factor-beta, and interferon-gamma mediators capable of inducing the fibroinflammation observed in IgG4-RD.<sup>14</sup>

The histopathology of AA does not include numerous plasma cells, and AA is not linked to IgG4-related disease. In our case, the alopecia represented AU based on the history and clinical features. The biopsy features of AA were obscured by the marked follicular dedifferentiation. Only traces of the infundibulum remained, and there was a loss of recognizable follicular isthmus, follicular canal formation, structured follicular sheaths, hairs, and sebaceous glands. The dedifferentiated follicles were transformed into expanded solid infundibular and pilar sheath epithelial structures outlined by arciform mantle zone-like cords. Dedifferentiation in the follicular bulb regions of miniaturized alopecia areata follicles resulted in numerous dispersed lobulated and cross-sectioned arciform epithelial follicular forms lacking evidence of trichogenesis or recognized as follicular bulbs. The dedifferentiation of the hair bulbs in our case can be distinguished from the telogen germinal units (TGUs) seen in longstanding AA (Fig. 6). The bulb region of follicles is the main target for the lymphocytic autoimmune pathology in AA. In AU, numerous miniaturized follicles are held in TGUs, recognized as crenated basaloid palisaded units featuring peripheral palisading of basaloid cells with a different central population (Fig. 6A) and also retained follicular differentiation as emerging follicular sheaths and retained telogen hairs within these miniaturized follicles. By contrast, the dedifferentiated follicles are multilobated, lack peripheral palisading of basaloid cells, and centrally have the same cell morphology as the peripheral cells and no evident trichogenesis (Fig. 6B). However, not all follicles in the scalp biopsies were dedifferentiated, and this allowed confirmation of the presence of underlying alopecia areata.

Although vitiligo was considered in the clinical differential diagnosis, scalp biopsies revealed that the clinical dyspigmentation was due to dermal melanin deposition scattered through the fibroinflammation and was most likely a consequence of follicular dedifferentiation and release of follicular melanin and could not be solely linked to vitiligo.

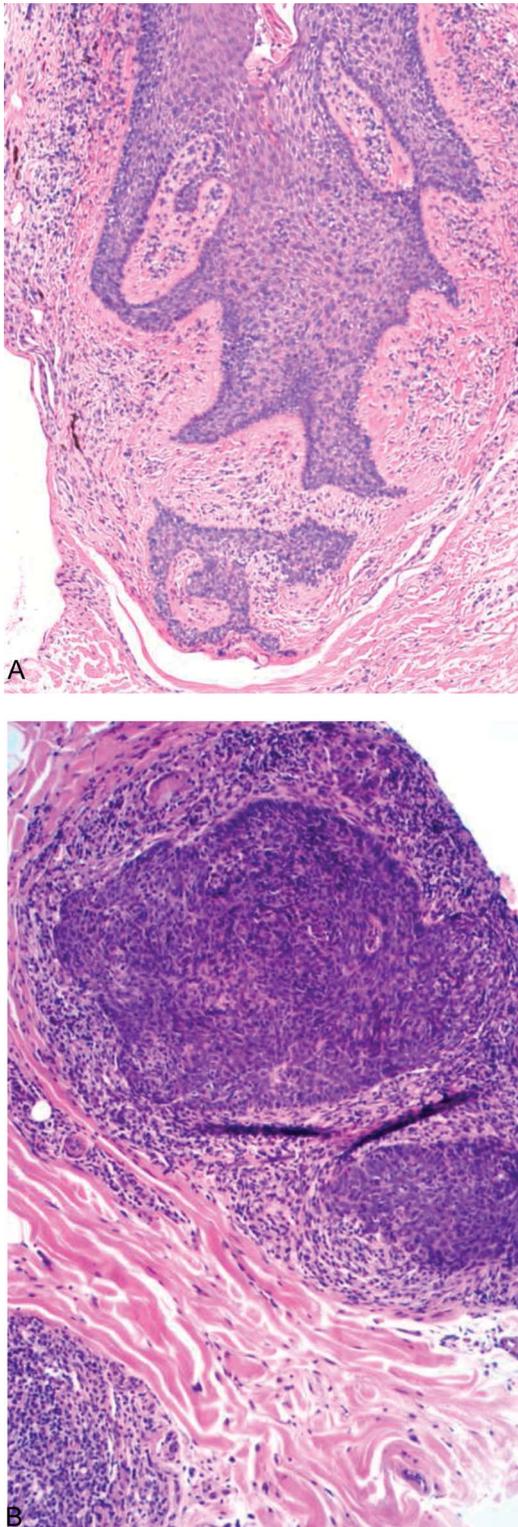
Follicular hamartomas as a basis for the dedifferentiated follicles was initially considered as follicular hamartomas are seen in the context of a rare syndrome of lupus erythematosus linked to myasthenia gravis. The medical history, clinical



**FIGURE 6.** Comparison histopathology of (A). Longstanding alopecia areata with TGUs that is crenated with peripheral palisade of basaloid cells and central paler cells (H&E,  $\times 400$ ) with (B). Dedifferentiated alopecia areata follicles with multilobated smooth epithelial forms without peripheral palisading and the same uniform cells through lobules (H&E,  $\times 100$ ).

presentation, ANA serology, and the histopathology lacking of lichenoid inflammation did not support lupus erythematosus and the fibroinflammation also needed to be integrated.

Marked progress has been made in studying the T-cell basis of AA. There are an expanding range of T-cell subsets that have been defined. Particularly important are Tregs with their complex roles in respect to protecting follicular immune privilege and also in their interaction with follicular stem cells underlying folliculogenesis and the maintenance of homeostasis and follicular hair cycles.<sup>20–22</sup> As an autoimmune process, in AA, loss of follicular immune privilege has been linked with reduced Tregs, leading to subsequent infiltration of follicular bulbs by pathogenic cytotoxic CD8 dominant T cells. The dedifferentiation of follicles in our case may represent disordered signaling to progenitor stem cells localized particularly to the bulge niche which is a major center for follicular homeostasis and maintaining follicular differentiation. These mesenchymal signals may be changed by the



**FIGURE 7.** Comparison of (A). Dedifferentiated follicles in alopecia areata conceptually related to interference by fibroinflammation of Treg lymphocyte-mediated follicular stem cell homeostasis (H&E,  $\times 200$ ) with (B). Basaloid folliculolymphoid hyperplasia with gross basaloid follicular dedifferentiation in the setting of folliculotropic mycosis and clonal T-cell-mediated interference of follicular stem cell homeostasis (H&E,  $\times 200$ ).

altered cytokine combinations produced by the extensive perifollicular fibroinflammation in the biopsies, altering normal mesenchymal signaling required by Treg-induced stem cell activation. Despite this, the preferable primary diagnosis for our patient's alopecia remains alopecia areata that had undergone dedifferentiation and modified by IgG4-related fibroinflammation rather than IgG4-RD.

CTCL was included in the initial provisional differential diagnoses, but the clinical presentation of a generalized lichenified dermatitis in the context of atopy and the presence of spongiotic dermatitis in all skin biopsies as well as negative peripheral blood and lymph node T-cell analysis excluded CTCL.

Follicular CTCL was also considered, but the clinical presentation and history of alopecia universalis differs from folliculotropic CTCL, which often has follicular papules and does not result in generalized hair loss. On histopathology, the pattern of follicular dedifferentiation was distinctive, and prominent folliculotropic lymphocytes, follicular mucinosis, or cerebriform T cells were absent. However, the follicular dedifferentiation in our case (Fig. 7A) could be contrasted with the features of a published rare form of follicular CTCL,<sup>23,24</sup> inducing gross basaloid follicular dedifferentiation (Fig. 7B). This striking form of basaloid dedifferentiation is shared with some forms of follicular mucinosis and occurs usually in patients with established mycosis fungoides, prominent folliculotropic cerebriform T cells. This is also a rare form of follicular dedifferentiation that may have a different pathogenesis and may represent a clonal expansion of follicular Treg cells capable of inducing profound basaloid follicular dedifferentiation.

Our case can also be contrasted to a report of an IgG4-related alopecia in a patient who had a circumscribed tumefactive patch of alopecia on the scalp and a mandibular plaque.<sup>25</sup> The scalp biopsy showed interfollicular fibroinflammation with a predominance of histiocytes, and the histopathology was initially diagnosed as sarcoid. Elevated IgG4-labeling plasma cells in the interfollicular fibroinflammatory infiltrate and perifollicular lymphocytic inflammation supported a cutaneous IgG4-RD. Dedifferentiation of follicles was not observed, and the hair growth was not restored with treatment leading to a diagnosis of localized cicatricial alopecia as a consequence of IgG4-RD. This case raises the issues of whether the follicular dedifferentiation in our case was dependent on the combined presence of atopy and AA that was modified by IgG4-related fibroinflammation and that an independent form of diffuse dedifferentiated follicular alopecia representing IgG4-RD also may exist.

Our case illustrates the features of a distinctive alopecia that appeared in the setting of a combination of defined individual skin diseases. In the final analysis of potential differential diagnoses in this case, both alopecia areata and atopic dermatitis were the skin diseases that appeared linked to the pathogenetic process resulting in a hitherto unrecognized fibroinflammatory dedifferentiated alopecia. However, the potential links to vitiligo, lupus erythematosus, and CTCL that were included in the discussion may still materialize in future cases of fibroinflammatory dedifferentiated alopecia, where alopecia areata may not be the primary alopecia and the

alopecia may be linked to LE or CTCL. Significant progress has been made in each of these skin diseases in reference to T-cell-driven inflammatory and immunological pathways. The intersection of these pathways may offer further insights into the complex events in our case in reference to T-cell modulation, AA, follicular dedifferentiation, and IgG4-RDs.

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