Granulomatous alopecia areata is a valid but rare histologic subset of a common disease

Margaret C. Green, DO, MSc, a Mary M. Braden, MD, b and Leonard C. Sperling, MD c
Bethesda and Prince Frederick, Maryland

Key words: alopecia areata; granuloma; uncommon; variant.

INTRODUCTION
Alopecia areata typically presents with a distinctive histopathologic pattern, including peribulbar lymphocytic inflammation with or without occasional eosinophils, follicular miniaturization, and an increase in catagen/telogen hairs. Pigment incontinence, which is proportional to the pigmentation of the patient’s hair, is often present within the peribulbar fibrous root sheath. 1-3 Only 3 cases of the granulomatous variant of alopecia areata have been reported, 3,4 and we now describe 2 additional cases of granulomatous alopecia areata. This histologic variant of alopecia areata represents a potential pitfall when evaluating the histopathology of a patient with hair loss. Granulomatous inflammation should not preclude the diagnosis of alopecia areata in the appropriate clinical-pathologic setting.

CASE REPORT
Case 1
A 34-year—old woman with Fitzpatrick skin type V presented with a 4-month history of hair loss that started as pruritic patches on the occipital aspect of the scalp. She denied any systemic symptoms. On examination, she had large, irregularly shaped, sharply demarcated zones of hair loss on the posterior part of the crown and occiput (Fig 1). Dermatoscopic examination of an affected zone showed patchy erythema and numerous “brown dots” as well as some obliterated ostia (Fig 2). A rapid plasma reagin test was nonreactive, and an antinuclear antigen test was negative. Iron and ferritin levels, dehydroepiandrosterone sulfate, free and total testosterone, angiotensin-converting enzyme, C3, C4, rheumatoid factor, and calcium levels were normal. Antibodies against double-stranded DNA, Smith, cardiolipin, and beta 2 glycoprotein were negative. The patient was slightly anemic, with a hemoglobin and hematocrit of 11.0 and 34.5, respectively. The patient declined intral cellular steroid injections and experienced modest improvement after several months of topical clobetasol application.

Hematoxylin-eosin-stained sections of punch biopsy specimens from the involved areas showed a normal interfollicular epidermis and a normal total hair count. Almost all follicles were greatly

From the Department of Dermatology, Walter Reed National Military Medical Center, Bethesda, a; Anne Arundel Dermatology, Prince Frederick, b; and Uniformed Services University of the Health Sciences, Bethesda, c.
Funding sources: None.
IRB approval status: Not applicable.
Correspondence to: Margaret C. Green, DO, MSc, Department of Dermatology, Walter Reed National Military Medical Center, Building 19, 3rd Floor, 8901 Wisconsin Avenue, Bethesda, MD 20889. E-mail: Margaret.c.green2.mil@mail.mil.

JAAD Case Reports 2022;21:169-72.
2352-5126
© 2022 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
https://doi.org/10.1016/j.jdcr.2021.12.029

Fig 1. Case 1. Patch of alopecia on the occipital aspect of the scalp demonstrating a large, irregular zone of marked hair loss with intact follicular ostia and abrupt transition to normal scalp (image courtesy of Dr Arash Koochek).
miniaturized, and most were in the catagen/telogen phase (Fig 3). Lymphocytic inflammation surrounded, infiltrated, and damaged or destroyed the follicular bulbar and suprabulbar zones in several areas. Some entire follicular units were replaced by granulomatous inflammation (Fig 4). Several eosinophils were also noted in the inflammatory infiltrate. The upper portions of most follicles were largely spared from inflammation, and there was no vacuolar interface alteration. Small foci of granulomatous inflammation with multinucleated giant cells were also present at the sites of damaged or destroyed infundibula. Most follicular lumina only contained small hair shafts and were filled and distended with orthokeratotic material.

**Case 2**

A 45-year-old man with Fitzpatrick skin type II presented with asymptomatic, discrete patches of hair loss scattered over the crown and occipital aspect of the scalp, in a pattern typical of alopecia areata. The lesions initially responded well to monthly intralesional steroid injections. Roughly 14 months from symptom onset, his alopecia actively worsened, and some areas became pruritic. Physical examination revealed widespread, severe, patchy alopecia affecting the crown and vertex of the scalp as well as subtle patchy erythema (Fig 5). There was also hair loss on the eyebrows and body. Laboratory tests (androstenedione, dehydroepiandrosterone sulfate, thyroid-stimulating hormone, T4, complete blood cell count, vitamin B12, iron, ferritin, folate,
rheumatoid factor, and sex hormone binding globulins) were unremarkable except for low vitamin D levels. A rapid plasma reagin test was nonreactive. He declined further intralesional steroids injections or a trial of tofacitinib.

Hematoxylin-eosin–stained sections from vertically and horizontally processed punch biopsies of the involved areas showed a normal interfollicular epidermis and a normal hair count. Most follicles were in the catagen/telogen phase, and peribulbar lymphocytic inflammation was moderately dense (Fig 6, A and B). However, many follicles also exhibited peribulbar granulomatous inflammation with multinucleated giant cells and multiple eosinophils surrounding several hair bulbs. Plasma cells, which can be a common component of infiltrates on the scalp, were found in association with the granulomatous inflammation (Fig 7).

**DISCUSSION**

Granulomatous inflammation has been reported rarely in alopecia areata. In the author’s (L.C.S.) experience, an occasional isolated follicle showing granulomatous destruction is not uncommon in otherwise typical cases of alopecia areata. This author (L.C.S.) reviewed 50 consecutive cases of alopecia areata (email, April 18, 2020) and found 2 cases showing granulomatous inflammation. In both instances, only a single follicular unit was affected, and the granulomas were in the papillary dermis, not the peribulbar region. In these cases, the author dismissed such isolated follicular destruction as a spurious finding. The 3 cases already described in the literature, in addition to our 2 cases described above, indicate that the peribulbar granulomatous pattern is a real but uncommon variant of alopecia areata. The authors of previously published cases of granulomatous alopecia areata speculated that the cause was a loss of immune privilege of the hair
follie during the anagen phase, leading to exposure of hair antigens and triggering a T-helper 1-type reaction, culminating in granuloma formation. These authors posit that past trauma or inflammation may have led to transient lymphohistiocytic inflammation that was followed by a granulomatous, foreign-body reaction directed against the follicular bulb epithelium; extensive laboratory and radiologic workups were undertaken to exclude underlying causes. In our cases, the clinical picture in combination with granulomatous inflammation associated with otherwise typical histologic features of alopecia areata led to the diagnosis of granulomatous alopecia areata.

When alopecia is associated with widespread granulomatous inflammation, sarcoidosis, syphilis, and the various forms of inflammatory, cicatricial alopecia (lichen planopilaris and central centrifugal cicatricial alopecia) would be included in the microscopic differential diagnosis. In sarcoidosis, the granulomas are not restricted to hair bulbs, and miniaturization of follicles is not seen. In syphilis, the granulomas might be associated with chronic inflammation, including plasma cells, which are not a feature of the infiltrate in typical cases of alopecia areata. However, some cases of syphilitic alopecia can be exact mimics of alopecia areata, and serologic testing would be required to exclude syphilis. This point is exemplified in case 2, where plasma cells could be found in the peribulbar infiltrate (Fig 7). In the various forms of cicatricial alopecia, the granulomas are usually found in the upper part of the dermis; in granulomatous alopecia areata, the granulomas are situated in the reticular dermis or superficial fat at the site of the hair bulbs. In addition, the various forms of inflammatory cicatricial alopecia are not associated with profound hair miniaturization. In summary, even clinically typical alopecia areata can rarely be associated with atypical histopathologic findings, namely peribulbar granulomatous inflammation affecting a few or even most follicles. This uncommon variant of a common disease should be welcomed into the family of unusual presentations of alopecia areata.

The authors wish to thank Drs Arash Koochek and Mark Wilke for sharing their cases, including clinical images and histologic glass slides.

Conflicts of interest
None disclosed.

REFERENCES
1. Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update: part I. Clinical picture, histopathology, and pathogenesis. J Am Acad Dermatol. 2010;62(2):177-188. quiz 189-190. https://doi.org/10.1016/j.jaad.2009.10.032
2. Sperling LC, Cowper SE, Knopp EA. An Atlas of Hair Pathology with Clinical Correlations. 2nd ed. New York & London: Informa Healthcare; 2012.
3. Paniz Mondolfi AE, Cressey BD, Ahmad A, Tapia-Centola B, Cohen LM, Mahmoodi M. Granulomatous alopecia: a variant of alopecia areata? J Cutan Pathol. 2013;40(4):357-360. https://doi.org/10.1111/j.1600-0560.2012.01216
4. Wilk M, Zelger BG, Zelger B. Granulomatous alopecia areata. J Cutan Pathol. 2014;41(3):329-331. https://doi.org/10.1111/j.1600-0560.2012.012277