Histopathologic Features of Alopecia Areata

**A New Look**

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**Background:** A peribulbar lymphocytic infiltrate is the expected histologic feature of alopecia areata, but it is absent in many scalp biopsy specimens. Other diagnostic criteria are needed.

**Objective:** To establish the histologic features of alopecia areata in scalp biopsy specimens taken from different types of alopecia areata, using follicular counts to relate biopsy findings to stages of the disease.

**Methods:** Fifty consecutive new patients with alopecia areata were studied. Four-millimeter punch biopsy specimens were taken from the scalp in areas of recent, active hair loss; old, inactive hair loss; or recent hair regrowth. Specimens were sectioned horizontally. Terminal and vellus-like hairs were counted. Inflammation and fibrosis around lower and upper follicles were rated.

**Results:** The histopathologic features of alopecia areata were not significantly affected by the sex, age, and race of the patient or by the type, percentage of hair loss, total duration, or regression of alopecia areata. The major factor affecting the histopathologic features was the duration of the current episode of alopecia areata. In the acute stage, bulbar lymphocytes surrounded terminal hairs in early episodes and miniaturized hairs in repeated episodes. In the subacute stage, decreased anagen and increased catagen and telogen hairs were characteristic. In the chronic stage, decreased terminal and increased miniaturized hairs were found, with variable inflammation. During recovery, increasing numbers of terminal anagen hairs from regrowth of miniaturized hairs and a lack of inflammation were noted.

**Conclusions:** The histopathologic features of alopecia areata depend on the stage of the current episode. Alopecia areata should be suspected when high percentages of telogen hairs or miniaturized hairs are present, even in the absence of a peribulbar lymphocytic infiltrate.

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**Alopecia Areata** is a common cause of nonscarring alopecia, occurring in 1.7% of Americans by age 50 years.1 It occurs in both sexes in all racial groups.2 Alopecia areata may present at any age, but it is most common in the third and fourth decades of life.2 A family history of alopecia areata exists in approximately 20% of patients.3,2 In 20% to 30% of patients, it is associated with other autoimmune diseases, such as type 1 diabetes mellitus.3 Alopecia areata may occur as a single, self-limiting episode, or it may recur at varying intervals over many years. Hair loss may occur on any part of the body, but it is most common and most obvious on the scalp. Typically, lesions of alopecia areata consist of 1 or more round, smooth, bald patches in which the scalp feels slightly depressed because of loss of the supportive effect of the hair shafts; exclamation mark hairs may be seen at the periphery of each patch. The pattern of scalp involvement may be patchy (scattered patches), mosaic (a mosaic of patches), confluent (a confluence of patches), or diffuse. The form of alopecia areata known as ophiasis consists of a broad band of hair loss around the margin of the scalp. In alopecia totalis, the whole scalp is affected; in alopecia universalis, all body hair is lost. These different forms of alopecia areata may evolve into one another during a single episode or with recurrent episodes.5

In the histologic assessment of scalp biopsy specimens from alopecia areata, a peribulbar lymphocytic inflammation is usually considered to be an essential finding in establishing the diagnosis.5,7 The lymphocytic infiltrate is rich in helper T cells, which are considered to be evidence of an autoimmune process.8 However, patients with alopecia areata may visit physicians at different times during and between episodes, when the peribulbar inflammation may be absent.

In the acute stage, a dense or moderate infiltrate develops around the anagen hair bulb. The infiltrate comprises lymphocytes and Langerhans cells, with eosinophils and plasma cells occasionally.9 This inflammation can lead to edema, microvesiculation, apoptosis, necrosis, and the ap-
The acute, subacute, and chronic phases of the disease. Biopsy specimens. Follicular counts were used to define stages of evolution by means of horizontally sectioned scalp mine the histopathologic features of alopecia areata in all infundibula often seen in alopecia areata. But they lack hair shafts, perhaps accounting for the empty may contain central pinkish remnants of inner root sheath, and therefore extrudes another 3 mm of hair tipped by the weakened hair shaft reaches the skin surface and is exposed to trauma. After approximately 2 weeks in catagen, the hair root ascends approximately 3 mm to the middle follicular level in telogen, like any normal follicle, and therefore extrudes another 3 mm of hair tipped by the expanded fracture. This is the typical exclamation point hair, which is destined for subsequent shedding, since it is a telogen hair. At the conclusion of telogen, some months later, a new hair grows. If there is no inflammation at this time, it may revert to a normal hair. If inflammation is still present, it is likely that the hair will be miniaturized. Miniaturized hairs may cycle for some time before inflammation subsides and allows regrowth of normal terminal hairs. Anagen inhibition results in a tapered-down hair shaft, such as that seen with chemotherapy. As it reaches the skin surface, it breaks off. If it continues to grow, the taper will reverse, and a short, pointed, dystrophic anagen hair will be produced. In due course, that hair can continue to cycle in different ways. It may persist for a while as a dystrophic anagen hair, which is eventually shed before reverting to a normal anagen hair; it may miniaturize for 1 or more cycles, depending on inflammation, followed by regrowth to a normal anagen hair with normal subsequent cycling; or, last, it may persist as a so-called nanogen hair before resumption of normal cycling. Nanogen hairs, found in the middle or upper dermis, are minute and cycle rapidly, showing mixed features of anagen, catagen, and telogen. They may contain central pinkish remnants of inner root sheath, but they lack hair shafts, perhaps accounting for the empty infundibula often seen in alopecia areata.

The purpose of this prospective study is to determine the histopathologic features of alopecia areata in all stages of evolution by means of horizontally sectioned scalp biopsy specimens. Follicular counts were used to define the acute, subacute, and chronic phases of the disease.

### METHODS

Fifty consecutive new patients with alopecia areata seen at the Baylor Hair Research and Treatment Center, Dallas, Tex, were included in the study. The age, sex, and race of each patient were recorded. A careful history was taken from each patient concerning general health, the presence of autoimmune diseases or atopy, and a family history of alopecia areata or autoimmune disease.

The types of alopecia areata diagnosed in this series, in order of severity, were diffuse, patch, ophiasis, mosaic, confluent, totals, and universalis. The duration of alopecia areata since onset of the first episode was reported as 1 to 3, 4 to 12, 13 to 24, 25 to 48, or 49 to 304 months. Duration of the current episode was reported as 1, 2, 3, 4 to 12, 13 to 24, or 25 to 244 months. The percentage of hair loss in the current episode was reported as 1% to 5%, 6% to 25%, 26% to 50%, 51% to 75%, 76% to 93%, or 96% to 100% in patients with active or regressing disease.

At the initial visit, one 4-mm scalp biopsy specimen was taken from an area of active or recent hair loss or from an area of recent regrowth. Where these were not present, an area of old hair loss was used for biopsy. Biopsy specimens were fixed in 10% formalin, embedded in paraffin, and processed routinely. At least 12 horizontal sections were cut and then stained with hematoxylin and eosin. All terminal anagen, catagen, and telogen hairs and vellus hairs (which included miniaturized hairs) were counted, as were follicular units and follicular stele (streamers). Anagen and telogen percentages and terminal-vellus ratios were calculated from these follicular counts. In addition, inflammation and fibrosis around lower and upper follicles were rated as nil, mild, moderate, or dense.

Follicular counts and inflammation ratings were correlated with the sex, age, and race of the patient; type of alopecia areata; percentage of hair loss; duration of the current episode; total duration of the disease; and regression during the current episode.

Follicular counts from the biopsy specimens from the 50 consecutive patients in this study were compared with those of 561 patients with alopecia areata who underwent biopsy at the Baylor Hair Research and Treatment Center between January 1, 1989, and December 31, 2002, and with 22 control subjects.

### RESULTS

Of the 50 new patients, 40 were white, 5 were Hispanic, 3 were Asian, and 2 were African American. There were 21 men and 29 women, with a mean age of 33 years. The number of patients with each type of alopecia areata were as follows: diffuse, 1; patch, 18; ophiasis, 10; mosaic, 5; confluent, 4; totalis, 6; and universalis, 6. Associated medical conditions consisted of atopy in 18 patients (36%), autoimmune disease in 6 (12%), and other conditions in 4 (8%). A history of familial alopecia areata was found in 11 patients (22%). Autoimmune disease was reported in the families of 28 patients (56%); however, this value was inflated by diabetes mellitus in which the type was not specified.

The mean follicular counts from biopsy specimens from the 50 patients matched those from the 561 patients with alopecia areata in the comparison group. The counts showed a large increase in vellus hairs, a reduction in terminal hairs, and a higher percentage of telogen hairs compared with controls (Table 1).

Follicular counts in men and women were similar. Follicular counts showed little variation up to age 60 years. The reduced counts in the only 2 patients in the 61- to 75-year-old age group may reflect senescence. Follicular counts

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Patients, No.</th>
<th>Age, Mean, y</th>
<th>Sex, M:F Ratio</th>
<th>Terminal-Vellus Ratio</th>
<th>Anagen/Telogen, %</th>
<th>Follicular Units, No.</th>
<th>Follicular Steleae, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>New AA patients</td>
<td>50</td>
<td>33</td>
<td>1:1.4</td>
<td>17</td>
<td>30</td>
<td>1:1.2</td>
<td>46/64</td>
</tr>
<tr>
<td>Total AA patients</td>
<td>561</td>
<td>31</td>
<td>1:2</td>
<td>17</td>
<td>13</td>
<td>30</td>
<td>1:1.3</td>
</tr>
<tr>
<td>Control subjects</td>
<td>22</td>
<td>43</td>
<td>1:0.7</td>
<td>35</td>
<td>5</td>
<td>40</td>
<td>7:1</td>
</tr>
</tbody>
</table>

Abbreviation: AA, alopecia areata.
differed somewhat in the 4 racial groups, but the numbers of nonwhites were too small for meaningful analysis.

Total follicular counts were similar in different types of alopecia areata, but there was a marked decrease in the anagen count with increasing severity of the disease, from 55% in the patch type to 30% in alopecia universalis (Table 2).

Follicular counts were correlated with percentage of hair loss, showing that the greater the hair loss, the greater the increase in telogen and vellus hairs (Table 2). Follicular counts by total duration of alopecia areata did not show obvious differences in anagen and telogen percentages. However, increasing duration could be correlated with an increasing proportion of vellus hairs. Changes in follicular counts were related to the duration of the current episode of alopecia areata (Table 2). The greatest loss of anagen hairs with relative increase in telogen hairs occurred in the early, acute stage of the disease. During the subsequent few months, the percentage of anagen hairs increased and the percentage of telogen hairs decreased (Figure 1). At the same time, terminal hairs decreased and vellus hairs increased (Figure 2). These anagen and telogen percentages and terminal-vellus ratios fluctuated with repeated episodes of alopecia areata. Follicular stelae numbers were increased above the 1 to 2 found in controls (Table 1) owing to an early increase in terminal hairs and a later increase in vellus (miniaturized) hairs. The greater number of stelae at 25 months vs 1 month reflects the higher number of vellus hairs at 25 months and the large increase in the percentage of telogen hairs at both times. The site and degree of follicular inflammation (which occurred in about one third of patients) also varied according to the duration of the current episode. A perifollicular lymphocytic infiltrate was more common around the hair bulb and the lower follicle (isthmus and infundibulum), and...
it appeared early in the current episode. In cases of chronic disease, with the increasing disappearance of terminal hairs due to miniaturization, a peribulbar infiltrate of variable intensity was often observed only around miniaturized hairs in the upper dermis. Fibrosis was relatively insignificant, not prominent around lower follicles but more obvious around upper follicles. With recovery, the number of terminal hairs increased and inflammation subsided.

**ACCURATE FOLLICULAR COUNTS**

Accurate follicular counts can be made on a routine basis only if scalp biopsy specimens are sectioned horizontally. It is important to evaluate sections taken through the lower or reticular dermis to capture the terminal hair bulbs and sections taken through the upper or papillary dermis to capture the miniaturized, velluslike hairs seen in alopecia areata.

Follicular counts in this study were not obviously affected by the sex, age, and race of the patient or by the type, percentage of hair loss, total duration, or regression of alopecia areata. However, follicular counts and follicular inflammation were related to the duration of the current episode. This provided interesting data regarding the extent, site, and timing of peribulbar lymphocytic inflammation and the changing anagen and telogen percentages and terminal-vellus ratios. A key observation was that whereas the peribulbar lymphocytic inflammation involved terminal hair bulbs in the initial acute episode, it mainly involved miniaturized hair

**Figure 3. The alopecia areata cycle. A severe episode of alopecia areata causes anagen arrest, with formation of an exclamation point hair. The affected hair may recycle as a normal hair or a miniaturized hair. A moderate episode causes anagen inhibition, forming a tapered dystrophic anagen hair, which may recycle as a normal, miniaturized, or nanogen hair (hematoxylin-eosin, original magnification for acute stage, ×40; subacute stage—catagen hairs, ×8; subacute stage—telogen hairs, ×20; chronic stage and recovery, ×20).**

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bulbs in chronic, repeated episodes, situated in the papillary dermis.

In the acute stage of an episode of alopecia areata, the first sign will be the inflammatory infiltrate around the terminal hair bulb, perhaps involving the dermal papilla (Figure 3). In the subacute stage, an increasingly large number of catagen hairs will be seen, and some telogen hairs will appear after a few weeks (Figure 3). As the hair bulb retracts upward in its journey to telogen level, the inflammatory infiltrate may persist in or around follicular stelae (streamers). In the chronic stage, there is a reversal of the terminal-vellus ratio, and many more miniaturized hairs will be seen at the expense of terminal hairs. The terminal-vellus ratio is likely to be 1:1 rather than the usual 7:1. A variable amount of inflammation will be seen and, if present, is more likely to be in the papillary dermis around miniaturized hair bulbs than in the reticular dermis or subcutaneous tissue because many terminal hairs have miniaturized and ascended to the upper dermis (Figure 3). Later, in the recovery stage, miniaturized hairs will grow back into terminal hairs so that the proportion of terminal to vellus hairs will start reverting to normal (Figure 3). Furthermore, little inflammation, if any, will be found. The percentage of anagen hairs will increase, with a corresponding decrease in telogen hairs. This situation can be complicated by recurrent episodes after the initial one, so mixtures of these findings must be expected in cases of chronic disease.

The important message, however, is that alopecia areata progresses through acute, subacute, and chronic stages. Thus, it can be diagnosed with some confidence, even when an inflammatory infiltrate is absent, based on increasing numbers of telogen hairs in the acute and subacute stages and increasing velluslike miniaturized hairs in the subacute and chronic stages.

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REFERENCES