Diagnostic Usefulness of a Peribulbar Eosinophilic Infiltrate in Alopecia Areata

Tae Young Yoon, MD, PhD; Dong Yoon Lee, MD; Young Jin Kim, MD; Ji Yeoun Lee, MD, PhD; Mi Kyeong Kim, MD, PhD

IMPORTANCE The histopathologic diagnosis of alopecia areata (AA) may be difficult in the chronic stage in which the presence of a peribulbar lymphocytic infiltrate is not definite. An eosinophilic infiltrate has been reported as a relatively common histopathologic finding and a helpful diagnostic feature in AA.

OBJECTIVE To investigate the frequency and diagnostic usefulness of an eosinophilic infiltrate around the hair bulbs or within the fibrous tracts during the chronic stage of AA.

DESIGN, SETTING, AND PARTICIPANTS A retrospective review was conducted at Chungbuk National University Hospital. A total of 162 scalp biopsy specimens of AA were analyzed.

MAIN OUTCOMES AND MEASURES The frequency of a peribulbar eosinophilic infiltrate in AA.

RESULTS In 30 of 162 specimens (18.5%) of AA in all stages, eosinophils were found around the hair bulbs with variable density but were not identified in the fibrous tracts of any specimen. Eosinophils around the hair bulbs were detected in 24 of 78 specimens (30.8%) of the acute stage of AA in which a peribulbar lymphocytic infiltrate was present, and eosinophils were densely infiltrated in 6 of these specimens (7.7%). In contrast, in the chronic stage of AA in which a peribulbar lymphocytic infiltrate was sparse or absent, eosinophils around the hair bulbs were found in only 6 of 84 specimens (7.1%); furthermore, eosinophils were sparsely present in all specimens. Pigmentary incontinence around the hair follicles was found in 58 of 84 specimens (69.0%), follicular miniaturization in 52 (61.9%), and shift to the catagen or telogen phase in 46 (54.8%).

CONCLUSIONS AND RELEVANCE An eosinophilic infiltrate around the hair bulbs or within the fibrous tracts is not a common finding in the histopathologic characteristics of AA, especially in the chronic stage of the disease. Thus, the diagnostic usefulness of the eosinophilic infiltrate is limited to few cases of AA in the chronic stage. Other histopathologic findings, such as pigmentary incontinence around the hair follicles, follicular miniaturization, and shift to the catagen or telogen phase, are more useful diagnostic features in the cases of AA not showing a definite peribulbar lymphocytic infiltrate.
Alopecia areata (AA) is a common form of nonscarring alopecia believed to be an autoimmune disease targeting the hair follicles on any part of the body, mainly the scalp. Although a peribulbar lymphocytic infiltrate, a so-called “swarm of bees,” is considered as the diagnostic histopathologic feature of AA, it may be subtle or even absent in the chronic stage of AA; therefore, other histopathologic features are required to establish the diagnosis. Increased hairs in the catagen or telogen phase, follicular miniaturization, and pigmen-
tary incontinence around the hair follicles are frequently found in AA, and the former 2 findings are more significant in long-standing lesions of AA. The presence of eosinophils around the hair bulbs or within the fibrous tracts has been reported as a relatively common finding in AA and was particularly helpful diagnostic feature when a peribulbar lymphocytic infiltrate was sparse or absent.

The primary aim of our study was to investigate the frequency and diagnostic usefulness of eosinophils around the hair bulbs or within the fibrous tracts in AA according to the presence or absence of a definite peribulbar lymphocytic infiltrate. We also determined the frequency of other histopathologic features of AA. We further analyzed scalp biopsy specimens of androgenetic alopecia (AGA) and trichotillomania to compare the frequency of eosinophils in AA with that in other nonscarring forms of alopecia and to determine the frequency of several histopathologic features shared among these 3 forms of alopecia.

Methods

Study Design
Specimens of all cases of AA diagnosed on the basis of clinical and histopathologic findings by an expert dermatopathologist (T.Y.Y.) at the Department of Dermatology, Chungbuk National University Hospital, Cheongju, South Korea, from January 1, 2003, to May 31, 2012, were retrospectively collected. Cases with uncertain diagnoses were excluded. All clinical forms of AA were included. A total of 177 scalp biopsy specimens obtained from 136 patients with AA were initially obtained. After a thorough review of all specimens, 15 of 177 were excluded because 7 specimens contained insufficient hair follicles to examine the histopathologic features and 8 specimens were sectioned vertically. All of the remaining specimens were obtained by 5-mm punch biopsy and sectioned horizontally. A total of 162 specimens from 128 patients were analyzed (Figure 1).

To compare the frequency of an eosinophilic infiltrate and several shared histopathologic features (eg, pigmentary incontinence around the hair follicles, shift to the catagen or telogen phase, or follicular miniaturization) among 3 forms of alopecia, 69 scalp biopsy specimens of AGA (43 specimens from 29 patients) and trichotillomania (26 specimens from 24 patients) diagnosed by the same dermatopathologist (T.Y.Y.) during the same period were also analyzed. Only the cases of AGA showing significant follicular miniaturization (terminal to vellus hair ratio of ≤2:1) and the cases of trichotillomania showing distorted follicular anatomy were included (Figure 1).

The histopathologic features of the specimens were examined to determine the presence of a peribulbar or peri-

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Association between the grade of a peribulbar lymphocytic infiltrate and that of peribulbar eosinophils. Statistical significance was established at \( P < .05 \). Statistical analysis was performed using SPSS, version 21 (SPSS Inc).

**Results**

The patients with AA comprised 78 females (57.4%) and 58 males (42.6%) (1.3:1.0 ratio). The mean age at diagnosis was 33.3 years (range, 15 months to 76 years). Disease duration showed a wide range, from 2 days to 40 years (Table 1).

Of 162 specimens of AA, 78 specimens (48.1%) showed a definite peribulbar lymphocytic infiltrate (acute stage, graded as 2+ or 3+) and 30 (18.5%) showed a peribulbar eosinophilic infiltrate with variable density. In all specimens, no eosinophils were found within the fibrous tracts. In the acute stage of AA, a peribulbar eosinophilic infiltrate was detected in 24 (30.8%) of 78 specimens, and eosinophils were densely infiltrated in 6 (7.7%) of those specimens. In contrast, in the chronic stage of the disease, a peribulbar eosinophilic infiltrate was found in only 6 (7.1%) of 84 specimens; furthermore, eosinophils were sparsely present in all of the specimens. Indeed, the grade of peribulbar eosinophils correlated with that of a peribulbar lymphocytic infiltrate (\( r = 0.39, P = .01 \)). Pigmentary incontinence around the hair follicles, follicular miniaturization, shift to the catagen or telogen phase, and extravasated erythrocytes within the hair follicles were found in 58 (69.0%), 52 (61.9%), 46 (54.8%), and 20 (23.8%) of 84 specimens of the chronic stage of AA, respectively. Extravasated erythrocytes and follicular miniaturization were significantly more frequent in the chronic stage than in the acute stage (\( P = .01 \) and \( P = .001 \), respectively). Although pigmentary incontinence and shift to the catagen or telogen phase seemed to be only slightly more frequent in the chronic stage than in the acute stage, the differences were statistically significant (\( P = .03 \) and \( P = .02 \), respectively) (Table 2).

There were 13 female and 16 male patients with AGA. The mean age at diagnosis was 35.2 years (range, 15-59), and disease duration ranged from 2 months to 30 years. Of 43 specimens of AGA, 23 (53.5%) showed a mild to moderate peri-infundibular lymphocytic infiltrate; however, there was no inflammatory infiltrate around the hair bulbs. Eosinophils were found around the lower infundibulum in 2 (4.7%) of 43 specimens. Seventeen (39.5%) specimens showed evidence of a shift to the catagen or telogen phase. Pigmentary incontinence around the hair follicles and extravasated erythrocytes within the hair follicles are not features of AGA, and they were not present in any specimens of AGA.

Of 24 patients with trichotillomania, 13 were female and 11 were male. The mean age at diagnosis was 10.1 years (range, 2-21), and disease duration ranged from 1 week to 5 years. An eosinophilic infiltrate, pigmentary incontinence, and extravasated erythrocytes were found around or within the traumatized follicles in 2 (7.7%), 20 (76.9%), and 15 (57.7%) of 26 specimens, and 22 specimens (84.6%) showed evidence of a shift to the catagen or telogen phase. Perifol-
Peribulbar eosinophilic infiltrate as diagnostic

Table 2. Histopathologic Characteristics of Alopecia Areata

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 162)</th>
<th>Acute Stage (N = 78)</th>
<th>Chronic Stage (N = 84)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophils</td>
<td>30 (18.5)</td>
<td>24 (30.8)</td>
<td>6 (7.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pigmentary incontinence</td>
<td>107 (66.0)</td>
<td>49 (62.8)</td>
<td>58 (69.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Extravasated erythrocytes</td>
<td>29 (17.9)</td>
<td>9 (11.5)</td>
<td>20 (23.8)</td>
<td>.01</td>
</tr>
<tr>
<td>Shift to the catagen or telogen phase</td>
<td>85 (52.5)</td>
<td>39 (50.0)</td>
<td>46 (54.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Follicular miniaturization</td>
<td>82 (50.6)</td>
<td>30 (38.5)</td>
<td>52 (61.9)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Table 3. Comparison of the Histopathologic Characteristics of 3 Forms of Nonscarring Alopecia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chronic stage of AA (n = 84)</th>
<th>AGA (n = 43)</th>
<th>Trichotillomania (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic infiltrate, %</td>
<td>51.9, Peribulbar</td>
<td>53.5, Peri-infundibular</td>
<td>None</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>7.1, Bulbs/fibrous tracts</td>
<td>4.7, Infundibulum</td>
<td>7.7, Distorted follicles</td>
</tr>
<tr>
<td>Pigmentary incontinence, %</td>
<td>69.0</td>
<td>None</td>
<td>76.9</td>
</tr>
<tr>
<td>Extravasated erythrocytes, %</td>
<td>23.8</td>
<td>None</td>
<td>57.7</td>
</tr>
<tr>
<td>Shift to the catagen or telogen phase, %</td>
<td>54.8</td>
<td>39.5</td>
<td>84.6</td>
</tr>
<tr>
<td>Follicular miniaturization, %</td>
<td>61.9</td>
<td>100.0</td>
<td>None</td>
</tr>
<tr>
<td>Distorted follicular anatomy, %</td>
<td>None</td>
<td>None</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Abbreviations: AA, alopecia areata; AGA, androgenetic alopecia.


dicular inflammation and follicular miniaturization are not features of trichotillomania, and they were not present in any specimens of trichotillomania.

There was no significant difference in the frequency of an eosinophilic infiltrate between AGA, trichotillomania, and the chronic stage of AA (P = .84), and the frequency was less than 10% in all of these forms of nonscarring alopecia. Although pigmentary incontinence around the hair follicles was more frequently found in trichotillomania than in the chronic stage of AA, the difference was not statistically significant (P = .09), and the frequency of that in the chronic stage of AA was more than 50%. Extravasated erythrocytes and shift to the catagen or telogen phase were significantly more frequent in trichotillomania than in the chronic stage of AA (both P < .001). Although the shift to the catagen or telogen phase, follicular miniaturization, and pigmentary incontinence around the hair follicles are frequently found in AA, they are not specific and can be observed in other types of nonscarring alopecia. The shift to the catagen or telogen phase and follicular miniaturization are also found in trichotillomania. Follicular miniaturization is the hallmark characteristic of AGA, and the number of hairs in the catagen or telogen phase also increases in AGA. Elston et al and Peckham et al reported that the presence of eosinophils around the hair bulbs or within the fibrous tracts was a relatively common finding in any stage of AA (44% of all cases and 18% of the cases without peribulbar inflammation in the study by Peckham et al), and that eosinophils were not present with significant frequency in AGA or trichotillomania. Thus, the presence of eosinophils around the hair bulbs or within the fibrous tracts was a helpful diagnostic feature of AA. However, El Darouti et al reported that eosinophils were found in only 11 (22%) of the 51 examined slides of established lesions of AA, and only 1 eosinophil was detected in the entire slide in 4 of those 11 cases.

In our study, the total frequency of an eosinophilic infiltrate in all cases of AA was only 18.5%, and the frequency of an eosinophilic infiltrate in the acute stage of AA was 30.8%. These results were significantly different from those in the study by
Peckham et al.³ (44% and 49%, respectively). Most notably, in the chronic stage of AA without a definite peribulbar lymphocytic infiltrate, which was difficult to differentiate histopathologically from AGA, the frequency of an eosinophilic infiltrate was only 7.1%, and it did not significantly differ from the frequency in AGA or trichotillomania. Moreover, the density of a peribulbar eosinophilic infiltrate was very sparse, and eosinophils were absent in the fibrous tracts. Therefore, the association between a peribulbar lymphocytic infiltrate and peribulbar eosinophils in our study suggests that a peribulbar eosinophilic infiltrate might be secondary to a lymphocytic infiltrate.

All of the other histopathologic features of AA, such as shift to the catagen or telogen phase, pigmentary incontinence around the hair follicles, and follicular miniaturization, were found more frequently when a peribulbar lymphocytic infiltrate was sparse or absent in our study. This result is consistent with the fact that the aforementioned features become more significant in the chronic stage of AA.¹,⁴,⁵ The combination of those 3 features with significant frequency can be found in the chronic stage of AA, but not in AGA or trichotillomania.

The main limitation of our study is the relatively small sample size of the control group (AGA and trichotillomania). The number of patients with biopsied samples of AGA or trichotillomania was much smaller than the number with AA in our clinic during the same period. However, to our knowledge, this is the largest study to investigate the frequency of an eosinophilic infiltrate in AA.

Conclusions

Our study demonstrates that an eosinophilic infiltrate around the hair bulbs or within the fibrous tracts is not a common finding in the histopathologic characteristics of AA (especially in the chronic stage), it is nonspecific and secondary to a peribulbar lymphocytic infiltrate, and its diagnostic usefulness is limited to few cases of the chronic stage of AA. The constellation of pigmentary incontinence around the hair follicles, follicular miniaturization, and shift to the catagen or telogen phase is more useful in the diagnosis of AA when a definite peribulbar lymphocytic infiltrate is sparse or absent.

Conflict of Interest Disclosures: None reported.

REFERENCES