Clinical manifestations of alopecia in autoimmune blistering diseases: A cross-sectional study

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Background: Alopecia is a complication of autoimmune blistering diseases (AIBDs) that affects patients' quality of life; however, it has generally been overlooked in patients with severe disease because it is regarded as a cosmetic issue.

Objective: To study the epidemiologic data and clinical presentations of alopecia in our cohort of patients with AIBDs.

Methods: Forty-one patients with AIBDs were assessed in this cross-sectional study. An assessment tool to collate patient information, including AIBD scalp involvement, trichoscopic findings, and Severity of Alopecia Tool II scores, was used.

Results: More than 70% of patients in our cohort had at least 1 type of alopecia, with 10% presenting with a nonspecific (end-stage) scarring alopecia. Elevated Dsg1 ratios were predictive of hair loss in pemphigus vulgaris (P < .001) and increased alopecia was associated with worse disease severity in bullous pemphigoid (P = .001).

Limitations: The small sample size and lack of severe cases.

Conclusion: There is a likelihood that 1 in 10 patients with AIBDs have a scarring alopecia related to their disease. To our knowledge, this is the first study including alopecia prevalence in patients with bullous pemphigoid, which was not significantly increased despite providing clues to disease severity. (JAAD Int 2023;10:6-13.)

Key words: alopecia; autoimmune blistering diseases; dermoscopy; pemphigoid; pemphigus; trichoscopy.

INTRODUCTION

Autoimmune blistering diseases (AIBDs) encompass a group of rare skin and mucosal diseases characterized by autoantibodies against adhesion proteins within the skin. These proteins, including Dsg1, Dsg3, bullous pemphigoid (BP) 180 antigens, and collagen VII, are also expressed in normal hair follicles. Although there have been several reports of alopecia associated with AIBDs, it has generally been overlooked in patients with severe AIBDs because it is regarded as a cosmetic issue. On the other hand, alopecia might have significant effects...
on patients' quality of life. The aim of the current study was to investigate the prevalence and type of alopecia in patients with AIBDs under trichoscopic guidance and to assess its association with disease severity.

**METHODS**

**Study design and participants**

An AIBD registry was used to approach all patients in a cross-sectional design, unless they were newly consented on the day of clinical review. Patients with a disproven original AIBD and those with neurologic conditions were excluded.

Participants were randomly selected new and follow-up adult patients with AIBD and consecutively recruited to minimize selection bias from a fortnightly outpatient clinic based at St George Hospital between May 2018 and September 2018. All participants gave written, informed consent according to the Declaration of Helsinki. The study was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC 08/STG/186).

A Registration and Assessment Tool was drawn up and administered to collect demographic and clinical data shown as Supplementary Material 1 (available via Mendeley at https://doi.org/10.17632/hn65fjkpzw.1). During the visit, AIBD severity was scored using the relevant validated scoring systems (Bullous Pemphigoid Disease Area Index [BPDAI], Pemphigus Disease Area Index [PDAI], and epidermolysis bullosa acquista [EBA] disease area index).

We modified an existing alopecia evaluation form, which has been used for routine evaluation in the Hair Unit of the Department of Dermatology and Venereology, Akdeniz University, Turkey (Supplementary Material 1). Specific definitions used in this study are shown in Supplementary Material 2 (available via Mendeley at https://doi.org/10.17632/hn65fjkpzw.1) regarding AIBDs.

We performed trichoscopic examination using a polarized-light handheld dermatoscope (DermLite DL4, 3Gen LLC), which allows scalp visualization at a 10-fold magnification, without an interface solution. No additional invasive procedures were performed unless it was part of routine standard of care.

**Statistical methods**

Data were analyzed by SPSS Statistics for Mac (v19.0; International Business Machines Corporation). Frequency and percentages were calculated for categorical and mean ± standard deviation for continuous variables. Both Fisher’s exact test and Mann-Whitney U test were used for categorical and continuous intergroup comparisons. Univariate and multivariate analysis were performed to evaluate the association of different variables with the severity of AIBDs and alopecia. A P value of < .05 was considered statistically significant. Participants with missing data on the Registration and Assessment Tool were followed up via phone call.

**RESULTS**

One hundred patients were approached in this study from the AIBD registry. Nineteen patients could not be reached because of outdated contact details. Furthermore, 33 patients declined participation because of distance to travel, frailty, or disinterest, and 7 patients were deceased. Forty-one patients with AIBDs were included in this study on voluntary basis, aged 26 to 92 years (mean, 63 years), including 13 men and 28 women (Table I).

Of the 41 patients included in the study, 29 (71%) had at least 1 type of alopecia, which was most prevalent in patients with pemphigus (Table II). The most prevalent alopecia phenotype was pattern hair loss (49%, n = 20), followed by telogen effluvium (10%, n = 4) and nonspecific (end-stage) scarring alopecia (10%, n = 4). Twelve patients (27%) had no hair disease. Only 4 patients (10%) had active scalp lesions during the visit. No participants had missing data.

**Alopecia and disease severity**

At the time of assessment, most patients (63%) had mild AIBD severity (Table I). Comparatively, more patients were in partial remission on more than minimal therapy (32%) than in any other stage of the disease.

In univariate analysis, increased hair shedding as a symptom (P = .033) and patterned hair loss (P = .001)
were prevalent in patients with AIBDs with alopecia, in contrast to those with no alopecia \( (P < .001) \) (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/hn65fjkpzw.1). No significant association was found between alopecia diagnosis and medical history, medications, personal or family history of hair disease, hair care and styling habits, or hair pull test.

The total Severity of Alopecia Tool II (SALT II) score was significantly higher in the pemphigus (mean ± SD = 20.6 ± 15.6) than the BP subgroup (mean ± SD = 11.4 ± 16.4) \( (P = .037) \), which also paralleled the longer duration of pemphigus onset than in pemphigoid \( (P = .032) \) (Table III).

Multivariate analyses showed that alopecia duration \( (P < .001) \) is an independent predictor of hair loss severity (SALT II total) but neither scalp lesions nor AIBD duration. In the pemphigus subgroup, Dsg1 ratios \( (P < .001) \) were associated with higher PDAI severity; however, the SALT II scores were not predictive. Specifically, in pemphigus vulgaris (PV), Dsg1 ratios \( (P < .001) \) were associated with higher SALT II scores, whereas a history of scalp lesions was not significantly associated with SALT II scores.

Multivariate analyses revealed that hair loss in patients with BP was associated with higher BPDAI total scores \( (P = .001) \). However, in these patients with BP, none of BP180, BP230, BPDAI total scores, or scalp lesions were predictors of SALT II scores.

### Trichoscopic features

The most common trichoscopic features in patients with AIBDs with alopecia included anisotrichosis \( (P = .002) \), honeycomb pigment pattern \( (P = .008) \), and epidermal scale (including white polygonal scaling and diffuse yellow scaling \( [P = .021] \) (Fig 1, A and B; Supplementary Table I).

We found an overall incidence of 10% \( (n = 4) \) of nonspecific (end-stage) scarring alopecia in 3 patients with pemphigus foliaceus and 1 patient with EBA. On trichoscopy, lesions were characterized by milky-red and white areas lacking follicular openings, yellow haemorrhagic crusts, epidermal scale, and hair casts.

### DISCUSSION

To our knowledge, this is the first study conducted using trichoscopy to determine the incidence of alopecia in a range of AIBDs. In addition, to our knowledge, this is the first study to quantify alopecia in AIBDs using the revised SALT II score, which determines percentage of scalp hair loss. There is still no universal tool that accurately quantifies hair loss and changes in hair density across all alopecia types, beyond those used for pattern hair loss (Ludwig and Sinclair scores). Therefore, we decided to subdivide scores clinically into hair thinning and baldness categories to further differentiate between diffuse (mostly pattern hair loss) or patchy alopecia, respectively.

### Alopecia and disease severity in AIBDs

In our study, 71% \( (n = 29) \) of patients had at least 1 phenotype of alopecia, yet only 10% of patients had active scalp lesions. This may be explained by 63% of patients with mild disease activity and the co-occurrence of alopecia commonly seen in these age groups.

### Pemphigus

In the pemphigus subgroup, SALT II (hair thinning and baldness) scores were not independent predictors of PDAI severity. In PV alone, despite an increased prevalence of alopecia (89%) and scalp lesions (67%), neither was correlated with pemphigus disease severity. This is perhaps skewed by the 3 patients with pemphigus with no visible active disease. This contrasts the findings of Daneshpazhooh et al\(^8\) in which anagen hair loss and scalp lesions were associated with severe PV disease in 61% of patients \( (n = 96) \) \( (P < .01) \).

Generally, the total SALT II scores were significantly higher in the pemphigus group than in the BP group. Most pertinently, pattern hair loss was observed in 67% \( (n = 12) \) of patients with pemphigus in nonlesional scalps, compared with 30% \( (n = 6) \) of patients with pemphigoid. This is even despite the average age of patients with pemphigoid being greater than that of patients with pemphigus, in which one would expect thinner hair and more pattern hair loss. One explanation of increased pattern hair loss prevalence is the higher proportion of patients with pemphigus with moderate disease severity (36% vs 13% of patients with BP) and the statistically different duration of AIBDs between the groups (7 years in pemphigus group vs 4 years in the pemphigoid group). Patients with active PV are usually quite sick and poorly nourished because of oral or esophageal involvement leading to loss of
protein and increased energy demands from denuded skin. Thus, systemic diseases such as pemphigus could cause increased hair-shedding cycles (telogen effluvium), which in return might cause early appearance of pattern-type hair loss because of decreased hair density. This could be the case in our cohort.

**Subepidermal blistering diseases**

On the other hand, in the BP group, SALT II scores were associated with BPDAI severity. One potential explanation is that more than half of the patients with BP (n = 8) had no hair disease, which would contribute to lower SALT II total scores compared with the pemphigus group. Further, the vast majority (89%) had mild BP disease severity. Reports of hair loss in subepidermal blistering diseases have mainly been associated with pattern hair loss, or conversely an erosive, “persistent denudation of the scalp.”10,11 The latter description has since been classified as mucous membrane pemphigoid, and scarring alopecia has been described when the scalp is affected; however, it is rare.12

**Antibody hypothesis**

Various types of hair loss are described in PV, including classic anagen effluvium, telogen hair loss, and tufted hair folliculitis.2,13-15 This may be because of higher levels of pemphigus antigens such as Dsg1 in the scalp.9,16-19 Interestingly, in our study, Dsg1 ratios (P < .001) were an independent predictor of hair loss in patients with PV. The role of Dsg1 antibodies in nonscarring alopecia is alluded to in the literature. In 2017, Yoshida et al18 reported a case of cutaneous PV associated with nonscarring alopecia and a dominant anti-Dsg1 to anti-Dsg-3 ratio that would normally be expected in pemphigus foliaceous. Similarly, in an earlier study, an initial high anti-Dsg3 to anti-Dsg1 ratio was observed in a patient with PV, which was associated with diffuse nonscarring alopecia as this ratio decreased.19

A specific example of a nonscarring alopecia present in the bullous literature is anagen shedding. Anagen shedding has been suggested to be characteristic in PV, which is different from physiologic anagen arrest and loss of dystrophic hair shafts, seen with treatments of chemotherapy (known as anagen effluvium).2 Although studies have reported a significant correlation between anagen shedding and serum anti-Dsg1 levels in patients with PV,17,20 our present study only identified 3 cases of positive anagen hair pull test out of 14 patients with PV. Pirmez21 was the first to report trichoscopic features in PV and suggests that hair casts in a patient with PV with anagen shedding is a sign of acantholysis of the outer root sheath to herald worse disease activity. Our findings of positive anagen hair pull test could be because of the same mechanism. We could not find any correlation between Dsg3 ratios and PV hair loss; therefore, the role of Dsg3 in hair loss remains confined to early Dsg3 knockout mouse models.22

There is limited literature reporting alopecia in BP; however, autoantibodies have also been suggested to play a role. In a case report of a patient with BP with alopecia areata (AA), BP autoantibodies were hypothesized to cause hair loss because of its association with other autoimmune diseases (such as AA as in this case), rapid response to steroid therapy, and the presence of lymphocytic cells around the hair follicles.23 On the other hand, another patient with BP with a low serum level of antibasement membrane zone antibodies has been described with scarring alopecia, which might suggest a minor role of autoantibodies in the pathogenesis of pseudopelade of Brocq.24 In our patients with BP,
although an elevated BP230 antibody ratio was associated with increased BP disease severity, neither BP230 nor BP180 ratios was associated with hair loss. This finding could suggest a small role for these antibodies in 6 of our 7 patients with nonscarring alopecia.

In EBA, reports of scarring alopecia have been linked to antibody formation against collagen VII in the basement membrane zone; however, even in severe cases, the scalp has often been spared.25 Our 2 patients with EBA demonstrated dichotomous responses paralleled in the literature. One patient with an extensive history of severe disease including esophageal dilatations, presented only with pattern hair loss, to concur with the idea that immune privilege of hair follicles is protective.26 The only cases of hair loss in EBA reported in the literature have been of nonspecific scarring alopecia.27-30

Inflammation hypothesis

Factors secondary to anti-Dsg antibody-mediated acantholysis, such as localized scalp infection, or the destruction of keratinocytes to trigger lymphocytic infiltration on lesional scalps could have resulted in alopecia in our patients.20 This was possible in our cohort of 3 patients with pemphigus foliaceous with active lesions and nonspecific scarring alopecia, 1 patient with PV with AA superimposed on pattern hair loss, and 1 patient with EBA with nonspecific scarring alopecia and trichoscopic findings of tufted hair and pustules.31,32

Autoimmune association

The association of pemphigus, BP, and linear IgA bullous disease with other autoimmune diseases such as vitiligo, AA, and rheumatoid arthritis is well documented in the context of multiple autoimmune syndrome.25,33-37 We identified 7 patients with autoimmune comorbidities such as rheumatoid arthritis, idiopathic thrombocytopenic purpura, autoimmune hepatitis, Sjogren disease, and AA. Despite this, the limited number of patients with autoimmune diseases in our study made it difficult to evaluate the autoimmune association and immunosuppressant effects of alopecia in AIBDs.

Limitations

Limitations included the small sample size because of the rarity of these diseases. Second, the lack of severe cases, which are usually managed in hospital, limited our analysis. A degree of ascertainment bias through a cross-sectional design, limited our population to the incidence of patients who were in partial remission or were routine patients who did not necessarily complain about hair loss. Many
patients had long-term male- and female-patterned hair loss and have adapted to their appearance so the prevalence of pattern hair loss in our study would be underestimated. On another level, most of our patients had a history of scalp involvement; however, they did not have active lesions during the study visit.

**Generalizability and future research**

Future studies could investigate developing a universal alopecia tool to include the assessment of hair density as well as hair loss. With no existing scoring system, we suggest that alopecia severity in pemphigus and pemphigoid could be ascertained by use of the PDAI and BPDAI scalp scores. Future
studies could also use phototrichogram to calculate hair loss objectively and enroll patients with severe disease to ensure generalizability. Local biopsies of the lesional and nonlesional scalp in patients with alopecia to test for specific cytokines could test any inflammatory origin. Furthermore, qualitative research on the psychologic effects of alopecia in these patients is useful to better assess the impact on quality of life. Lastly, given a longer duration, this study could lead to a prospective international cohort study on trichoscopic findings in AIBDs.

CONCLUSION

Alopecia is pervasive in patients with AIBDs and may be physiological and pathological. One in 10 patients with AIBDs have a scarring alopecia that is likely related to their bullous disease, and it remains the possibility that the incidence of alopecia is higher than reported because hair examination has not been routinely performed in patients with AIBDs. Furthermore, scalp involvement was not an indicator of alopecia prevalence in PV or BP. Although Dsg1 ratios and BP230 ratios were both positive predictors of PDAI and BPDAI severity, there remains numerous hypotheses for the cause of alopecia in AIBDs, with scope for future studies including more severe bullous diseases and the development of a universal tool to measure alopecia.

Conflicts of interest

None disclosed.

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