



Scalp Involvement In Pemphigus: A Retrospective Cohort Study Of Clinical And Immunopathologic Features

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ABSTRACT Introduction: Pemphigus is a rare autoimmune blistering disease characterized by the presence of autoantibodies against desmogleins, leading to skin and mucosal blisters and erosions. Scalp involvement is common but poorly characterized.

Objectives: This study investigated the prevalence, clinical patterns, immunopathological features, and correlations with disease severity and serological markers of scalp involvement.

Methods: A retrospective cohort study was conducted at the Dermatology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, including patients diagnosed with pemphigus from 2012 to 2024. Scalp involvement was assessed through clinical examination and pull test. Data collected included demographics, disease subtype, anti-desmoglein antibody titers, PDAI scores, treatments, and outcomes.

Results: Among 115 patients, 57.4% had scalp involvement. Male sex was significantly associated with scalp lesions ($P=0.0148$). Patients with scalp involvement had higher anti-Dsg1 titers (mean

206.4 vs. 74.2 IU/mL, $P < 0.001$) and higher PDAI scores (mean 43.9 vs. 32.1, $P = 0.006$). Disease severity stratification also differed significantly between groups ($P = 0.0147$). Three clinical phenotypes were identified: scaling without alopecia, crusting and erosions (further stratified into circumscribed and confluent forms), and extensive patchy alopecia, each associated with specific clinical and serological characteristics.

Conclusions: Scalp involvement is common in pemphigus and correlates with higher anti-Dsg1 titers and disease severity. Recognizing distinct scalp phenotypes may support earlier diagnosis and more targeted management.

Introduction

Pemphigus is a rare group of autoimmune blistering diseases characterized by blisters and erosions of the skin and mucous membranes. The disease is mediated by autoantibodies against desmosomal proteins, primarily desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3), leading to the loss of keratinocyte adhesion and acantholysis [1-3]. The two most common subtypes, pemphigus vulgaris (PV) and pemphigus foliaceus (PF), have distinct clinical and immunologic profiles [4,5].

Scalp involvement has been reported in up to 50% of pemphigus cases [6-9], but its incidence, specific clinical phenotypes, immunopathological features, and prognostic significance remain poorly characterized [10]. While erosions and crusting are the most commonly described lesions, alopecia is rarely reported, and the underlying mechanisms remain unclear [11-14]. However, clinical observations suggest a broader spectrum of scalp manifestations, including desquamation and nonscarring alopecia, suggesting a phenotypic heterogeneity that has not been systematically characterized in the literature.

Despite its prevalence, scalp pemphigus is often underdiagnosed or misdiagnosed, as its presentation may mimic seborrheic dermatitis, psoriasis, or cicatricial alopecia [12,15,16]. Hair cover complicates lesion detection, and topical therapies are often impractical or ineffective, potentially increasing the psychological burden on patients. In addition, the relationship between scalp involvement and overall disease severity or therapeutic response remains uncertain. Further investigation is needed to define the clinical, prognostic, and therapeutic implications of scalp involvement in pemphigus [10,17-19].

Objectives

The aim of this study was to evaluate the clinical, serological, and immunopathological characteristics of patients with pemphigus involving the scalp, to assess both its prevalence and the specific features of scalp lesions, and to compare patients with and without scalp involvement.

Methods

A retrospective observational cohort study was conducted at the Department of Dermatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. The study included patients diagnosed with pemphigus vulgaris, foliaceus, or vegetans who were followed up between 2012 and 2024. Data collection included comprehensive medical history, clinical findings, laboratory analyses, instrumental diagnostics, histological examinations, direct and indirect immunofluorescence results, and treatment regimens. For each patient, relevant variables were recorded, including pemphigus subtype, age at diagnosis, sex, age at study entry, anti-Dsg1 and anti-Dsg3 antibody levels at diagnosis, disease severity as assessed by the Pemphigus Disease Area Index (PDAI), treatments, and follow-up. Scalp involvement was assessed clinically using specific parameters, including erythema, crusts, erosions, scaling, and alopecia, with additional assessment of hair follicle involvement through the pull test. The extent of scalp involvement was quantified using the PDAI. Clinical assessments were consistently performed by the same dermatologists with experience in autoimmune blistering diseases, reducing inter-observer variability and potential bias.

Patients were divided into two groups based on the presence or absence of scalp involvement. Comparisons were made with respect to demographic characteristics, clinical parameters, immunopathological findings, and therapeutic responses. Pemphigus severity was stratified into three categories using the PDAI scoring system: mild (PDAI < 15), moderate (PDAI 15–44), and severe (PDAI ≥ 45). Patients were excluded if they lacked a confirmed diagnosis based on histological and immunofluorescence examination, had both anti-Dsg1 and anti-Dsg3 levels below 20 U/mL, or had incomplete data on key study variables (e.g., scalp involvement description, PDAI scores, antibody levels). No data imputation was performed. Descriptive statistical analyses were performed for all variables. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Results

Cohort Description and Subgroup Comparison

A total of 115 patients with pemphigus were included in the study (67 females, 48 males), with a mean age at diagnosis of 53.9 years \pm 15.6. Among them, 66 (57.4%) had scalp involvement either at disease onset or during subsequent disease flares. The most common subtype was PV (88/115, 76.5%), followed by PF (26/115, 22.6%); a single case of pemphigus vegetans (PVe) (0.9%) was recorded.

The mean age at diagnosis was 51.3 years for patients with scalp involvement and 57.3 years for those without. This difference was statistically significant ($P=0.0389$). Regarding sex distribution, scalp involvement was observed in equal proportions of males and females (34 males and 32 females), whereas females predominated in the non-scalp group (35 females and 14 males). Logistic regression revealed a significant association between male sex and scalp lesions ($P=0.0148$). The distribution of pemphigus subtypes was similar between the two groups. PV accounted for 50 out of 66 (75.8%) patients with scalp involvement and 38 out of 49 (77.6%) patients without scalp involvement. PF was present in 24.2% and 20.4% of patients in the scalp-involved and non-scalp-involved groups, respectively. The only PVe case occurred in the non-scalp group (2.0%).

Anti-Dsg1 levels were significantly higher in patients with scalp involvement (mean 206.4 IU/mL, range 1–1176) compared to those without (mean 74.2 IU/mL, range 1–410.4) ($P=0.0001$). Anti-Dsg3 levels were not significantly different between groups (scalp group: mean 165.5 IU/mL, range 0–1206; non-scalp group: mean 204.3 IU/mL, range 0–2451) ($p=0.512$).

The mean PDAI was higher in patients with scalp involvement (mean 43.9, range 11–120) than in those without (mean 32.1, range 9–118; $p = 0.006$). Disease severity stratification confirmed this trend ($P=0.0147$): among patients with scalp involvement, 4.5% had mild disease (PDAI <15), 53% had moderate disease (PDAI 15–44), and 42.4% had severe disease (PDAI \geq 45). In patients without scalp involvement, 12.2% had mild disease, 69.4% had moderate disease, and 18.4% had severe disease.

Regarding treatment, all patients with scalp involvement and almost all patients without scalp involvement (96%) received systemic corticosteroids. Rituximab was used more frequently in the group with scalp involvement (33/66, 50%, mean cycles 1.88) than in the group without scalp involvement (11/49, 22.4%, mean cycles 2.18). In a refined logistic regression model, rituximab treatment was significantly associated with scalp involvement ($P<0.05$). Patients with alopecia achieved complete hair regrowth after rituximab, albeit with a relapse rate of 50%.

The mean follow-up duration was five years. During follow-up, 18/66 (27.3%) of patients with scalp involvement were lost to follow-up (including 12 deaths, 18.2%). Among those without scalp involvement, 22/49 (44.9%) were lost to follow-up (including five deaths, 10.2%). Despite higher mortality in the scalp-involved group, the difference was not statistically significant. Clinical and serological comparisons between groups are shown in Table 1.

Clinical and Immunopathological Phenotypes of Scalp Involvement

Among the 66 patients with scalp involvement, three main clinical phenotypes emerged based on dermatological examination and pull test: i) scaling without alopecia; ii) crusting and erosions; iii) extensive patchy alopecia. The crusting and erosions phenotype was further stratified into two subgroups, circumscribed and confluent, according to the extent of scalp involvement.

Scaling without Alopecia

This pattern, observed in nine patients (13.64%, five males and four females), was characterized by diffuse desquamation without crusts, erosions, or alopecia. All patients had a negative pull test, indicating no follicular involvement. Trichoscopy confirmed the absence of follicular damage, showing yellow-white scales with preserved follicular ostia (Figure 1). PF was the predominant subtype (8/9 patients), with one case of PV. The mean PDAI in this group was 42.1. Anti-Dsg1 titers were elevated (mean 376.41 IU/mL), reflecting the predominance of PF, while anti-Dsg3 levels were low (mean 139.31 IU/mL, median 2.0 IU/mL). The mean age at diagnosis was 54.2 years. Three patients achieved complete remission; five experienced at least one relapse.

Circumscribed Crusting and Erosions

This was the most common phenotype, affecting 45 patients (68.18%, 22 males and 23 females). Lesions involved less than two scalp quadrants and were accompanied by a positive pull test showing anagen hair loss. Trichoscopic examination showed erythema, yellow scales, and hemorrhagic dots and globules. (Figure 2). PV was the predominant subtype (38/45), with seven cases of PF. The mean PDAI score was 40.8. Mean anti-Dsg1 and anti-Dsg3 titers were 170.84 and 166.85 IU/mL, respectively. The mean age at diagnosis was 51.3 years. Most patients required systemic immunosuppression; 19 received rituximab. Twenty patients achieved remission, and 28 had at least one relapse.

Confluent Crusting and Erosions

This more severe form, seen in eight patients (12.12%, seven males and one female), involved extensive lesions in more

Table 1. Patient characteristics summary.

Characteristics	Scalp involvement	No scalp involvement	p-value
Total patients	66	49	-
Mean age at diagnosis (years)	51.3	57.3	0.0389
Female	32	35	-
Male	34	14	0.0148
Pemphigus vulgaris	50 (75.8%)	38 (77.6%)	0.463
Pemphigus foliaceus	16 (24.2%)	10 (20.4%)	-
Pemphigus vegetans	0 (0%)	1 (2%)	-
Mean PDAI score (range)	43.9 (11–120)	32.1 (9–118)	0.006
Mild PDAI (<15)	3 (4.5%)	6 (12.2%)	0.0147*
Moderate PDAI (15-44)	35 (53%)	34 (69.4%)	-
Severe PDAI (≥45)	28 (42.4%)	9 (18.4%)	-
Mean Dsg1 level (IU/mL) (Range)	206.4 (1–1176)	74.2 (1–410.4)	0.0001
Mean Dsg3 level (IU/mL) (Range)	165.5 (0–1206)	204.3 (0–2451)	0.512
Rituximab use	33 (50.0%)	11 (22.4%)	<0.05 (refined model)
Mean rituximab cycles	1.88	2.18	-
Azathioprine use	19 (28.8%)	9 (18.4%)	-
Cyclophosphamide use	10 (15.2%)	5 (10.2%)	-
Methotrexate use	3 (4.5%)	1 (2.0%)	-
Mycophenolate Mofetil use	4 (6.1%)	1 (2.0%)	-
Dapsone use	2 (3.0%)	1 (2.0%)	-
Lost to follow-up or died	18 (27.3%)	22 (44.9%)	-
Mortality rate	12 (18.2%)	5 (10.2%)	-

*p = 0.0147 refers to the overall comparison of PDAI severity category distribution between groups.

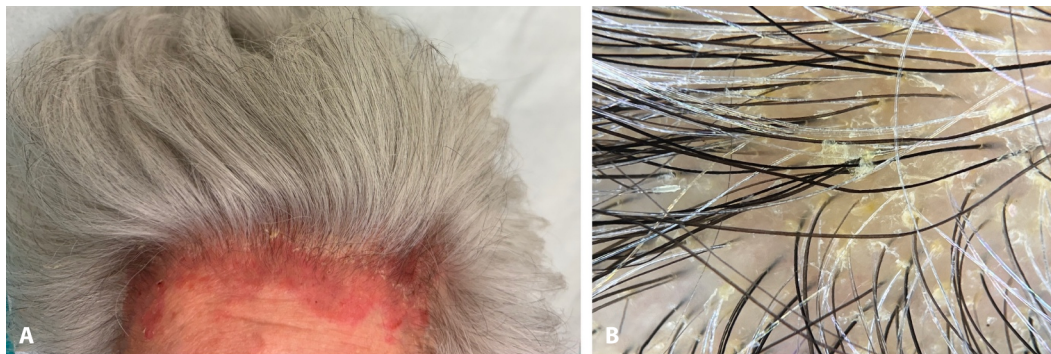


Figure 1. Clinical presentation of the scaling without alopecia phenotype. A) Diffuse scaling of the scalp without erosions, crusts, or visible hair loss in a patient with PF. Pull test was negative and no evidence of follicular involvement was observed. B) Trichoscopy shows yellow-white scales, with preserved follicular openings and no signs of follicular damage.

than two scalp quadrants and a positive pull test in the anagen phase (Figure 3A). Trichoscopic features were analogous to those observed in circumscribed lesions. All patients had PV and the majority were male (7/8). The mean PDAI score was 53.5. Mean antibody titers were 184.58 IU/mL (anti-Dsg1) and 191.96 IU/mL (anti-Dsg3). The mean age at

diagnosis was 50.5 years. Two patients achieved remission (Figure 3B), while six experienced multiple relapses.

Extensive Patchy Alopecia

This phenotype, present in four female patients (6.06%), was defined by large nonscarring alopecic patches with minimal



Figure 2. Circumscribed crusting and erosions phenotype: clinical and trichoscopic findings. A) Erythematous plaque with overlying crusts and erosions on the parietal scalp involving less than two quadrants. B) Trichoscopic examination shows erythema, yellow scales, and hemorrhagic dots and globules. C) Pull test performed on the lesional area shows active hair loss. D) Positive pull test with extracted anagen hairs characterized by intact hair bulbs and outer root sheaths.



Figure 3. Confluent crusting and erosions phenotype: before and after treatment. A) Extensive erosive and crusted lesions involving more than two quadrants of the scalp in a patient with pemphigus vulgaris. B) Complete clinical remission of scalp lesions after treatment with rituximab.

crusting or erosion (Figure 4). All had a strongly positive pull test suggesting anagen effluvium. Trichoscopic examination showed nonscarring alopecia with preserved follicular ostia and absence of erythema, scaling, or perifollicular

inflammation (Figure 4B). Three had PV and one had PF. This subgroup had the highest mean PDAI (64), with elevated antibody titers (anti-Dsg1: 268.28 IU/mL; anti-Dsg3: 156.63 IU/mL). The mean age at diagnosis was 45.5 years.

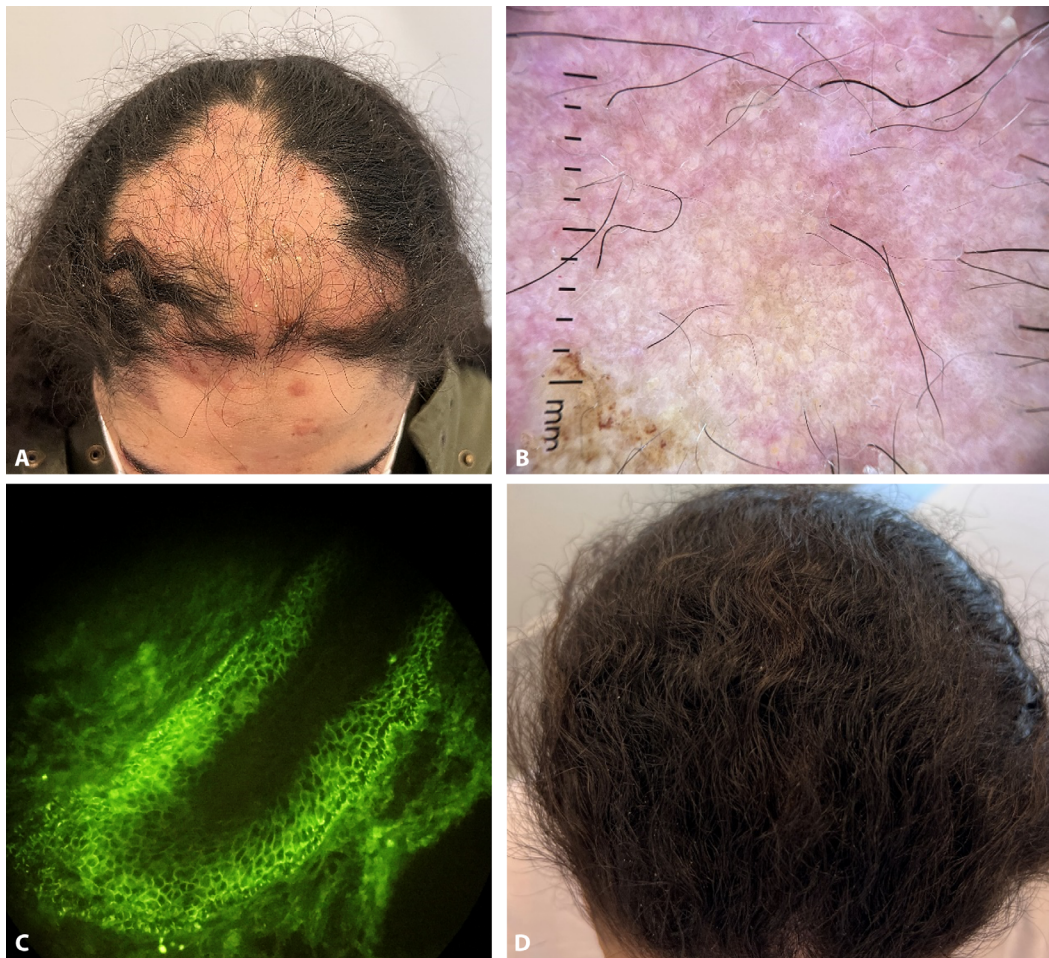


Figure 4. Extensive patchy alopecia phenotype. A) Clinical picture showing multiple large non-scarring alopecic patches on the scalp with minimal epidermal changes and no visible inflammation. B) Trichoscopic examination shows nonscarring alopecia with preserved follicular ostia and absence of erythema, scaling, or perifollicular inflammation. C) Direct immunofluorescence on a scalp hair follicle showing intercellular IgG deposition along the outer root sheath of the hair follicle, suprabasal clefting, and acantholytic keratinocytes. D) Complete hair regrowth after rituximab therapy.

All were treated with rituximab; one received cyclophosphamide. Hair regrowth occurred in all cases (after a mean of 1.5 cycles), although two experienced relapses.

A schematic illustration of the three clinical phenotypes, highlighting the differences in epidermal and follicular involvement, is shown in Figure 5. Clinical features of each pattern are summarized in Table 2.

Discussion and Conclusions

Reported rates of scalp involvement in pemphigus vary widely, from 9.5% to 60% [7,9], largely due to the heterogeneity in case definitions and study populations. For example, some studies considered only alopecia, while others included minor erosions or crusts [12-14]. The impact of methodology is evident in the study by Veraitch et al., who found a rate of 5.4% using alopecia alone [12]. Other cohorts reported different rates: approximately 30% in the study by Arya et al. [7] and 9.5% in the study by Salmanpour et al. [9].

In our retrospective observational cohort of 115 patients, scalp involvement was documented in 57.4% of cases, suggesting that scalp involvement is more common than traditionally recognized.

To address the variability in definitions, we proposed a structured clinical classification of scalp pemphigus into four clinical patterns, grouped into three main phenotypes: i) scaling without alopecia; ii) circumscribed and confluent crusting and erosions; iii) extensive patchy alopecia.

In the present study, most patients with scalp involvement had PV, in keeping with epidemiological data from European populations [20]. However, our findings also included a significant proportion of PF [21].

Although pemphigus overall is more prevalent in females, with an estimated female-to-male ratio of 1.5:1 [4,20], our data suggest that scalp involvement may follow a different distribution. In our cohort, male sex was significantly associated with the presence of scalp lesions ($P=0.0148$). This sex difference in the prevalence of scalp involvement

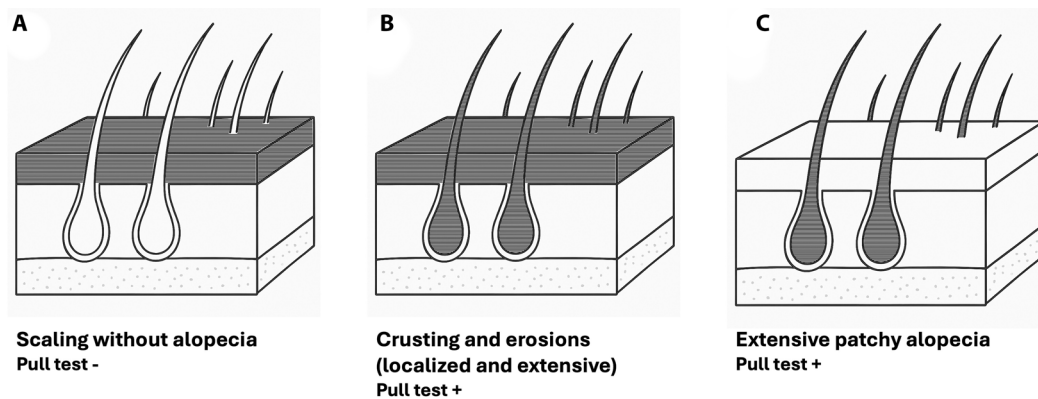


Figure 5. Representative images of the three main clinical phenotypes identified in the study: A) scaling without alopecia, characterized by diffuse desquamation in the absence of erosions or hair loss; B) crusting and erosions, presenting as erosive and crusted lesions on the scalp associated with a positive pull test; C) extensive patchy alopecia, showing large alopecic patches with minimal inflammation and a strongly positive pull test.

Table 2. Clinical patterns of scalp involvement in pemphigus patients.

Clinical pattern	No. of patients (M/F)	Pemphigus subtype distribution	Mean age at diagnosis (Years)	Mean PDAI	Mean Dsg1 (IU/mL)	Mean Dsg3 (IU/mL)	Remission	Relapse rate
Scaling without alopecia	9 (5M/4F)	PF (8), PV (1)	54.2	42.1	376.41	139.31 (median 2.0)	33.3% (3/9)	55.6% (5/9)
Circumscribed crusting and erosions	45 (22M/23F)	PV (38), PF (7)	51.3	40.8	170.84	166.85	44.4% (20/45)	62.2% (28/45)
Confluent crusting and erosions	8 (7M/1F)	PV (8)	50.5	53.5	184.58	191.96	25% (2/8)	75% (6/8)
Extensive patchy alopecia	4 (0M/4F)	PV (3), PF (1)	45.5	64	268.28	156.63	100% (4/4)	50% (2/4)

Abbreviations: M: male, F: female, PF: pemphigus foliaceus, PV: pemphigus vulgaris, PDAI: Pemphigus Disease Area Index, Dsg1/Dsg3: desmoglein 1/3 (IU/mL). Remission refers to complete lesion resolution; relapse indicates recurrence after remission.

is supported by Esmaili et al., who found scalp lesions in 48% of pemphigus vulgaris patients, with a higher prevalence in males (61.1%) compared to females (40.7%) [8]. Interestingly, the subgroup of patients with extensive patchy alopecia in our study consisted entirely of female patients. These sex-specific discrepancies raise the possibility that sex-specific factors—hormonal, genetic or immunological—may influence desmoglein expression or the inflammatory response at the follicular level [8].

In our study, serological analysis revealed a robust association between scalp involvement and elevated anti-Dsg1 antibody levels. Patients with scalp lesions had higher anti-Dsg1 titers than did those without (mean 206.4 vs 74.2 IU/mL; $P=0.0001$), confirming the pathogenic role of anti-Dsg1 [22]. Fard et al. also reported that high anti-

Dsg1 titers were strongly correlated with scalp lesions, including alopecia [22]. While Dsg3 antibody levels were also elevated in the subgroup of patients with scalp involvement, they were not significantly different from the non-involved group. Notably, when patients were stratified by clinical phenotype, anti-Dsg1 levels were consistently high across all subtypes, whereas elevated anti-Dsg3 levels were observed in patients with alopecia or crusts/erosions. This would suggest a distinct immunologic profile among scalp phenotypes.

The differential expression of desmosomal proteins in the hair follicle may help to explain these findings. Wu et al. showed that Dsg1 localizes to the inner root sheath and to the inner layers of the outer root sheath. Dsg3 distribution depends on keratinization, i.e., it spans the full thickness of the outer root sheath in trichilemmal areas but is largely

confined to the basal layer in epidermal-type regions, such as the infundibulum [23]. Dsg3 is also expressed in the hair medulla, supporting a potential role in hair shaft anchorage [23].

Fard et al. found that a positive anagen pull test correlates with higher anti-Dsg1, with no between-group difference in anti-Dsg3; because all patients were anti-Dsg3-positive, they inferred that anagen hair loss requires simultaneous inactivation of Dsg1 and Dsg3 [22]. In this context, a positive pull test may be regarded as the scalp analogue of the Nikolsky sign, that is, a sign of active disease at the level of the follicular epithelium. Consistently, in our cohort anti-Dsg1 alone was associated with superficial erosions and scaling and a negative pull test, whereas follicular involvement and alopecia occurred only when anti-Dsg1 and anti-Dsg3 were both elevated with a positive pull test. This pattern is consistent with the mouse model by Hanakawa et al., in which only Dsg1/Dsg3 double-knockout mice developed anagen hair loss [24].

In our study, despite the consistent presence of elevated anti-Dsg1 titers across clinical subtypes, some cases challenged the assumption that both Dsg1 and Dsg3 must be involved for alopecia to occur. One patient with PF and extensive patchy alopecia exhibited high anti-Dsg1 titers but lacked anti-Dsg3 antibodies, suggesting that other follicular antigens may play a role. Desmogleins 2 and 4, for instance, have been detected in specific compartments of the hair follicle: Dsg2 in less differentiated cells of the follicular bulge and basal outer root sheath, and Dsg4 in differentiated regions such as the hair shaft cortex and inner root sheath cuticle [25,26]. Kljuic et al. even proposed desmoglein 4 as a possible autoantigen in PV [26].

Taken together, our findings indicate that while high anti-Dsg1 levels are likely necessary for the development of scalp lesions, they may not be sufficient to cause alopecia. Additional factors, including co-targeting of Dsg3 or other desmosomal proteins as well as inflammatory triggers, may contribute to the pathogenesis of hair loss.

Scalp involvement was also associated with higher PDAI scores (mean 43.9 vs 32.1; $P=0.006$), and PDAI severity category distribution also differed significantly between groups ($P=0.0147$). This confirms earlier findings by Sar-Pomian et al., who identified scalp lesions as markers of disease severity and prolonged course [27,28]. Our classification may help to refine disease severity assessments and guide tailored treatment strategies.

Interestingly, scalp involvement was not uniformly predictive of poor therapeutic outcome. Patients with scalp lesions, especially those with extensive patchy alopecia, responded well to rituximab, often achieving complete hair regrowth. Nevertheless, relapse was common (50%), suggesting a need for retreatment or maintenance [12]. Although

the association with prior therapies did not reach statistical significance ($P=0.0521$), patients with scalp lesions were more frequently managed with rituximab, consistent with therapeutic escalation in more severe or refractory disease.

Finally, although mortality appeared to be higher in patients with scalp involvement (18.2% vs 10.2%), this difference did not reach statistical significance. This may be influenced by the limited sample size, variability in patient follow-up, or the effects of contemporary immunosuppressive regimens.

This study has several limitations due to its retrospective observational design. As a single-center study, its generalizability may be limited due to potential geographic, genetic, or environmental differences between populations. Retrospective data collection might also have introduced selection and information bias, particularly in the presence of incomplete clinical data. We addressed missing data by excluding participants, which may have reduced the study's representativeness. The relatively high loss to follow-up, including deaths, may have underestimated long-term outcomes and limited the precision of recurrence and prognosis estimates.

Nevertheless, our study may provide valuable insights regarding the prevalence, clinical diversity, and immunopathogenesis of scalp involvement in pemphigus. The identification of distinct clinical phenotypes and their correlation with serological profiles may aid in better stratifying disease presentation and treatment decisions.

These findings support incorporating scalp assessment into routine scoring and motivate studies on follicular desmogleins and other target antigens. Clarifying these factors, alongside clinical variables such as sex, may enable more personalized management.

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