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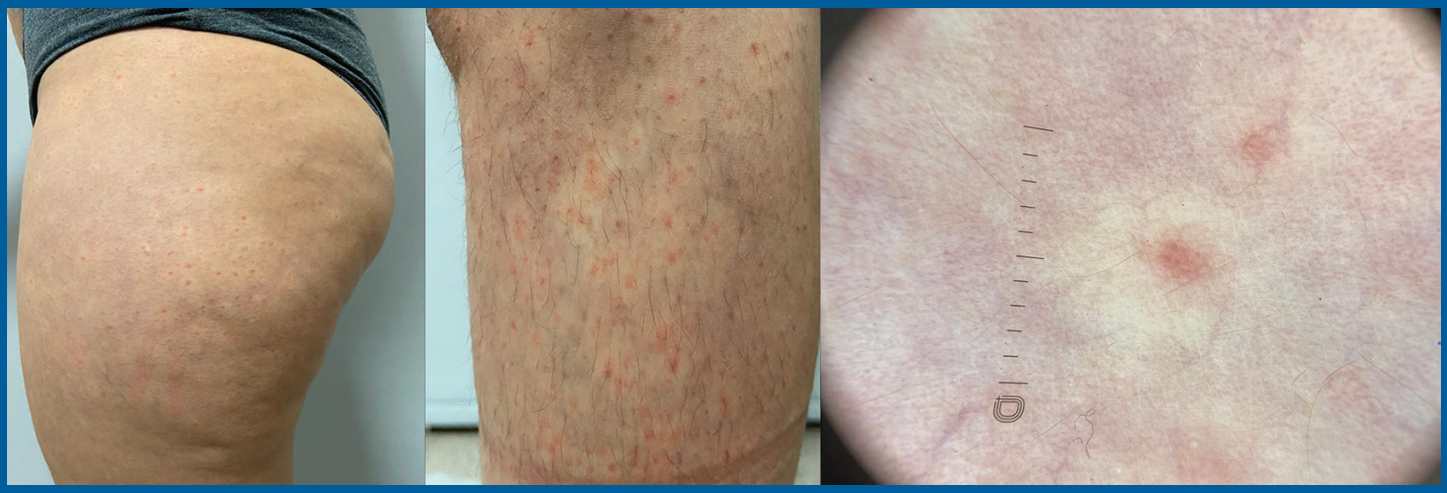

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CONTENTS

Original Article

Diagnostic Value of NLR, PLR, hsCRP, and MPV for Assessing Disease Severity in Adult Atopic Dermatitis

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Abstract

Aim: Atopic dermatitis (AD) is a chronic inflammatory disease with systemic involvement. Severity is usually assessed using the scoring AD (SCORAD) index, but this method is partly subjective. Blood-derived markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), high-sensitivity C-reactive protein (hsCRP), and mean platelet volume (MPV) may provide objective indicators. This study evaluated their diagnostic value in assessing disease severity in adults with AD.

Materials and Methods: A cross-sectional study was conducted among 112 adults with AD at Ho Chi Minh City Hospital of Dermato-Venereology Hospital from March to September 2024. Demographics, clinical features, and SCORAD scores were recorded. Laboratory analyses included NLR, PLR, hsCRP, and MPV. Receiver operating characteristic (ROC) analysis determined the ability of these markers to identify severe AD (SCORAD ≥ 51).

Results: A total of 112 patients were included (62.5% female; mean age 48 years); 20% had severe AD (median SCORAD 30.7). Higher SCORAD was associated with increased neutrophils, NLR, PLR, and hsCRP, and with decreased lymphocytes (all $P < 0.05$). NLR best predicted severe AD, with an area under the receiver operating characteristic curve (AUROC) of 0.805 (cut-off 2.59; sensitivity 77.3%; specificity 80.0%), followed by PLR (AUROC: 0.754) and hsCRP (AUROC: 0.734), whereas MPV showed no predictive value (AUROC: 0.530; $P = 0.663$).

Conclusion: NLR, PLR, and hsCRP are simple, low-cost, and reliable biomarkers that correlate with AD severity, with NLR showing the highest diagnostic accuracy. Incorporating these indices may improve objective assessment and serve as an adjunctive tool in clinical practice.

Keywords: Atopic dermatitis, biomarkers, C-reactive protein, lymphocytes, neutrophils, platelets

Introduction

Atopic dermatitis (AD), the most common chronic inflammatory skin disease, imposes a substantial psychosocial burden by affecting appearance and reducing quality of life. Its complex pathogenesis involves immune dysregulation, impaired skin barrier function, and alterations of the commensal microbiota.[1] The disease is not confined to localized skin manifestations but also presents as a systemic inflammatory condition, often associated with other allergic diseases such as asthma and allergic rhinitis.[1,2] The global prevalence of AD is estimated to be as high as 30% in children and 2–10% in adults, and these rates continue to rise annually.[2-4] In addition to cutaneous symptoms, clinical and epidemiological factors including age, sex, age of onset, a history of allergic rhinitis, and personal and family histories of asthma play important roles in disease progression and severity stratification.[5] The integration of epidemiological and clinical characteristics forms the foundation for a more comprehensive and accurate model for assessing disease severity. Evaluating the severity of AD is a key factor in management and treatment selection. The scoring AD (SCORAD) index is a widely used and reliable clinical tool for disease severity assessment.[5] This score comprises three main components: the extent of disease; intensity (redness, swelling, oozing/crusts, scratch marks, lichenification, dryness); and subjective symptoms,

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including itch and sleeplessness, over the last three days. The total SCORAD ranges from 0 to 103, with disease severity classified as mild (< 25), moderate (25–50), or severe (≥ 51).[5-7] However, the method remains subjective as it depends on both physician and patient assessments. Consequently, blood-based biomarkers reflecting systemic inflammation are receiving increasing attention. Parameters such as white blood cell count, neutrophils, lymphocytes, eosinophils, platelet count, mean platelet volume (MPV), and high-sensitivity C-reactive protein (hsCRP) may serve as indicators of inflammatory activity.[2] Furthermore, systemic inflammatory ratios such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are readily obtained from a complete blood count, correlate strongly with systemic inflammation in chronic inflammatory diseases. Their low cost and broad applicability make them particularly advantageous.[2,5,8,9] No study in Vietnam has evaluated the NLR, PLR, or their associations with clinical features and disease severity in AD. Establishing threshold values for these indices is essential to enhance objectivity and clinical applicability. Therefore, this study aimed to assess MPV, NLR, PLR, eosinophil-to-lymphocyte ratio (ELR), dNLR, hsCRP, SCORAD scores, and the related demographic and clinical factors in adults with AD, with the aim of developing a more objective clinical tool to assess severity in practice.

Materials and Methods

Participants

Patients aged ≥ 18 years diagnosed with AD who attended Ho Chi Minh City Hospital of Dermato-Venereology Hospital for consultation and treatment between March 2024 and September 2024 were included.

Inclusion criteria were: a confirmed diagnosis of AD according to the Hanifin and Rajka criteria, modified by the American Academy of Dermatology in 2014;[10] age ≥ 18 years; and willingness to participate in the study. Exclusion criteria were: treatment with systemic corticosteroids or cytotoxic drugs within the past month; history of cardiovascular disease, chronic liver disease, end-stage chronic kidney disease, acute or chronic infections, malignancy, or systemic immune-related or immunodeficiency disorders; treatment with medications affecting platelet count or function within the past two weeks; and pregnancy or breastfeeding.

Sample Size and Sampling Method

The sample size was calculated for estimating a single proportion. We used $P = 0.325$ based on the proportion of patients in SCORAD group III (SCORAD ≥ 51) reported by Jiang and Ma,[5] and an acceptable margin of error (d) of 0.065. Using the standard formula for a single proportion ($n = Z^2 \cdot p \cdot (1–p)/d^2$, with Z corresponding to 95% confidence), the required sample size was 97. Allowing for 10% sample loss or unusable samples, the minimum target sample size was increased to 107. A total of 112 participants were recruited for the study. A consecutive convenience sampling method was used to enroll eligible patients until the required sample size was reached.

Data Collection Procedure

Data were recorded on a standardized case-report form that included the following: demographic characteristics (age, sex); personal history (allergic rhinitis, bronchial asthma); family history (bronchial asthma); dermatological examination findings. Clinical examination included the classification of disease stage (acute, subacute, or chronic), the determination of lesion sites and body surface area involvement (BSA%), and the detailed description of lesion morphology (redness, swelling, oozing/crusts, scratch marks, lichenification, and dryness). Photographs of representative lesions were also taken. Disease severity was assessed using the SCORAD index. Venous blood samples were collected into two tubes, one containing EDTA and the other heparin, and transferred to the Medic Hoa Hao Laboratory. Hematological parameters were analyzed using the SIEMENS ADVIA® 2120i automated hematology analyzer, which uses flow cytometry combined with laser fluorescence to identify and classify blood cell lineages, providing counts of red blood cells, white blood cells, and platelets, as well as MPV. Erythrocyte sedimentation rate was measured using the Ves-Matic Easy system based on automated optical detection. hsCRP levels were determined by an immunoturbidimetric assay using the Full Range hsCRP kit (Cat. No. CP3847 or CP3849). The procedure involved mixing serum samples with reagents containing anti-CRP antibodies, measuring optical turbidity, and automatically calculating hsCRP concentration. All laboratory analyses were performed in accordance with standard operating procedures, with both internal and external quality control measures applied regularly to ensure accuracy and reproducibility of results.

Study Variables

Age was calculated as the survey year minus the year of birth (in years). Sex was classified into two categories: male and female. Personal history of allergic rhinitis was recorded as a categorical variable with two values: yes or no. Personal and family history of bronchial asthma were also recorded as categorical variables (yes/no).

Disease severity was assessed using the SCORAD index, a quantitative variable developed by the European Task Force on AD in 1993 and calculated by the formula SCORAD = A/5 + 7B/2 + C, where A represents the percentage of BSA affected (BSA%), B is the total score of six clinical signs (0–18), and C is the sum of two subjective symptoms, pruritus and sleep loss (0–20). SCORAD severity categories were defined as follows: mild (< 25), moderate (25–50), and severe (≥ 51). This categorical variable thus comprised three levels. Laboratory variables included hematological and inflammatory markers, all treated as quantitative variables: peripheral blood neutrophil count (10^3/mm^3), lymphocyte count (10^3/mm^3), platelet count (K/mL), and MPV (fL). Inflammatory indices were calculated as follows: MPV, NLR, PLR, ELR, and dNLR. hsCRP (mg/L) was also measured.

Table 1. Clinical, demographic characteristics and laboratory results of the participants

	Value	n (%)/median (IQR)/mean ± SD
Age (years)		48 (32–61)
Gender	Male	42 (37.5)
	Female	70 (62.5)
Age of onset (years)		35 (22–49.5)
Age at onset categories	2 years	0 (0)
	2–12 years	12 (10.7)
	12–60 years	91 (81.3)
	> 60 years	9 (8.0)
History of allergic rhinitis	Yes	18 (16.1)
	No	94 (83.9)
History of bronchial asthma	Yes	10 (8.9)
	No	102 (91.1)
Family history of bronchial asthma	Yes	12 (10.7)
	No	100 (89.3)
WBC count, 10^9/L		8.6 (6.9–10.6)
Eosinophils, 10^9/L		0.28 (0.12–0.45)
Neutrophils, 10^9/L		5.0 (4.0–6.2)
Lymphocytes, 10^9/L		2.4 (1.8–2.9)
Platelet count, 10^9/L		295.5 ± 71.6
MPV, fL		9.3 (8.9–9.9)
NLR		2.1 (1.5–3.0)
PLR		114.0 (97.8–153.8)
ELR		0.059 (0.026–0.109)
dNLR		1.49 (1.07–1.92)
hsCRP, mg/L		1.7 (0.8–4.0)
SCORAD score		30.7 (15.1–40.2)
Categorize by SCORAD	Group I SCORAD (0-24)	39 (35)
	Group II SCORAD (25-50)	51 (45)
	Group III SCORAD (51-103)	22 (20)

WBC: White blood cell, NLR: Neutrophils to lymphocytes ratio, PLR: Platelet to lymphocyte ratio, MPV: Mean platelet volume, hsCRP: High-sensitivity C-reactive protein, SCORAD: Scoring atopic dermatitis index, ELR: Eosinophil-to-lymphocyte ratio, SD: Standard deviation, IQR: Interquartile range

Statistical Analysis

Data were managed using Microsoft Excel 365 (Windows OS) and analyzed with SPSS version 20 (IBM Corp., Armonk, NY, USA). The distribution of quantitative variables was assessed using the Shapiro–Wilk test. Variables with normal distribution were compared using one-way ANOVA with Tukey's post-hoc test, whereas non-normally distributed variables were analyzed using the Kruskal–Wallis test followed by Mann–Whitney U tests for pairwise comparisons. Receiver operating characteristic (ROC) curve analysis was used to evaluate the ability of MPV, NLR, PLR, ELR, dNLR, and hsCRP to discriminate patients in group III (SCORAD 51–103). The ROC curve was considered acceptable at ≥ 0.7 and good at ≥ 0.8. Youden's index was applied to calculate sensitivity and specificity and to determine the optimal cut-off values for predicting severe AD. A *P*-value < 0.05 was considered statistically significant.

Ethical Considerations

This study received approval from the Ethics Committee in Biomedical Research of Ho Chi Minh City Dermatology Hospital (approval number: 418/CN-BVDL, date: 29.02.2024). Written informed consent was obtained from all adult participants prior to enrollment, consistent with the Declaration of Helsinki (revised 2013).

Results

The study included 112 patients with a mean age of 48 years (range: 32–61). Females predominated, comprising 70 cases (62.5%) compared with 42 males (37.5%) (Table 1). The mean age at symptom onset was 35 years (22–49.5 years), and the majority (81.3%) of patients developed symptoms between 12 and 60 years. No cases of onset were recorded before 2 years of age, and only 8% had onset after 60 years of age. A history of allergy was reported in 18 patients (16.1%). A personal history of bronchial asthma accounted for only 8.9% (10 cases), whereas a family history of asthma accounted for 10.7% (12 cases). The median white blood cell count was 8.6 × 10^9/L (6.9–10.6), which is within the normal range. Neutrophils were 5.0 × 10^9/L (4.0–6.2), eosinophils were 0.28 × 10^9/L (0.12–0.45), and lymphocytes were 2.4 × 10^9/L (1.8–2.9); all values were within normal limits. The platelet count was 295.5 ± 71.6 × 10^2/L, which is within the normal range. MPV was 9.3 fL (8.9–9.9); the inflammatory ratios included NLR 2.1 (1.5–3.0), PLR 114.0 (97.8–153.8), ELR 0.059 (0.026–

0.109), and dNLR 1.49 (1.07–1.92). The hsCRP level was 1.7 mg/L (0.8–4.0). The median SCORAD score was 30.7 (15.1–40.2). Based on the SCORAD classification, group I (0–24 points) accounted for 35%, group II (25–50 points) for 45%, and group III (51–103 points) for 20%. Most patients belonged to the moderate group, suggesting that the disease generally presented with mild to moderate clinical manifestations.

Comparison of mean neutrophil counts across the three SCORAD-based groups revealed a clear upward trend (Table 2). Group III had the highest mean value, 5.82 (4.96–7.40) × 10^9/L, and the overall difference among the three groups was statistically significant ($P = 0.003$). Pairwise analysis revealed that this difference was most pronounced between group I and group III ($P < 0.001$). Lymphocyte counts, in contrast, showed a progressive decline with increasing disease severity, from 2.45 (2.01–2.93) × 10^9/L in group I to 1.70 (1.32–2.34) × 10^9/L in group III. This trend was highly significant ($P < 0.001$). Pairwise comparisons indicated that the largest difference was again observed between group I and group III ($P < 0.001$), and a significant difference was observed between group I and group II ($P < 0.001$). However, no statistically significant difference was observed between group II and group III ($P = 0.851$). Systemic inflammatory indices, including NLR, PLR, and hsCRP, also rose steadily from mild to severe disease, with the highest levels recorded in group III. All showed statistically significant differences among the three groups ($P \leq 0.001$). For NLR in particular, the differences were striking ($P < 0.001$). Pairwise analysis demonstrated that the greatest difference was observed between groups I and III ($P = 0.001$), while a significant difference was also observed between groups I and II ($P = 0.001$). No significant difference was observed between groups II and III ($P = 0.788$).

ELR values showed slight variation among the three groups, but the overall comparison was not statistically significant ($P = 0.057$). Pairwise analyses indicated no meaningful differences among groups I, II, and III ($P = 0.840$ for I vs. II; $P = 0.053$ for I vs. III; $P = 0.118$ for II vs. III).

dNLR values demonstrated a similar pattern, with no significant overall difference across the three groups ($P = 0.063$). Pairwise comparisons showed no significant differences between groups I and II ($P = 0.576$) or between groups II and III ($P = 0.229$); however, groups I and III differed significantly ($P = 0.049$). Similarly, hsCRP levels increased with disease severity, rising from 0.8 (0.4–1.1) mg/L in group I to 3.0 (2.2–4.7) mg/L in group III. The overall difference across the three groups was highly significant ($P < 0.001$). Pairwise comparisons confirmed that the most pronounced difference was between groups I and III ($P < 0.001$), and a significant difference was also observed between groups II and III ($P < 0.001$).

The diagnostic performance of MPV, NLR, PLR, ELR, dNLR, and hsCRP for identifying group III patients (SCORAD ≥ 51) is summarized in Table 3 and illustrated in Figure 1. MPV showed poor diagnostic value, with an AUROC of 0.530 [95% confidence interval (CI): 0.391–0.668; $P = 0.663$]. Moreover, NLR demonstrated the strongest diagnostic performance, with an AUROC of 0.805 (95% CI: 0.707–0.903; $P < 0.001$). At the cut-off value of 2.59, NLR achieved a sensitivity of 77.3% and a specificity of 80.0%. Additionally, PLR demonstrated good predictive ability, with an AUROC of 0.754 (95% CI: 0.621–0.856; $P < 0.001$), a sensitivity of 59.1% and a specificity of 90.0%. ELR demonstrated limited diagnostic value, with an AUROC of 0.589 (95% CI, 0.447–0.731; $P = 0.196$). At the cut-off level of 0.116, ELR provided a sensitivity of

Table 2. Laboratory results of patients according to SCORAD

	Group I (n = 39) SCORAD (0–24)	Group II (n = 51) SCORAD (25–50)	Group III (n = 22) SCORAD (51–103)	P[b]	GI-II P[a]	GI-III P[a]	GII-III P[a]
WBC count, 10^9/L	7.89 (6.08–9.33)	8.76 (6.80–19.62)	8.83 (7.51–11.26)	0.089	0.560	0.036	0.095
Neutrophils, 10^9/L	4.26 (3.61–5.24)	5.13 (4.01–6.17)	5.82 (4.96–7.40)	0.003	0.076	0.001	0.044
Lymphocytes, 10^9/L	2.45 (2.01–2.93)	2.51 (1.89–3.20)	1.70 (1.32–2.34)	< 0.001	< 0.001	< 0.001	0.851
Platelet count, 10^9/L	288.46 ± 67.12	291.22 ± 66.20	318.05 ± 88.41	0.209[c]	0.107[d]	0.111[d]	0.804[d]
MPV, fL	9.3 (8.8–9.9)	9.3 (8.8–9.9)	9.5 (8.9–9.9)	0.794	0.916	0.662	0.662
NLR	1.7 (1.4–2.3)	2.1 (1.5–2.6)	3.4 (2.6–5.0)	< 0.001	0.001	0.001	0.788
PLR	110.3 (99.2–140.0)	108.5 (95.6–140.4)	186.2 (115.1–290.8)	0.001	0.527	0.001	0.139
ELR	0.055 (0.029–0.095)	0.074 (0.018–0.097)	0.079 (0.300–0.140)	0.057	0.840	0.053	0.118
dNLR	1.26 (1.07–1.63)	1.36 (1.00–1.76)	2.09 (1.59–2.38)	0.063	0.576	0.049	0.229
hsCRP, mg/L	0.8 (0.4–1.1)	2.4 (1.1–6.5)	3.0 (2.2–4.7)	< 0.001	< 0.001	< 0.001	0.339

[a]Mann-Whitney U test. [b]Krusal-Wallis test. [c]One-way ANOVA test. [d]Tukey's test
WBC: White blood cell, NLR: Neutrophils to lymphocytes ratio, PLR: Platelet to lymphocyte ratio, MPV: Mean platelet volume, hsCRP: High-sensitivity C-reactive protein, SCORAD: Scoring atopic dermatitis index, ELR: Eosinophil-to-lymphocyte ratio

Table 3. Diagnostic accuracy of different formulae with regard to high SCORAD score

	AUROC (95% CI)	*P*-value	Cut-off	Sensitivity, %	Specificity, %
MPV, fL	0.530 (0.391–0.668)	0.663	9.35	59.1	55.6
NLR	0.805 (0.707–0.903)	< 0.001	2.59	77.3	80.0
PLR	0.754 (0.621–0.886)	< 0.001	174.5	59.1	90.0
ELR	0.589 (0.447–0.731)	0.196	0.116	36.4	86.4
dNLR	0.737 (0.610–0.863)	0.001	1.85	72.7	83.0
hsCRP, mg/L	0.734 (0.639–0.828)	< 0.001	1.78	90.9	61.1

NLR: Neutrophils to lymphocytes ratio, PLR: Platelet to lymphocyte ratio, MPV: Mean platelet volume, hsCRP: High-sensitivity C-reactive protein, AUROC: Area under the receiver operating characteristic curve, CI: Confidence interval, SCORAD: Scoring atopic dermatitis index, ELR: Eosinophil-to-lymphocyte ratio

36.4% and a specificity of 86.4%. dNLR showed moderate diagnostic performance, with an AUROC of 0.737 (95% CI: 0.610–0.863; $P = 0.001$). Using a cut-off value of 1.85, dNLR achieved a sensitivity of 72.7% and a specificity of 83.0%. However, hsCRP demonstrated an AUROC of 0.734 (95% CI: 0.639–0.828; $P < 0.001$), characterized by high sensitivity (90.9%) but lower specificity (61.1%). A comparative analysis using the DeLong test confirmed that NLR was the most reliable predictor of high SCORAD scores, outperforming the other indices.

Discussion

Principal Finding

The study group had a median SCORAD score of 30.7 (15.1–40.2), with 65.2% of patients classified as moderate to severe. Regarding inflammatory indices, the median NLR in adult AD patients was 2.1 (1.5–3.0), and the median serum hsCRP was 1.7 (0.8–4.0) mg/L. Neutrophils, NLR, PLR, and hsCRP increased significantly with increasing SCORAD scores. Among them, NLR and hsCRP were the most reliable indicators of disease severity. NLR, in particular, showed the strongest diagnostic performance, with an AUROC of 0.805 (95% CI: 0.707–0.903; $P < 0.001$), a cut-off of 2.59, sensitivity of 77.3%, and specificity of 80.0%.

Comparing with Previous Studies

In our study, 26.8% of patients were aged ≥ 60 years, consistent with Chan et al.[11] in the United Kingdom, who reported a prevalence of 7.7% in adults and 11.6% among the elderly, with more severe disease in the latter group. This highlights the importance of early detection in older adults. A female predominance was also observed (62.5%; female-to-male ratio = 1.67:1), aligning with findings of Mora et al.[12] in Spain (59.4%; 1.46:1) and Koppes et al.[13] (63.3%). This pattern has been attributed to estradiol and other female sex hormones, which may exacerbate Th2-mediated inflammation in AD. Supporting evidence from animal studies shows that estradiol can directly promote mast cell degranulation and trigger allergic sensitization.[14-16]

Comorbid allergic conditions were common, with 16.1% of patients reporting allergic rhinitis and 8.9% reporting asthma. These rates were lower than those reported in Ravnborg et al.[17] meta-analysis (25.7% for asthma; 21% in physician-diagnosed cases) and in Knudgaard et al.,[18] who found allergic rhinitis in 40.5% of patients with AD compared with

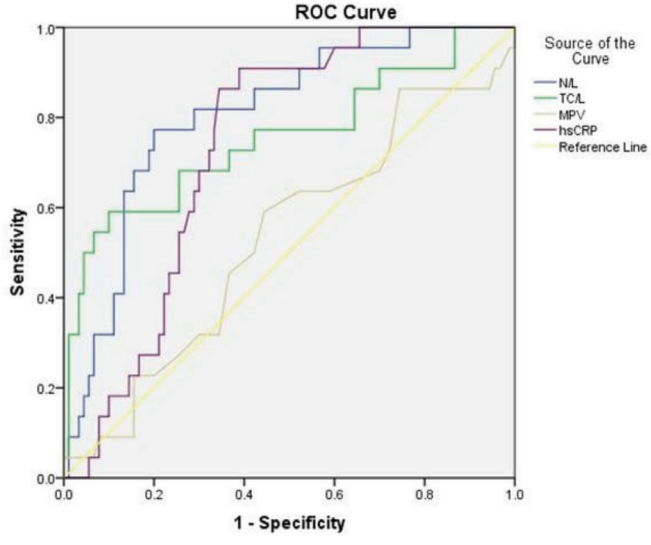

Figure 1. Receiver operating characteristic (ROC) curves showing the sensitivity and specificity of NLR, PLR, MPV, and hsCRP with respect to Group III SCORAD (51–103). NLR (blue line), PLR (green line), MPV (beige line), and hsCRP (purple line); the reference line is shown in yellow

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MPV, Mean platelet volume, hsCRP: High-sensitivity C-reactive protein, SCORAD: Scoring atopic dermatitis index

18.0% of controls. Such variability may reflect differences in population characteristics, diagnostic criteria, and study design. The frequent comorbidity of AD, asthma, and allergic rhinitis, often described as the "atopic triad", reflects shared pathogenic mechanisms, including immunoglobulin E (IgE) elevation, Th1/Th2 imbalance, and mast cell activation, supporting the concept of the atopic march.

Our results showed that total leukocyte count and NLR increased significantly with higher SCORAD scores, reflecting systemic inflammation in AD. This trend is consistent with the findings of Sekar et al.,[19] who reported significant increases in both NLR and PLR from mild to severe groups, although the absolute values in our study were lower. In contrast, MPV did not differ significantly across severity groups, which is inconsistent with Sekar et al.,[19] who observed a significant decrease, but consistent with Batmaz,[20] who reported no significant differences in NLR, PLR, or MPV. These discrepancies suggest that NLR may be influenced by population characteristics and study design; nonetheless, recent evidence, particularly from Sekar et al.,[19] reinforces the value of NLR and PLR, especially NLR, as markers for disease severity stratification. Similarly, Dogru and Citli[21] demonstrated that, in children, NLR increased with higher SCORAD scores and was positively correlated with disease severity, supporting the presence of systemic inflammation at an early stage. NLR, which reflects the imbalance between innate and adaptive immunity, therefore emerges as a simple, low-cost, and reliable inflammatory marker for severity stratification in both pediatric and adult patients, with particular utility in resource-limited clinical settings. Regarding hsCRP, our findings align with those of Vekaria et al.[22] and Nguyen and Chau,[23] confirming that CRP levels increase with disease severity and can be used as a stratification tool. In contrast, MPV did not show significant differences in our study, consistent with Batmaz,[20] but contrary to Sekar et al.[19] and Bostan Gayret et al.[24] This indicates that MPV is more susceptible to variability related to population differences and laboratory conditions. Taken together, NLR, PLR, and hsCRP, particularly NLR, appear to be reliable inflammatory markers for assessing disease severity and monitoring disease progression; however, MPV currently lacks the stability required for routine clinical application.

Analysis of predictive markers for severe AD (group III) in our study identified NLR as the most prominent indicator. This finding is consistent with Jiang and Ma,[5] who reported an AUC of 0.778 with a lower cut-off value (1.75), yielding a sensitivity above 90% but a specificity of only 58.6%. NLR reflects immune imbalance: neutrophil counts rise as part of the inflammatory response, whereas lymphocytes—particularly regulatory T cells—decline, impairing the regulation of inflammation.[25] Consequently, elevated NLR is typically associated with more severe disease and extensive skin involvement. Supporting this, Inokuchi-Sakata et al. [25] demonstrated a direct relationship between NLR and SCORAD scores. Beyond AD, numerous studies have linked NLR with other allergic and autoimmune diseases, including pediatric allergic rhinitis (Dogru and Citli),[21] asthma, and systemic lupus erythematosus.[26-28] These lines of evidence strengthen the biological rationale for applying NLR as a prognostic marker of disease severity in AD.

From a pathophysiological perspective, interleukin (IL)-17 plays a pivotal role in chronic cutaneous inflammation. It not only promotes neutrophil production but also induces the release of tissue-degrading enzymes (such as metalloproteinases and elastase) and reactive oxygen species, thereby exacerbating skin damage and disease severity.[29] At the same time, reduced regulatory T-cell activity limits the ability to suppress inflammation, sustaining a chronic inflammatory state that is difficult to control.[30] These mechanisms provide a biological explanation for why patients with elevated NLR often present with more severe clinical manifestations, poorer treatment response, and a higher likelihood of persistent disease.

Study Limitations

Our study has several limitations. First, the study was conducted at a single center with a relatively modest sample size; therefore, the findings may not fully capture the diversity of the epidemiological and clinical characteristics of AD patients across regions of Vietnam. Second, the cross-sectional design only allowed assessment of associations at a single time point, without evaluating longitudinal changes in MPV, NLR, PLR, ELR, dNLR, and hsCRP during disease progression or after treatment. Third, we focused exclusively on four peripheral blood inflammatory markers and did not include other immuno-inflammatory markers such as cytokines (IL-4, IL-13, IL-17), serum IgE, or novel molecular biomarkers, all of which could further elucidate disease pathogenesis and enhance predictive value. Fourth, due to limited resources and technical constraints, we were unable to include a well-matched healthy control group stratified by age, sex, and comorbidities, which limits the ability to fully exclude potential confounding factors.

Clinical Implications

The findings of this study suggest that routine, low-cost, and easily implemented blood tests —MPV, NLR, PLR, ELR, dNLR, and hsCRP— may serve as useful adjunctive tools for assessing disease severity in AD. Incorporating these indices into clinical practice could enable physicians to identify patients at higher risk of severe disease at an earlier stage, thereby facilitating closer monitoring and timely adjustment

of therapeutic regimens. In addition, monitoring changes in NLR and hsCRP during treatment may provide valuable information on therapeutic response, helping to guide treatment strategies and improve disease control.

Conclusion

The study demonstrated that total leukocyte count, NLR, PLR, and hsCRP all increased progressively with higher SCORAD scores, reflecting systemic inflammation in patients with AD. Among these markers, NLR showed the strongest diagnostic performance, with a cut-off value of 2.59, suggesting its potential as a simple, low-cost, and easily applicable clinical indicator for risk stratification and treatment decision-making. Multicenter studies with longitudinal designs are warranted to validate and further explore the clinical utility of these indices in routine practice.

Ethics

Ethics Committee Approval: This study received approval from the Ethics Committee in Biomedical Research of Ho Chi Minh City Dermatology Hospital (approval number: 418/CN-BVDL, date: 29.02.2024).

Informed Consent: Written informed consent was obtained from all adult participants prior to enrollment, consistent with the Declaration of Helsinki (revised 2013).

Footnotes

Conflict of Interest: The author declare that they have no conflict of interest.

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Original Article

Evaluation of Information Quality and Readability of Artificial Intelligence–Powered Chatbots in Systemic Isotretinoin Use

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Abstract

Aim: This study aimed to evaluate and compare the readability and quality of information in responses generated by artificial intelligence (AI) models to patients' frequently asked questions about systemic isotretinoin, a medication commonly prescribed in dermatology.

Materials and Methods: Thirty-four frequently asked questions from patients using isotretinoin were prepared by a team of dermatology specialists. These questions were posed to three AI-based text-generation tools (ChatGPT, Gemini 2.0, and Copilot), and the responses were analyzed. The resulting texts were compared in terms of readability levels [Flesch Reading Ease score (FRES), Flesch-Kincaid Grade Level (FKGL), Simple Measure of Gobbledygook (SMOG), Gunning Fog index (GFOG), Coleman-Liau index (CLI), and automated readability index (ARI)], sentence lengths, and content quality, which was evaluated by dermatologists.

Results: None of the AI models achieved the optimal readability threshold (FRES ≥ 60). Readability metrics differed significantly among models. Gemini produced responses that were significantly less readable and more complex than those produced by ChatGPT and Copilot across all readability indices, including FRES, FKGL, SMOG, GFOG, CLI, and ARI; post-hoc analyses confirmed differences between Gemini and the other models. Sentence counts also differed significantly, with Gemini generating longer responses than Copilot. In contrast, Likert-based quality scores and response appropriateness were comparable across models, with no statistically significant differences observed.

Conclusion: This study demonstrates that AI models produce academic responses that are difficult for those unfamiliar with medical terminology to understand, and can generate outputs with variable readability in health-related content. These findings highlight the need for careful evaluation of AI-based content for use in healthcare.

Keywords: Artificial intelligence, isotretinoin, readability, quality

Introduction

Chatbots are computer programs that can understand and respond to speech and text in a human-like manner using various algorithms. Large language models are used to simulate human conversation. Many companies are using this technology to develop their own chatbots.[1,2] A major milestone in this field was the introduction of ChatGPT in 2022. These chatbots have various applications, including serving as dialogue systems, providing language translation, and generating content. Alongside ChatGPT, other chatbots utilizing large language models have been launched.[1,3] Microsoft Copilot is another chatbot with different functionalities. Unlike ChatGPT, it can search the internet and update its knowledge base.[4] Google Gemini, developed in collaboration with Google teams, integrates different types of information: text, code, audio, images, and video to serve as a writing, planning, and learning assistant.[1] Besides these,

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there are currently over 5,100 chatbots, approximately 100 of which are used in healthcare applications.[5] Chatbots offer advantages such as improving diagnostic accuracy, supporting personalized treatment plans, facilitating the translation of the latest medical literature into clinical practice, and contributing to patient education, thereby enhancing healthcare services.[5,6]

Many dermatological diseases have a chronic course and require long-term follow-up and treatment. However, patients do not always have easy access to a dermatologist. Therefore, patients increasingly turn to online platforms, including social media and artificial intelligence (AI) chatbots, to obtain information about their diseases and the medications they use. Although these assistive tools are well-designed, concerns remain regarding the accuracy, currency, and reliability of the medical information they provide, and regarding the transparency with which user data are handled. To address these concerns, various studies on AI chatbots have been conducted in different specialties.[6–9] In this study, we investigated the readability and reliability of chatbot responses to the most frequently asked questions about isotretinoin, a medication commonly prescribed in dermatology outpatient clinics.

Materials and Methods

Chatbots

Chatbots were selected considering factors such as user fees, login requirements, and inspiration from previous similar studies. The chatbots selected for the study and their versions were ChatGPT 4, Google Gemini 2.0, and Microsoft 365 Copilot; the readability and quality of the responses from these chatbots were evaluated. In the remainder of this paper, these chatbots are referred to as ChatGPT, Gemini, and Copilot. The chatbots were accessed using a personal computer (MacBook Air M2) connected to a home broadband connection. Data were collected between July 1 and July 5, 2025.

Questions

The questions about isotretinoin, the most frequently prescribed active ingredient in dermatologic practice, were prepared by expert dermatologists. Of the prepared questions, 34 were selected. Each question was asked individually to the chatbots, and the responses were recorded in separate documents for review and analysis. Responses were examined by two dermatologists specializing in the field. All items were evaluated jointly by two dermatologists. Both the 5-point Likert scale ratings and the appropriateness classifications (appropriate, incomplete, and inappropriate) were determined by discussion and assigned by consensus. Since the ratings were not performed independently, interrater reliability analysis was not applicable. The British Association of Dermatologists' guidelines were taken as the criterion for response accuracy (Supplementary).[10] The Likert scale developed by Kumari et al.,[11] shown in Table 1, was used to evaluate the accuracy of responses. Furthermore, chatbot responses were classified into three categories: "appropriate", "incomplete", and "inappropriate". An appropriate response was defined as accurate, complete, and consistent with what an expert would advise a patient in the same situation; an inappropriate response was defined as inconsistent with expert opinion or containing incorrect information; and an incomplete response was defined as correct and relevant but lacking sufficient detail. Prior to each question, the chatbot sessions were reset.

Readability Analysis

After the accuracy of the responses had been verified by two independent dermatologists, a readability analysis was performed for each response. The following measures were used: Flesch Reading Ease score (FRES), Flesch-Kincaid Grade level (FKGL), Simple Measure of Gobbledygook (SMOG), Gunning Fog index (GFOG), Coleman-Liau index (CLI), and automated readability index (ARI). In addition, sentence lengths for each response were compared.

Flesch Reading Ease Score: It is a measure of text readability calculated based on the average number of words per sentence and the average number of syllables per word. Scores range from 0 to 100, with higher scores indicating easier readability. Scores between 70 and 80 correspond to approximately an eighth-grade reading level.[12]

Flesch-Kincaid Grade Level: A readability measure that determines reading difficulty according to the United States school grade level. Scores range from 0 to 18, with higher scores indicating greater difficulty. Scores above 12 indicate that the text is written in an academic style.[13]

Simple Measure of Gobbledygook: Designed to assess the appropriateness of a text for the reader's age. It counts ten sentences from the beginning, middle, and end of the text to determine the level. It counts words with three or more syllables across 30 sentences. The syllable counts are then converted to a corresponding reading-grade level.[14]

Gunning Fog Index: This metric determines how difficult a text is to read based on sentence and word length. Scores range from 1 to 18, with each score corresponding to the number of years of education needed to understand the text. To facilitate comprehension by the general public, an average score of 8 is recommended. Scores of 17 and above are considered primarily understandable to individuals with postgraduate education.[15]

Coleman-Liau Index: CLI is a readability assessment that measures how challenging a text is and helps determine its appropriate grade level. It is commonly used in the USA and several other countries. Unlike many other grade-level estimators, CLI relies on the number of characters per word rather than on the number of syllables per word.[16]

Automated Readability Index: This measure estimates the number of years of education required to understand a text on first reading. It takes into account the average number of characters per word and the average number of words per sentence. ARI uses a specific formula to determine the grade level of the text.[17]

Statistical Analysis

Data were analyzed using SPSS for Windows, version 26.0. Descriptive statistics—including mean, standard deviation, median, and percentage distributions—were used to summarize the data. The Kruskal-Wallis test was applied to compare continuous and ordinal variables, such as readability scores and Likert-scale ratings, across the three AI models. For categorical variables, such as response appropriateness, the chi-square test was employed. A *P*-value of less than 0.05 was considered statistically significant.

Results

In our study, 34 questions regarding systemic isotretinoin use were asked of each of three AI chatbots. While a FRES of ≥ 60 is required for optimal readability, none of the examined models reached this threshold. With the exception of FRES, none of the models achieved an acceptable readability level on the other five measures; all models scored well above the thresholds, indicating generally low readability of the content (Table 1).

Readability scores differed significantly among the three AI models across all objective indices (FRES: $P = 0.013$; FKGL: $P = 0.002$; SMOG: $P < 0.001$; GFOG: $P = 0.006$; CLI: $P = 0.003$; ARI: $P < 0.001$). Dunn-Bonferroni post-hoc analyses indicated that these differences were consistently driven by Gemini. Compared with both ChatGPT and Copilot, Gemini produced responses that were significantly less readable, as reflected by lower FRES scores (vs. ChatGPT: $P = 0.011$; vs. Copilot: $P = 0.010$) and higher grade-level indices (FKGL: $P = 0.002$ for both comparisons; SMOG: $P = 0.001$ and $P < 0.001$; GFOG: $P = 0.005$ and $P = 0.007$; CLI: $P = 0.002$ and $P = 0.006$; ARI: $P < 0.001$ for both). No significant differences were observed between ChatGPT and Copilot on any readability metric (Table 1).

Sentence counts also differed significantly ($P = 0.009$); Gemini generated longer responses than Copilot ($P = 0.003$); other pairwise comparisons were not significant.

Likert scale ratings evaluating the quality of responses were similar across models (median = 4), with no statistically significant difference observed ($P = 0.259$). Similarly, the distribution of response appropriateness did not differ significantly among models ($P = 0.701$), and most responses were rated as appropriate (Table 1).

Discussion

Today, increasing and unmet healthcare demands are leading individuals to seek information from alternative sources. Among these, online tools are the most frequently used due

Table 1. Comparison of the relevance and readability of responses from three AI models to questions asked by isotretinoin users

	ChatGPT (Mean ± SD)	Gemini (Mean ± SD)	Copilot (Mean ± SD)	*P*-value*
Flesch Reading Ease score	-2.66 ± 15.08	-11 ± 12.76	-2.71 ± 13.26	**0.013**
Flesch-Kincaid Grade level	16.91 ± 2.33	18.67 ± 1.37	16.97 ± 2.16	**0.002**
Simple Measure of Gobbledygook	12.7 ± 1.58	13.97 ± 1	12.62 ± 1.85	**< 0.001**
Gunning Fog index	18.85 ± 3.17	20.77 ± 2.09	18.95 ± 2.72	**0.006**
Coleman-Liau index	19.12 ± 2.49	20.8 ± 1.75	19.44 ± 1.89	**0.003**
Automated readability index	12.73 ± 2.51	14.85 ± 1.41	12.8 ± 2.12	**< 0.001**
Sentence count	13.79 ± 5	16.88 ± 6.71	12.18 ± 3.04	**0.009**
Likert scale (1–5)	4.35 (median:4)	4.18 (median:4)	4.09 (median:4)	0.259
Appropriateness** Appropriate Incomplete inappropriate	26 (76.5%) 8 (23.5%) 0 (0.0%)	24 (70.6%) 8 (23.5%) 2 (5.9%)	24 (70.6%) 9 (26.5%) 1 (2.9%)	0.701

*Kruskal-Wallis test; **chi-square test
SD: Standard deviation, AI: Artificial intelligence

to their accessibility. Previous studies have shown that a significant proportion of patients turn to online resources for information regarding their diseases and treatments.[18,19]

Our current study provides insight into the performance and reliability of chatbot responses in the medical context. Chatbots are increasingly used across many fields, including medicine. Due to growing healthcare needs and various limitations, unmet demands are increasingly being addressed through tools such as online chatbots. Our study found that chatbots provided answers that varied in length and readability to the same questions. Even though we selected the questions and responses from a publicly accessible online guide, each chatbot generated content and response lengths that differed. While a FRES of ≥ 60 is required for optimal readability, none of the examined models reached this threshold.

When examining accuracy and appropriateness scores, we found that the three chatbots demonstrated similar performance. Similar to our findings, a previous study comparing ChatGPT and Google Bard on educational questions posed by patients with obstructive sleep apnea found the responses from both chatbots to be appropriate and accurate.[20] However, other studies in dermatology, hematology, neurosurgery, lung cancer, and urology have shown differing accuracy rankings among ChatGPT, Gemini, and Copilot.[21] These varying results may be related to differences in the algorithms used by chatbots, the training data, which can vary by country, and updates made to chatbots over time. While accuracy rates differ across studies, one common finding in our study is that no chatbot achieved 100% accuracy.

Statistically significant differences in readability scores were most pronounced between ChatGPT and Gemini and between Gemini and Copilot. Across readability scales, Gemini consistently received significantly higher scores than the other two chatbots, indicating lower readability and increased response complexity. Examination of sentence lengths across all three AI chatbots revealed a significant difference between Gemini and Copilot. Gemini provided longer and more detailed answers with the highest number of sentences, while Copilot offered shorter answers with simpler sentence structures.

Across all readability indices (FRES, FKGL, GFOG, ARI, SMOG, and CLI), the responses generally corresponded to a university-level or higher reading difficulty. Negative FRES values, particularly pronounced in Gemini, were attributable to very long sentences and the use of multisyllabic terms, as reflected in the formula: FRES = 206.835−(1.015 × average words per sentence)−(84.6 × average syllables per word). When the subtraction components exceed 206.835, negative scores occur, indicating exceptionally high textual complexity.[12] These findings align with previous studies evaluating chatbot readability in lung cancer, radiology, urology, and chronic kidney disease contexts, all of which reported low readability levels.[17,21-26] However, a discipline-specific study in urology has reported different readability outcomes.[27]

Likert-scale ratings of response quality were similar across models, and no statistically significant differences were found. The quality of chatbot responses ranged from 81.8% to 87; none achieved the perfect score of 5 and therefore cannot be considered 100% reliable. This finding is consistent with previous studies comparing AI chatbots.[1,21-23,28-30] The quality and accuracy observed in our study suggest that chatbots may be useful for providing relatively accurate information about diseases. Consequently, they may provide valuable assistance to individuals concerning systemic isotretinoin, one of dermatology's fundamental treatment options. Chatbots could educate patients about the use, side effects, and treatment process of systemic isotretinoin, and about when to seek professional medical support. Additionally, by answering simple questions, chatbots can support patients in managing their treatment, thereby reducing the workload on the healthcare system and enabling dermatologists to devote more time to complex and serious cases.

Study Limitations

This study has several limitations. First, only three chatbots were selected, excluding other online platforms accessible to patients. Although the accuracy of responses was evaluated jointly by two dermatologists, inter-rater agreement statistics were not reported. This limitation is acknowledged and could be addressed in future studies by including measures such as Cohen's kappa. The question list was limited and prepared based on the most frequently asked questions in dermatology outpatient clinics. In real life, patient queries may be more diverse and multifaceted.

Conclusion

This study demonstrated that responses generated by chatbots about systemic isotretinoin, which is one of the most frequently prescribed treatments in dermatology, have readability levels corresponding to university education and above, making them relatively difficult to read. The highest response quality reached 87%, and no chatbot provided answers with 100% quality. Although the selected questions focused on a specific drug, the responses were based on publicly available online guidelines. Moreover, individuals of diverse ages and educational backgrounds who initiate systemic isotretinoin treatment in dermatology clinics may consult AI chatbots for information.

The high readability of these responses could lead to misinterpretation of information. This indicates that people seeking information through AI chatbots might be misled, potentially resulting in unnecessary anxiety and increased demand for consultations with doctors, thereby placing an excessive burden on the healthcare system. Conversely, if readability is low for matters requiring urgent intervention, this may delay necessary treatment and negatively impact patients' health.

For healthcare professionals, higher readability levels may be advantageous, providing more detailed and informative content. In the future, it would be beneficial to program chatbots to generate responses tailored to different age groups and educational levels. This approach could make AI chatbots more accessible and effective for diverse populations. More comprehensive and large-scale studies are needed to explore this further.

Ethics

Ethics Committee Approval: Ethical approval was not obtained for the study as it involved publicly accessible data and did not include any patient-specific information.

Informed Consent: Not applicable.

Authorship Contributions

Surgical and Medical Practices: H.A.K., E.Ö., Concept: H.A.K., C.A.G., Design: H.A.K., C.A.G., Data Collection or Processing: E.Ö., Analysis or Interpretation: C.A.G., Literature Search: H.A.K., Writing: H.A.K., E.Ö.

Conflict of Interest: The authors declared that they have no conflict of interest.

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Original Article

Evaluation of Super Response in Plaque-Type Psoriasis Patients Treated with IL-17 and IL-23 Inhibitors

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Abstract

Aim: Biologic treatments have become important for optimal disease control in patients with moderate to severe plaque psoriasis. The term "super response" is used to describe a faster and more sustained response to biologic treatment. This study aimed to determine the characteristics of non-super-responder (NSR) and super-responder (SR) patients with psoriasis receiving interleukin (IL)-17 or IL-23 inhibitors.

Materials and Methods: Patients with plaque psoriasis who were treated with IL-17 or IL-23 inhibitors between 2020 and 2024 were retrospectively analyzed. A super response was defined as a psoriasis area and severity index (PASI) 100 response at week 16 that was maintained through week 28. The patients were divided into the NSR and SR groups and compared in terms of sociodemographic characteristics, clinical findings, biological treatments, and lipid profiles.

Results: A total of 200 patients were included in the study; 96 (48%) were SRs. The frequency of super response was significantly higher among patients with an initial PASI score of ≥ 10 (P = 0.041). Compared with the SR group, the NSR group was more likely to have a history of biologic therapy (P = 0.002). Continued use of the same biological agent was more frequent among SRs (P = 0.019). In the multivariate logistic regression analysis, prior biologic therapy was independently associated with a lower likelihood of achieving a super response [odds ratio (OR) = 0.30; 95% confidence interval (CI): 0.15–0.61; P = 0.001]. Additionally, low high-density lipoprotein (HDL) levels were identified as independent negative predictors of super response (OR = 0.44; 95% CI: 0.24–0.81; P = 0.008).

Conclusion: Prior biologic therapy and HDL level were identified as the most important factors associated with super response.

Keywords: IL-17/IL-23 inhibitors, psoriasis, super response

Introduction

Psoriasis is a chronic, immune-mediated systemic inflammatory disease that affects approximately 2–3% of the population worldwide.[1] Recent studies have revealed that the T-cell-mediated immune response is central to the pathogenesis of psoriasis. Specifically, pathogenic T cells that produce high levels of interleukin (IL)-17 in response to IL-23 stimulation were shown to be the main drivers of the disease.[2]

Biologic agents developed based on this knowledge led to a significant paradigm shift in the treatment of psoriasis. Clinical trial data on monoclonal antibodies targeting the IL-17 signaling pathway (secukinumab, ixekizumab, and bimekizumab) and the newer IL-23p19 antagonists (tildrakizumab, guselkumab, and risankizumab) have provided further evidence that these cytokines are major triggers of the pathogenesis of psoriasis.[2,3] These findings confirm the central role of the IL-17/IL-23 axis in the pathogenesis of psoriasis and provide the scientific basis for focusing treatment strategies on this axis.

The elucidation of these different pathogenetic pathways has enabled the development of new targeted treatment approaches. The widespread and diverse use of biologics has

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led to the emergence of new concepts in the literature, one of which is the term "super response".[3] Researchers have generally defined the concept of super response based on the initial response rate and the maintenance of that response over time.[4] However, there is no consensus on the definition of "super response" specific to psoriasis.[5] Table 1 summarizes the definition of "super response" for patients receiving IL-17 or IL-23 inhibitor therapy.[5-17]

The aim of the present study was to determine the sociodemographic and clinical characteristics of patients with psoriasis classified as non-super-responders (NSRs) and super responders (SRs) to IL-17 or IL-23 inhibitor treatment. A secondary objective was to determine the preferred treatment modalities for patients with SR status. Our findings are expected to contribute to the identification of biomarkers that predict clinical response in this group.

Materials and Methods

Study Design

This single-center, retrospective, cross-sectional, observational analysis included patients with moderate-to-severe plaque psoriasis who presented to the dermatology and venereal diseases outpatient clinic of Trakya University Faculty of Medicine between January 2020 and December 2024. Approval was obtained from the Ethics Committee of Trakya University (approval number: 15/11, date: 25.08.2025).

Inclusion Criteria

1) Age over 18 years,

2) Clinical and histopathological diagnosis of plaque psoriasis,

3) Use of IL-17 or IL-23 inhibitor therapy at the standard dose,

4) Regular follow-up for at least 28 weeks,

5) Informed consent.

Patients diagnosed with guttate, erythrodermic, or pustular psoriasis who were receiving IL-17 or IL-23 inhibitors in combination with any systemic therapy (acitretin, methotrexate, apremilast) or with ultraviolet therapy were excluded from the study.

Definition of Super Responder

In our study, super response was defined as a 100% improvement in psoriasis area and severity index (PASI) score (PASI 100) at week 16 that was maintained at week 28. To determine NSR and SR status, PASI scores at baseline (pre-treatment) and at 16 and 28 weeks after the start of treatment were extracted from patient records and evaluated. Patients who met the specified criteria were divided into the NSR and SR groups. The groups were compared in terms of gender, age, disease duration, comorbidities and psoriatic arthritis (PsA), smoking and alcohol use, body mass index (BMI), dermatological life quality index (DLQI), biologic agent used, number of prior systemic treatments, history of biologic use before the current treatment, drug continuity, drug regimen changes, and high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol values.

Table 1. Definitions of SR to IL-17 and IL-23 inhibitors in patients with psoriasis vulgaris

Authors	Publication date	Biologic agent	Definition of SR status
Morelli et al.[7]	December 2021	Secukinumab	Maintaining PASI 100 response up to weeks 88 and 100
Feldman et al.[6]	March 2022	Tildrakizumab	PASI 90 response at week 28
Reich et al.[8]	August 2022	Guselkumab	PASI 100 response at weeks 20 and 28
Ruiz-Villaverde et al.[9]	September 2022	Guselkumab	PASI 0 at weeks 12 and 24
Mastorino et al.[11]	December 2022	IL-17 and IL-23 inhibitors	In bio-naive patients, PASI 100 response at week 16 and maintained at week 100
Rompoti et al.[10]	January 2023	Brodalumab	PASI ≤ 1 at week 12 or week 16
Herranz-Pinto et al.[14]	July 2023	Guselkumab	PASI ≤ 2 after the third dose of guselkumab and PASI ≤ 1 maintained after subsequent doses for at least 52 weeks
Menéndez Sánchez et al.[15]	July 2023	IL-23 inhibitors	PASI 0 at week 16 and 24
Kim et al.[13]	October 2023	IL-17A, IL-23, TNF, and IL-12/23 inhibitors	PASI 100 response at weeks 48-52
Schäkel et al.[17]	October 2023	Guselkumab	PASI 100 response at weeks 20 and 28
Di Giulio et al.[5]	September 2025	IL-23 inhibitors	PASI ≤ 1 at week 16 and maintained at weeks 28 and 52
Zhang et al.[12]	October 2025	IL-17 inhibitors	PASI 0 before week 4 and maintained at week 24
Kojanova et al.[16]	October 2025	Guselkumab	PASI 0 at week 16 and 24

IL: Interleukin, PASI: Psoriasis area and severity index, TNF: Tumor necrosis factor, SR: Super-responder

The Charlson comorbidity index (CCI) estimates mortality risk for patients with various comorbidities. The prognosis is estimated based on 19 criteria, including age, with total scores ranging from 0 to 33.[18] In our study, CCI was assessed at the initiation of biologic therapy. Switching patterns between IL-17 and IL-23 inhibitors were classified into mutually exclusive categories, ensuring that each patient was included in only one treatment modification group.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25. Non-parametric and categorical statistical methods were used to compare the sociodemographic and clinical characteristics of the NSR and SR groups. Because continuous variables did not meet the assumption of normality, comparisons of these variables (e.g., age and CCI score)were performed using the Mann-Whitney U test. The number of previous systemic treatments was also compared between groups using the Mann-Whitney U test, and the results were reported as Z values. Categorical variables, including gender, smoking and alcohol use, disease duration, comorbidity status, and baseline PASI and DLQI scores, were analyzed using the Pearson chi-square test or Fisher's exact test when expected cell counts were insufficient; Fisher's exact test was specifically used for comparisons involving ≥ 2 previously used biologic agents due to small cell counts. Logistic regression analysis was conducted to determine the effects of age, gender, baseline PASI score, prior biologic therapy, and HDL levels on the likelihood of achieving a super response. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). *P*-values less than 0.05 were considered statistically significant.

Results

A total of 200 patients were included in the study, 48% (n = 96) of whom were SRs. The mean age was 46.2 years, and males accounted for 54% of the sample. Over 70% of the patients had a disease duration longer than 10 years. There were no statistically significant differences in demographic factors, such as age, sex, smoking, and alcohol use, between the NSR and SR groups. Clinical characteristics such as disease duration, comorbidity, CCI, PsA, and BMI were also comparable between the groups ($P > 0.05$). A baseline PASI ≥ 10 was more common in the SR group ($P = 0.041$), while there was no difference in the frequency of baseline DLQI ≥ 10 between NSRs and SRs ($P > 0.05$) (Table 2).

Low HDL levels were significantly more common in the NSR group than in the SR group (51.0% vs. 33.3%, $P = 0.012$), whereas no significant between-group differences were observed for LDL ($P = 0.889$) or total cholesterol ($P = 0.472$) (Table 3).

Biologic treatment consisted of IL-17 inhibitors in 52% (n = 104) and IL-23 inhibitors in 48% (n = 96) of patients. Among biologic agents, the proportion of patients receiving guselkumab was numerically lower in super responders than in NSR (17.7% vs. 30.8%, $P = 0.032$). No statistically significant differences were observed for risankizumab ($P = 0.235$), ixekizumab ($P = 0.051$), or secukinumab ($P = 0.192$). Compared with the NSR group, SR patients were less likely to have received biologic therapy previously and more likely to have used only one biologic ($P = 0.002$ and $P = 0.007$, respectively). SR patients were more likely to continue receiving the same biologic agent, while NSR patients were more likely to switch drug regimens ($P = 0.019$) (Table 4).

Multivariate logistic regression analysis, including age, sex, baseline PASI score, prior biologic therapy use, and HDL levels, demonstrated that prior biologic therapy use was independently associated with a lower likelihood of achieving super response (OR = 0.30; 95% CI: 0.15–0.61; $P = 0.001$). Additionally, low HDL levels were identified as an independent negative predictor of super response (OR = 0.44; 95% CI: 0.24–0.81; $P = 0.008$). No significant associations were observed for age, sex, or baseline PASI score in the multivariate model ($P > 0.05$; Table 5).

Table 2. Sociodemographic and clinical characteristics of NSR and SR patients

	Non-super-responders (n = 104)	Super responders (n = 96)	Total (n = 200)	X^2/Z	*P**
Age, mean ± SD, range	47.48 ± 13.56 (20–76)	45.24 ± 13.55 (18–75)	46.32 ± 13.57 (18–76)	-1175.00	0.240
Sex, n (%)					
Male	51 (49)	57 (59.4)	108 (54)	2147.00	0.143
Female	53 (51)	39 (40.6)	92 (46)		
Smoking, n (%)					
Current-smoker	55 (52.9)	50 (52.1)	105 (52.5)	1201.00	0.549
Ex-smoker	17 (16.3)	21 (21.9)	38 (19)		
Never-smoker	32 (30.8)	25 (26)	57 (28.5)		

Table 2. Continued

	Non-super-responders (n = 104)	Super responders (n = 96)	Total (n = 200)	X^2/Z	*P**
Alcohol, n (%)					
Current drinker	28 (26.9)	20 (20.8)	48 (24)	2708.00	0.258
Social drinker	16 (15.4)	23 (24)	39 (19.5)		
Never-drinker	60 (57.7)	53 (55.2)	113 (56.5)		
Disease duration, n (%) (years)					
< 5	14 (13.5)	12 (12.5)	26 (13)	0.04	0.840
5-10	14 (13.5)	19 (19.8)	33 (16.5)	1452.00	0.228
> 10	76 (73.1)	65 (67.7)	141 (70.5)	0.69	0.406
BMI (kg/m²), n (%)					
Normal (< 25)	27 (26)	26 (27.1)	53 (26.5)	0.03	0.857
Overweight (25 to < 30)	44 (42.3)	32 (33.3)	76 (38)	1706.00	0.191
Obese (≥ 30)	38 (39.6)	33 (31.7)	71 (35.5)	1344.00	0.246
CCI, mean ± SD, range	1.38 ± 1.67 (0–7)	1.4 ± 1.48 (0–6)	1.04 ± 1.57 (0–7)	-0.645	0.519
PsA*, n (%)**	39 (37.5)	25 (26)	64 (32)	3012.00	0.083
Comorbidities**, n (%)**	39 (37.5)	42 (43.8)	81 (40.5)	0.81	0.368
Baseline PASI ≥ 10, n (%)	29 (27.9)	40 (41.7)	69 (34.5)	4196.00	0.041**
Baseline DLQI ≥ 10, n (%)	18 (17.3)	16 (16.7)	34 (17)	0.02	0.904

*Pearson chi-square, Fisher's exact test, Mann-Whitney U test
**Statistically significant
***Rheumatologist-diagnosed psoriatic arthritis
****Comorbidities included hypertension, diabetes, coronary artery disease, and non-alcoholic fatty liver disease
SD: Standard deviation, BMI: Body mass index, CCI: Charlson comorbidity index, PsA: Psoriatic arthritis, PASI: Psoriasis area and severity index, DLQI: Dermatological life quality index

Table 3. Lipid profiles of NSRs and SRs

	Non-super-responders (n = 104)	Super responders (n = 96)	Total	X^2	*P**
Low HDL (females < 50 mg/dL and males < 40 mg/dL)	53 (51)	32 (33.3)	85 (42.5)	6348.00	0.012**
High LDL (≥ 130 mg/dL)	40 (38.5)	36 (37.5)	76 (38)	0.02	0.889
Total cholesterol (≥ 200 mg/dL)	35 (33.7)	37 (38.5)	72 (36)	0.52	0.472

*Pearson chi-square
**Statistically significant
HDL: High-density lipoprotein, LDL: Low-density lipoprotein, NSRs: Non-super-responders, SRs: Super-responders

Table 4. Treatment characteristics of NSR and SR patients

	Non-super-responders (n = 104)	Super responders (n = 96)	Total (n = 200)	X^2/Z	*P**
Biologic agent used					
Guselkumab (IL-23 inh.)	32 (30.8)	17 (17.7)	49 (24.5)	4604.00	0.032**
Risankizumab (IL-23 inh.)	28 (26.9)	19 (19.8)	47 (23.5)	1412.00	0.235
Ixekizumab (IL-17 inh.)	21 (20.2)	31 (32.3)	52 (26)	3798.00	0.051
Secukinumab (IL-17 inh.)	23 (22.1)	29 (30.2)	52 (26)	1699.00	0.192
Number of previous systemic treatments***	1.71 ± 1.2 (1–6)	1.25 ± 0.82 (1–5)	1.49 ± 1.06 (1–6)	-2720.00	0.007**
Previous biologic agent use******	38 (36.5)	15 (15.6)	53 (26.5)	9.6	0.002**

Table 4. Continued

	Non-super-responders (n = 104)	Super responders (n = 96)	Total (n = 200)	X^2/Z	*P**
Number of previously used biologic agents***					
1	32 (30.8)	14 (14.6)	46 (23)	7385.00	0.007**
≥ 2	6 (5.8)	1 (1.04)	7 (3.5)	4208.00	0.067
Continuation of the same biologic agent	88 (84.6)	91 (94.8)	179 (89.5)	5501.00	0.019**
Switch from IL-17 inh. to IL-23 inh.	9 (8.7)	3 (3.1)	12 (6)	2706.00	0.100
Switch from IL-23 inh. to IL-17 inh.	7 (6.7)	2 (2.1)	9 (4.5)	2509.00	0.173

*Pearson chi-square, Fisher's exact test, Mann-Whitney U test
**Statistically significant
***Refers to all conventional systemic drugs received for psoriasis vulgaris and the total number of different drugs tried
****History of exposure to any biologic prior to the current biologic treatment; biologic-experienced patient
*****Number of biologic agents received prior to the current biologic therapy
IL: Interleukin, inh.: Inhibitor, NSR: Non-super-responder, SR: Super-responder

Table 5. Results of multivariate analysis of age, sex, baseline PASI, prior biologic use, and HDL as predictors of SR status

	B	OR (95% CI)	*P*-value*
Age	0.019	1.02 (0.996–1.043)	0.102
Sex	0.398	1.489 (0.818–2.707)	0.192
Baseline PASI***	0.482	1.62 (0.859–3.055)	0.136
Prior biologic therapy	-1.210	0.298 (0.147–0.606)	0.001**
Low HDL****	-0.826	0.438 (0.237–0.809)	0.008**

*Logistic regression analysis. The B value indicates the effect of each variable on log-odds (logarithmic probability)
**Statistically significant
***Baseline PASI: Patients with PASI ≥ 10 before initiation of biologic therapy
****Low HDL: Females < 50 mg/dL and males < 40 mg/dL
PASI: Psoriasis area and severity index, HDL: High-density lipoprotein, SR: Super-responder, OR: Odds ratio, CI: Confidence interval

Discussion

The most common form of psoriasis is plaque-type (psoriasis vulgaris), which affects both genders equally. Recent literature reports the age at onset in Türkiye as 44.5 years.[19,20] Although our study included a small sample of patients, their sociodemographic data were consistent with the literature.

Increasing evidence indicates that SR psoriasis patients may exhibit a distinct endotype with clinical features that differ from those of NSR patients.[21] Studying SRs helps us understand which patient subgroups derive the greatest benefit from biologic agents and implement personalized treatment strategies.[5,8] Despite advances in psoriasis treatment, it remains a clinical challenge because a subset of patients, unlike SRs, do not respond to biologic therapies.[21] Recent studies have reported that approximately 6.5% of psoriasis patients are treatment-resistant.[22]

The concept of super response was first used in the literature in 2019 by Talamonti et al.,[23] who found that carriers of the HLA-Cw6 allele showed a better treatment response to ustekinumab. A similar study conducted in HLA-Cw6-positive and -negative psoriasis patients receiving secukinumab showed that HLA-Cw6 allele positivity was associated with a better response.[7]

One of the most important studies on this subject is GUIDE, a phase IIIb study. The study evaluated SR patients who were treated with guselkumab and showed that the most decisive factors in achieving SR status were a disease duration longer than two years and a history of biologic therapy.[17] Higher SR rates have been reported in recent studies. Zhang et al.[12] reported an SR rate of 64.7%, while Di Giulio et al.[5] reported an SR rate of 63.8%. In our study, this rate was 48%. Higher rates may result from increased awareness of super response among clinicians.

There is no consensus on the effect of sex on SR status. Menéndez Sánchez et al.[15] reported that men were more prevalent among NSRs receiving IL-23 inhibitors, whereas Mason et al.[24] suggested that female sex was associated with NSR status. Although male dominance was noted in our SR group, the difference did not reach statistical significance.

Other factors affecting SR status include lower BMI, biologic naivety,[16] and comorbidities such as obesity, hypertension, and diabetes.[25] Ruiz-Villaverde et al.[9] reported that SR patients

were predominantly younger and had lower BMI, although they did not observe statistically significant differences. Similarly, our SR group was relatively young and had a lower BMI. This association may be related to a lower baseline inflammatory load in SR patients.

Disease duration has also gained relevance in the evaluation of SRs. For psoriasis, a disease duration of 2 years or less has been defined as short, and a disease duration of 2 years or more has been defined as long.[5] SR rates appear better in patients with shorter disease duration.[5,12] As net disease durations could not be determined in our study, these data could not be interpreted. In Türkiye, the use of biologic agents is permitted only after conventional treatment. For these reasons, it is challenging to identify psoriasis patients with a short disease duration and to evaluate the effectiveness of biologic treatment in the early stages of the disease.

In our study, no statistically significant association was found between disease duration and SR status. Furthermore, disease duration and biologic-naive status should be considered distinct clinical variables. This observation underscores the potential importance of timely initiation of biologic therapy, rather than relying solely on disease duration or biologic-naive status when making treatment decisions.[5,11-15]

Although PASI values indicate disease severity, it has been emphasized that PASI elevations may also be associated with recent markers of systemic inflammation.[26] The burden of systemic inflammation determines not only the severity of the disease but also the accompanying endothelial damage, the presence of metabolic syndrome, and the cardiovascular risk.[27] Previous studies on the relationship between high PASI and SR status have yielded contradictory results. In our study, there was a higher proportion of patients with baseline PASI $\geq$ 10 in the SR group. These findings are consistent with those of Mastorino et al.[11] and Liu et al.[21] found that baseline PASI did not differ significantly between NSR and SR patients. In another study, SR status was associated with low baseline PASI.[25] Although higher baseline PASI scores may indicate greater disease severity, biologic-naive status should nevertheless be considered an independent clinical variable, distinct from disease severity. Therefore, the higher super response rates observed in patients with elevated baseline PASI scores should not be interpreted solely as a consequence of biologic-naive status. Instead, baseline disease severity may represent a distinct clinical factor influencing treatment response. Additional studies are needed to clarify the relationship between PASI and super response.

In psoriasis, dyslipidemia results from chronic inflammation and increased levels of oxidized lipids in psoriatic skin.[28] Numerous studies have demonstrated lower HDL levels in patients with psoriasis than in healthy controls. In our study, patients with low HDL values were less likely to achieve SR status. This is similar to a study by Liu et.,[21] in which HDL was the most prominent predictor among all patients. Low HDL was associated with an 87% reduction in the likelihood of achieving a PASI 90 response at 52 weeks. In another study, failure of multiple biologic treatments was found to be more frequent among patients with psoriasis who had a history of hyperlipidemia.[29] The persistent systemic inflammatory environment in psoriasis patients may contribute to reduced treatment efficacy and partially explain these findings. However, further research is needed to confirm the relationship between HDL levels and SR.

When the effect of previous treatment on SR status was evaluated, we observed no difference between the groups with respect to the conventional systemic treatments received. This is consistent with earlier studies showing that conventional treatments received before starting biologic therapy do not affect SR status.[13,27] However, previous exposure to biologic treatments has an effect. Multi-treatment resistance in psoriasis is defined according to the number of discontinued biologic agents ($\geq$ 2 to $\geq$ 9) and biologic classes ($\geq$ 2, $\geq$ 3, or 4).[30] In our study, there was no statistically significant difference between NSR and SR patients in the proportion previously exposed to 2 or more biologic agents. However, this result should be interpreted with caution, given the small number of patients with a history of using two or more biologic agents.

Achieving a super response also affects treatment duration for patients with psoriasis. Although our study was limited to 28 weeks, consistent with other studies, a higher proportion of SR patients continued the same drug treatment compared with NSR patients.[11,21] Being familiar with the characteristics of SR patients and personalizing treatment are important for treatment continuity.

SR rates vary depending on the biologic agents used. One study reported that SRs were more likely to receive IL-17 inhibitor therapy, with ixekizumab and brodalumab showing the highest SR rates.[11] In a study evaluating SR to IL-23 inhibitors, the proportion of SRs was higher in the risankizumab group than in groups receiving other IL-23 inhibitors.[15] In another study, no difference in SR rates was observed among IL-23 inhibitors.[5] In our study, subgroup analyses showed comparable rates of achieving a super response among patients treated with IL-23 inhibitors (guselkumab, risankizumab) and those treated with IL-17 inhibitors (ixekizumab, secukinumab). The highest SR rate was observed among patients receiving ixekizumab, whereas the lowest was observed among those receiving guselkumab. A recent meta-analysis showed that the PASI 75 response rates were highest for bimekizumab, brodalumab, and ixekizumab. In the network meta-analysis,

the PASI 90 response rate was similar between IL-17 and IL-23 agents, with bimekizumab producing the fastest response.[31] In another study, the highest PASI 75 response rate at week 52 was observed with guselkumab; however, that study was also conducted retrospectively. In our study, the unequal distribution of patient subgroups receiving biological therapies makes it difficult to interpret these findings. Additionally, our data collection ended at Week 28, which limits our ability to evaluate long-term SR.

Study Limitations

Limitations of our study include its retrospective design and the small number of patients in the subgroups. Moreover, follow-up was limited to 28 weeks. Finally, certain sociodemographic (e.g., socioeconomic level) values, clinical (e.g., genital involvement) values, and laboratory values (e.g., C-reactive protein concentration, sedimentation rate) could not be evaluated due to missing data.

Conclusion

Sociodemographic characteristics did not appear to significantly influence SR status. Prior biologic therapy and low HDL levels were independently associated with a lower likelihood of achieving a super response, whereas baseline PASI score was not independently associated with a super response after multivariate adjustment. The finding that SRs are more likely to continue the same biologic agent is an important contribution to our understanding of the characteristics of the SR patient group.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Trakya University (approval number: 15/11, date: 25.08.2025).

Informed Consent: Written informed consent was obtained from all patients before study initiation for participation and for the use of anonymized clinical data in scientific research.

Footnotes

Surgical and Medical Practices: M.Ü., M.C.G., Y.G.Ü., Concept: M.Ü., M.C.G., Y.G.Ü., Design: M.Ü., M.C.G., Y.G.Ü., Data Collection or Processing: M.Ü., M.C.G., Y.G.Ü., Analysis or Interpretation: M.Ü., M.C.G., Y.G.Ü., Literature Search: M.Ü., M.C.G., Y.G.Ü., Writing: M.Ü., M.C.G., Y.G.Ü.

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Original Article

Pyoderma Gangrenosum in Clinical Practice: Five Years of Experience from a Tertiary Referral Center

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Abstract

Aim: Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis that causes a high wound burden. Diagnosis is difficult, and treatment is inconsistent. We aimed to describe clinical features, treatments administered, outcomes, and the safety profile of those treatments in a tertiary-center cohort.

Materials and Methods: We performed a single-center retrospective study (2020–2025). PG was diagnosed by clinicopathologic assessment using the PARACELSUS scoring system and by exclusion of mimicking conditions. Responses were predefined: [complete response (CR), ≥ 75% ulcer reduction without active inflammation or new ulcers], [partial response (PR), 30–< 75% with supportive signs], and [no response (NR), < 30% or progression]. We recorded total treatment duration (TTD) and total number of treatments (TNTs).

Results: Fourteen patients were included (7 women, 7 men; mean age 53.0). The ulcerative subtype was most common (n = 12/14, 85.7%); pathergy was present in 35.7% (n = 5/14). The lower limbs were the most frequent sites (n = 5/14, 35.7%). First-line therapy consisted mainly of topical and/or systemic corticosteroids (CR 57.1%, PR 7.1%, NR 35.7%). Second-line regimens (steroids, cyclosporine, colchicine, adalimumab) resulted in CR, PR, and NR rates of 28.6%, 28.6%, and 42.9%, respectively. Third-line therapy (steroids, intravenous immunoglobulin, or cyclosporine) produced PR in all cases. Infliximab, administered as fourth-line therapy (n = 3), achieved CR in 66.7% and PR in 33.3%; one wound infection occurred. The overall TTD was 4.61 ± 4.48 months (median 3, range 1.5–18) and TNT was 1.93 ± 1.21 (median 2, range 1–4). Adverse events occurred in 35.7% of patients overall and in 44.4% of steroid-exposed patients, typically at 3 months. TTD correlated with adverse events [r = 0.74; P = 0.002; 95% confidence interval (0.34, 0.91)]. No statistically significant sex-related differences were observed in treatment response distribution, TTD, or TNT (P > 0.05); however, descriptive trends suggested that females tended toward longer TTD, whereas males exhibited higher TNT.

Conclusion: Corticosteroids are effective, but time-dependent toxicity is common. Early steroid-sparing strategies are advisable. Infliximab showed favorable response rates in refractory PG. Structured wound care should accompany all pharmacologic treatments. Larger prospective studies are needed.

Keywords: Pyoderma gangrenosum, skin ulcer, therapy

Introduction

Pyoderma gangrenosum (PG) is a rare, chronic neutrophilic dermatosis characterized by rapidly progressive, painful ulcerations.[1] Despite its rarity, it carries a disproportionately high clinical impact owing to substantial wound burden, tissue-destructive potential, and an unpredictable course.

PG may occur in isolation or in association with systemic conditions such as inflammatory bowel disease, rheumatoid arthritis, and hematologic malignancies, though idiopathic forms are common.[1,2]

Clinical presentations are heterogeneous, ranging from classical ulcerative to pustular, bullous, and vegetative variants.[3] As no specific diagnostic markers exist, PG remains a diagnosis of exclusion,[4,5] and diagnostic delays are common.

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The disease course is highly variable, and reliable prognostic markers remain lacking.[6,7]

Contemporary management of PG rests on two coequal pillars: structured wound care and disease-directed anti-inflammatory therapy. Wound care is a core therapeutic modality that requires standardized protocols addressing cleansing, moisture balance, infection prevention, pain management, periwound skin protection, and compression or offloading when indicated. In parallel with structured wound care, systemic corticosteroids and immunosuppressive agents such as cyclosporine remain the cornerstone of first-line therapy.[8,9] In refractory cases, biologic agents, including anti-tumor necrosis factor (TNF) agents such as infliximab and adalimumab, have shown efficacy.[10,11] More recently, therapies targeting interleukin pathways or B cells have been trialed, though their role remains uncertain and, in some cases, paradoxically associated with PG induction.[12-15] Despite these therapeutic advances, the absence of standardized treatment algorithms or universally accepted guidelines continues to limit evidence-based clinical practice.

The lack of standardized guidelines creates an urgent need for high-quality, real-world data to inform evidence-based management strategies.

The present study aims to evaluate the clinical characteristics, treatment modalities, treatment safety, and therapeutic responses of patients with PG treated at a tertiary center over a five-year period. By examining long-term outcomes and exploring potential sex-related differences, this work seeks to contribute valuable real-world data that may support more individualized and standardized approaches to PG management.

Materials and Methods

This single-center, retrospective cohort study was conducted between 2020 and 2025 at a tertiary referral center. The diagnosis of PG was established based on clinical presentation, histopathological findings, and exclusion of alternative causes, using the PARACELSUS scoring system as a structured diagnostic aid.[16] All patients had PARACELSUS scores consistent with a definite or probable diagnosis of PG. Clinical data were collected from electronic medical files and patient charts. Patients with incomplete medical records or uncertain diagnoses were excluded. Extracted variables included demographic and clinical characteristics, treatment regimens, and treatment outcomes.

Treatment outcomes were categorized retrospectively based on the information available in patient records:

- A complete response (CR) was defined as a ≥ 75% reduction in ulcer surface area together with the absence of active inflammation and no new or satellite ulcers.
- Partial response (PR) was defined when the charts reflected a 30% to < 75% reduction in ulcer surface area, accompanied by at least two supportive findings such as decreased erythema, a ≥ 2-point reduction on a 10-point visual analog scale (when available), decreased exudation, evidence of re-epithelialization or flattening of lesion margins, and the absence of new or satellite ulcers.
- No response (NR) was defined as a < 30% reduction in ulcer surface area, or any documented progression, including new or satellite ulcer formation, lesion enlargement, or worsening inflammatory features.

These cut-off values were determined based on previously published PG cohorts and treatment response classifications to ensure comparability with existing literature.[17-19]

In addition, two treatment-related variables were analyzed for each patient. The total treatment duration (TTD) was defined as the number of months; the total number of treatments (TNT) was defined as the total number of distinct treatment regimens administered per patient from the date of diagnosis to the achievement of complete clinical response. TNT was regarded as an indirect indicator of treatment resistance.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as numbers (n) and percentages (%), and continuous variables as mean ± standard deviation, median, minimum, and maximum values. The distribution of continuous variables was assessed using the Shapiro-Wilk test. Given the limited sample size and the frequent deviations from normality, non-parametric tests were applied. The Mann-Whitney U test was used for comparisons between two independent groups, the Kruskal-Wallis H test was used for comparisons among more than two groups, and Spearman's rank correlation coefficient was used for assessing associations between continuous variables. Spearman's correlation was selected as the primary measure of association because it is robust to non-normal distributions and small sample sizes; however, given the limited number of observations (n = 14) and the reduced statistical power in subgroup analyses, correlation results should be interpreted with caution. To aid interpretation, 95% confidence intervals (CIs) were calculated alongside *P*-values where applicable. Point-biserial correlation (equivalent to Spearman for binary variables) was used to assess associations between dichotomous and continuous variables. Categorical variables were compared using the chi-square test or Fisher's

exact test, as appropriate. Statistical significance was set at $P < 0.05$.

Ethical approval for this study was obtained from the Uşak University Non-Interventional Clinical Research Ethics Committee (approval number: 807-807-28, date: 24.07.2025). The study was conducted in accordance with the principles of the Declaration of Helsinki. No identifiable personal information was collected, and all data were anonymized prior to analysis.

Results

Patient Selection and Demographics

A total of 19 patients with a recorded diagnosis of PG were initially identified from hospital archives. Following the exclusion of cases with incomplete medical records or uncertain diagnoses, 14 patients (7 females and 7 males) met the eligibility criteria and were included in the final analysis.

The mean age of the study population was 53.0 ± 13.5 years (range 31–73). Female patients had a mean age of 55.85 ± 12.99 years (range 31–73), while male patients were slightly younger with a mean of 49.42 ± 13.50 years (range 36–69). The average disease duration across the cohort was 18.0 ± 34.3 months (median 6 months, range 0–108). Female patients had a shorter disease duration (mean 13.29 ± 17.42 months, median 4 months, range 0–48) compared with males (mean 23.90 ± 47.05 months, median 3 months, range 1–108), although variability was greater in the male subgroup.

Disease Characteristics

The majority of patients presented with the ulcerative subtype, which was observed in all female patients (7/7; 100%) and in 5 out of 7 male patients (71.4%). Bullous and pustular variants were each identified in one male patient (14.3%). Pathergy positivity was observed in 5 of 14 patients (35.7%), with no significant difference between sexes.

The lower extremities were the most frequently affected anatomical sites, affecting 2 female patients (28.6%) and 3 male patients (42.9%). Other affected regions included the gluteal region (1 female, 2 males), the upper extremities (1 female, 1 male), the abdomen (1 female), the back (1 female), and the face (1 female, 1 male). The detailed anatomical distribution and subgroup comparisons are illustrated in Figure 1.

Comorbidities were frequently observed across both sexes. Among female patients, the most common comorbid conditions were diabetes mellitus, obesity, and hepatosteatosis. In male patients, hypertension was the most frequent condition. A detailed summary of individual comorbidities is presented in Table 1.

Treatment Outcomes

Response rates were calculated per treatment line, not per individual medication. As shown in Figure 2, systemic and topical corticosteroids were the most frequent first-line therapies, together accounted for the majority of initial treatment regimens. In this group (n = 14), CR, PR, and NR were observed in 57.1% (n = 8/14), 7.1% (n = 1/14), and 35.7% (n = 5/14), respectively. Second-line therapies included agents such as systemic corticosteroids, combined systemic and topical corticosteroids, cyclosporine, colchicine, and adalimumab. Among these patients (n = 7), CR occurred in 28.6% (n = 2/7), PR in 28.6% (n = 2/7), and NR in 42.9% (n = 3/7). In the third-line group (n = 3), all patients were treated with systemic corticosteroids, intravenous immunoglobulin, or cyclosporine, and all demonstrated PR (100.0%, n = 3/3). Infliximab, administered as a fourth-line option, resulted in CR in 66.7% (n = 2/3) and PR in 33.3% (n = 1/3).

When stratified by sex, no statistically significant differences in overall response distribution were observed between female and male patients ($\chi^2 = 0.96$, $P = 0.62$). However, descriptive trends were noted: female patients showed a higher proportion of CR than male patients (50.0% vs. 40.0%), whereas male

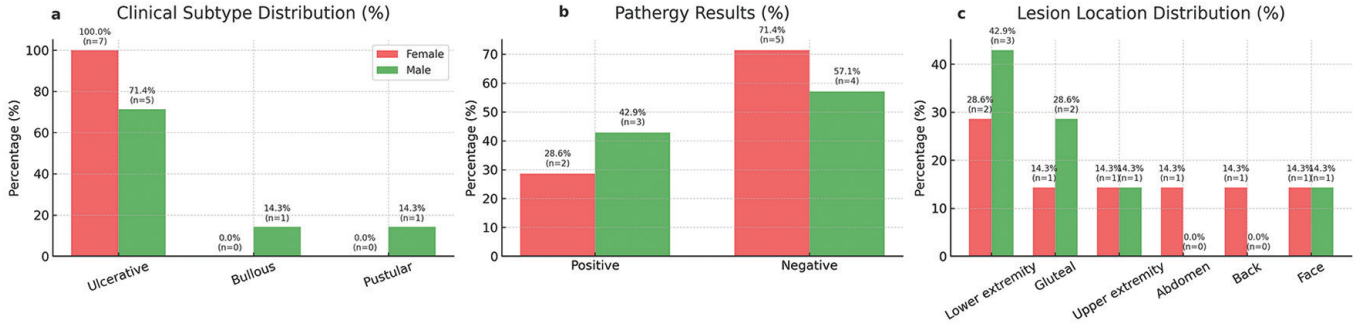

Figure 1. Sex-specific distribution of key disease characteristics, demonstrating variations in clinical subtypes (a), pathergy reactivity (b), and anatomical localization of lesions (c)

Table 1. Comorbidities observed in the study population, stratified by sex; percentages are calculated within each sex group and totals exceed 100% because some patients had more than one comorbid condition

Comorbidity	Female n (%)	Male n (%)
Diabetes mellitus	3 (42.9)	1 (14.3)
Obesity	2 (28.6)	1 (14.3)
Hepatosteatosis	2 (28.6)	1 (14.3)
Heart failure	1 (14.3)	0 (0.0)
Arrhythmia	1 (14.3)	0 (0.0)
Coronary artery disease	1 (14.3)	1 (14.3)
Hypertension	0 (0.0)	2 (28.6)
Asthma	0 (0.0)	1 (14.3)
Brucellosis	0 (0.0)	1 (14.3)
Essential thrombocythemia	0 (0.0)	1 (14.3)
Hypothyroidism	1 (14.3)	0 (0.0)
Behçet's disease	1 (14.3)	0 (0.0)
Morphea	1 (14.3)	0 (0.0)
Peripheral vascular disease	0 (0.0)	1 (14.3)
History of trauma/surgery	0 (0.0)	1 (14.3)

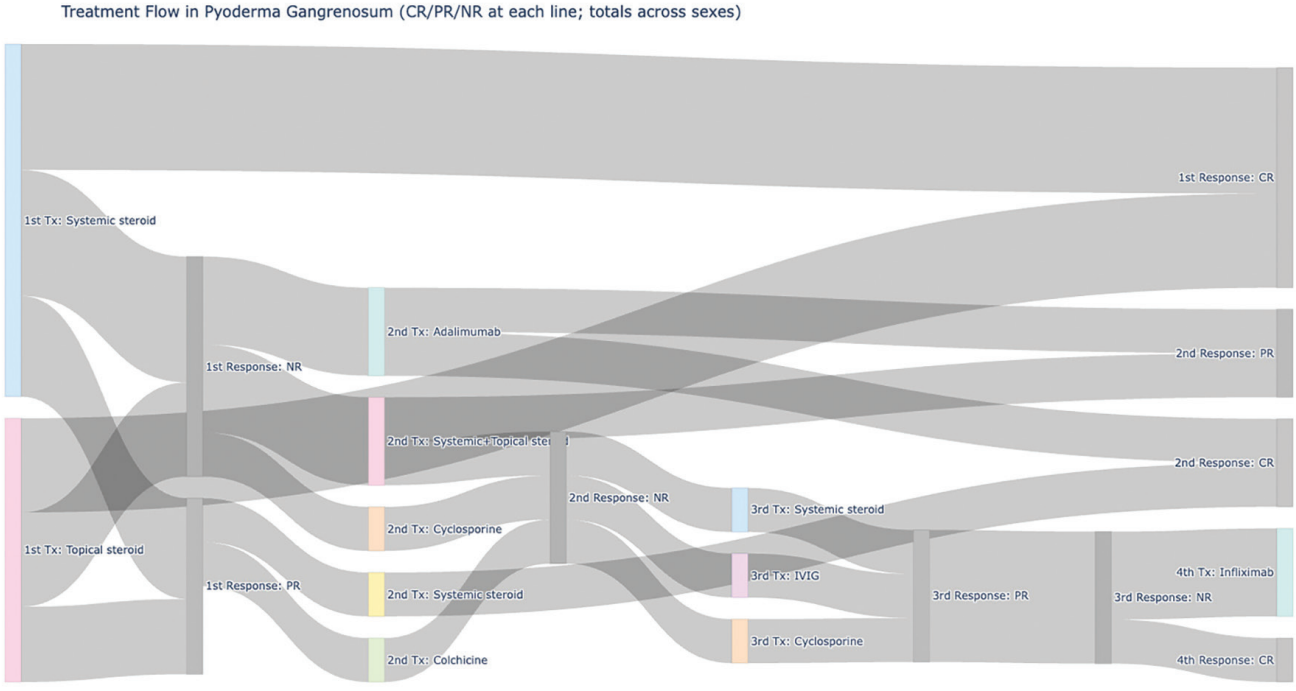

Figure 2. Treatment flow in pyoderma gangrenosum across sequential therapy lines. The diagram illustrates first-line corticosteroid-based regimens, subsequent transitions to second-, third-, and fourth-line agents, and their corresponding clinical responses
CR: Complete response, PR: Partial response, NR: No response

patients more frequently demonstrated PR than female patients (33.3% vs. 16.7%). NR rates were comparable between the sexes (33.3% vs. 26.7%).

Adverse Events and Reasons for Treatment Discontinuation

Adverse events were observed in 5 of 14 patients (35.7%). Among patients exposed to systemic corticosteroids in any treatment line (n = 9), adverse events occurred in 4 patients (44.4%), with some individuals experiencing more than one reaction. Corticosteroid-associated events included hyperglycemia in 2/9 (22.2%), weight gain in 1/9 (11.1%), and fatigue with purpura or ecchymosis in 1/9 (11.1%); iatrogenic Cushing's syndrome was recorded in 1/9 (11.1%). In patients receiving systemic corticosteroid therapy, adverse events were most commonly observed within the early treatment period,

emerging at 3.7 ± 0.6 months (median 3 months, range: 3–5) after initiation.

Among patients exposed to infliximab (n = 3), a wound-site infection developed in one patient during the 3rd week of treatment. No statistically significant differences were observed between female and male patients regarding the occurrence of adverse events. A detailed breakdown of adverse events is provided in Table 2, with proportions calculated relative to the number of patients exposed to each therapy.

Total Treatment Duration and Total Number of Treatments

In the overall cohort, the TTD was 4.61 ± 4.48 months (median 3, range 1.5–18), and the TNT was 1.93 ± 1.21 (median 2, range 1–4). When stratified by sex, TTD was longer in females at 6.03 ± 5.88 months (median 3, range 1.5–18) compared with males at 3.19 ± 1.93 months (median 2.62, range 2–7.5). Conversely, TNT was higher in males at 2.14 ± 1.34 (median 2, range 1–4) compared with females at 1.71 ± 1.11 (median 1, range 1–4).

Correlation Analyses

No correlation was found between disease duration, presence of comorbidity, or pathergy positivity and either TTD or TNT ($P > 0.05$). No correlation was detected between disease duration and the occurrence of adverse events ($P > 0.05$). No statistically significant associations were found between sex and TTD, TNT or the occurrence of adverse events ($P > 0.05$). Additionally, the overall response distribution did not differ by sex ($\chi^2 = 0.96$, $P = 0.62$).

A significant positive correlation was observed between TTD and the occurrence of adverse events [Spearman r = 0.74, $P = 0.002$; 95% CI (0.34, 0.91)]. Although not statistically significant, females tend to have longer TTD (6.03 ± 5.88 months vs. 3.19 ± 1.93 months in males, $P > 0.05$), whereas males exhibited higher TNT (2.14 ± 1.34 vs. 1.71 ± 1.11, $P > 0.05$).

Discussion

When evaluating the demographic and disease-specific characteristics of our cohort, we observed patterns that are largely consistent with those reported in the existing literature: the predominance of the ulcerative subtype, the frequent involvement of the lower extremities, the frequency of pathergy positivity, and the occurrence of comorbid conditions such as diabetes and cardiovascular disease.[20-22] Although our cohort consists of a limited number of patients, it nevertheless provides a representative sample reflecting the typical clinical spectrum of PG. This supports the external validity of our observations and suggests that the findings may be generalizable, at least in part, to the broader patient population.

Our observations indicate that treatment selection often did not adhere to a uniform, stepwise algorithm, with decisions appearing to be guided by clinical judgment and patient-specific considerations. First-line therapies most commonly consisted of topical, intralesional, and systemic corticosteroids. In cases of inadequate response, systemic corticosteroids were frequently combined with topical or intralesional preparations rather than being replaced by other immunosuppressive agents. Notably, cyclosporine was rarely used as initial therapy and was instead reserved for later lines of treatment. This finding differs from the prevailing literature, where cyclosporine is more often considered in earlier stages.[8-10,23] The tendency to postpone cyclosporine use in our study may be related to the older age of our patients, the presence of comorbidities, and concerns regarding its strong immunosuppressive effects, which could further limit its suitability.

Systemic corticosteroids were associated with the majority of adverse reactions in our cohort, most of which emerged after approximately three months of therapy. This observation highlights the critical window during which the risk of corticosteroid-related adverse events becomes most pronounced. In line with this, a recent review emphasized that long-term tolerability of corticosteroids is limited by their

Table 2. Treatment-related adverse events observed in patients. The drug-event relationship was determined based on temporal association, biological plausibility, and exclusion of alternative causes. Percentages are calculated relative to the number of patients exposed to each therapy

Therapy	Patients exposed (n)	Adverse events (n, %)
Systemic corticosteroids	9	**4 (44.4%)**
Hyperglycemia		2 (22.2%)
Weight gain		1 (11.1%)
Fatigue with purpura/ecchymosis		1 (11.1%)
Iatrogenic Cushing's syndrome		1 (11.1%)
Infliximab	**3**	**1 (33.3%)**
Wound site infection		1 (33.3%)

adverse effects and a cohort study reported that prolonged prednisone exposure was associated with higher mortality.[24,25] To mitigate these complications, the early introduction of corticosteroid-sparing agents within the first three months of treatment may be advisable. Such an approach could reduce cumulative corticosteroid exposure and improve long-term tolerability while maintaining disease control. However, due to incomplete documentation, no specific conclusions could be drawn regarding corticosteroid dosages in relation to adverse events. Nevertheless, the average starting dose of systemic prednisolone in our cohort was between 0.5 and 1 mg/kg/day, consistent with commonly reported initial dosing regimens in the literature.

In our cohort, infliximab was typically reserved for the later stages of treatment. Nevertheless, we observed that it produced the most successful clinical responses, with all treated patients achieving either complete or partial remission. Notably, one patient developed a wound-site infection during the induction phase of biologic therapy, underscoring the need for careful monitoring for infectious complications.

Although adalimumab was also employed, its outcomes were less consistent than those observed with infliximab, indicating a potential advantage of infliximab over other anti-TNF agents. Previous reports similarly highlight infliximab as the anti-TNF agent with the highest rates of response in PG.[25,26] This may be because infliximab dosing is adjusted for body weight.

Although our study is limited to make a definitive comparison, our findings suggest that the efficacy of anti-TNF agents remains high regardless of comorbidities in line with literature.[27,28] Yet, their preferential use may be justified when comorbid conditions, such as inflammatory bowel disease, offer additional therapeutic benefits. Interestingly, paradoxical cases of PG induced by anti-TNF agents have also been reported in the literature, highlighting the complexity of the underlying pathogenesis and the need for further mechanistic research, and such paradoxical reactions should be kept in mind in clinical practice.[29,30]

Sex-related descriptive trends, although not statistically significant ($P > 0.05$), were observed in our cohort. Female patients achieved complete remission more frequently, yet required longer treatment durations (TTD), suggesting a tendency to be late responders. In contrast, male patients more commonly exhibited PRs and required a greater number of treatment lines (TNT), which may indicate a greater degree of treatment resistance. While our sample size is limited and these findings were not statistically significant, they nevertheless raise the possibility of underlying sex-related differences in treatment dynamics that merit further exploration in larger cohorts. Although this has not been specifically addressed in prior studies, it is well established that immune responses differ between sexes,[31] and this could naturally influence the efficacy of immunosuppressive agents.

In our series, the risk of adverse events increased with longer cumulative treatment duration, a pattern that was particularly pronounced among patients receiving systemic corticosteroids. These observations underscore the need to optimize treatment duration to balance efficacy and safety. One potential strategy would be to use standardized disease severity assessment tools at baseline to guide the selection of appropriately potent therapies from the outset. Tailoring treatment intensity to disease severity may reduce both TTD and the cumulative burden of adverse effects. Ultimately, larger studies are warranted, and the development of internationally accepted guidelines will be essential to standardize treatment decisions and improve long-term outcomes in PG.

Finally, our observations underscore the role of wound care as a primary therapeutic modality alongside systemic treatment. In our cohort, as is frequently the case in general dermatologic practice, standardized wound care protocols were inconsistently applied during the treatment course, which may have influenced healing outcomes and the accuracy of therapeutic response assessment. Appropriate wound management, including meticulous infection control and prevention of secondary colonization, should accompany every treatment line as a standard component of care.[32,33] Accordingly, structured wound care should be initiated as early as possible while diagnostic and etiologic evaluations proceed.

Additionally, optimization of comorbid conditions and general supportive measures may complement pharmacologic treatment.

Study Limitations

This study has inherent limitations, including its retrospective, single-center design and small sample size. Consequently, the statistical power was limited, and correlation analyses largely remained descriptive rather than conclusive. Furthermore, the duration of resistance to prior treatments could not be systematically assessed among patients who received infliximab, and time-to-response data were not available, which limits interpretation of comparative treatment efficacy. Nonetheless, the study provides valuable real-world insights into treatment burden, sex-related variability, and therapeutic aspects of PG. Future multicenter prospective studies with standardized outcome measures are needed to validate these findings and to support the development of evidence-based management guidelines.

Conclusion

PG remains a complex disease that requires individualized management. While corticosteroids are widely used, their adverse effects argue for the early introduction of corticosteroid-sparing strategies. Infliximab produced consistent, favorable responses in our cohort, supporting its use in refractory cases. Wound care should be positioned as a primary therapeutic modality, delivered in parallel with pharmacologic treatment and implemented using standardized protocols that address cleansing, moisture balance, infection prevention, pain control, and protection of periwound skin, including compression or offloading when indicated. Optimization of comorbidities and other supportive measures complements this dual approach. This study provides real-world data that may support more individualized and more standardized care. Larger prospective studies and international guidelines are needed to further standardize management and improve outcomes.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Uşak University Non-Interventional Clinical Research Ethics Committee (approval number: 807-807-28, date: 24.07.2025).

Informed Consent: No identifiable personal information was collected, and all data were anonymized prior to analysis.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.G., S.Ü., Concept: E.G., S.Ü., Design: E.G., S.Ü., Data Collection or Processing: E.G., S.Ü., Analysis or Interpretation: E.G., Literature Search: E.G., S.Ü., Writing: E.G.

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Case Report

Finally, She Smiled: A Case of Granulomatous Cheilitis Treated with Tofacitinib

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Abstract

Granulomatous cheilitis (GC) is a rare, idiopathic inflammatory disorder usually affecting young adults. Various treatment modalities have been suggested in the literature, but some cases remain recalcitrant and result in significant emotional distress owing to facial disfigurement. We present a 20-year-old woman with a two-year history of asymptomatic lip swelling, diagnosed as biopsy-proven GC and refractory to topical corticosteroids, tacrolimus, intralesional corticosteroids, and systemic corticosteroids. After failure of these therapies, oral tofacitinib (5 mg twice daily) for 3 months, administered with emollients, resulted in a significant improvement in swelling and disfigurement. The exact etiology of GC remains unknown, but T-helper 1-driven cytokines contribute to granuloma formation via the Janus kinase-signal transducer and activator of transcription pathway. In this refractory case, tofacitinib, a JAK1/3 inhibitor, showed promising results. While this suggests potential as a therapeutic option in recalcitrant GC, larger studies are needed to establish efficacy, safety, and the role in treatment algorithms. Known risks of JAK inhibitors, including infections, thromboembolism, cardiovascular events, and malignancy, should be considered.

Keywords: Granulomatous cheilitis, Janus kinase inhibitors, lip swelling, non-caseating granuloma, refractory cheilitis, tofacitinib

Introduction

Granulomatous cheilitis (GC), or Miescher's cheilitis, is a rare, idiopathic inflammatory condition characterized by persistent, non-tender swelling of one or both lips, predominantly affecting young adults.[1] It is considered a monosymptomatic variant of Melkersson-Rosenthal syndrome, which may include facial paralysis and fissured tongue.[2] The chronic disfigurement caused by GC often leads to significant emotional distress and reduced quality of life.[3]

The etiology of GC remains unclear, with proposed triggers including genetic predisposition, hypersensitivity reactions (e.g., to food additives or dental materials), and microbial agents like *Mycobacterium tuberculosis* or *Borrelia burgdorferi*.[4,5] Associations with systemic conditions such as Crohn's disease and sarcoidosis suggest a shared granulomatous pathology.[6] Histologically, GC is marked by non-caseating granulomas with epithelioid histiocytes, lymphocytes, and lymphoedema.[6] Immunologically, T-helper 1 (Th1) cells drive granuloma formation through cytokines like interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which signal via the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway.[7] IFN-γ activates JAK1/JAK2-STAT1, promoting macrophage polarization and granuloma maintenance, whereas TNF-α contributes via overlapping inflammatory cascades.

Clinically, GC presents with insidious lip swelling, often affecting the upper lip, which may initially be episodic but

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becomes persistent.[8] The diagnosis relies on clinical findings and biopsy to rule out mimicking conditions. A systematic review from India reported a mean onset age of 26 years, with 75% of cases being monosymptomatic.[8] Treatment is challenging due to the lack of randomized trials and variable response rates.[9] Standard therapies include topical, intralesional, or systemic corticosteroids, which often yield temporary relief.[10] Other options like antibiotics (e.g., metronidazole), immunosuppressants (e.g., thalidomide), and biologics (e.g., anti-TNF agents) have inconsistent outcomes.[11] Surgical interventions like cheiloplasty or radiofrequency therapy are reserved for severe cases but carry relapse risks.[12]

Recent evidence highlights JAK inhibitors as promising for granulomatous skin diseases by targeting the JAK-STAT pathway.[1] Tofacitinib has shown efficacy in conditions like granuloma annulare and necrobiosis lipoidica, while upadacitinib achieved high response rates in refractory GC.[4,5] This report presents a case of biopsy-proven GC successfully treated with tofacitinib after failure of conventional therapies, adding to emerging evidence on JAK inhibition in refractory granulomatous dermatoses.

Case Report

A 20-year-old female presented with a two-year history of asymptomatic swelling of both lips, with insidious onset and gradual progression, resulting in noticeable facial disfigurement. No pain, itching, or systemic symptoms (fever, weight loss, gastrointestinal complaints) were reported. No allergies, dental procedures, or family history noted.

Examination revealed diffuse, non-tender, soft-to-firm swelling of both lips, more prominent on the upper lip, without erythema, scaling, or ulceration (Figure 1a). The oral mucosa was spared; no facial palsy, fissured tongue, or lymphadenopathy was noted.

Laboratory tests [complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum angiotensin converting enzyme (ACE), antinuclear antibody, antineutrophilic cytoplasmic antibody] were normal. Patch testing was negative. Lip biopsy confirmed non-caseating granulomas with epithelioid histiocytes and lymphocytes, consistent with GC.[1]

Patient was previously treated with topical clobetasol propionate 0.05% ointment (twice daily, 4 weeks), topical tacrolimus 0.1% ointment (twice daily, 6 weeks), intralesional triamcinolone acetonide 10 mg/mL (biweekly, 3 months), systemic prednisolone 1 mg/kg/day (tapered over 8 weeks)—transient improvement were noted with recurrence and refractoriness. Systemic corticosteroids were discontinued approximately 2 months before initiation of tofacitinib.

After informed consent and baseline screening (tuberculosis Quantiferon, viral serology, and lipid profile), oral tofacitinib 5 mg twice daily and an emollient were initiated. She was counseled on risks (infections, thromboembolism, cardiovascular events, malignancy). At 1 month, partial reduction was noted (Figure 1b); at 3 months, near-complete resolution with a normal contour (Figure 1c) was achieved. dermatology life quality index improved from 18 to 4. No adverse events were noted. Tofacitinib was tapered over the next month. Remission was noted at 6-month follow-up.

Discussion

This case illustrates tofacitinib's potential in refractory GC where conventional therapies failed. The pathogenesis of GC involves Th1-mediated granuloma formation via IFN-γ and TNF-α signaling through the JAK-STAT pathway.[7,13] JAK inhibition disrupts this process and may be to broad corticosteroids by targeting specific cytokine signaling rather than causing non-selective immunosuppression, thereby reducing the risk of relapse in cytokine-driven granulomatous inflammation.

Conventional treatments yield inconsistent results much of the time. Intralesional corticosteroids are usually the first-line agents, but relapses are common.[2,8] Metronidazole is also effective in some cases.[10] Even thalidomide has shown efficacy but its use is limited by neurological adverse effects.[11] Radiofrequency therapy has also been tried in some cases.[12]

JAK inhibitors target multiple cytokines in granulomatous conditions. Tofacitinib induced remission in necrobiosis lipoidica and granuloma annulare has been reported.[4,8] Also there are case reports showing upadacitinib achieved 80% complete response in refractory GC, including Crohn's-associated.[4] Our patient's rapid response aligns with the hypothesis that JAK inhibition targets core inflammation.

Differential diagnosis includes orofacial Crohn's disease, sarcoidosis, foreign body granulomas, infectious granulomatous diseases (tuberculosis, deep fungal infections).[13] But normal serum ACE and no systemic symptoms argued against sarcoidosis; no gastrointestinal symptoms and normal labs also excluded Crohn's disease. Even the biopsy lacked caseation or organisms. The negative Quantiferon test and no travel/endemic exposure ruled out tuberculosis and negative special stains excluded fungal etiology.[14] There was no history of injection of foreign material.

Tofacitinib at low doses generally favorable, but JAK inhibitors carry risks like serious infections, thromboembolism, cardiovascular events (e.g., MACE), malignancy (Food and Drug Administration boxed warnings based on ORAL

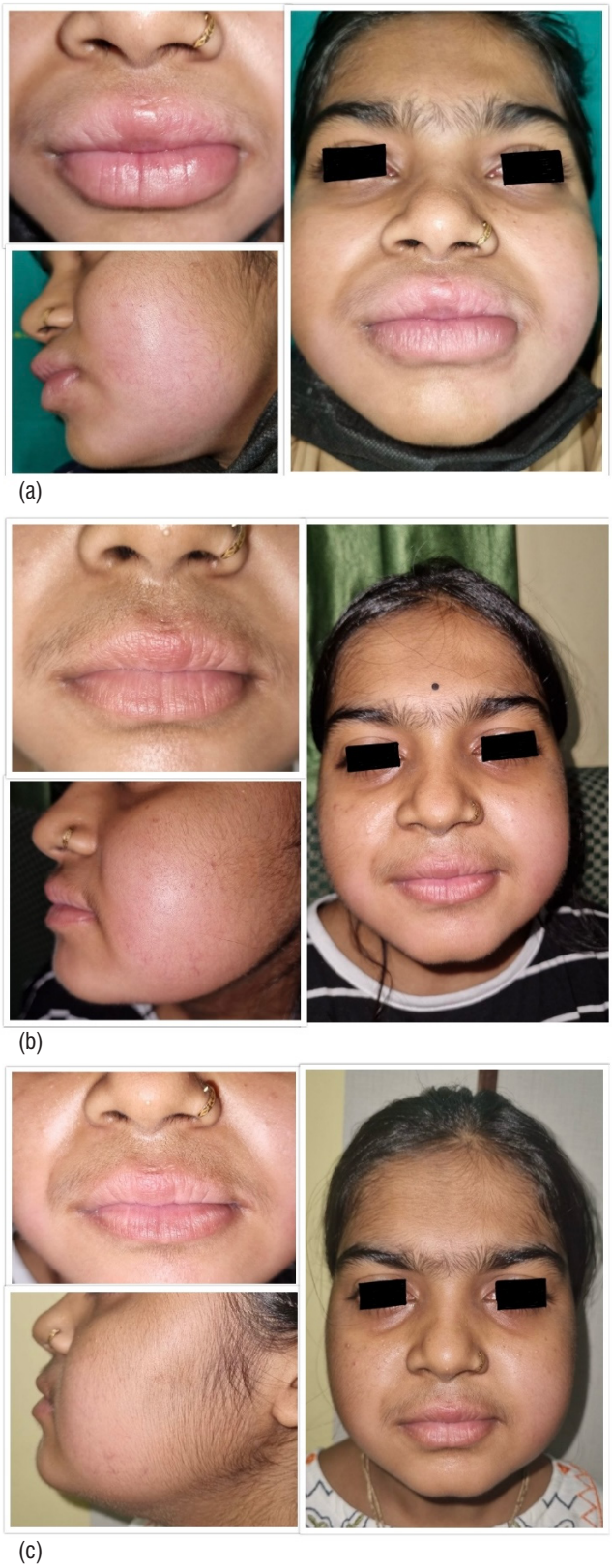

Figure 1. (a) Diffuse, non-tender, soft-to-firm swelling over both lips. (b) Partial reduction in swelling at 1 month after starting tofacitinib. (c) Near-complete resolution of lip swelling with restoration of normal lip contour at 3 months after starting tofacitinib

Surveillance trial in rheumatoid arthritis, extrapolated class-wide).[15] So, it should be used with caution in at-risk patients. In our case, it was low-dose, short-term use. No adverse events were noted.

Our case adds to limited reports of tofacitinib in GC (mostly upadacitinib data), demonstrates efficacy post-multiple failures, highlights quality-of-life benefit and contributes preliminary evidence for JAK inhibitors in recalcitrant GC.

We have limitations, including a single case and a short follow-up period. Also, it cannot establish causality or superiority. Prospective trials are needed for efficacy and safety positioning against corticosteroids.[16]

Conclusion

This case suggests that tofacitinib may be effective in refractory GC, improving clinical outcomes and quality of life without observed adverse effects. However, the evidence is exploratory and derived from case reports and case series. Larger controlled studies are required to confirm efficacy, long-term safety, and potential role as a first-line or alternative therapy, while balancing benefits against known JAK inhibitor risks.

Footnotes

Informed Consent: Patient consent for publication of images obtained.

Authorship Contributions

Concept: S.P., Design: S.M., Literature Search: S.P., Writing: S.M.

Conflict of Interest: The authors declared that they have no conflict of interest.

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Case Report

Rapid Clinical Improvement with Pentoxifylline in Pigmented Purpuric Dermatosis: A Case Report and UV-F Dermoscopy Findings

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Abstract

Pigmented purpuric dermatoses (PPD) are chronic capillaritides characterized by petechiae, purpura, and brown macules. We present a biopsy-confirmed case of Schamberg disease with rapid clinical improvement following a 2-week course of oral pentoxifylline. A 25-year-old woman presented with an approximately 5-year history of recurrent asymptomatic petechial eruptions affecting the upper and lower extremities. Dermoscopy demonstrated reddish, round-to-oval globules and dots on a brownish background. Ultraviolet-induced fluorescence (UV-F) dermoscopy enhanced the visibility of active petechial foci and assisted in selecting an optimal biopsy site. Histopathology revealed a superficial perivascular lymphocytic infiltrate with focal erythrocyte extravasation and pigment-laden macrophages in the papillary dermis; features of leukocytoclastic vasculitis were absent. After failure of topical high-potency corticosteroids and topical calcineurin inhibitors, controlled-release pentoxifylline 600 mg once daily was initiated. Near-complete clinical resolution was observed by day 14. Treatment was discontinued because of nausea and vomiting, and remission persisted at 2-month follow-up. This case suggests that pentoxifylline may be associated with early clinical improvement in selected patients with PPD and highlights UV-F dermoscopy as a practical adjunct for identifying active purpuric foci and selecting a biopsy site.

Keywords: Dermoscopy, pentoxifylline, pigmented purpuric dermatosis, purpura, Schamberg disease

Introduction

Pigmented purpuric dermatoses (PPD) constitute a spectrum of relatively rare, chronic, benign disorders characterized by petechiae, purpura, and yellow-brown pigmentation, most commonly involving the lower extremities, although the upper extremities and trunk may also be affected.[1,2] Histopathologic features include superficial perivascular lymphocytic infiltrate, erythrocyte extravasation, and hemosiderin deposition.[1] Although the condition is benign, it may lead to cosmetic concerns; therefore, treatment is often symptomatic. Various therapies, including topical corticosteroids, phototherapy, and systemic agents such as griseofulvin, cyclosporine, and rutoside with vitamin C, have been reported; however, a standardized protocol is lacking.[1,2] Pentoxifylline has emerged as a promising option due to its hemorheologic and anti-inflammatory properties.[2,3]

Case Report

A 25-year-old woman with no significant medical history presented with recurrent, asymptomatic petechial eruptions

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on the upper and lower extremities that had been present for approximately 5 years. Physical examination revealed diffuse "cayenne pepper" purpuric macules and brownish-yellow discoloration, more prominent on the lower extremities (Figure 1a). Dermoscopy showed reddish round-to-oval globules and dots on a brownish background (Figure 2a). Under ultraviolet-induced fluorescence (UV-F) dermoscopy (DermLite DL5, 365-nm UVA LEDs), the purpuric foci became more distinct, aiding in the selection of an optimal biopsy site (Figure 2b).

Histopathologic examination of a punch biopsy specimen revealed, in the papillary dermis, a superficial perivascular lymphocytic infiltrate, focal erythrocyte extravasation, and pigment-laden macrophages, consistent with Schamberg disease (Figure 3). Direct immunofluorescence was not performed. In this case, leukocytoclastic vasculitis was considered unlikely based on the absence of neutrophilic infiltration, leukocytoclasia, and fibrinoid necrosis on histopathology, together with clinicopathologic findings consistent with PPD. The patient was referred to the rheumatology department for further evaluation. The patient had positive antinuclear antibodies with a homogeneous pattern at a titer of 1:1280. Rheumatology evaluation revealed the absence of symptoms, such as joint pain and Raynaud's phenomenon; other systemic rheumatologic investigations were negative. Further investigations, including anti-dsDNA, antineutrophil cytoplasmic antibodies, and extractable nuclear antigen profiles, were negative. The rheumatology department did not suspect vasculitis or connective tissue disease and recommended an annual follow-up.

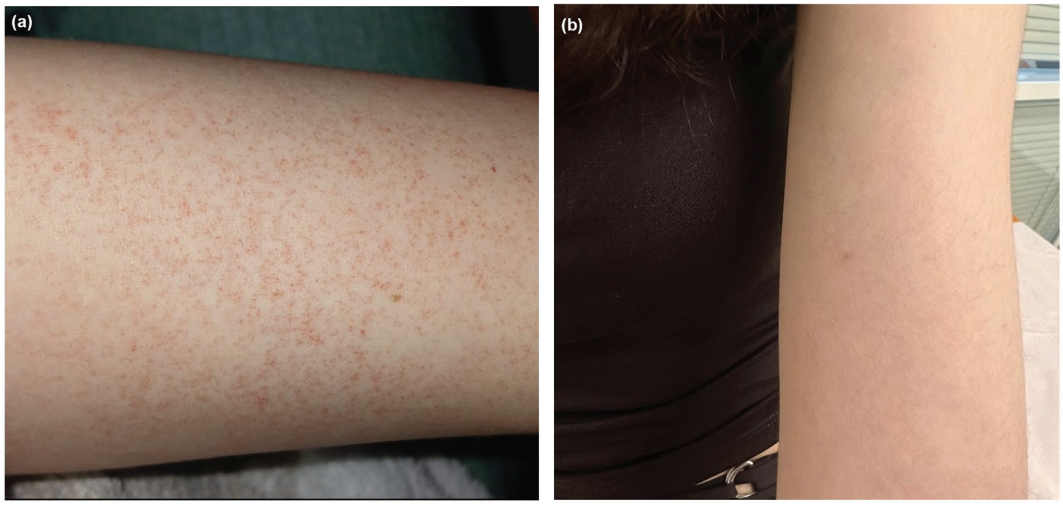

Figure 1. Clinical photographs. (a) Non-blanchable petechial and purpuric macules on the upper extremities. (b) Marked resolution of the lesions observed on day 14 after initiation of oral pentoxifylline therapy

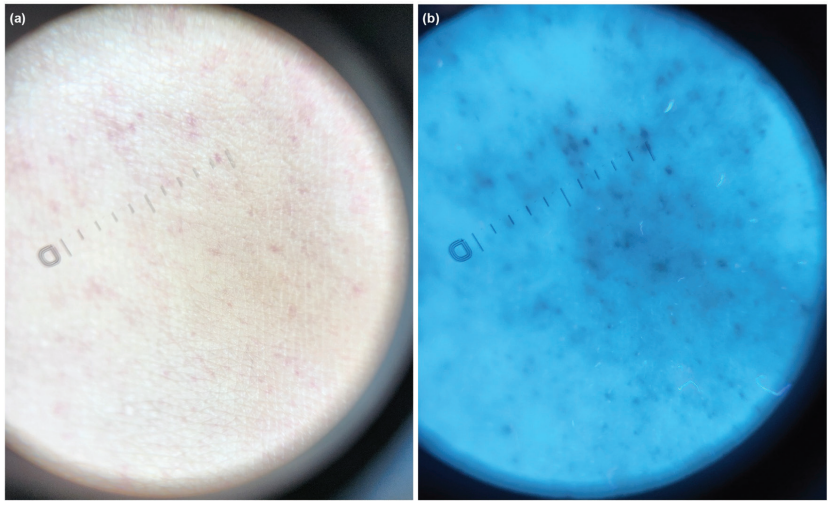

Figure 2. Dermoscopic and ultraviolet-induced fluorescence (UV-F) findings. (a) Dermoscopy showing numerous reddish round-to-oval globules and dots on a brownish background. (b) UV-F dermoscopy (DermLite DL5, 365-nm UVA LEDs) enhancing the visibility of purpuric foci and facilitating biopsy-site selection
UV-F: Ultraviolet-induced fluorescence

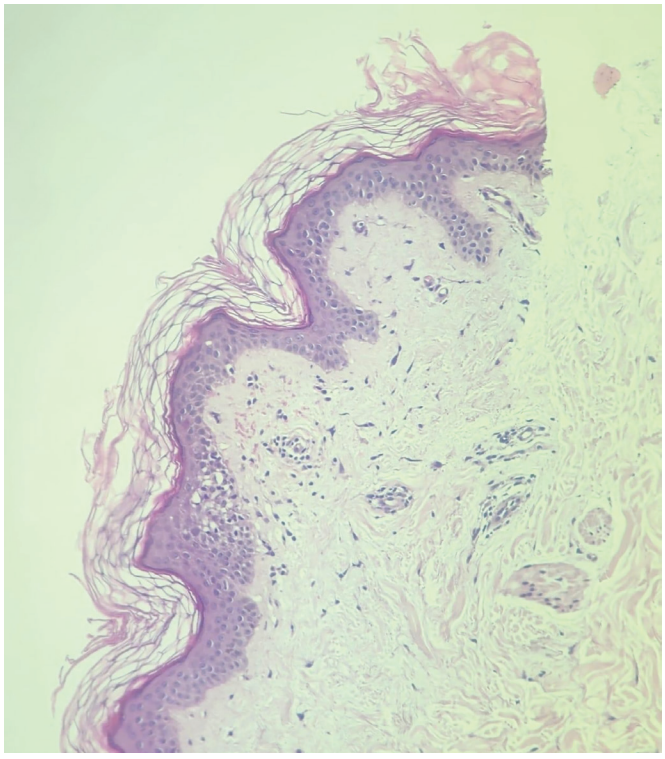

Figure 3. Histopathologic features. The histopathologic image demonstrates superficial perivascular lymphocytic infiltrate, focal erythrocyte extravasation, and pigment-laden macrophages in the papillary dermis; no neutrophilic infiltrate or fibrin deposition is identified, arguing against leukocytoclastic vasculitis (H&E, original magnification ×100)
H&E: Hematoxylin and eosin

After the patient failed to respond to 8 weeks of topical high-potency corticosteroids and topical calcineurin inhibitors, controlled-release pentoxifylline 600 mg once daily was initiated. After approximately 14 days, near-complete resolution of the chronic purpuric lesions was observed (Figure 1b). Pentoxifylline was discontinued because of gastrointestinal adverse effects (nausea and vomiting). At a 2-month follow-up, the patient remained in remission.

Discussion

Treatment of PPD remains difficult, and the current literature is based predominantly on case reports and small case series rather than large controlled studies.[2] Pentoxifylline is among the therapies reported for PPD.[1,2] In the available literature, successful responses to pentoxifylline have been described in patients with PPD, Schamberg disease, and granulomatous PPD.[1,3,4] However, the published evidence is not fully consistent.[1,3] Small studies of Schamberg disease reported marked improvement in a subset of patients after 8 weeks of treatment, whereas another small trial did not demonstrate objective histopathologic improvement despite some subjective clinical benefit.[3] In addition, a more recent case of granulomatous PPD showed significant improvement after 2 months of oral pentoxifylline, with no relapse 6 months after discontinuation of treatment.[4] Against this background, the near-complete response observed in our patient by day 14 appears comparatively early. The patient is currently being followed up in our clinic, with no recurrence.

Pentoxifylline decreases blood viscosity, inhibits platelet aggregation, reduces endothelial adhesion molecule expression, and suppresses pro-inflammatory cytokines including tumor necrosis factor-alpha, interleukin (IL)-1, and IL-6.[3] Pentoxifylline has also been proposed as a treatment that may suppress adhesion of inflammatory T cells to the endothelium via intercellular adhesion molecule-1–mediated interactions.[4] These mechanisms may help explain the clinical benefit observed in our patient. Gastrointestinal adverse effects, such as nausea and vomiting, are among the most commonly reported side effects of pentoxifylline and were also observed in our case.[3]

Because PPD can follow a chronic and relapsing course, it may be difficult to distinguish spontaneous remission from treatment-related improvement in a single case. In our patient, several findings suggest a possible therapeutic contribution of pentoxifylline, including an approximately 5-year history of recurrent lesions, histopathological findings consistent with PPD, inadequate response to 8 weeks of topical treatment, and a close temporal association between pentoxifylline initiation and rapid clinical improvement. Nevertheless, spontaneous remission cannot be entirely excluded. Additional case reports and larger controlled studies are required to better define the efficacy of pentoxifylline in PPD.

In our case, UV-F dermoscopy improved the visibility of active purpuric foci and aided biopsy-site selection. Conventional dermoscopic findings reported in PPD include red round-to-oval globules, diffuse brownish-orange background pigmentation, red dots, brown network, twisted red loops, and linear vessels.[5] Under 365-nm UV-F dermoscopy, hemoglobin-rich or erythrocyte-extravasation-related areas may appear darker because of increased ultraviolet absorption.[6] A similar optical effect may explain the enhanced visibility of active petechial foci in our patient and facilitate biopsy-site selection in lesions with subtle contrast under conventional dermoscopy.

Conclusion

Pentoxifylline may be associated with early clinical improvement in selected patients with PPD. UV-F dermoscopy may serve as a useful, non-invasive adjunct for highlighting

active purpuric foci and guiding biopsy-site selection. Further controlled studies are needed to better define the therapeutic role of pentoxifylline in PPD.

Footnotes

Informed Consent: Written informed consent was obtained from the patient for publication of the case details and accompanying images.

Authorship Contributions

Surgical and Medical Practices: E.B.A., N.S., S.K., Concept: E.B.A., N.S., Design: E.B.A., N.S., Data Collection or Processing: E.B.A., N.S., S.K., B.T., Analysis or Interpretation: E.B.A., N.S., B.T., Literature Search: E.B.A., Writing: E.B.A., N.S., S.K., B.T.

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Case Report

Crusted Scabies Confined to the Scalp Mimicking Seborrheic Dermatitis in an Immunosuppressed Liver Transplant Recipient: A Case Report

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Abstract

Crusted scabies is a severe, highly contagious variant of scabies that predominantly affects immunocompromised individuals. Although it usually involves extensive areas of the body, isolated scalp involvement in adults is exceedingly rare. This report describes a case of crusted scabies confined to the scalp in a 63-year-old male liver transplant recipient receiving everolimus therapy. The case emphasizes the importance of considering atypical presentations of scabies in immunosuppressed patients and highlights the diagnostic value of dermoscopy in challenging clinical scenarios.

Keywords: Everolimus, immunosuppression therapy, scabies, scalp dermatoses, seborrheic dermatitis, transplantation

Introduction

Crusted scabies, also known as Norwegian scabies, is a rare but severe infestation caused by *Sarcoptes scabiei* var. *hominis*. It is characterized by hyperkeratotic, crusted plaques that contain numerous mites and is most commonly observed in individuals with impaired immune function, including organ transplant recipients and patients receiving immunosuppressive therapy.[1]

Scalp-only involvement in adults is extremely uncommon and may mimic inflammatory scalp disorders such as seborrheic dermatitis or psoriasis.[2] This report presents a rare case of crusted scabies confined to the scalp in a liver transplant recipient undergoing everolimus therapy.

Case Report

A 63-year-old male who had undergone liver transplantation one year prior presented to the dermatology clinic with persistent pruritus and scaling of the scalp. His post-transplant treatment regimen included everolimus 0.25 mg twice daily and ursodeoxycholic acid 250 mg once daily. His medical history was notable for diabetes mellitus and benign prostatic hyperplasia.

Two years before the current presentation, the patient had been diagnosed with classic scabies and had been treated with six courses of permethrin cream. Although generalized pruritus and body lesions resolved after treatment, scalp itching persisted. The patient sought medical evaluation multiple times and was diagnosed with seborrheic dermatitis; topical corticosteroid lotion was prescribed without clinical improvement (Figure 1a, b).

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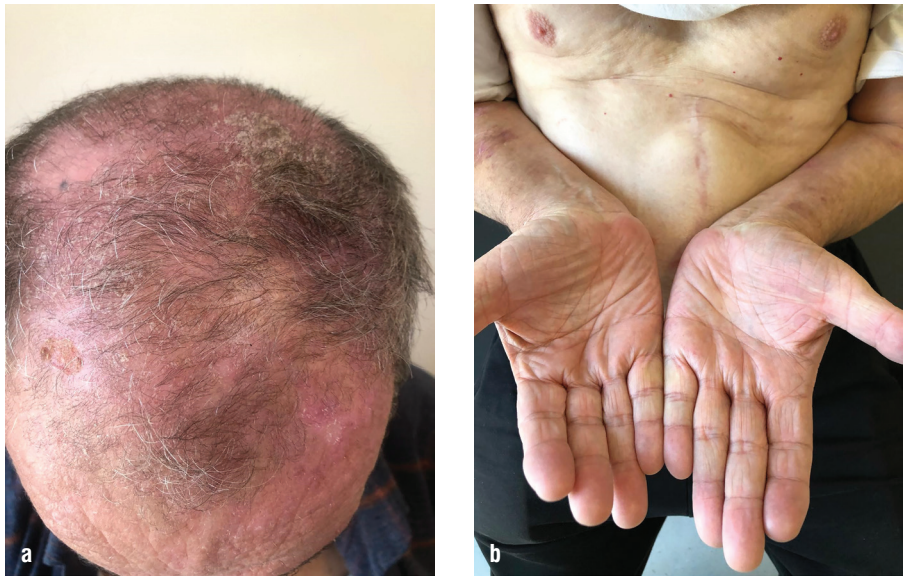

Figure 1. (a) Erythematous and scaly plaques on the scalp, b) only a few cherry angiomas observed on the hands and trunk

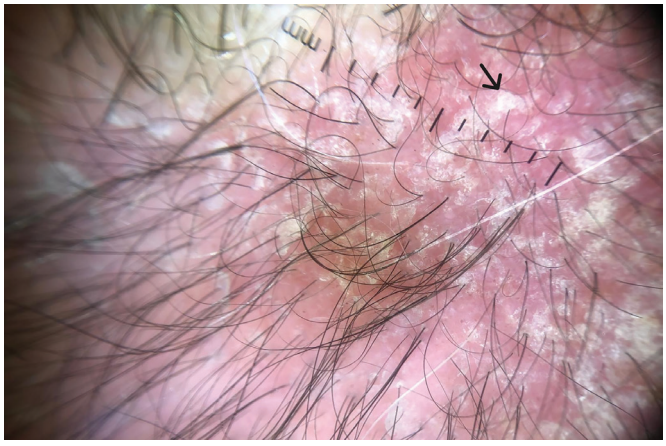

Figure 2. Numerous burrows were observed on dermoscopic examination of the scalp. The arrow indicates the characteristic "delta wing jet" sign at the end of a burrow

Dermatological examination revealed diffuse erythema with localized, fine, compact scaling on the scalp. Dermoscopic evaluation demonstrated the characteristic "delta wing jet" sign suggestive of *Sarcoptes scabiei* infestation (Figure 2). Microscopic examination of scalp scrapings revealed more than ten live mites and numerous eggs in a single field, confirming the diagnosis of localized crusted scabies.

Treatment was initiated with permethrin cream applied for three consecutive days and was repeated one week later. Following therapy, complete resolution of lesions was achieved and pruritus subsided (Figure 3a, b).

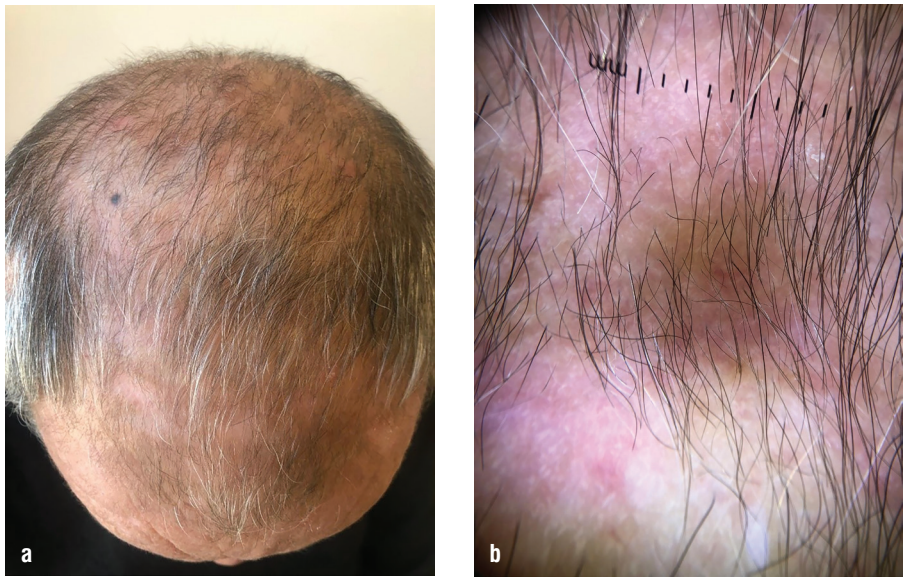

Figure 3. (a) Clinical appearance of the scalp after treatment, b) dermoscopic examination of the scalp after treatment

Discussion

Crusted scabies is a severe form of scabies characterized by a high parasite burden and extensive hyperkeratotic lesions. It most frequently occurs in individuals with significant immunosuppression, including patients with human immunodeficiency virus infection, patients with malignancies, patients with autoimmune diseases, or organ transplant recipients.[2] While classic scabies typically involves interdigital spaces, wrists, and the trunk, crusted scabies may present with atypical locations, which may lead to delayed diagnosis.

Although scalp involvement is uncommon in classic scabies, crusted scabies affecting the scalp has been reported in immunosuppressed patients. In a patient with systemic lupus erythematosus, an occipital plaque initially misdiagnosed as psoriasis was later confirmed as crusted scabies by biopsy.[3] Similarly, dermatomyositis patients receiving immunosuppressive therapy have been reported to develop crusted lesions involving the scalp and face.[4] In an adult T-cell leukemia patient positive for human T-lymphotropic virus type 1, scalp and auricular crusted lesions were initially attributed to leukemia-related skin manifestations.[5] Additionally, pediatric patients with scalp involvement have been misdiagnosed as tinea capitis prior to microscopic confirmation of scabies.[6]

Conclusion

The present case represents a rare instance of crusted scabies confined to the scalp in an adult liver transplant recipient. Persistent, treatment-resistant scalp pruritus in immunosuppressed individuals should prompt consideration of scabies in the differential diagnosis. Dermoscopy and microscopic examination are essential tools for early and accurate diagnosis. In such patients, inclusion of the scalp in topical treatment regimens may help prevent persistent infestation and relapse.

Footnotes

Informed Consent: Written informed consent was obtained from the patient for publication of the case details and images.

Conflict of Interest: The author declared that they have no conflict of interest.

Financial Disclosure: The author declared that this study received no financial support.

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Recurrent Eruptive Pseudoangiomatosis with Initial Onset After COVID-19 Vaccination: A Case Report

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Dear Editor,

Eruptive pseudoangiomatosis (EP) is an acute, self-limiting exanthem characterized by bright red angioma-like papules that typically resolve within a few weeks. It has been reported following infections with echoviruses, enteroviruses, cytomegalovirus, Epstein-Barr virus, adenovirus, parvovirus B19, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), predominantly in children but also in adults. Recurrent EP is an exceptionally rare condition in the literature. We describe a unique case of long-term recurrent EP that initially developed after coronavirus disease-2019 (COVID-19) vaccination.

A 34-year-old woman with a history of allergic asthma only presented with a two-week history of pruritic, erythematous papules, predominantly on her arms and legs. Her history revealed that she first experienced similar lesions approximately 3.5 years earlier; these lesions emerged about one month after her second dose of the mRNA COVID-19 vaccine (Pfizer–BioNTech) and resolved spontaneously within 2 weeks. She reported that the eruptions had recurred several times over the subsequent 3.5 years, although she could not recall the exact number of episodes. She denied any medication use preceding the recurrences. At the time of her presentation, she reported a flu-like illness; however, she did not recall any antecedent infections during previous episodes. Dermatological examination revealed blanchable erythematous papules with a more prominent peripheral hypopigmented halo, distributed over the bilateral lower extremities (from the gluteal region to the dorsum of the feet), upper extremities (from the elbows to the dorsum of the hands), and the palmoplantar regions (Figure 1a-d). The mucosae were normal. Dermoscopic examination demonstrated dotted vessels over a reticular vascular network with a peripheral halo, findings that may correspond to perilesional vasoconstriction or transient dermal edema, as suggested in previous descriptions of EP (Figure 1e). In ultraviolet mode, the vascular pattern and perivascular halo were also visualized (Figure 1f). Histopathological examination of two 4-mm punch biopsy specimens taken from lower-extremity lesions revealed surface orthokeratosis and mild spongiosis in the granular layer of the epidermis. The superficial dermis showed dilated dermal vessels with vascular endothelial proliferation, accompanied by a predominantly lymphocytic perivascular inflammatory infiltrate. Endothelial swelling was not prominent, and there was no evidence of leukocytoclasia or fibrinoid necrosis. The patient was diagnosed with EP based on clinical, dermoscopic, and histopathological findings, and was treated symptomatically with a topical corticosteroid and an oral antihistamine. Several conditions may enter the differential diagnosis of EP, including cherry angiomas, viral exanthems, and early leukocytoclastic vasculitis. However, in the present case, the characteristic blanchable vascular papules with a surrounding pale halo, together with the dermoscopic

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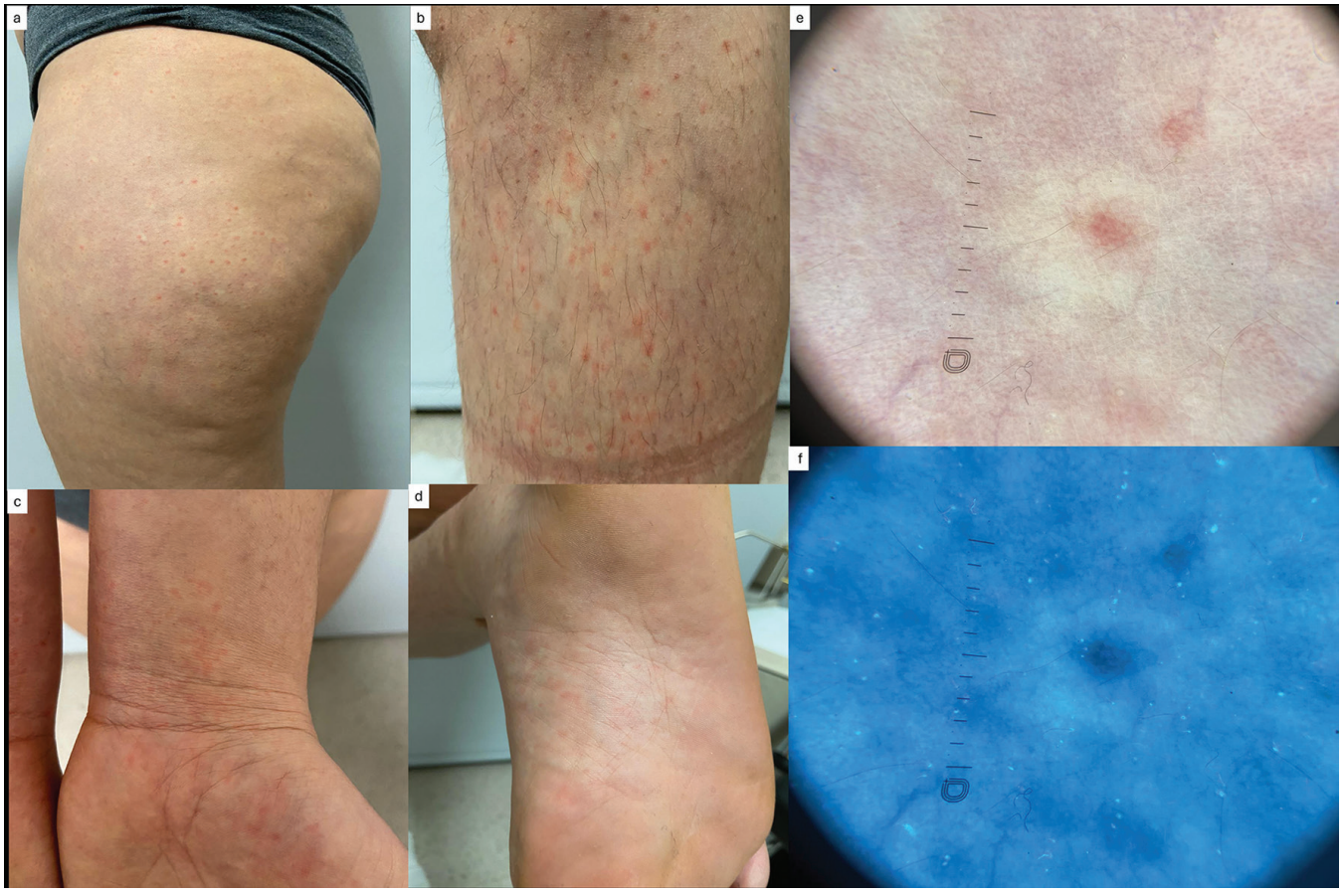

Figure 1. (a–d) Blanchable erythematous papules with a prominent peripheral hypopigmented halo on the lower and upper extremities and palmoplantar areas. (e) Polarized dermoscopy using DermLite DL5 showed dotted vessels over a reticular vascular network with a peripheral halo. (f) Ultraviolet mode demonstrating the vascular pattern and perivascular halo

and histopathologic findings and the absence of vasculitic features, supported the diagnosis of EP.

Since the emergence of COVID-19, accumulating data indicate that SARS-CoV-2 infection and vaccination can act as initial triggers for multiple dermatologic disorders that subsequently follow their natural history. Newly developed or reactivated conditions such as chronic spontaneous urticaria and psoriasis have been documented after COVID-19 infection or immunization, with many of these patients later exhibiting spontaneous recurrences consistent with their well-known relapsing behavior.[1] These findings support the concept that COVID-19–related immune activation may function as an initiating stimulus in predisposed hosts.

However, for EP, post-COVID or post-vaccination cases reported in the literature have almost exclusively presented as an acute, self-resolving, single-episode pattern. To date, all reported instances of EP related to COVID-19 vaccination have occurred after the ChAdOx1 nCoV-19 (Covishield) vaccine; to our knowledge, no published cases have been reported following mRNA (BNT162b2) vaccination (Table 1). Although the onset of the first episode in our patient occurred shortly after COVID-19 vaccination, a temporal association alone does not establish a causal relationship.

To our knowledge, a long-term, intermittently recurrent course extending over several years—particularly following an initial vaccine-associated onset—has rarely, if ever, been documented previously. Our patient's case, therefore, broadens the recognized clinical spectrum of EP and raises the possibility that an initial COVID-19 vaccination may trigger a sustained state of vascular or immunologic reactivity, thereby predisposing the patient to subsequent spontaneous recurrences. Furthermore, because EP has been associated with various potential triggers, most notably viral infections, there may be an additional trigger preceding the recurrent episodes in our patient. However, no prior viral serologic or polymerase chain reaction testing was performed to confirm this possibility, which is a limitation. In addition, the patient was unable to reliably recall the exact number of recurrences or the precise intervals between episodes, representing another limitation of this retrospective history. Given the rarity of chronic-recurrent EP, we believe this case contributes to the

Table 1. Reported cases of eruptive pseudoangiomatosis and corresponding data from our patient's first episode

Study	Number of cases	Age (year)	Sex	Vaccine type	Vaccine dose	Time to onset after vaccination (days)	Associated pruritus	Time to resolution (days)
Mohta et al.[4]	5	24–48	1 M, 4 F	Covishield	NA	5.2	3/5 cases	2–8
Prarthana et al.[3]	1	36	M	Covishield	First and second dose	NA	NA	14
Mohta et al.[2]	53	18–30	NA	Covishield	47 cases after second dose	5.3	5/53 cases	10–14
Current case	1	34	F	BioNTech/Pfizer	Second dose	30	Yes	14

M: Male, F: Female, NA: Not available

expanding spectrum of cutaneous reactions associated with COVID-19 vaccines and may raise clinical awareness of its benign but prolonged course. Further case accumulation is needed to better understand this association. Therefore, the potential role of alternative triggers, including viral infections, should also be considered when interpreting the temporal relationship observed in this case.

Footnotes

Informed Consent: Written informed consent was obtained from the patient for publication of clinical data and images.

Authorship Contributions

Surgical and Medical Practices: S.K.Y., N.E.A., Concept: S.K.Y., N.E.A., Design: S.K.Y., Data Collection or Processing: S.K.Y., N.E.A., Analysis or Interpretation: S.K.Y., N.E.A., Literature Search: S.K.Y., Writing: S.K.Y.

Conflict of Interest: The authors declared that this study received no financial support.

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Erratum

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Tabak GH, Karaduman A, Şener B. Evaluation of serum zonulin levels in patients with recurrent aphthous stomatitis. Turk J Dermatol. 2026;20(1):33-38.

On page 5 of the manuscript, the Conflict of Interest section required revision. Accordingly, the necessary correction has been indicated in bold within the text below.

The uncorrected version is as follows:

Conflict of Interest: The authors declared that they have no conflict of interest.

The corrected version is as follows:

Conflict of Interest: One of the authors, Ayşen Karaduman, is a member of the Associate Editor of the Turkish Journal of Dermatology. However, she was not involved in any stage of the editorial decision-making process for this manuscript. The manuscript was evaluated independently by editors from other institutions. The other authors declare no conflicts of interest.