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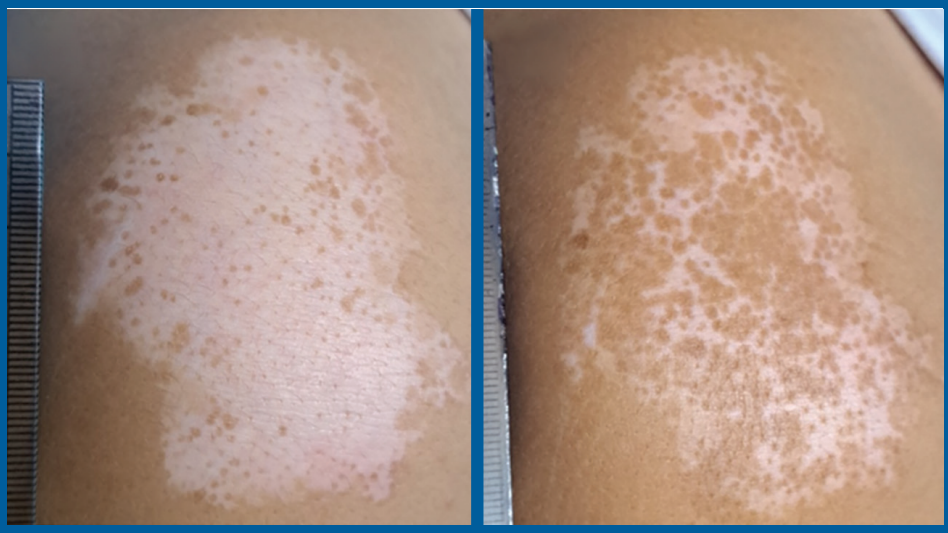

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CONTENTS

Review

Paradoxical Psoriasis Associated With JAK Inhibitors: Current Evidence, Proposed Mechanisms, and Clinical Management

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Abstract

The use of Janus kinase (JAK) inhibitors has been rapidly increasing, particularly in immune-mediated conditions, including severe and treatment-refractory inflammatory bowel disease, rheumatologic disorders, and dermatologic conditions such as atopic dermatitis (AD). By inhibiting the JAK/signal transducer and activator of transcription signaling pathway, these agents suppress proinflammatory cytokine production and modulate immune responses. However, as a consequence of this potent immunomodulatory activity, immune-mediated paradoxical reactions—most notably paradoxical psoriasis—may occasionally occur. Although paradoxical psoriasis associated with JAK inhibitors has only rarely been reported in the literature, its true incidence is likely higher. This review synthesizes the current evidence, discusses the proposed pathophysiological mechanisms, and provides an updated perspective on clinical management strategies. This comprehensive evaluation is expected to enhance clinical awareness of paradoxical psoriasis arising during JAK inhibitor therapy and to contribute to improved diagnostic and therapeutic approaches.

Keywords: Immune-mediated adverse reactions, Janus kinase inhibitors, JAK/STAT pathway, paradoxical psoriasis

Introduction

Janus kinase (JAK) inhibitors are pharmacologic agents that inhibit intracellular enzymes of the JAK family involved in cytokine and growth-factor signaling. In recent years, they have gained a prominent role in the treatment of a wide range of immune-mediated diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), spondyloarthropathies, psoriasis, psoriatic arthritis, atopic dermatitis (AD), and alopecia areata. By selectively or broadly inhibiting the JAK/signal transducer and activator of transcription signaling pathway, these agents simultaneously modulate multiple cytokine-driven immune mechanisms, resulting in rapid and potent anti-inflammatory effects.

While these broad immunological effects offer therapeutic advantages, the multidimensional modulation of immune responses may also lead to unexpected immunological disequilibrium in some patients. One of the most notable examples of this phenomenon is paradoxical psoriasis. This entity is defined as the new onset of psoriasis or the exacerbation of pre-existing psoriasis during treatment for another condition. Unlike classical psoriasis, paradoxical psoriasis typically regresses after discontinuation of the offending agent, and relapse is uncommon. Although initially most frequently associated with tumor necrosis factor (TNF) inhibitors, cases have also been described with interleukin (IL)-

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4/13 and IL-17A inhibitors.[1] Although still rare, paradoxical psoriasis associated with JAK inhibitors has increasingly been recognized and has drawn clinical attention (Table 1).[2-8]

The aim of this narrative review is to summarize the currently available evidence regarding paradoxical psoriasis associated with JAK inhibitors, to discuss the proposed pathophysiological mechanisms, to review clinical management strategies, and to present an illustrative case of a psoriasiform eruption occurring during upadacitinib therapy. Although the number of reported cases remains limited, the available literature provides valuable insights into the clinical spectrum, potential mechanisms, and therapeutic approaches to this uncommon adverse event.

Reported Cases in the Literature

One of the first reported cases of paradoxical psoriasis associated with JAK inhibitors was described by Shibata et al.[2] in a 25-year-old patient with juvenile idiopathic arthritis. Shortly after initiation of tofacitinib, sterile palmoplantar pustular lesions developed on the palms and soles, which regressed markedly upon drug discontinuation and recurred after re-introduction. This clinical course provided some of the earliest evidence that tofacitinib may trigger palmoplantar pustulosis-like psoriasiform eruptions.[2]

Koumaki et al.[3] reported a case of palmoplantar pustulosis in a patient receiving baricitinib for RA, in whom the lesions resolved after withdrawal of the drug and recurred upon re-challenge. The authors suggested that the mechanism of baricitinib-associated palmoplantar pustulosis remains unclear, but alterations in T-cell–mediated cytokine pathways may be involved.[3] Similarly, Di Domizio et al.[4] described a psoriasiform eruption in a patient with RA who was treated with baricitinib and suggested that JAK1/2 inhibition led to a cytokine imbalance, particularly increased expression of IL-6, IL-8(CXCL8), and IL-36G. These cytokines were proposed to promote neutrophil accumulation and IL-23A activation, thereby driving JAK-independent inflammatory pathways and triggering paradoxical psoriasis.[4]

Erol and Ertaş[5] reported the development of psoriasiform plaques in a patient with RA during the third month of tofacitinib therapy. The lesions were clinically and histopathologically consistent with psoriasis and showed marked improvement after drug discontinuation, leading to their classification as a paradoxical psoriasiform reaction. The authors hypothesized that suppression of several downstream cytokines, including interferon-α (IFN-α), may disturb the balance between IFN-α and IFN-γ and/or reshape Th1/Th17 responses, thereby contributing to the development of paradoxical psoriatic inflammation.[5]

Table 1. Reported cases of paradoxical psoriasis and psoriasiform eruptions associated with JAK inhibitor therapy in the literature and the present case

Author year	Age/ gender	JAK inhibitor	Indication	Clinical phenotype	Onset	Previous psoriasis	Family history	Biopsy	Outcome
Shibata et al.[2]	25/F	Tofacitinib	Juvenile idiopathic arthritis	Palmoplantar pustulosis–like eruption	10 days	No	No	Yes	Near-complete clearance after discontinuation; recurrence after reintroduction
Koumaki et al.[3]	56/M	Baricitinib	Rheumatoid arthritis	Palmoplantar pustulosis–like eruption	5 years	No	No	Yes	Near-complete clearance after discontinuation; recurrence after rechallenge
Di Domizio et al.[4]	68/F	Baricitinib	Rheumatoid arthritis	Plaque-type psoriasiform eruption	3 weeks	No	No	Yes	Resolved within 2 months after discontinuation and topical corticosteroids
Erol and Ertaş[5]	45/M	Tofacitinib	Rheumatoid arthritis	Plaque-type psoriasiform eruption	3 months	No	No	Yes	Improved after discontinuation
Ferrucci et al.[6]	44/M	Upadacitinib	Atopic dermatitis	Plaque psoriasis	3 weeks	Yes	NR	Yes	Recurrence of psoriasis during upadacitinib treatment; improvement after discontinuation and methotrexate reintroduction
Becker et al.[7]	20/M	Abrocitinib	Atopic dermatitis	Plaque psoriasis	7 months	No	No	Yes	Resolution after dose reduction
Özkır et al.[8]	12/F	Tofacitinib	Alopecia totalis	Psoriasis flare	4 months	Yes	NR	No	Significant regression after discontinuation, NB-UVB phototherapy, and topical treatment
Present case 2025	43/M	Upadacitinib	Ulcerative colitis	Plaque-type psoriasiform eruption with pustulation	6 months	No	No	Yes	Marked improvement with topical mometasone furoate while continuing upadacitinib (3-month follow-up)

F: Female, M: Male, NR: Not reported, NB-UVB: Narrowband ultraviolet B phototherapy, JAK: Janus kinase

Two patients with AD who developed paradoxical psoriasis during JAK inhibitor therapy have also been reported. In a patient with severe AD who developed psoriasis while receiving dupilumab, disease flares recurred shortly after switching to upadacitinib. This clinical course suggests that Th2 blockade may relatively enhance the Th1/Th17 axis, thereby promoting psoriasiform inflammation, and that JAK1 inhibitors may not fully prevent a phenotypic shift in some individuals. It has also been proposed that incomplete suppression of TYK2-mediated IL-12/IL-23 pathways may contribute to the persistence of psoriatic responses.[6] In another reported patient with severe AD, new eruptions clinically and histologically compatible with psoriasis appeared approximately seven months after initiation of abrocitinib. This observation supports the notion that, despite broad cytokine inhibition, JAK1 inhibitors may paradoxically induce a Th2 → Th17 phenotypic shift.[7] Although JAK inhibitors are theoretically effective for both AD and psoriasis due to their wide-ranging cytokine blockade, they may paradoxically precipitate psoriatic inflammation.

Another case in the literature involved an adolescent patient with alopecia totalis receiving tofacitinib.[8] The patient had a history of psoriasis, and it was postulated that JAK inhibitor–induced cytokine disequilibrium, particularly disruption of the IFN-α/IFN-γ axis, may have triggered psoriatic inflammation. Marked regression of the lesions after drug discontinuation supported the diagnosis of a drug-induced paradoxical reaction.

In our case, a 43-year-old male with ulcerative colitis presented to our dermatology outpatient clinic with a one-month history of erythema and scaling on the soles of both feet that began after approximately six months of treatment with upadacitinib 30 mg/day. The patient had previously failed multiple therapies for ulcerative colitis, including 5-aminosalicylic acid derivatives, systemic corticosteroids, azathioprine, adalimumab, and infliximab. No concomitant medications were used at the time of lesion onset. There was no personal or family history of psoriasis. Dermatological examination revealed erythematous, scaly plaques with scattered pustules on the bilateral plantar surfaces (Figure 1). Histopathological examination demonstrated epidermal parakeratosis, hyperkeratosis, focal areas of hypogranulosis, and focal intraepidermal pustule formation, accompanied by occasional eosinophils within the dermis (Figure 2). Based on the clinical and histopathological findings, a diagnosis of paradoxical psoriasis was favored. Given the excellent control of ulcerative colitis and the localized nature of the lesions, upadacitinib therapy was continued, and topical mometasone furoate was initiated, resulting in marked clinical improvement during a three-month follow-up. Although the temporal relationship between upadacitinib exposure and lesion onset, the absence of personal or family history of psoriasis, and the lack of concomitant medications support a possible association, causality should be interpreted with caution. Because upadacitinib therapy was continued and neither dechallenge nor rechallenge could be assessed, a definitive causal relationship cannot be established in this case.

The pathogenesis and molecular mechanisms of paradoxical psoriasis associated with upadacitinib have not yet been fully elucidated; however, it has been proposed that selective JAK1 inhibition may disturb cytokine homeostasis in genetically predisposed individuals and thereby precipitate this adverse event. To the best of our knowledge, paradoxical psoriasis associated with JAK inhibitor therapy in the context of UC has not previously been reported. Although this case is compatible with a paradoxical dermatologic reaction associated with upadacitinib, causality should be interpreted with caution because neither dechallenge nor rechallenge could be assessed.

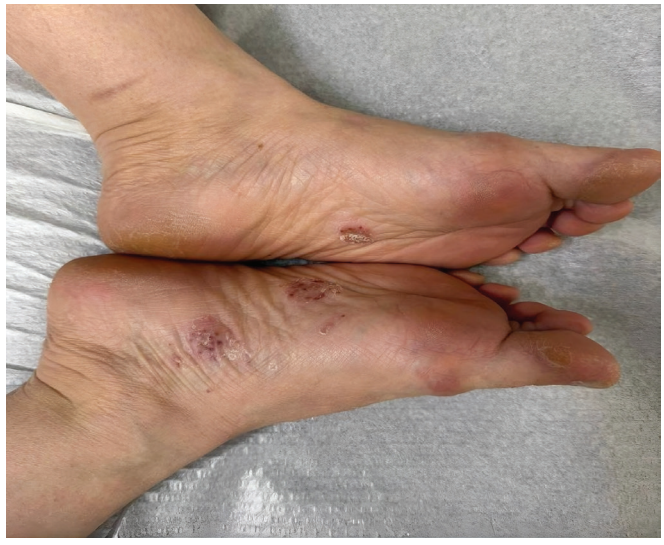

Figure 1. Clinical image of the lesion on the foot

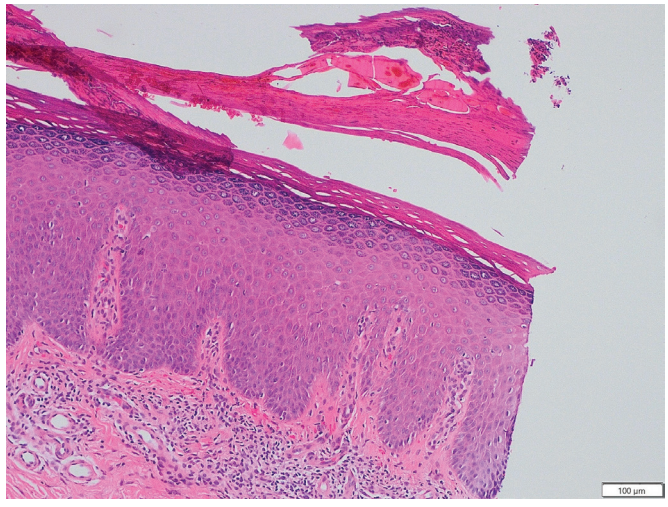

Figure 2. Histopathology showing psoriasiform epidermal hyperplasia with focal intraepidermal pustules and parakeratosis (H&E ×100)
H&E: Hematoxylin and eosin

Nevertheless, it adds to the limited literature on paradoxical dermatologic reactions associated with JAK inhibitor therapy. It also has clinical relevance for improving the understanding of the safety profile of JAK inhibitors and for optimizing patient selection.

Proposed Pathophysiological Mechanisms of Paradoxical Psoriasis

Paradoxical reactions comprise various inflammatory manifestations that may both respond to and be triggered by modern immunomodulatory therapies targeting similar immunologic pathways. These reactions include paradoxical psoriasis, hidradenitis suppurativa, lichenoid eruptions, granulomatous reactions, eczematous eruptions, and neutrophilic dermatoses. Their pathogenesis is multifactorial, involving both drug-related immunologic effects and patient-specific genetic or microbial factors. Most frequently implicated mechanisms include shifts in T-cell polarization, disruption of negative feedback loops, secondary immune responses driven by anti-drug antibodies, and immune activation mediated by interactions between monoclonal antibodies and Fc receptors on myeloid cells.[9] Although paradoxical psoriasis has been most commonly associated with TNF inhibitors due to their long-standing clinical use, reports of paradoxical psoriasis linked to other biologic agents have increasingly accumulated.

Biologic agents remain the class of drugs most frequently associated with paradoxical reactions; however, in recent years a limited but growing number of similar cutaneous phenomena have also been reported with oral small-molecule JAK inhibitors. These agents suppress multiple cytokine pathways simultaneously, generating a broad immunomodulatory effect. Paradoxical psoriasis associated with JAK inhibition appears to arise from a complex immunologic process that cannot be explained by a single mechanism. One prominent hypothesis suggests that JAK inhibition suppresses IFN-α signaling while relatively enhancing IFN-γ–mediated responses, thereby increasing inflammatory gene expression in keratinocytes and triggering psoriatic changes.[10] This hypothesis resembles the pathogenic model proposed for paradoxical psoriasis associated with TNF inhibitors.

Another proposed mechanism, particularly in RA, involves suppression of Th1/Th17 cells within the synovium, leading to expansion of pathogenic T-cell subsets in peripheral lymph nodes—similar to mechanisms described for TNF inhibitors.[11] This aberrant T-cell redistribution may facilitate cutaneous psoriasiform reactions.

Additional studies have suggested that JAK1/2 blockade may shift cytokine balance toward JAK-independent inflammatory axes, particularly IL-8/IL-36–driven pathways, resulting in increased expression of epithelial gene products involved in psoriatic inflammation.[12] This immunologic reprogramming can promote keratinocyte proliferation, neutrophilic infiltration, and the amplification of psoriatic inflammation, creating a permissive environment for paradoxical psoriasis.

In AD, psoriasiform eruptions arising during JAK inhibitor therapy have been interpreted as supporting the Th2 → Th17 phenotypic shift hypothesis. Reduction of Th2 activity—especially following potent IL-4/IL-13 inhibition—may lead to relative dominance of the Th17/IL-23 axis. Such a shift may increase susceptibility to paradoxical psoriasis, particularly in AD subsets characterized by heightened IL-17 expression and histopathologic features overlapping with psoriasis.

Collectively, these mechanisms highlight the complex interplay of genetic predisposition, cytokine imbalance, and treatment-related modulation of immune pathways, which likely underpins the clinical heterogeneity of paradoxical psoriasis observed across rheumatologic, dermatologic, and IBD populations. Considering the shared features of our case with previously published reports, it may be hypothesized that JAK blockade contributes to cytokine alterations in genetically predisposed individuals, thereby facilitating paradoxical psoriatic inflammation. However, the exact mechanisms remain uncertain and require further investigation. Future studies incorporating cytokine profiling and genetic biomarkers may facilitate the development of risk-stratification strategies to predict psoriasiform reactions in patients receiving JAK inhibitors.

Clinical Presentation and Diagnosis

Paradoxical psoriasis typically differs from classic psoriasis in that lesions may exhibit eczema-like areas, less sharply demarcated borders, focal erosions, and incompletely developed silvery scale.[13] Although paradoxical psoriasis associated with JAK inhibitors presents a heterogeneous clinical spectrum, several recurring features have been noted in the literature. The most commonly reported phenotype resembles classic plaque-type psoriasis, followed by a palmoplantar pustulosis–like pustular variant.

Histopathologically, paradoxical psoriasis is often indistinguishable from *de novo* psoriasis. However, cases associated with TNF inhibitors demonstrate a wide histologic spectrum, including eczematous spongiotic patterns, psoriasiform patterns mimicking classic psoriasis (with intraepidermal or subcorneal neutrophilic microabscesses), and lichenoid interface dermatitis.[14] The presence of scattered eosinophils or plasma cells may provide supportive evidence for a drug-related process.

Across all reported cases of JAK inhibitor–associated paradoxical psoriasis, the histopathology consistently demonstrates psoriasiform epidermal hyperplasia, neutrophilic infiltration, and varying degrees of parakeratosis. These features suggest that JAK inhibitors may alter cytokine balance in a way that promotes keratinocyte proliferation and neutrophil-mediated inflammation, thereby initiating paradoxical psoriatic disease.

Clinical Management and Therapeutic Approach

The primary step in clinical management is confirming the possibility of a drug-induced paradoxical reaction. Accurate recognition of paradoxical psoriasis is essential to avoid unnecessary treatment changes and to maintain drug survival. Although no universal treatment algorithm has been established, evidence from published cases indicates that management strategies should be guided by the severity of the paradoxical psoriasis, the pattern of psoriatic involvement, and the status of the underlying disease for which the drug was initiated. Accordingly, individualized decision-making and a multidisciplinary approach are crucial.

Management strategies should be tailored according to disease severity. In patients with mild and localized eruptions, continuation of JAK inhibitor therapy is often feasible, with adequate symptom control achieved through topical therapies and/or phototherapy. In moderate disease, additional therapeutic interventions may be warranted while carefully balancing the benefits of ongoing JAK inhibitor treatment against the severity of the cutaneous adverse event. In severe, extensive, or treatment-refractory cases, dose reduction or discontinuation of the offending agent should be considered, taking into account the activity of the underlying disease and the availability of alternative treatment options.

In most patients, lesions improve following discontinuation or dose reduction of the implicated drug. Topical corticosteroids, keratolytics, vitamin D analogues, and narrowband ultraviolet B phototherapy are commonly employed to control cutaneous manifestations. When continuation of JAK inhibitor therapy is necessary because of active underlying disease, close multidisciplinary collaboration is essential. Ultimately, treatment decisions should be individualized according to the severity of skin involvement, the degree of disease control, and the feasibility of maintaining JAK inhibitor therapy.

Conclusion

JAK inhibitors have emerged as highly effective therapies for a broad range of immune-mediated conditions due to their extensive cytokine blockade. Nonetheless, they may rarely induce unexpected cutaneous reactions such as paradoxical psoriasis. The limited number of published cases suggests that this reaction cannot be explained by a single pathogenic pathway but rather reflects a complex interplay among cytokine imbalance, T-cell polarization, and individual genetic susceptibility. Early recognition and personalized management are essential to achieving adequate control of psoriatic reactions and to ensuring continuity of JAK inhibitor therapy. Future studies focusing on immunologic and genetic predictors of risk are expected to deepen our understanding of these reactions and enhance clinical decision-making.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: S.Y., Concept: S.Y., S.A.T., Design: S.Y., S.A.T., Data Collection or Processing: S.Y., S.A.T., M.A., Literature Search: S.Y., S.A.T., M.A., S.D., P.O., Writing: S.Y., S.A.T., M.A., S.D., P.O.

Footnotes

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Original Article

Comparative Efficacy of Topical Tacrolimus Versus Tyrosine as Co-Therapy to NB-UVB in Vitiligo: A Randomized Intra-Individual Controlled Clinical Trial

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Abstract

Aim: This study aimed to investigate the efficacy of topical tyrosine versus tacrolimus as co-therapies in vitiligo patients undergoing narrowband ultraviolet B (NB-UVB) therapy.

Materials and Methods: Three comparable vitiligo patches were selected from each patient (n = 67) and randomly assigned to tyrosine 2% plus NB-UVB (group I), tacrolimus 0.1% plus NB-UVB (group II), and NB-UVB alone (control). Topical treatments were applied twice daily, while NB-UVB phototherapy was administered twice weekly at the minimal erythema dose for three months.

Results: Repigmentation differed significantly among the study groups ($P < 0.001$). The tacrolimus plus NB-UVB group showed the highest repigmentation [median (interquartile range): 60.0% (37.0–70.0)], followed by the tyrosine plus NB-UVB group [28.0% (16.0–46.0)], while the NB-UVB alone group demonstrated the lowest repigmentation [12% (10.0–21.0)]. Estimated effect size showed that pairwise comparisons between each active treatment group (groups I and II) and the control group for responder status (≥ 25% repigmentation) were significant (McNemar's test, $P < 0.001$). Odds ratios were 5.5 (95% confidence interval: 2.3–13.1) for group I vs. control, and 89 for group II vs. control. Across all study groups, the stepwise linear regression model demonstrated that a shorter time since the last disease activity and a lower vitiligo area scoring index were the strongest predictors of a higher vitiligo extent score by target area.

Conclusion: Combination therapy appears to be more effective for the management of vitiligo. Tacrolimus combined with NB-UVB achieved the highest repigmentation outcomes, whereas tyrosine combined with NB-UVB may represent a promising, safe, and potentially beneficial adjunct. Early initiation of the treatment may improve repigmentation, particularly in patients with limited disease severity.

Keywords: Vitiligo, narrowband UVB, phototherapy, tacrolimus, tyrosine

Introduction

Vitiligo is a chronic, acquired pigmentary disorder characterized by autoimmune destruction of melanocytes, resulting in hypochromic or achromic macules and patches affecting the skin and mucous membranes.[1]

The pathogenesis of vitiligo is multifactorial. A central mechanism involves an autoimmune response in which melanocyte-specific autoantibodies and cytotoxic $CD8^+$ T-cells contribute to melanocyte destruction. In addition, impaired melanocyte adhesion, associated with reduced expression of adhesion molecules, may increase melanocyte detachment and susceptibility to immune-mediated damage.[2]

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Although several therapeutic options are available, few treatments effectively achieve both disease stabilization and repigmentation. Phototherapy remains one of the most effective treatment modalities for vitiligo. Ultraviolet (UV) radiation, particularly narrowband ultraviolet B (NB-UVB; 311–312 nm), has demonstrated significant efficacy in suppressing autoreactive cytotoxic T-cells, inducing melanocyte differentiation, and stimulating residual melanocytes in perilesional skin and melanocyte precursors in hair follicles, thereby promoting repigmentation.[3,4]

Calcineurin inhibitors also contribute to repigmentation through immunomodulatory mechanisms. By suppressing T-cell activation, these agents reduce inflammation-mediated melanocyte damage and may indirectly enhance melanogenesis. Tyrosinase, the key enzyme in melanin synthesis, plays a central role in this process, as its activity directly determines melanin production.[5]

Tyrosine, an essential amino acid and the primary substrate for melanin synthesis, has been explored *in vitro* as a potential therapeutic adjunct for vitiligo. Furthermore, tyrosine has been shown to influence tyrosinase activity in both normal and vitiligo-affected skin, supporting its possible role in melanogenesis.[6,7]

Evidence from human studies further indicates that topically applied tyrosine can penetrate the epidermis and contribute to melanin production. In a pilot study, the application of a 0.2% tyrosine cream to sun-exposed forearm skin produced visible tanning in all volunteers after 24 hours, whereas a tyrosine-free control produced erythema alone.[7] Additionally, tyrosine-derived nanospheres have been shown to effectively transport lipophilic agents across the stratum corneum into the deep dermis, achieving up to ninefold greater delivery than conventional formulations.[8] Collectively, these findings support the principle that tyrosine-based compounds can penetrate human skin and serve as substrates for melanin production.

Despite growing evidence regarding the potential role of tyrosine metabolism in vitiligo, its clinical relevance in enhancing repigmentation of human vitiliginous skin remains insufficiently explored. Therefore, the present study aimed to investigate the efficacy and safety of topical tyrosine 2% compared with those of topical tacrolimus 0.1% in promoting skin repigmentation among patients with vitiligo who were candidates for NB-UVB therapy.

Materials and Methods

Study Design, Setting, and Study Period

This randomized, intra-individual, controlled clinical trial was conducted in patients with non-segmental vitiligo (NSV) at the outpatient dermatology clinic of a university hospital between August 2025 and February 2026. Sample size was calculated with G*Power software (version 3.1.9.4) for paired proportions using McNemar's test, assuming a two-tailed α of 0.05, 80% power, an odds ratio (OR) of 3.5, and a discordant proportion of 0.40; these assumptions were based on previously reported efficacy rates of 74.35% for combined tacrolimus and phototherapy and 45.3% for phototherapy.[9] The minimum required sample size was 63 patients; to account for a 10% anticipated dropout, 69 patients were enrolled, of whom 67 completed the study.

Ethical Considerations and Consent

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Faculty of Medicine, Minia University, Egypt (approval no: 1614/07/2025; date: 14 June 2025). The study was registered at ClinicalTrials.gov (Identifier: NCT07532330). Written informed consent, including consent for clinical photography, was obtained from all participants prior to enrollment. Participants were thoroughly informed about the treatment procedures, assessment methods, expected outcomes, and potential adverse effects.

Eligibility Criteria

Patients aged 18–65 years with NSV who were candidates for NB-UVB therapy were eligible for inclusion in the study. Pregnant or lactating women and patients who had received any systemic or topical treatment within the preceding three months were excluded.

Baseline Assessment

A full medical history was obtained from all participants, including personal history (age and sex), present history (disease duration and time since the last episode of disease activity), and family history of vitiligo.

A general clinical and dermatological examination was performed for all participants, including confirmation of the diagnosis of vitiligo using Wood's lamp examination, assessment of disease extent using the vitiligo area scoring index (VASI),[10] and determination of Fitzpatrick skin type.

Treatment Protocol

For each patient, three comparable vitiligo patches, matched as closely as possible for lesion duration and anatomical site, were selected and randomly assigned to one of the following treatment groups using a manual shuffling method (drawing cards), which was repeated independently for each patient:

Group I: NB-UVB combined with topical tyrosine 2% cream (Tyromax® Cream, Vaxil Pharma, Egypt), a liposomal formulation designed to enhance skin penetration, applied twice daily to the first patch.

Group II: NB-UVB combined with topical tacrolimus 0.1% ointment (Treczimus® 0.1% ointment, Marcyrl Pharmaceutical Industries, Egypt) applied twice daily to the second patch.

Group III: NB-UVB alone to the third patch as a control.

NB-UVB phototherapy was delivered twice weekly over a three-month period. All patients started treatment at a fixed dose of 200 mJ/cm². Subsequent dose adjustments ranged from 10% to 20% per session, with the goal of achieving a mild, non-painful pink erythema lasting less than 24 hours (minimal erythema dose). In the absence of erythema, the dose was increased; conversely, if bright red, persistent, or painful erythema occurred, phototherapy was withheld until complete resolution.

Patches were clearly marked and monitored to ensure adherence to treatment, and care was taken to avoid overlap between patches.

Clinical Assessment of Treatment Outcome

Standardized photographs were obtained at baseline and after three months of treatment using the same camera for all patients. Imaging parameters, including lighting, background, and distance, were kept consistent across all sessions. Treatment outcomes were subsequently evaluated by two independent, non-blinded physicians using the following measures:

The Vitiligo Extent Score by Target Area (VESTA): It is a semi-objective assessment tool that uses reference images to evaluate the percentage of repigmentation within a target lesion. It accounts for both marginal and perifollicular repigmentation patterns. The vitiligo extent score by target area (VESTA) comprises three components: (1) reference images for marginal repigmentation; (2) reference images illustrating perifollicular repigmentation; and (3) a formula used to calculate the total percentage of repigmentation. This calculation combines the fully repigmented area (%) with the percentage of perifollicular repigmentation within the remaining depigmented area.[11]

Clinical Improvement Grade: Clinical improvements grading is a subjective assessment tool based on physician visual assessment, generally categorized as follows:

< 25% Improvement: Mild.

25%–50% Improvement: Moderate.

51%–75% Improvement: Good.

> 75% Improvement: Excellent.[12]

Treatment response was assessed at 3 months for each lesion. The percentage of repigmentation was calculated relative to the baseline lesion area. A patient was considered a responder for a given treatment if the lesion treated with that agent achieved ≥ 25% repigmentation (based on VESTA score repigmentation percent) at the 3-month follow-up. Lesions with < 25% repigmentation were classified as non-responders. This threshold was chosen based on studies demonstrating that at least 25% repigmentation constitutes a clinically meaningful improvement and correlates with patients' satisfaction and willingness to continue treatment.[13] Therefore, this cut-off is considered clinically valid.

Side-effect monitoring: patients were monitored for side effects at each follow-up visit. Monitoring included assessment of visible, persistent erythema, as well as patient-reported, long-lasting (> 24 hours) erythema, irritation, or itching associated with application of topical treatment.

Statistical Analysis

All data were collected, tabulated, and analyzed using SPSS version 26 for Windows (SPSS Inc., Chicago, IL, USA) and R version 4.5.0 (R Core Team, 2025). Normality of quantitative data was assessed using the Shapiro-Wilk test. Qualitative variables were expressed as frequencies and percentages, and differences between groups were evaluated using Fisher's exact test. For quantitative variables (repigmentation percentage), values were expressed as the median [interquartile range (IQR)] when the data were non-normally distributed. The Friedman test was used for overall comparison among the three paired groups, followed by the Wilcoxon signed-rank test for pairwise comparisons. The median difference between each pair was estimated using the Hodges-Lehmann estimator with 95% confidence intervals (CIs). Stepwise linear regression was performed to identify independent predictors of the VESTA score; standardized coefficients (β) and *P*-values were reported, and model fit was assessed using R^2 and the F test. For the binary outcome (responder status, defined as ≥ 25% repigmentation based on VESTA score), pairwise comparisons between each active treatment group (groups I and II) and the control group were performed

using McNemar's test for paired proportions (R version 4.5.0, McNemar's test function). When zero discordant pairs were present, a continuity correction (adding 0.5 to each cell) was applied to calculate the matched OR. The proportion of discordant pairs was reported as an additional measure of within-subject effect size. A two-tailed *P*-value < 0.05 was considered statistically significant.

Results

A total of 69 patients were enrolled in the study. One patient was lost to follow-up, and another discontinued treatment because of a non-study-related accident. Consequently, 67 patients completed the study and were included in the final analysis.

Baseline Demographic and Clinical Characteristics

The patients' age mean ± standard deviation (SD) was 32.4 ± 11.1 years. Males constituted 59.7% of the sample, while females constituted 40.3%. The disease durations mean ± SD was 5.3 ± 4.9 years, and the time elapsed since the last disease activity mean ± SD was 4.0 ± 4.4 months. A positive family history of vitiligo was reported in 37.3% of patients. The VASI score mean ± SD was 8.1 ± 4.4, and majority of patients had Fitzpatrick skin type III (67.2%), followed by type IV (32.8%).

Clinical Evaluation

The VESTA score intraclass correlation coefficient was 0.974 (95% CI: 0.966–0.980, $P < 0.001$), indicating excellent agreement between raters. It demonstrated a statistically significant difference in repigmentation among the study groups *P*-value < 0.001. Group II (combined tacrolimus and NB-UVB) exhibited the highest repigmentation, with a median (IQR) of 60.0% (37.0–70.0). This was followed by group I (combined tyrosine and NB-UVB) with a median (IQR) of 28.0% (16.0–46.0). In contrast, group III (NB-UVB alone) showed the lowest repigmentation, with a median (IQR) of 12% (10.0–21.0). Pairwise comparisons revealed statistically significant differences between all groups. The median difference between group I and group II was -19.0% [95% CI: -24.0–(-14.5); $P < 0.001$], indicating significantly higher repigmentation in group II. Group I showed a median increase of 15.5% (95% CI: 9.5–23.5) compared with group III ($P < 0.001$). The largest effect was observed between groups II and III, with a median difference of 40.13% (95% CI: 31.0–47.0) in favor of group II ($P < 0.001$) (Table 1).

A statistically significant difference in the distribution of clinical improvement grades was observed among the three groups ($P < 0.001$). Group II (combined tacrolimus and NB-UVB) demonstrated the most favorable clinical outcomes, with the majority of patients achieving either good (50.7%) or excellent (14.9%) improvement. In contrast, group I (combined tyrosine and NB-UVB) showed predominantly mild (37.4%) to moderate (38.8%) improvement, with only 13.4% and 10.4% of patients demonstrating good and

Table 1. Clinical assessment of treatment outcome in the studied patients (n = 67)

	Group I tyrosine 2% + NB-UVB	Group II tacrolimus 0.1% + NB-UVB	Group III NB-UVB (control)	Group I vs. group II	Group I vs. group III	Group II vs. group III
VESTA score (%)	Median (IQR)			Median differences (CI)		
	28.0 (16–46)	60.0 (37–70)	12.0 (10.0–21)	-19 [-24.0–(-14.5)]	15.5 (9.5–23.5)	40.13 (31.0–47.0)
***P*-value**	**< 0.001***			**< 0.001***	**< 0.001***	**< 0.001***
Clinical improvement grade	n (%)					
Mild	25 (37.4%)	8 (11.9%)	43 (64.2%)			
Moderate	26 (38.8%)	15 (22.5%)	24 (35.8%)			
Good	9 (13.4%)	34 (50.7%)	0 (0.0%)			
Excellent	7 (10.4%)	10 (14.9%)	0 (0.0%)			
***P*-value**	**< 0.001***			**< 0.001***	**< 0.001***	**< 0.001***

Friedman's test for non-parametric quantitative data between the three groups
Wilcoxon test for non-parametric quantitative data between each two groups
Hodges-Lehmann test for median differences and confidence interval
Positive median differences indicate higher repigmentation in the first group compared to the second
Fisher's exact test for qualitative data
NB-UVB: Narrowband ultraviolet B, VESTA: Vitiligo extent score by target area, IQR: Interquartile, CI: Confidence interval
*Statistically significant *P*-value ($P < 0.05$)

excellent improvement, respectively. Group III (NB-UVB alone) exhibited predominantly mild improvement (64.2%), while the remaining 35.8% showed moderate improvement; no patients achieved good or excellent responses. Pairwise comparisons revealed a significantly greater improvement in group II compared with both groups I and III ($P < 0.001$ for both comparisons). Additionally, group I demonstrated significantly greater improvement than group III ($P < 0.001$; Table 1, Figures 1–3).

None of the patients included in the present study reported any clinically significant or treatment-limiting side effects.

The best-fitting stepwise linear regression model demonstrated the effects of different variables on the VESTA score. Across the studied groups, shorter time since the last disease activity and lower VASI scores were the strongest predictors of higher VESTA scores, with standardized coefficients (β) of -0.37 ($P = 0.016$) and -0.66 ($P < 0.001$), respectively in group I, standardized coefficients (β) of -0.41 ($P = 0.001$) and -0.61 ($P < 0.001$), respectively in group II, and standardized coefficients (β) of -0.38 ($P = 0.014$) and -0.65 ($P < 0.001$), respectively in group III (Table 2).

Effect Size Estimation

For the binary outcome (responder status defined as ≥ 25% VESTA repigmentation score), the responder proportions were 59.7% (40/67) in group I (tyrosine plus NB-UVB), 85.1% (57/67) in group II (tacrolimus plus NB-UVB), and 19.4% (13/67) in group III (NB-UVB alone). These proportions differ from those obtained with clinical improvement grading owing to differences in methodology between the two assessment tools. These proportions were analyzed using McNemar's paired comparisons, which showed statistically significant differences between each active treatment group (groups I and II) and the control group ($P < 0.001$ for each). Between group I and the control group, 33 subjects responded only to tyrosine plus NB-UVB, and 6 subjects responded only to NB-UVB (OR = 5.5; 95% CI: 2.3–13.1; discordant proportion 0.582). Between group II and the control group, 44 patients responded only to tacrolimus plus NB-UVB, and none responded only to NB-UVB (OR = 89; continuity correction; discordant proportion 0.657; 95% CI not estimable due to zero_cell) (Table 3).

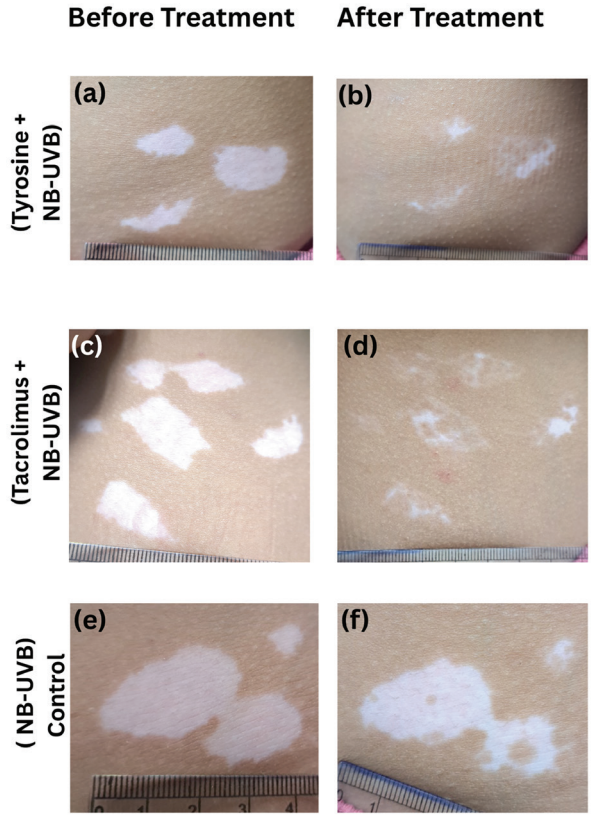

Figure 1. Clinical outcomes of the three treatment modalities in a female patient with non-segmental vitiligo. (a, b) Tyrosine 2% plus narrowband ultraviolet B (NB-UVB) group, showing baseline lesion on the trunk (a) and excellent improvement after 3 months (b). (c, d) Tacrolimus 0.1% plus NB-UVB group, showing baseline lesion on the trunk (c) and excellent improvement after 3 months (d). (e, f) NB-UVB only group, displaying baseline lesion on the trunk (e) and mild improvement after 3 months (f)

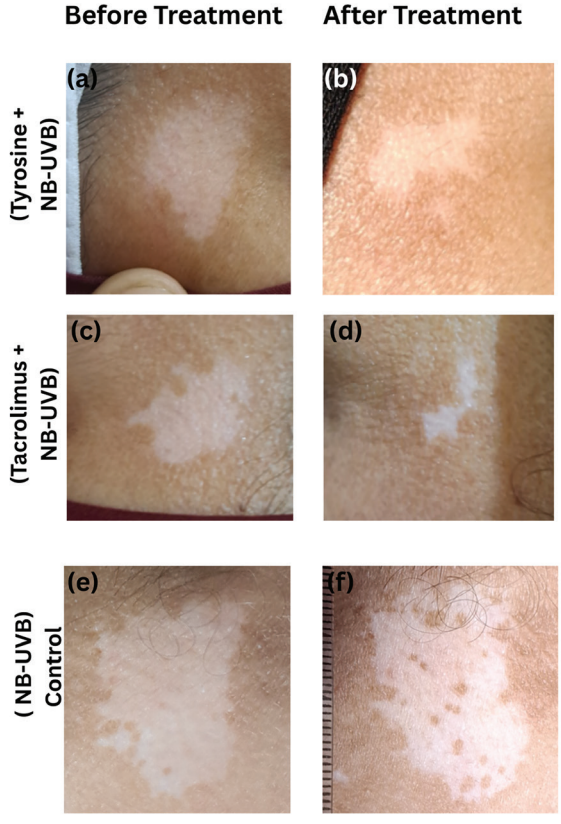

Figure 2. Clinical outcomes of the three treatment modalities in a female patient with non-segmental vitiligo. (a, b) Tyrosine 2% plus narrowband ultraviolet B (NB-UVB) group, showing baseline lesion on the face (a) and good improvement after 3 months (b). (c, d) Tacrolimus 0.1% plus NB-UVB group, showing baseline lesion on the face (c) and excellent improvement after 3 months (d). (e, f) NB-UVB only group, displaying baseline lesion on the neck (e) and mild improvement after 3 months (f)

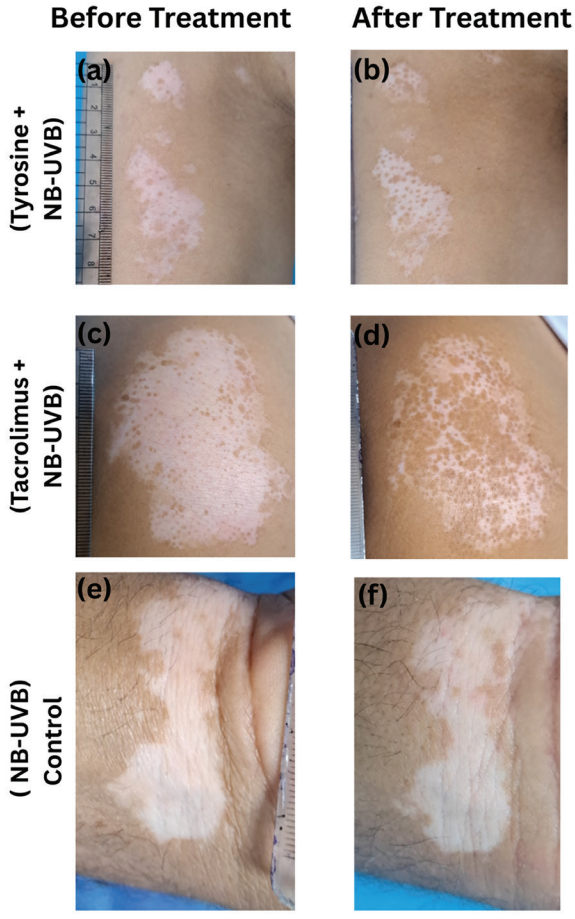

Figure 3. Clinical outcomes of the three treatment modalities in a male patient with non-segmental vitiligo. (a, b) Tyrosine 2% plus narrowband ultraviolet B (NB-UVB) group, showing baseline lesion on the upper limb (a) and moderate improvement after 3 months (b). (c, d) Tacrolimus 0.1% plus NB-UVB group, showing baseline lesion on the upper limb (c) and excellent improvement after 3 months (d). (e, f) NB-UVB only group, displaying baseline lesion on the upper limb (e) and mild improvement after 3 months (f)

Discussion

Vitiligo is a complex disorder characterized by a multifactorial pathogenesis arising from the interplay of genetic predisposition, metabolic influences, and immune responses, ultimately leading to the destruction of melanocytes.[14] Therefore, therapeutic strategies that target immune suppression, stimulate melanocyte activity, and modulate the metabolic environment are essential for effective disease management.

In the present study, NB-UVB demonstrated efficacy in the treatment of vitiligo when used alone or in combination with tyrosine or tacrolimus.

Phototherapy represents a cornerstone in the management of generalized vitiligo, acting not only to stabilize active disease but also to promote repigmentation. The primary mechanisms include the induction of T-cell apoptosis, the downregulation of inflammatory cytokines and the stimulation, migration, and proliferation of melanocyte stem cells originating from hair follicles. Furthermore, phototherapy enhances the production of melanogenic growth factors, such as endothelin-1 (ET-1).[15]

Notably, our result revealed that, patients receiving tyrosine plus NB-UVB had a substantially higher chance of achieving a clinical response compared to NB-UVB alone.

Tyrosine serves as the principal amino acid precursor for all forms of melanin, including eumelanin and pheomelanin, in the skin, hair, and eyes. In melanocytes, tyrosine is converted by the enzyme tyrosinase into L-DOPA and subsequently into dopaquinone, initiating the melanogenesis pathway.[16] Both L-tyrosine and L-DOPA function not only as substrates but also as positive regulators of melanogenesis, contributing to melanogenic homeostasis within melanocytes.[17]

UV radiation enhances melanogenesis in part by upregulating tyrosinase expression and increasing its utilization of L-tyrosine.[16] Because tyrosinase uses L-tyrosine as its rate-limiting substrate, variations in tyrosine availability or competition at this step can directly influence melanin production and overall pigmentation.[18] Moreover, metabolomic analyses of plasma from patients with vitiligo have demonstrated an enrichment of the tyrosine metabolism pathway, suggesting potential alterations of this pathway in vitiligo pathophysiology. Notably, evidence indicates that vitiliginous skin retains the capacity to synthesize melanin from tyrosine.[19]

These mechanisms may account for the therapeutic benefit of tyrosine observed in the present study. By increasing the availability of a critical substrate for melanin synthesis, tyrosine may enhance melanogenic activity in residual or partially functional melanocytes, particularly when combined with phototherapy-induced stimulation. Accordingly, the addition of tyrosine to NB-UVB may facilitate repigmentation primarily through the metabolic enhancement of melanogenesis.

Moreover, our results demonstrated that patients treated with tacrolimus combined with NB-UVB were substantially more likely to achieve a clinically meaningful repigmentation compared with NB-UVB alone. This finding is consistent with multiple randomized trials and meta-analyses showing greater repigmentation with tacrolimus combined with NB-UVB or excimer light than with phototherapy alone. In particular, the meta-analyses by Arora et al.[20] and Dong et al.[21] reported that combining tacrolimus with phototherapy significantly increased the proportion of patients achieving ≥ 75% repigmentation (excellent response) compared with phototherapy alone.

Table 2. Linear regression for factors affecting VESTA score in each group (n = 67)

		Standardized coefficient β	(95% CI)	*P*-value
Group I tyrosine 2% + NB-UVB	**Age**	-0.153	(-0.78–0.11)	0.131
	Sex	-0.04	(-14.44–13.85)	0.967
	Disease duration	0.28	(-0.20–2.86)	0.088
	Time since last disease activity	-0.37	[-3.55–(-0.38)]	**0.016***
	Family history	-0.03	(-12.09–15.14)	0.823
	VASI score	-0.66	[-4.87–(-2.16)]	**< 0.001***
	Fitzpatrick skin type	0.05	(-8.21–13.30)	0.638
Group II tacrolimus 0.1% + NB-UVB	**Age**	-0.12	(-0.67–0.12)	0.166
	Sex	0.00	(-12.50–12.51)	0.999
	Disease duration	0.18	(-0.43–2.28)	0.175
	Time since last disease activity	-0.41	[-3.74–(-0.94)]	**0.001***
	Family history	0.05	(-9.54–14.54)	0.679
	VASI score	-0.61	[-4.66–(-2.27)]	**< 0.001***
	Fitzpatrick skin type	-0.05	(-12.30–6.72)	0.560
Group III NB-UVB (control)	**Age**	-0.12	(-0.22–0.06)	0.273
	Sex	-0.06	(-5.41–3.56)	0.682
	Disease duration	0.27	(-0.08–0.89)	0.103
	Time since last disease activity	-0.38	[-1.14–(-0.13)]	**0.014***
	Family history	-0.01	(-4.45–4.19)	0.953
	VASI score	-0.65	[-1.51–(-0.65)]	**< 0.001***
	Fitzpatrick skin type	0.07	[-4.51–(-2.32)]	0.523

Dependent variable; vitiligo extent score by target area (VESTA)
VASI: Vitiligo area scoring index, CI: Confidence interval, NB-UVB: Narrowband ultraviolet B
Reference categories: female sex, negative family history, and Fitzpatrick skin type IV
*Statistically significant *P*-value ($P < 0.05$)

Table 3. McNemar paired comparisons for responder status (≥ 25% repigmentation) (n = 67)

Comparison	OR (95% CI)	*P*-value	Discordant proportion
Group I (tyrosine 2% + NB-UVB) vs. Group III (NB-UVB only)	5.5 (2.3–13.13)	**< 0.001***	0.582 (58.2%)
Group II (tacrolimus 0.1% + NB-UVB) vs. Group III (NB-UVB only)	**89^**	**< 0.001***	0.657 (65.7%)

McNemar's chi-squared test was applied for binary outcome (responder status defined as ≥ 25% repigmentation)
^Continuity correction applied (0.5) due to zero cell; 95% CI estimate is unstable and not calculable
*Statistically significant *P*-value ($P < 0.05$)
CI: Confidence interval, OR: Odds ratio, NB-UVB: Narrowband ultraviolet B

Tacrolimus plays a key role in inhibiting T-cell–mediated autoimmunity by blocking the calcineurin/nuclear factor of activated T-cells signaling pathway, which is essential for T-cell activation and the production of pro-inflammatory cytokines. This immunosuppressive effect reduces the autoimmune response responsible for melanocyte destruction in vitiligo. In addition, tacrolimus promotes melanocyte growth, migration, and function. It has been shown to increase the expression of endothelin-B (ETB) receptors on melanoblasts and enhance the production of matrix metalloproteinases (MMP-2 and MMP-9), which facilitate melanocyte migration and contribute to repigmentation.[22]

Moreover, the dual action of UVB-induced ET-1 production and tacrolimus-induced ETB receptor expression creates a favorable microenvironment for melanocyte recruitment and

repigmentation.[23,24] This synergistic interaction may explain the enhanced therapeutic efficacy observed when these two modalities are combined in the treatment of vitiligo.

However, our results demonstrated that the addition of tacrolimus to NB-UVB produced significantly greater repigmentation than tyrosine. This difference may be attributed to tacrolimus's ability to target multiple pathogenic mechanisms of vitiligo through its potent immunomodulatory effects and stimulatory effect on melanocyte migration and proliferation.[22] In contrast, tyrosine acts primarily via a single targeted pathway in its role as a melanin precursor.[17]

The influence of the treatment modalities studied, NB-UVB alone or combined with tyrosine or tacrolimus, on the progression of vitiligo suggests that early initiation of these therapies may be beneficial in limiting disease progression and enhancing repigmentation. This effect appears to be more pronounced in patients with limited disease severity. This is supported by the regression findings, which identified shorter time since last disease activity and lower VASI scores as significant predictors of higher VESTA scores across the studied groups.

Study Limitations

This study is limited by its short follow-up, lack of external funding, and single-center design, which may limit generalizability and preclude assessment of the long-term durability of repigmentation. Although the intra-individual design reduces inter-patient variability, residual site-specific differences in treatment response cannot be excluded. Additionally, the non-blinded design of this controlled clinical trial may represent a source of assessment bias. Moreover, the discrepancy between the semi-objective VESTA assessment and the subjective clinical grading, particularly near the 25% response threshold, represents an additional limitation. Therefore, VESTA-based responder analysis was prioritized for effect size estimation.

Conclusion

Combination therapy appears to offer superior efficacy in the management of vitiligo, potentially shortening the time required to achieve noticeable repigmentation, with NB-UVB phototherapy remaining the therapeutic cornerstone. Tacrolimus in combination with NB-UVB achieved the highest repigmentation outcomes, whereas tyrosine combined with NB-UVB may represent a safe and potentially beneficial adjunct. Early initiation of NB-UVB, with or without tyrosine or tacrolimus, may improve repigmentation and limit disease progression, particularly in patients with less severe disease.

Recommendation

Given that this is, to our knowledge, the first clinical study evaluating topical tyrosine in vitiligo, these findings require further validation through large-scale, multicenter trials with extended follow-up to confirm these results and delineate potential synergistic effects of combining NB-UVB, tacrolimus, and tyrosine. Furthermore, comprehensive mechanistic studies are needed to elucidate the role of topical tyrosine in melanogenesis and repigmentation.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Faculty of Medicine, Minia University, Egypt (approval no: 1614/07/2025; date: 14 June 2025). The study was retrospectively registered at ClinicalTrials.gov (Identifier: NCT07532330).

Informed Consent: Written informed consent, including consent for clinical photography, was obtained from all participants prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.M.A., Concept: M.H.A.M., Design: M.H.A.M., A.M.A., H.A.Z., Data Collection or Processing: A.M.A., Analysis or Interpretation: H.A.Z., Literature Search: M.H.A.M., A.M.A., Writing: M.H.A.M., A.M.A., H.A.Z.

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

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Original Article

Association of *SOCS1* and *SOCS3* Gene Polymorphisms with Vitiligo Phenotypes: A Case-Control Study

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Abstract

Aim: Suppressors of cytokine signaling (SOCS) proteins maintain immune homeostasis and are implicated in autoimmune diseases. This case-control study investigated the role of *SOCS1* (rs33989964) and *SOCS3* (rs4969168, rs4969170) gene polymorphisms in vitiligo susceptibility, and examined their potential associations with distinct clinical features to evaluate their contribution to phenotypic heterogeneity in vitiligo.

Materials and Methods: This study included 100 patients with non-segmental vitiligo and 100 age- and sex-matched healthy controls. Genotyping of *SOCS1* (rs33989964) and *SOCS3* (rs4969168 and rs4969170) polymorphisms was performed using TaqMan probe-based polymerase chain reaction. A post-hoc power analysis yielded an estimated statistical power of 98.9% for allelic analyses and 96.2% for genotypic analyses, indicating adequate power for the overall analyses.

Results: The primary analysis revealed no significant association between SOCS polymorphisms and overall vitiligo susceptibility ($P > 0.05$). However, uncorrected exploratory subgroup analyses indicated potential clinical correlations: The *SOCS1* rs33989964 del/del genotype exhibited a preliminary association with progressive disease [$P = 0.025$; odds ratio (OR) = 5.27, 95% confidence interval (CI): 1.08–25.78]. For *SOCS3* rs4969168, the AA genotype demonstrated a potential, uncorrected association with the absence of triggering factors ($P = 0.031$) and the Koebner phenomenon ($P = 0.049$; OR = 4.75, 95% CI: 1.07–21.01), while the A allele was more frequent among patients with familial autoimmunity ($P = 0.036$; OR = 1.83, 95% CI: 1.03–3.23). Additionally, the *SOCS3* rs4969170 AA genotype showed a potential association with poliosis ($P = 0.024$; OR = 2.77, 95% CI: 1.12–6.85), and its A allele was associated, as an uncorrected exploratory finding, with both poliosis ($P = 0.006$; OR = 1.97, 95% CI: 1.21–3.22) and leukotrichia ($P = 0.048$; OR = 1.65, 95% CI: 1.002–2.72).

Conclusion: *SOCS1* and *SOCS3* polymorphisms do not confer overall vitiligo susceptibility. However, these uncorrected exploratory subgroup analyses suggest that they may be associated with adverse clinical features, including progressive disease, familial autoimmunity, Koebner phenomenon, poliosis, and leukotrichia. These findings suggest that *SOCS* variants may act as modulators of disease phenotype and phenotypic variation rather than susceptibility. These uncorrected associations warrant validation in larger, independent, multivariable cohorts.

Keywords: Genetic polymorphism, JAK-STAT pathway, *SOCS1, SOCS3,* vitiligo

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Introduction

Vitiligo is an acquired, chronic autoimmune disorder characterized by the appearance of depigmented macules resulting from the selective destruction of functional melanocytes. At the core of its immunopathogenesis lies a breakdown in immune tolerance, which permits autoreactive CD8+ cytotoxic T lymphocytes to infiltrate the epidermis. Once at the target tissue, these cells secrete high levels of pro-inflammatory cytokines, most notably interferon-gamma (IFN-γ). This establishes a feedback loop that promotes progressive melanocyte loss, continuously recruits additional autoreactive T cells to the lesion site, and drives disease progression.[1]

At the cellular level, the destructive impact of IFN-γ and other pro-inflammatory cytokines is largely orchestrated through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway.[2] To maintain immunological homeostasis and prevent collateral tissue damage, this robust signaling cascade must be tightly restrained. This essential "braking" function is performed by the Suppressor of cytokine signaling (SOCS) family, particularly *SOCS1* and *SOCS3*.[3] Utilizing their unique kinase inhibitory regions, these proteins directly bind to JAK kinases, suppressing JAK catalytic activity, effectively halting STAT hyperactivation and shielding tissues from cytokine-driven pro-inflammatory cascades.[2,3]

Functional single nucleotide polymorphisms within the *SOCS1* and *SOCS3* genes can alter protein expression or stability, potentially disrupting this negative feedback loop. Furthermore, dysregulation or genetic variants of *SOCS1* and *SOCS3* have been widely implicated in the pathogenesis of systemic and cutaneous autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and atopic dermatitis.[4-7] Despite their central role in immune regulation and the clinical relevance of JAK-STAT modulation, the impact of *SOCS1* and *SOCS3* gene polymorphisms on vitiligo remains unexplored. Therefore, this study aims to evaluate the association of specific polymorphisms in *SOCS1* (rs33989964) and *SOCS3* (rs4969168, rs4969170) with overall susceptibility to vitiligo, and to perform exploratory analyses of their potential associations with distinct clinical features, thereby enhancing our understanding of how these variants may act as modulators of vitiligo's phenotypic heterogeneity.

Materials and Methods

Study Population

This case-control study was conducted at the Dermatology Outpatient Department of Uludağ University Faculty of Medicine between March 2019 and June 2019. Approximately 140 patients with suspected depigmentation disorders were screened for eligibility during the initial recruitment phase. Following clinical evaluation, 40 patients who did not meet the inclusion criteria or who declined to participate were excluded, yielding 100 eligible patients. Concurrently, healthy volunteers, comprising patients' relatives and unrelated individuals, were invited to participate to form the control group. Consequently, a final cohort of 200 participants, comprising 100 patients clinically diagnosed with non-segmental vitiligo (NSV) and 100 healthy volunteers matched for age, sex, and ethnicity, was consecutively enrolled in the study. To account for familial genetic influences, the study population was categorized into two cohorts, each subdivided into two subgroups (n = 50 per group). The patient cohort consisted of Group 1 and Group 2. Group 1 comprised vitiligo patients who participated individually, without any relatives enrolled in the study. Group 2 included vitiligo patients with a relative participating in the study. The Healthy Control Cohort consisted of Groups 3 and 4. Group 3 comprised the healthy first- or second-degree relatives of the patients in Group 2. Group 4 included healthy individuals with no personal or familial history of vitiligo, serving as an independent control group. Patients with other concurrent autoimmune diseases were excluded from the study to evaluate the potential genetic association between SOCS polymorphisms and vitiligo. Demographic and clinical parameters—including age, sex, disease triggers, age at onset, disease duration, clinical subtype, disease stage, presence of leukotrichia, poliosis, halo nevus, Koebner phenomenon, and family history of autoimmune diseases—were recorded for all participants. Disease onset was categorized as early-onset (< 12 years) or late-onset (≥ 12 years).[7] Disease activity was defined by the presence of the Koebner phenomenon, the development of new lesions within the past 12 months, or the progression of existing lesions.[8]

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Uludağ University Institutional Ethics Committee (date: 05 March 2019; approval no: 2019-5/9), and written informed consent was obtained from all participants prior to sample collection.

Genetic Analysis

Polymorphisms in the *SOCS1* and *SOCS3* genes were selected from the National Center for Biotechnology Information database (Table 1). Genomic DNA was isolated from peripheral blood samples using the Blood-Animal-Plant DNA Preparation Kit (Jena Bioscience, Germany, PP213) according to the manufacturer's protocol. DNA concentration and purity were assessed spectrophotometrically to ensure high-quality templates for downstream analysis. Genotyping was performed

Table 1. *SOCS1* rs33989964, *SOCS3* rs4969168, and *SOCS3* rs4969170 polymorphisms

Chromosomes	Genes	Locus	Polymorphisms	Alleles	The effect of polymorphism on expression
16p13.13	*SOCS1*	-1478 rs33989964	Deletion	TG > del	**del allele/del/del genotype:** Reduced promoter activity and decreased *SOCS1* protein expression[9]
17q25.3	*SOCS3*	+1383 rs4969168	SNP	A > G	**Variant alleles:** Altered mRNA stability and post-transcriptional regulation via 3' UTR modification[10]
17q25.3	*SOCS3*	-4874 rs4969170	SNP	A > G	**A allele/AA genotype:** Enhanced promoter activity, leading to increased levels of *SOCS3* mRNA and protein[11]

SOCS: Suppressor of cytokine signaling, del: Deletion, SNP: Single nucleotide polymorphism, 3' UTR: 3′ untranslated region

by allelic discrimination assay using the TaqMan system with specific primer-probe mixes and quantitative polymerase chain reaction (qPCR) ProbesMaster (Jena Bioscience, Germany). The PCR reactions were carried out in a total volume of 20 µL, containing 10 µL of qPCR ProbesMaster, 1 µL of Primer-Probe Mix, 7 µL of PCR-grade water, and 2 µL of genomic DNA. Amplification was performed on a Bio-Rad CFX Real-Time PCR Detection System with the following thermal cycling conditions: initial denaturation at 95 °C for 2 minutes, followed by 40 cycles of 95 °C for 15 seconds and 60 °C for 1 minute. To ensure quality control, genotyping analyses were performed blinded to case/control status, and 10% of the samples were randomly selected and re-genotyped to confirm reproducibility, yielding a 100% concordance rate. To align with modern genomic databases and TaqMan assay outputs, the *SOCS1* rs33989964 deletion polymorphism is denoted TG > del, corresponding to the historical CA > del nomenclature.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was utilized to assess the normality of continuous variables. For comparisons involving more than two groups with normally distributed data, a one-way analysis of variance was applied. Categorical variables, including genotype and allele frequencies, were analyzed using Pearson's chi-square test, Fisher's exact test, or the Fisher–Freeman–Halton test, as appropriate. To assess genetic susceptibility and intrafamilial allele segregation, comparative analyses were conducted using three specific stratification models: (i) overall susceptibility (Group 1 + 2 vs. Group 3 + 4); (ii) intrafamilial genetic segregation (Group 2 vs. Group 3); and (iii) background risk allele carriage (Group 3 vs. Group 4).

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the relative disease risk conferred by variant alleles across different genetic models (e.g., allelic, dominant, and recessive). In instances where zero observations occurred within a contingency table cell, the Haldane–Anscombe correction (adding 0.5 to each cell) was applied to allow for OR and CI estimation, although such small cell counts can lead to wide CIs and statistical instability. However, in specific clinical subgroup analyses in which a reliable OR could not be computed because a genotype was completely absent, the association was evaluated solely on the exact *P*-value. Genotype frequencies in the control group were tested for Hardy–Weinberg equilibrium (HWE) using a goodness-of-fit chi-square test, with $P > 0.05$ indicating conformity. A two-tailed *P*-value < 0.05 was considered statistically significant for the primary susceptibility analyses; however, for the secondary clinical subgroup evaluations, *P*-values were interpreted as nominal, uncorrected, exploratory signals because no corrections for multiple testing were applied. A post-hoc power analysis was conducted using G*Power software (version 3.1.9). Based on the genotype distribution data, the input parameters were set as follows: a moderate effect size ($w = 0.3$), a statistical significance level (α) of 0.05, and a total sample size of 200 individuals. The calculation yielded an estimated statistical power of 98.9% for the allelic analysis (degrees of freedom = 1) and 96.2% for the genotypic analysis (degrees of freedom = 2). These results indicate adequate power for the overall analyses. However, we acknowledge that this approach neither substitutes for an a priori sample size calculation nor resolves the limited statistical power of the exploratory clinical subgroup analyses.

Results

Demographic and baseline clinical characteristics were similarly distributed between the patient and control groups, with generalized vitiligo being the most prevalent clinical subtype among the cases (Table 2). Disease onset was primarily observed before early adulthood, although a distinct subgroup presented with late-onset vitiligo. While most patients reported no specific precipitating event, emotional stress was the most frequent trigger among those with identifiable precipitating factors, followed by ultraviolet (UVB) exposure and physical trauma (Table 3).

Table 2. Age and gender distribution of patient and control subgroups

	Group 1 (patient)	Group 2 (patient)	Group 3 (control)	Group 4 (control)	*P*
n	50	50	50	50	
Age					0.917
Mean age ± SD	34.76 ± 16.04	34.7 ± 17.95	34.49 ± 11.49	36.40 ± 9.53	
Median age; min-max	35;7–73	35.5;6–74	35;9–64	38;7–54	
Gender					0.278
Female	26	28	28	35	
Male	24	22	22	15	

Statistically significant *P*-values ($P < 0.05$) are indicated in bold where applicable
SD: Standard deviation, min: Minimum, max: Maximum

Table 3. Clinical and demographic characteristics of vitiligo patients

	n
n	100
Age (years) Mean ± SD Median; min-max	 34.73 ± 16.94 35;6–74
Age of onset of disease (years) Mean ± SD Median; min-max Early onset (< 12 years) Late onset (> 12 years) Unknown	 26.71 ± 17.11 25.5 (1–71) 24 75 1
Disease duration (years) Mean ± SD Median; min-max	 6.43 ± 6.63 4;1–35
Triggering factors Stress Ultraviolet Trauma No Unknown	 29 6 3 47 15
Clinical type Generalized Focal Acral/acrofacial	 55 18 27
Disease stage Active-progressive Stable	 50 50
Koebner phenomenon Yes No	 20 80
Halo nevus Yes No Unknown	 8 87 5
Leukotrichia Yes No	 34 66
Poliosis Yes No	 17 83
Family history of autoimmune disease Yes No Unknown	 40 55 5

"Unknown" categories represent missing clinical data for specific parameters
SD: Standard deviation, min: Minimum, max: Maximum

The genotype distributions of all investigated polymorphisms in the control group were consistent with the HWE ($P = 0.618$ for *SOCS1* rs33989964; $P = 0.613$ for *SOCS3* rs4969168; and $P = 0.477$ for *SOCS3* rs4969170). According to our stratification models, the evaluation of overall susceptibility (Group 1 + 2 vs. Group 3 + 4) revealed no significant differences in genotype or allele frequencies for any of the investigated polymorphisms ($P > 0.05$). Similarly, intrafamilial genetic segregation analysis (Group 2 vs. Group 3) and background risk evaluation (Group 3 vs. Group 4) did not reach statistical significance (Table 4).

Further stratifications based on clinical and demographic variables indicated several potential genotype-phenotype correlations among the vitiligo patients (Tables 5 and 6). Regarding disease activity, at an uncorrected level, the *SOCS1* rs33989964 del/del genotype was observed to be more frequent among patients with progressive disease than among those with stable disease (TG/del + TG/TG genotypes) ($P = 0.025$; OR = 5.27, 95% CI: 1.08–25.78). Evaluation of the *SOCS3* rs4969168 variant showed a potential association with the Koebner phenomenon, with the AA genotype more frequent in affected patients; this was an uncorrected exploratory finding ($P = 0.049$; OR = 4.75, 95% CI: 1.07–21.01). This AA genotype was also suggestively associated with the absence of identifiable triggering factors at disease onset ($P = 0.031$). However, due to the small sample size within this specific subgroup, which necessitated exact statistical corrections, the corresponding OR exhibited a wide CI that crossed 1.0 (OR = 0.08, 95% CI: 0.003–2.07). In addition to these clinical features, the *SOCS3* rs4969168 A allele demonstrated an unadjusted, exploratory association with a positive family history of autoimmune diseases ($P = 0.036$; OR = 1.83, 95% CI: 1.03–3.23). Regarding follicular involvement, the *SOCS3* rs4969170 polymorphism was potentially associated with both poliosis and leukotrichia. Specifically, the AA genotype ($P = 0.024$; OR = 2.77, 95% CI: 1.12–6.85) and the A allele ($P = 0.006$; OR = 1.97, 95% CI: 1.21–3.22) demonstrated a potential uncorrected association with the presence of poliosis, while carriage of the A allele showed a borderline uncorrected exploratory association with leukotrichia ($P =$

0.048; OR = 1.65, 95% CI: 1.002–2.72). Certain ORs in these clinical subgroups exhibit wide CIs due to small sample sizes, necessitating the Haldane-Anscombe correction. Given this statistical instability and the fact that the reported *P*-values are exploratory and uncorrected for multiple testing, these clinical correlations should be interpreted cautiously as preliminary signals.

Table 4. Genotype and allele distribution of the polymorphisms *SOCS1* rs33989964, *SOCS3* rs4969168, *SOCS3* rs4969170 in patients with vitiligo and healthy controls

	Patient (P)		Control (C)			*P* (P-C)
Polymorphisms	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Total**	
SOCS1 rs33989964						
TG/TG	21	20	23	25	89	0.577
TG/del	24	24	21	20	89	
del/del	5	6	6	5	22	
TG	66	64	67	70	267	0.458
del	34	36	33	30	133	
SOCS3 rs4969168						
GG	27	30	26	34	117	0.491
AG	18	17	22	14	71	
AA	5	3	2	2	12	
G	72	77	74	82	305	0.411
A	28	23	26	18	95	
SOCS3 rs4969170						
GG	12	9	10	9	40	0.414
AG	21	27	27	30	105	
AA	17	14	13	11	55	
-G	45	45	47	48	185	0.616
A	55	55	53	52	215	

SOCS: Suppressor of cytokine signaling; del: deletion. $P < 0.05$ was considered statistically significant

Table 5. Significant associations between clinical/demographic features and *SOCS1* and *SOCS3* polymorphisms

***SOCS1* rs33989964**	**Genotype**										**Alleles**		
	TG/TG	**TG/del**	**del/del**	***P***	**del/del**	**TG/TG + TG/del**	***P***	**TG/TG**	**TG/del + del/del**	***P***	**TG**	**del**	***P***
Stage of disease													
Progressive	18	23	9	0.076	9	41	**0.025**	18	32	0.443	59	41	0.075
Stable	23	25	2		2	48		23	27		71	29	
***SOCS3* rs4969168**	**Genotype**										**Alleles**		
	AA	**AG**	**GG**	***P***	**GG**	**AG + AA**	***P***	**AA**	**AG + GG**	***P***	**G**	**A**	***P***
Triggering factors													
Yes	0	13	25	0.070	25	13	0.241	0	38	**0.031**	63	13	0.055
No	6	16	25		25	22		6	41		66	28	
Koebner phenomenon													
Yes	4	5	11	0.073	11	9	0.840	4	16	**0.049**	27	13	0.256
No	4	30	46		46	34		4	76		122	38	
Familial autoimmunity													
Yes	4	17	19	0.138	19	21	0.053	4	36	0.236	55	25	**0.036**
No	2	16	37		37	18		2	53		90	20	

Table 5. Continued

SOCS3 rs4969170	Genotype										Alleles		
	AA	AG	GG	*P*	GG	AG + AA	*P*	AA	AG + GG	*P*	G	A	*P*
Leukotrichia													
Yes	14	16	4	0.148	4	30	0.104	14	20	0.114	24	44	0.048
No	17	32	17		17	49		17	49		66	66	
Poliosis													
Yes	9	8	0	**0.024**	0	17	**0.020**	9	8	**0.032**	8	26	0.006
No	22	40	21		21	62		22	61		82	84	

SOCS: Suppressor of cytokine signaling; del: deletion. $P < 0.05$ was considered to be statistically significant

Table 6. Significant associations and risk estimates (odds ratios)

Clinical parameter	Polymorphism	Model/comparison	*P*-value	OR (95% CI)
Disease progression	*SOCS1* rs33989964	del/del vs. TG/TG + TG/del	0.025	5.27 (1.08–25.78)
Koebner's phenomenon	*SOCS3* rs4969168	AA vs. AG + GG	0.049	4.75 (1.07–21.01)
Absence of triggering Factors	*SOCS3* rs4969168	AA vs. AG + GG	0.031	0.08[†] (0.003–2.07
Familial autoimmunity	*SOCS3* rs4969168	A allele frequency	0.036	1.83 (1.03–3.23)
Poliosis	*SOCS3* rs4969170	AA vs. AG + GG (recessive)	0.024	2.77 (1.12–6.85)
Poliosis	*SOCS3* rs4969170	GG vs. AG + AA (dominant)	0.020	N/A[‡†] (-)
Poliosis	*SOCS3* rs4969170	A allele frequency	0.006	1.97 (1.21–3.22)
Leukotrichia	*SOCS3* rs4969170	A allele frequency	0.048	1.65(1.002–2.72)

[†]Haldane–Anscombe Correction: Applied to estimate the OR and 95% CI due to zero observations in contingency table cells
[‡]Zero Frequency: A reliable odds ratio could not be computed because of the complete absence of the specified genotype in the clinical subgroup
CI: Confidence interval, N/A: Not applicable, OR: Odds ratio, SOCS: Suppressor of cytokine signaling

Discussion

To the best of our knowledge, the current study represents the first investigation into the association between *SOCS1* and *SOCS3* gene polymorphisms and NSV. The primary finding of our study is the lack of significant association between the investigated SOCS polymorphisms and overall susceptibility to disease onset. Instead, uncorrected exploratory subgroup analyses suggest that *SOCS1* and *SOCS3* variants may act as modulators of specific clinical phenotypes and disease severity and may be more closely related to phenotypic variation than to overall disease susceptibility. This observation aligns with existing literature on other autoimmune conditions, where *SOCS* variants often influence clinical heterogeneity rather than absolute risk.[4]

Specifically, our study revealed a preliminary, uncorrected association between the *SOCS1* rs33989964 del/del genotype and progressive vitiligo (OR = 5.27). Mechanistically, this potential link parallels recent discoveries regarding human *SOCS1* haploinsufficiency, wherein loss-of-function variants lead to severe autoimmunity characterized by hyperactivation of the JAK/STAT pathway.[12] Although functional protein activity was not directly evaluated in our cohort, the reduced promoter activity associated with the del/del genotype may fail to provide the necessary negative feedback against IFN-γ-driven CD8+ T-cell cytotoxicity. Consequently, this dysregulated signaling might facilitate the heightened proinflammatory environment required for progressive melanocyte destruction.[13]

Regarding follicular involvement, the *SOCS3* rs4969170 polymorphism exhibited potential associations with both poliosis (AA genotype and A allele) and leukotrichia (A allele). These genotype-phenotype correlations can be elucidated by existing functional in vitro data, which demonstrate that the AA genotype at the *SOCS3* rs4969170 promoter locus enhances transcriptional activity, leading to increased *SOCS3* mRNA and protein expression.[14] In the context of vitiligo, this constitutive overexpression of *SOCS3* is hypothesized to act as a negative regulator that excessively suppresses downstream signaling. Because the balanced activation of STAT3 is crucial for the survival, proliferation, and migration of melanocyte stem cells located in the follicular bulge, its potential inhibition by genetically driven overexpression of *SOCS3* may impair the regenerative capacity of the hair follicle, which may clinically manifest as leukotrichia and poliosis. However, due to the limited sample sizes in these clinical subgroups, these secondary findings must be interpreted with caution, as they represent uncorrected exploratory signals rather than definitive prognostic markers.

Furthermore, evaluation of the *SOCS3* rs4969168 variant showed a potential association with Koebner phenomenon, with the AA genotype being more frequent in affected

patients, which was an uncorrected finding (OR = 4.75). This AA genotype was also potentially associated with the absence of identifiable triggering factors at disease onset. Although the corresponding OR exhibited a wide CI due to the small sample size in this subgroup, this association suggests that the variant may indicate an intrinsic genetic predisposition contributing to spontaneous immune dysregulation, potentially circumventing the need for external environmental stimuli. Additionally, the *SOCS3* rs4969168 A allele was observed to be more prevalent among patients with a positive family history of autoimmune diseases, as an uncorrected exploratory finding (OR = 1.83). Collectively, these exploratory clinical correlations support the hypothesis that *SOCS3* polymorphisms act as potential systemic modulators of immune tolerance, extending their impact beyond localized depigmentation to a broader autoimmune diathesis.

The lack of an overall association with susceptibility in our cohort is consistent with previous research on SOCS polymorphisms across various immune-mediated and malignant diseases in the Turkish population. Studies evaluating the *SOCS1* rs33989964 polymorphism found no association with overall susceptibility to ulcerative colitis or colorectal cancer, and similarly, the *SOCS3* variants showed no significant association with psoriasis in Turkish cohorts.[15-17] Conversely, the *SOCS1* rs33989964 del/del genotype has been significantly associated with disease characteristics in hematological malignancies, such as multiple myeloma, and in gastric cancer.[9,10]

Although these studies encompass diverse disease groups, the consistent finding is that *SOCS* polymorphisms rarely confer overall disease susceptibility but may influence clinical course or prognosis. Importantly, the lack of significant associations in Turkish populations for autoimmune diseases such as ulcerative colitis, psoriasis, and vitiligo (including our study) may also reflect ethnic and genetic background differences that shape *v* gene function.

Furthermore, our observation that *SOCS* polymorphisms may influence disease characteristics rather than overall susceptibility aligns with the concept of gene–environment interactions in multifactorial diseases. In the dermatological context, *SOCS3* functions as a key JAK/STAT modulator in immune-mediated diseases triggered by environmental factors. For instance, in atopic dermatitis, *SOCS3* regulates Th2-mediated allergic responses provoked by environmental allergens and pathogens.[11]

Similarly, in psoriasis, environmental triggers such as mechanical stress and trauma exacerbate inflammation, a process in which *SOCS3* expression is often dysregulated, leading to sustained STAT3 activation.[18] Furthermore, chronic UVB exposure has been shown to directly suppress *SOCS3* expression in the skin, thereby amplifying local inflammatory responses.[18] Together, these findings underscore that genetic polymorphisms rarely act in isolation but rather function within complex biological networks shaped by environmental exposures. In this context, our study's observation that SOCS variants were not directly associated with vitiligo susceptibility but showed exploratory correlations with clinical features such as Koebner phenomenon, leukotrichia, and disease progression suggests that *SOCS* variants may modulate the phenotypic expression of vitiligo in conjunction with environmental triggers, including psychological stress, UVB exposure, or local trauma.

Given the uncorrected exploratory associations observed between *SOCS* variants and adverse clinical features, our findings suggest that these genetic variants may impair the negative feedback regulation of the JAK/STAT signaling pathway, potentially contributing to melanocyte destruction mediated by IFN-γ and interleukin-6.[2,19]

Ultimately, this highlights the potential role of the SOCS/JAK/STAT signaling axis in vitiligo pathogenesis. Targeted modulation of this pathway, potentially through topical or systemic SOCS mimetics and through selective JAK inhibitors, may offer therapeutic avenues for patients with progressive and refractory variants of vitiligo.[2,20]

Study Limitations

Several limitations of this study should be acknowledged. First, while the overall sample size (n = 200) provided a basis for evaluating general susceptibility, the limited number of patients in specific clinical subgroups restricted the statistical power of the sub-phenotype analyses, necessitating the use of exact *P*-values and the Haldane-Anscombe correction for zero frequencies. Because of these small subgroup sizes, multivariable logistic regression, adjusted for confounding clinical variables, could not be performed reliably. Furthermore, no formal multiple testing correction (such as Bonferroni) was applied to the subgroup analyses to avoid substantially increasing the risk of Type II (false-negative) errors; therefore, these uncorrected clinical associations should be interpreted as exploratory findings rather than definitive risk factors.

Second, the study was conducted within a specific demographic cohort, the Turkish population, which may limit the generalizability of the findings to populations with different genetic backgrounds. Third, the cross-sectional, hospital-based design inherently restricts the ability to establish definitive causal relationships, and because some healthy controls were relatives of patients, a potential lack of statistical independence due to familial clustering could not be entirely excluded. The

absence of functional molecular assays, such as measuring *SOCS1* and *SOCS3* mRNA or protein expression in skin biopsies or serum, prevents direct confirmation of the biological mechanisms by which these genetic variants exert their phenotypic effects; consequently, our mechanistic explanations remain hypothetical and are based on existing literature.

Conclusion

The primary finding of this case-control study *is* that *SOCS1* (rs33989964) and *SOCS3* (rs4969168, rs4969170) gene polymorphisms may not confer overall susceptibility to NSV. However, uncorrected exploratory subgroup analyses suggest that these variants may influence the clinical phenotype and disease severity. Our preliminary data suggest that the *SOCS1* rs33989964 del/del genotype is potentially associated with progressive vitiligo, whereas the *SOCS3* rs4969168 AA genotype is potentially associated with an increased frequency of the Koebner phenomenon. Additionally, the *SOCS3* rs4969170 AA genotype exhibited an exploratory correlation with follicular depigmentation, particularly poliosis. These results suggest that *SOCS* variants may act as modulators of disease phenotype and may be more closely related to phenotypic variation than to overall disease susceptibility. Identifying these genetic modulators provides deeper insights into the complex pathogenesis of vitiligo; however, these exploratory signals require further validation in larger, independent, multivariable cohorts before they can be considered clinically actionable.

Ethics

Ethics Committee Approval: The study protocol was approved by the Uludağ University Institutional Ethics Committee (date: 05 March 2019; approval no: 2019-5/9).

Informed Consent: Written informed consent was obtained from all participants prior to sample collection.

Authorship Contributions

Surgical and Medical Practices: E.I.Y., H.S., Ş.G.T., E.B.B., K.A., S.Y., Concept: E.I.Y., H.S., Ş.G.T., E.B.B., K.A., S.Y., G.Ö., H.B.O., Design: E.I.Y., H.S., Ş.G.T., E.B.B., K.A., S.Y., G.Ö., H.B.O., Data Collection or Processing: E.I.Y., H.S., Ş.G.T., H.B.O., Analysis or Interpretation: E.I.Y., H.S., G.Ö., Literature Search: E.I.Y., H.S., Writing: E.I.Y., H.S., Ş.G.T., E.B.B., K.A., S.Y., G.Ö., H.B.O.

Footnotes

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Original Article

Reappraisal of Acne Vulgaris Pathogenesis: The Role of Tissue Inhibitor of Metalloproteinase-2 (TIMP-2)

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Abstract

Aim: Acne vulgaris is a persistent inflammatory condition affecting the pilosebaceous unit. Tissue inhibitor of metalloproteinase-2 (TIMP-2) is an endogenous inhibitor of matrix metalloproteinase-2 (MMP-2) that controls MMP-2 proteolytic activity. This study was designed to evaluate serum and gene expression levels of TIMP-2 in patients with acne vulgaris compared with healthy controls, and to correlate these results with available clinical data.

Materials and Methods: This case-control study included 83 cases of acne vulgaris and 83 normal controls. Disease severity was estimated by the Global Acne Grading System (GAGS). Real-time polymerase chain reaction was used to determine *TIMP-2* gene expression, and serum TIMP-2 levels were assessed by enzyme-linked immunosorbent assay.

Results: Comparison between cases and controls showed statistically significant differences in mean serum levels and TIMP-2 expression levels, with levels higher in cases than in controls ($P < 0.001$ for both). Significant positive correlations were observed between mean serum TIMP-2 levels and the GAGS score, NAST classification, and *TIMP-2* gene expression ($P < 0.001$ for all). Significant positive correlations were observed between *TIMP-2* gene expression and both the GAGS score and the NAST classification ($P < 0.001$ for both).

Conclusion: Serum TIMP-2 levels and *TIMP-2* gene expression are significantly elevated in patients with acne vulgaris and positively correlate with disease severity. These findings suggest that TIMP-2 may play a role in acne pathogenesis and could serve as a biomarker of disease activity.

Keywords: Acne vulgaris, tissue inhibitor of metalloproteinase-2, matrix metalloproteinase-2, polymerase chain reaction, enzyme-linked immunosorbent assay

Introduction

Acne vulgaris ranks as one of the most prevalent dermatological problems affecting the pilosebaceous unit, which is made up of the hair follicle, shaft, and sebaceous gland.[1] Acne vulgaris typically begins in adolescence, reaches a peak prevalence of about 95% between the ages of 14 and 19 and often resolves by the middle of one's 20s.[2]

Acne vulgaris commonly presents as pimples, nodules, pustules, and cysts, and these lesions can often result in pigmentation and scarring. Patients with severe acne may have permanently disfiguring scars, which may negatively affect their appearance and their psychological health.[3]

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Acne has a complex, heterogeneous pathophysiology. The main pathogenic factors include androgen stimulation of sebaceous secretion, increased sebum secretion, and follicular hyperkeratinisation. It has been suggested that microbial colonization by *Cutibacterium acnes (C. acnes)* increases perifollicular inflammation, which is a crucial early step in the development of acne vulgaris.[4]

Many matrix metalloproteinases (MMPs), including MMP-1, MMP-2, MMP-3, MMP-9, and MMP-13, can be stimulated by *C. acnes*.[5] MMPs' primary function is to degrade all components of the extracellular matrix. However, they also play a part in inflammation, cell development, proliferation, and remodeling, as well as influencing the production and release of cytokines and chemokines.[6]

Tissue inhibitor of metalloproteinase-2 (TIMP-2) is an endogenous inhibitor of MMP-2, regulating its proteolytic activity.[7] TIMP-2, located on the long arm of chromosome 17, locus number (25), has been shown to regulate the proteolytic activity of MMP-2 through the enzyme's production of a 1:1 stoichiometric suppressive complex.[8]

TIMP-2 and MMP-2 interact via a mechanism more complex than a simple inhibitor-substrate interaction. The relation between TIMP-2 and MMP-2 is concentration-dependent. At low concentrations, TIMP-2 can bind to membrane type-1 MMP and the carboxyl-terminal hemopexin-like domain of MMP-2, activating pro-MMP-2 and promoting its maturation. At high concentrations, TIMP-2 can bind MMP-2 via its N-terminal domain, thereby inhibiting MMP-2 activity.[9]

The study aims to assess TIMP-2 messenger ribonucleic acid (mRNA) expression and serum TIMP-2 levels in patients with acne vulgaris of varying grades and to correlate these findings with available clinical data.

Materials and Methods

In this case-control study, 83 patients with acne vulgaris served as the case group, and 83 age- and gender-matched healthy subjects served as the control group.

Inclusion Standards

The following individuals were recruited to participate in the study after obtaining informed consent: patients presenting with acne vulgaris who had not received treatment for three months, had no history of skin resurfacing, and had not used oral isotretinoin in the previous six months.

Exclusion Standards

Exclusion criteria are as follows: patients with a history of diabetes mellitus; patients who are obese; females with polycystic ovary syndrome; patients with chronic or acute hepatitis; patients with liver cirrhosis; patients with benign or malignant tumours; patients with inflammatory bowel disease; patients with chronic pancreatitis; patients with cardiovascular diseases, autoimmune disorders, malignancy, or asthma; patients receiving drugs that cause acneiform eruptions; patients with a known history of lipid metabolic disorder or those taking drugs that affect lipid metabolism; subjects with acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), or any other cutaneous or fibrotic lesions.

Sample Size Calculation

A study proposing to evaluate the effect of TIMP-2 mRNA expression on acne vulgaris of varying severity, compared with healthy controls. A previous study showed that the distribution of the GC genotype for the TIMP-2 (-418 G/C) polymorphism differed between the patient and control groups, 14.8% vs. 33.3%, respectively.[10] Thus, the sample size for the current study, to detect a significant effect at $P < 0.05$ with 80% power was calculated using the following formula:

$$p = \frac{p_1 + rp_2}{1+r}$$

$$n \geq \frac{\left[Z_{1-\alpha/2}\sqrt{(r+1)p(1-p)} + Z_{1-\beta}\sqrt{rp_1(1-p_1)+p_2(1-p_2)}\right]^2}{r(p_2-p_1)^2}$$

In the above formula, Z1-α/2 = 1.96; β = 0.2; r = 1. So, n = 83. Thus, at least 166 individuals should be recruited for the study, with at least 83 in each group. n is the minimum sample size for the group. Z1-α/2 denotes the standardized value corresponding to the specified confidence level. At 95% confidence interval (CI), it is 1.96, and at 99% CI (1% type I error), it is 2.58. The sample consisted of 166 patients.

Consent to Participate and Ethics

Prior to the initiation of the study, ethical approval was obtained from the Research Ethics Committee, Institutional Review Board, Faculty of Medicine, Menoufia University (approval no: DERMA 27; approval date: 27 October 2022). The study was conducted in accordance with the principles of the Declaration of Helsinki. Cases were consecutively recruited from the Outpatient Clinic of Dermatology, Andrology and STDs at Menoufia University Hospitals. Each participant

provided written informed consent before the start of the study, which was approved by the Local Ethical Research Committee of Menoufia Faculty of Medicine. One of the patients' parents provided consent for the patients under the age of eighteen. Every enrolled patient underwent thorough history-taking and a detailed dermatological examination. Along with other clinical information, the following were gathered: onset, progression, lesion location, aggravating factors (food, stress, pregnancy, menstruation, sun exposure, etc.), and family history.

Clinical evaluation of the enrolled patients was performed in accordance with Nast et al.,[11] who assessed acne vulgaris as follows: the microcomedone gave rise to non-inflammatory lesions, including both closed (whiteheads) and open (blackheads) comedones. Inflammatory lesions were either deep or superficial. The terms papules and pustules refer to superficial inflammatory lesions measuring ≤ 5 mm in diameter. In more severe cases, lesions could progress to nodules or deep pustules.

Evaluation of Acne Vulgaris Severity

Acne vulgaris was categorized according to the method described by Tan.[12] Mild acne was defined as the presence of < 20 comedones, < 15 inflammatory lesions, or < 30 total lesions. Moderate acne was defined as 20–100 comedones, 15–50 inflammatory lesions, or a total lesion count of 30–125. Severe acne vulgaris was defined as the presence of more than five cysts, more than 100 comedones, more than 50 inflammatory lesions, or a total lesion count of more than 125.

Acne Vulgaris Lesion Scoring

The severity score is the result of adding up the six regional subscores, which are obtained by multiplying the factor for each region (two seconds for the forehead and cheeks, one second for the nose and chin, and three seconds for the chest and back) by the most severely weighted lesion within that region (1 for ≥ 1 comedone, 2 for ≥ 1 papule, 3 for ≥ 1 pustule, and 4 for ≥ 1 nodule). Global Acne Grading System (GAGS) scoring methodology was based on a quantitative scoring system.[13]

Sampling and Preparation

A total of 5 mL of venous blood was collected from each participant and divided into two aliquots. Accordingly, 3 mL was placed in a standard tube, allowed to clot for 30 minutes at room temperature, and then centrifuged for 10 minutes at 4,000 revolutions per minute. The serum was separated and stored for the determination of TIMP-2 (ng/mL) by enzyme-linked immunosorbent assay (ELISA). Additionally, 2 mL of blood was collected into a Vacutainer tube containing EDTA for mRNA extraction, and the extract was stored at -80 °C until the RT-PCR step.

Protein and Gene Analysis

Human serum TIMP-2 concentrations (ng/mL) were measured using the SUN RED (ST) ELISA kit (Shanghai). Quantitative real-time PCR was performed using the *TIMP-2* gene as the target and GAPDH as the housekeeping (reference) gene. We used the miRNeasy Mini preparations (catalogue number 217004, Qiagen, Germany) for whole RNA extraction, combining silica-membrane purification with phenol/guanidine-based lysis. A Thermo Scientific (USA) NanoDrop 2000 spectrophotometer, set to measure absorbance at 260 and 280 nm, was used to determine the RNA concentration. A high-capacity cDNA synthesis kit with an inhibitor (Thermo Fisher Scientific, Applied Biosystems, USA) was used for reverse transcription (RT) of RNA into cDNA. RT was conducted using 10 µL of RNA in a 20 µL reaction volume, and 2 µL of RT random primers, 2 µL of dNTP mix, 1 µL of RNase inhibitor, and 1 µL of reverse transcriptase MultiScribe, and 2 µL nuclease free water. Incubation was done in a 2720 thermal cycler (Applied Biosystems, Singapore), single cycle at 25 °C for 5 minutes, for 60 minutes at 42 °C, and 70 °C for 5 minutes.

The expression levels of TIMP2 and GAPDH were quantified by qRT-PCR. The TIMP-2 forward primer was 5′ ACCCTCTGTGACTTCATCGTGC 3′, and the TIMP-2 reverse primer was 5′ GGAGATGTAGCACGGGATCATG 3′. The GAPDH forward primer was 5′CTCTGCTCCTCCTGTTCGAC3′, and the GAPDH reverse primer was 5′ TTAAAAGCAGCCCTGGTGAC3′. Each reaction for each gene was performed in a final volume of 20 mL, 5 µL of nuclease-free water was used. 3 µL of cDNA mix. 10 µL mL SYBR Green 2x QuantiTect PCRMaster. One mL forward primer, 1 mL reverse primer. The mix was incubated at 94 °C for 3 min, followed by 60 cycles; denaturation at 94 °C for 30 s, for 40 s for annealing at 55 °C and extension at 72 °C for 31 s.

All experimental conditions were carefully controlled, and PCR amplification efficiency was verified. Comparable amplification efficiencies for the target and housekeeping genes were assumed. The melting curve was produced (Figures 1 and 2). Higher Ct values were associated with

***TIMP-2* expression = $2^{-\Delta\Delta Ct}$**	
ΔΔCt =	**ΔCt Acne vulgaris sample-ΔCt control sample**
ΔCt acne vulgaris sample =	Ct (*TIMP-2* mRNA)–Ct (*GAPDH* mRNA)
ΔCt control =	Ct (*TIMP-2* mRNA)–Ct (*GAPDH* mRNA)

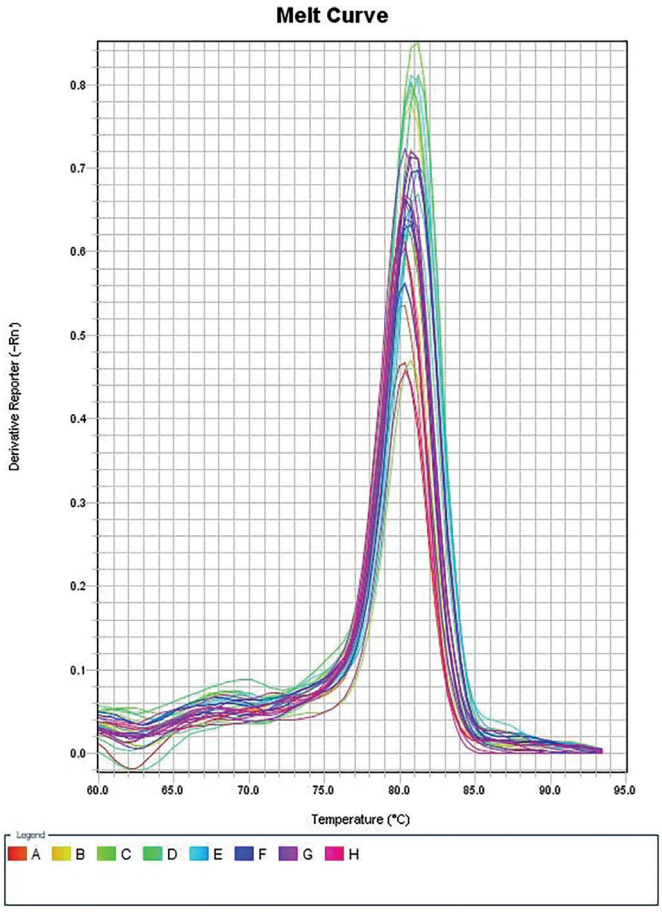

Figure 1. Melting curve of GAPDH

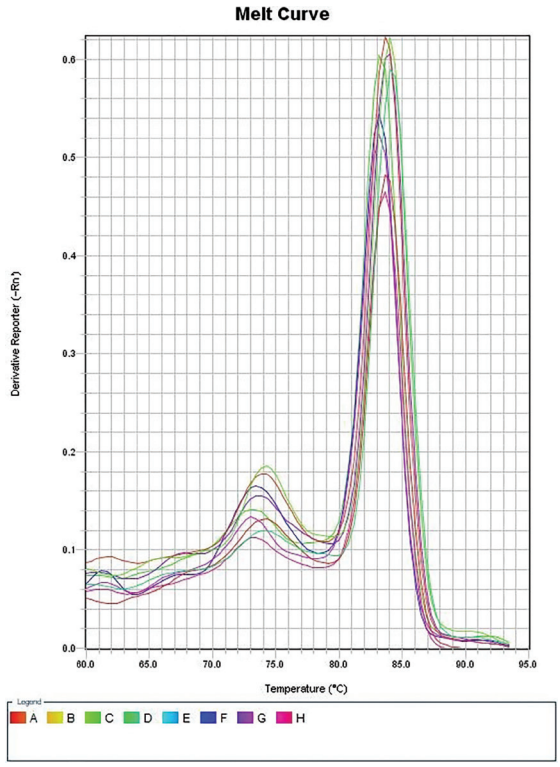

Figure 2. Melting curve of TIMP-2
TIMP-2: Tissue inhibitor of metalloproteinase-2

lower RNA levels. The relative quantification values for each unique gene were determined using the $2^{-\Delta\Delta Ct}$ formulation[14] in the following manner:

TIMP-2 expression = $2^{-\Delta\Delta Ct}$	
ΔΔCt =	ΔCt Acne vulgaris sample - ΔCt Control sample
ΔCt acne vulgaris sample =	Ct (*TIMP-2* mRNA) – Ct (*GAPDH* mRNA)
ΔCt control =	Ct (*TIMP-2* mRNA) – Ct (*GAPDH* mRNA)

Statistical Analysis

For the statistical analysis, an IBM personal computer running the statistical programs Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and SPSS version 20.0 (IBM Corp., Armonk, NY, USA) was used. Descriptive statistics were performed as follows: categorical data were presented as numerical counts (N) and percentages (%), and quantitative data were presented as mean (X), range, and standard deviation (SD). Among the analytical procedures employed were the Spearman correlation coefficient test (r), the Mann–Whitney U test (U), the chi-square test (X^2), and the Kruskal–Wallis test (K). At $P \leq 0.05$, the significance threshold was applied.

Results

This case-control study included 35 males (42.2%) and 48 females (57.8%). Ages ranged from 16 to 28 years, with 20.82 ± 2.69 years for the mean ± SD value. Controls consisted of 35 (42.2%) males and 48 (57.8%) females, with ages ranging from 16 to 28 years. Mean ± SD value was 20.82 ± 2.69 years.

Clinical information for the studied cases of acne vulgaris is presented in Table 1.

Appraisal of Mean Serum TIMP-2 Level and Mean Expression Level of *TIMP-2* Gene Between Patients and Control Subjects

Upon studying the mean serum level of TIMP-2 and the mean expression level of the *TIMP-2* gene, there were statistically significant differences, both being higher in cases (63.58 ± 29.80 ng/mL) than in control subjects (22.36 ± 7.88 ng/mL) ($P < 0.001$ for both) (Table 2).

Relationship Between the Mean Serum Level of TIMP-2 (ng/mL) and Clinical Information of the Studied Patients

A significant association between the mean serum TIMP-2 level (ng/mL) and aggravating factors such as sun exposure (*P*

= 0.018) was observed. Additionally, significant relationships were found between the mean serum TIMP-2 level (ng/mL) and acne lesions on the back ($P < 0.001$) and chest ($P = 0.001$), NAST classification ($P < 0.001$), disease severity ($P = 0.01$), and GAGS grade ($P < 0.001$) (Table 3).

Table 1. Clinical facts of studied patients (n = 83)

Studied variables		n	%
Onset	Gradual	56	67.5
	Acute	27	32.5
Disease course	Progressive	49	59.0
	Stationary	34	41.0
Duration/years	Range	1.0–6.0	
	$\bar{x} \pm SD$	3.14 ± 1.34	
Family history	Positive	44	53.0
	Negative	39	47.0
Site	Face	83	100.0
	Back	63	75.9
	Chest	22	26.5
Aggravating factor	No	25	30.1
	Yes[#]	58	69.9
	Spicy food	21	25.3
	Sun	35	42.2
	Stress	52	62.7
	Menses	36	43.3
NAST classification	Non-inflammatory	36	43.4
	Inflammatory	47	56.6
Disease severity	Mild	27	32.5
	Moderate	28	33.7
	Severe	28	33.7
GAGS grade	Mild	36	43.4
	Moderate	24	28.9
	Severe	23	27.7
GAGS score	Min–max	6.0–37.0	
	X ± SD	18.89 ± 10.13	
	Median (IQR)	21.0 (9.0–31.0)	

X: Mean, n: Number, %: Percentage, [#]: More than one answer, SD: Standard deviation, IQR: Interquartile range, GAGS: Global Acne Grading System

Correlation Between Serum TIMP-2 (ng/mL) and Age of Cases in Years, Disease Duration in Years, GAGS Score, and *TIMP-2* Gene Expression

There were statistically significant positive correlations between mean serum TIMP-2 level (ng/mL) and duration of disease in years (r = 0.265, $P = 0.015$), GAGS score (r = *0.852), P < 0.001,* and *TIMP-2* gene expression level (r = 0.695), $P < 0.001$ (Figure 3a-c).

Relationship Between Mean *TIMP-2* Gene Expression Level and Clinical Information of the Studied Patients

Significant associations were observed between the mean expression level of the *TIMP-2* gene and (1) acne lesions on the chest ($P = 0.031$), (2) NAST classification ($P < 0.001$), and (3) GAGS grade ($P < 0.001$) (Table 4).

Correlation Between *TIMP-2* Gene Expression and Age of Cases in Years, Disease Duration in Years, and GAGS Score

Significant positive correlations were observed between *TIMP-2* gene expression and duration of disease in years (r = 0.286, $P = 0.009$), and between *TIMP-2* gene expression and GAGS score (r = 0.672, $P < 0.001$) (Figure 4a and b respectively).

ROC Curve for Serum TIMP-2 (ng/mL) and Expression of the *TIMP-2* Gene to Distinguish Cases from Control Subjects

For serum TIMP-2 (ng/mL), the receiver operating characteristic (ROC) curve showed a cut-off value of ≥ 31, with a sensitivity of 92.77%, specificity of 80.72%, and an area under the curve (AUC) of 0.969, which was statistically significant ($P < 0.001$). In comparison, *TIMP-2* gene expression at a cut-off value of ≥ 1.5 had a sensitivity of 93.98% and specificity of 100.0%. The AUC was 0.996 (*P*

Table 2. Evaluation of serum TIMP-2 (ng/mL) and *TIMP-2* gene expression levels between cases and controls

	Cases (n = 83)	Controls (n = 83)	U	*P*
Serum TIMP-2 (ng/mL)				
Min–max	30.0–120.0	7.50–34.0	213.000*	< 0.001*
Mean ± SD	63.58 ± 29.80	22.36 ± 7.88		
Median (IQR)	47.0 (43.0–88.0)	22.0 (17.0–31.0)		
***TIMP-2* gene**				
Min–max	1.35–6.80	0.52–1.50	25.000*	< 0.001*
Mean ± SD	3.74 ± 1.51	1.02 ± 0.23		
Median (IQR)	3.20 (2.80–4.0)	1.0 (0.86–1.17)		

SD: Standard deviation, IQR: Interquartile range, U: Mann–Whitney test, *P*: For comparison between diverse groups, TIMP-2: Tissue inhibitor of metalloproteinase-2, Min-max: Minimum-maximum
*: $P \leq 0.05$ is the level of significance

Table 3. Relationship between serum TIMP-2 (ng/mL) and clinical data of the studied cases (n = 83)

	n	Serum TIMP-2 (ng/mL)		Test of sig.	*P*
		X ± SD	Median (min–max)		
Sex					
Male	**35**	63.84 ± 29.19	47.0 (31.0–112.0)	U = 815.500	0.821
Female	**48**	63.39 ± 30.54	47.0 (30.0–120.0)		
Onset					
Gradual	**56**	64.76 ± 30.62	47.0 (30.0–120.0)	U = 748.0	0.938
Acute	**27**	61.15 ± 28.42	47.0 (31.0–112.0)		
Course					
Stationary	**34**	59.87 ± 30.79	44.50 (30.0–112.0)	U = 673.50	0.139
Progressive	**49**	66.16 ± 29.13	60.0 (31.0–20.0)		
Aggravating factor					
No	**25**	53.98 ± 25.58	44.0 (31.0–110.0)	U = 545.50	0.074
Yes[#]	**58**	67.72 ± 30.73	53.0 (30.0–120.0)		
Spicy food	**21**	59.66 ± 30.02	45.0 (31.0–120.0)	U = 581.50	0.466
Sun	**35**	73.26 ± 32.03	87.0 (30.0–120.0)	U = 585.0*	0.018*
Stress	**52**	67.98 ± 30.56	53.0 (30.0–120.0)	U = 606.0	0.059
Menses'	36	68.28 ± 30.32	59.50 (30.0–120.0)	U=707.50	0.202
Family history					
No	**39**	69.18 ± 29.96	60.0 (30.0–120.0)	U = 669.0	0.084
Yes	**44**	58.63 ± 29.10	45.0 (31.0–120.0)		
Site[#]					
Face	**83**	63.58 ± 29.80	47.0 (30.0–120.0)	–	–
Back	**63**	70.12 ± 29.93	60.0 (30.0–120.0)	U = 231.0*	< 0.001*
Chest	**22**	78.27 ± 27.30	86.0 (45.0–120.0)	U = 358.50*	0.001*
NAST classification					
Non-inflammatory	**36**	38.55 ± 5.89	39.50 (30.0–47.0)	U = 24.0*	< 0.001*
Inflammatory	**47**	82.76 ± 26.28	88.0 (45.0–120.0)		
Disease severity					
Mild	**27**	54.67 ± 30.36	43.0 (31.0–120.0)	K = 9.247*	0.010*
Moderate	**28**	67.16 ± 32.46	48.25[a] (30.0–112.0)		
Severe	**28**	68.61 ± 25.24	60.0[a] (43.0–120.0)		
GAGS grade					
Mild	**36**	38.55 ± 5.89	39.50 (30.0–47.0)	K = 64.475*	< 0.001*
Moderate	**24**	66.48 ± 18.01	60.0[a] (45.0–90.0)		
Severe	**23**	99.74 ± 22.68	110.0[ab] (47.0–120.0)		

SD: Standard deviation, GAGS: Global Acne Grading System, U: Mann–Whitney test, TIMP-2: Tissue inhibitor of metalloproteinase-2, K: Kruskal–Wallis test, *P*: For comparison between diverse groups using a post-hoc test (Dunn's test with Bonferroni adjustment for multiple comparisons) n: Number, *P*: For comparison between diverse groups
*: $P \leq 0.05$ is the level of significance, X: Mean
[a]: Significance with mild, [b]: Significance with moderate

< 0.001), indicating a significant ability to distinguish acne vulgaris cases from controls (Figure 5a).

ROC Curve for Serum TIMP-2 (ng/mL) and *TIMP-2* Gene Expression to Discriminate Disease Severity

A ROC curve was applied to serum TIMP-2 (ng/mL) and *TIMP-2* gene expression to determine their sensitivity and specificity for stratifying disease severity. Serum TIMP-2 at a cut-off value of ≥ 47 had a sensitivity of 60.71% and specificity of 61.82%. The AUC was 0.645, with a statistically significant result ($P = 0.031$). In comparison, *TIMP-2* gene expression at a cut-off value of ≥ 3.1 had a sensitivity of 50.0% and specificity of 49.09%. The AUC was 0.548, which was not statistically significant ($P = 0.479$) (Figure 5b).

Discussion

Acne vulgaris is an inflammatory skin disorder that affects the pilosebaceous unit. It may present as non-inflammatory lesions, inflammatory lesions, or a combination of both. The pathogenesis of acne is multifactorial and involves several factors: *C. acnes* activity, excess sebum production, and follicular hyperproliferation.[15]

Table 4. Relationship between mean *TIMP-2* gene expression level and clinical data of the studied cases (n = 83)

	n	*TIMP-2* gene		Test of sig.	*P*
		Mean ± SD	Median (min–max)		
Sex					
Male	**35**	3.86 ± 1.47	3.40 (1.35–6.50)	U = 753.500	0.423
Female	**48**	3.64 ± 1.56	3.05 (1.35–6.80)		
Onset					
Gradual	**56**	3.87 ± 1.48	3.20 (1.35–6.80)	U = 625.0	0.201
Acute	**27**	3.46 ± 1.57	3.0 (1.35–6.50)		
Course					
Stationary	**34**	3.70 ± 1.63	3.05 (1.35–6.80)	U = 795.0	0.724
Progressive	**49**	3.76 ± 1.44	3.20 (1.35–6.60)		
Aggravating factor					
No	**25**	3.46 ± 1.26	3.20 (1.35–6.50)	U = 643.0	0.413
Yes[#]	**58**	3.85 ± 1.61	3.15 (1.35–6.80)		
Spicy food	**21**	3.79 ± 1.57	3.20 (1.35–6.60)	U = 650.0	0.992
Sun	**35**	4.09 ± 1.81	3.10 (1.35–6.60)	U = 745.50	0.381
Stress	**52**	3.87 ± 1.65	3.05 (1.35–6.80)	U = 725.0	0.444
Menses	**36**	3.74 ± 1.68	3.15 (1.35–6.80)	U = 840.0	0.956
Family history					
No	**39**	3.87 ± 1.42	3.40 (1.35–6.50)	U = 721.0	0.209
Yes	**44**	3.62 ± 1.60	3.0 (1.35–6.80)		
Site[#]					
Face	**83**	3.74 ± 1.51	3.20 (1.35–6.80)	–	–
Back	**63**	3.92 ± 1.62	3.40 (1.35–6.60)	U = 463.50	0.075
Chest	**22**	4.18 ± 1.71	4.0 (1.35–6.50)	U = 462.50*	0.031*
NAST classification					
Non-inflammatory	**36**	2.86 ± 0.31	2.80 (2.30– 3.40)	U = 276.0*	< 0.001*
Inflammatory	**47**	4.41 ± 1.72	4.0 (1.35–6.80)		
Disease severity					
Mild	**27**	3.52 ± 1.26	3.0 (2.30–6.50)	K = 1.081	0.583
Moderate	**28**	3.90 ± 1.71	3.30 (1.35–6.60)		
Severe	**28**	3.78 ± 1.56	3.50 (1.35–6.80)		
GAGS grade					
Mild	**36**	2.86 ± 0.31	2.80 (2.30–3.40)	K = 48.799*	< 0.001*
Moderate	**24**	3.08 ± 1.0	3.10 (1.35–4.0)		
Severe	**23**	5.80 ± 1.08	6.30[ab] (3.40–6.80)		

SD: Standard deviation, U: Mann–Whitney test, TIMP-2: Tissue inhibitor of metalloproteinase-2, K: Kruskal–Wallis test, GAGS: Global Acne Grading System, Pairwise comparison bet. every 2 groups were done using post-hoc test (Dunn's test with Bonferroni adjustment for multiple comparisons)
n: Number, *P*: For comparison between diverse groups
*: $P \leq 0.05$ is the level of significance; X: Mean
[a]: Significance with mild, [b]: Significance with moderate

MMP-2 is a Zn+2-dependent endoproteinase that is involved in the disruption of sebaceous glands.[16] TIMP-2 is a unique inhibitor within the TIMP family that inhibits the proteolytic activity of MMP-2.[17]

The balance between TIMPs and MMPs controls the modification of the extracellular matrix and the imbalance between them may lead to the development of acne and other inflammatory disorder.[5]

Although TIMP-2 is classically recognized as an inhibitor of MMP-2, its increased expression may represent a compensatory response to enhanced extracellular matrix remodeling and inflammation associated with acne pathogenesis. Elevated TIMP-2 levels may reflect an attempt to counterbalance increased MMP activity and limit tissue damage during chronic inflammatory processes. Furthermore, TIMP-2 has been reported to exert biological functions beyond MMP inhibition, including regulation of cell proliferation, apoptosis, and tissue

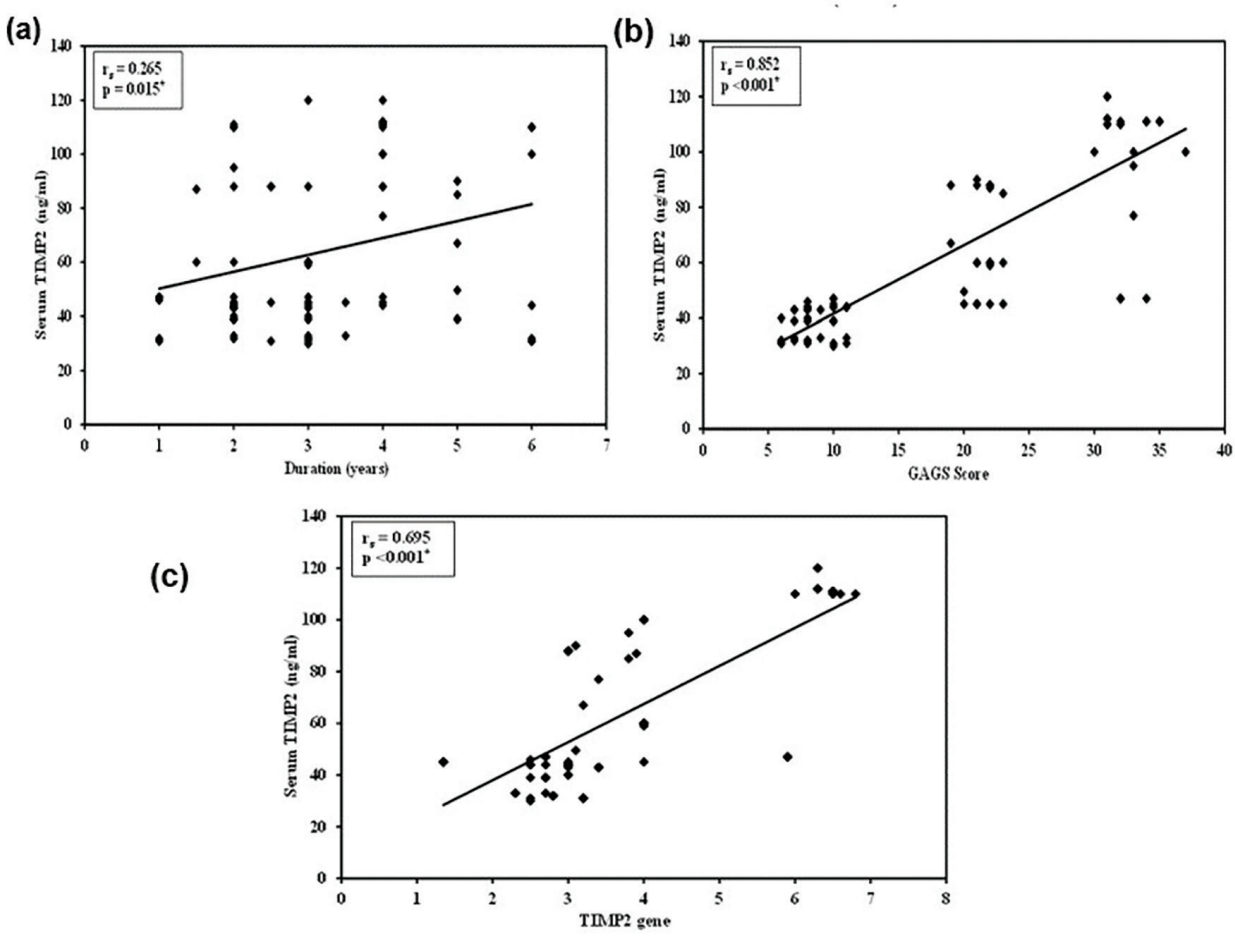

Figure 3. Correlation between serum TIMP-2 (ng/mL) and disease duration in years (r = 0.265, *P* = 0.015) (a), GAGS score (r = 0.852), (b) and serum *TIMP-2* level (r = 0.695), (*P* < 0.001 for both) and *TIMP-2* gene expression (c)
TIMP-2: Tissue inhibitor of metalloproteinase-2, GAGS: Global Acne Grading System

remodeling. Therefore, increased circulating TIMP-2 may serve as a marker of ongoing inflammatory and remodeling events rather than a direct pathogenic factor.[18]

The elevated serum TIMP-2 levels and gene expression observed in patients with acne vulgaris may represent a compensatory regulatory response to the inflammatory and extracellular matrix remodeling processes associated with the disease. As TIMP-2 is a major endogenous inhibitor of MMP-2 and plays an important role in maintaining extracellular matrix homeostasis, its upregulation may reflect an attempt to counterbalance increased proteolytic activity and tissue remodeling during inflammation. Similar regulatory functions of TIMP-2 have been described in several inflammatory and tissue-remodeling conditions.[19] Beyond its inhibitory activity against MMPs, TIMP-2 contributes to tissue homeostasis through MMP-independent mechanisms, including the regulation of cellular proliferation, angiogenesis, and tissue remodeling. Therefore, increased TIMP-2 expression may also reflect a broader protective response to ongoing inflammatory processes.[20] However, MMP-2 levels were not measured in the current study. Consequently, the proposed compensatory role of TIMP-2 cannot be directly confirmed, and our findings should be interpreted as demonstrating an association between increased TIMP-2 levels and acne severity rather than establishing a causal mechanism. Future studies that evaluate both TIMP-2 and MMP-2 are warranted to clarify their interaction in the pathogenesis of acne vulgaris.

Papakonstantinou et al.[21] investigated the expression of MMPs and their inhibitors in the facial sebum of patients with acne, both before and after isotretinoin treatment, and documented the presence of TIMP-2 in the sebum of acne patients, which was not influenced by isotretinoin treatment. Other studies investigated TIMP-2 tissue expression in acne patients, including Saint-Jean et al.[22] which found that TIMP-2 expression was significantly stronger in papules of patients prone to acne scars compared to patients not prone to scars.

The expression of TIMP-2 was studied only in sebum and tissue cultures, but not in the blood of acne vulgaris

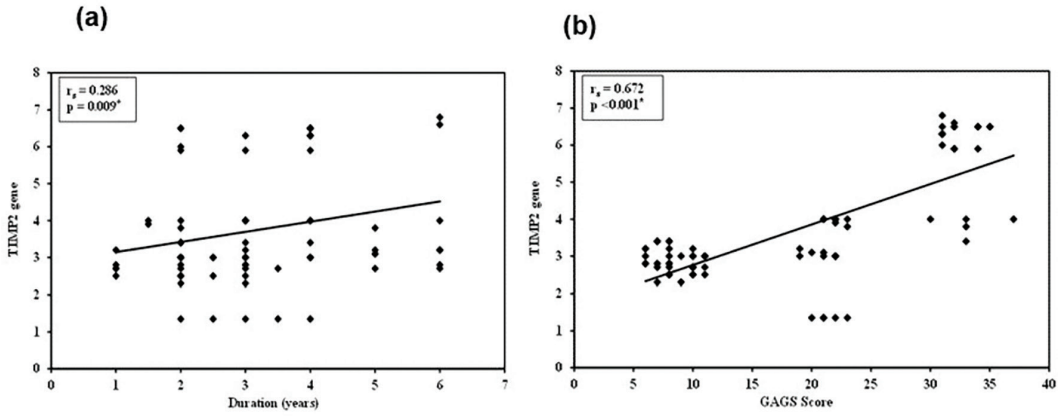

Figure 4. Correlation between *TIMP-2* gene expression and disease duration in years (a) (r = 0.286), and GAGS score (b) (r = 0.672)
TIMP-2: Tissue inhibitor of metalloproteinase-2, GAGS: Global Acne Grading System

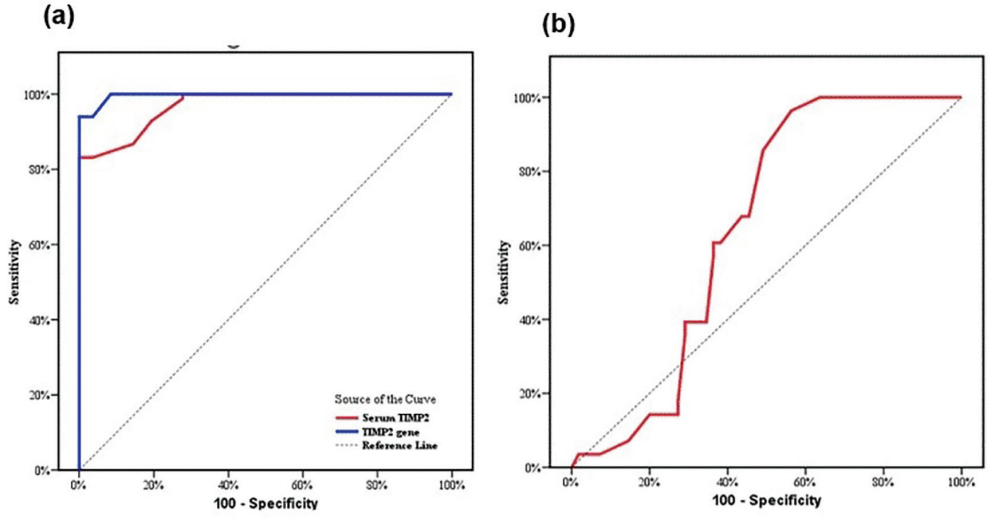

Figure 5. (a) ROC curve for serum TIMP-2 (ng/mL) and *TIMP-2* gene expression to discriminate cases from controls. (b) ROC curve for serum TIMP-2 and *TIMP-2* gene expression to discriminate disease severity
ROC: Receiver operating characteristic, TIMP-2: Tissue inhibitor of metalloproteinase-2

patients,[21,22] whereas the current study aimed to assess serum TIMP-2 levels in cases of acne vulgaris to better understand its role in acne vulgaris etiopathogenesis.

This study found that mean serum TIMP-2 levels were significantly higher in acne vulgaris patients than in control subjects. Indeed, a significant relationship between the mean serum TIMP-2 level and aggravating factors, such as sun exposure and pregnancy, was observed.

This may be explained by the rising TIMP-2 level, which decreases MMP-2. Gao et al.[16] stated that there may be an increase in proinflammatory cytokine production leading to systemic inflammation if MMP-2 activity declines below baseline. Additionally, they reported that lipid dysregulation, including decreased liver X receptor-α levels and increased hepatic triglyceride production, was caused by MMP-2 deficiency, and that similar dysregulation was also reported in acne.

The concentration of TIMP-2 is higher in acne lesions on the back and chest. Dagnelie et al.[23] reported that cases with acne on the back exhibit a loss of *C. acnes* phylotypes, particularly phylotype IA1, thereby activating innate immunity. Saint-Jean et al.[22] documented a distinct innate immunity profile in the normal skin of back acne patients with and without acne scars. In patients who developed scars, considerable overexpression of TLR-4, interleukin (IL)-2, IL-10, TIMP-2, and the transcription factor JUN, alongside decreased MMP-9 protein levels, was observed.

The results of this investigation showed significant positive correlations between mean serum TIMP-2 levels and both disease duration (years) and NAST classification; TIMP-2

serum levels were significantly higher among patients with prolonged disease duration and inflammatory lesions. This finding was consistent with Gao et al.,[16] who confirmed that inhibited MMP-2 activity may lead to overexpression of IL-1α and β, tumor necrosis factor-α, and triglycerides, thus promoting inflammation and lipid dysregulation in acne.

The current study supported the use of TIMP-2 as a marker for the diagnosis of acne vulgaris, with a cut-off value of ≥ 31, yielding a sensitivity of 92.77%, specificity of 80.72%, and an AUC of 0.969, with a statistically significant result ($P < 0.001$). It can also be used to detect the severity of acne vulgaris, as serum TIMP-2 shows significant diagnostic performance in discriminating between severe and mild/moderate disease at a cut-off of ≥ 47, with a sensitivity of 60.71% and specificity of 61.82%. AUC was 0.645 with a statistically significant result ($P = 0.031$)

This suggests that acne patients with high TIMP-2 levels are more likely to develop severe, extensive disease and scarring. Chuah and Goh[24] suggested that predicting the susceptibility to severe acne is very important, as early treatment is easier and prevents the serious side effects of post-acne scarring.

Many studies have investigated the *TIMP*-2 gene polymorphism in acne vulgaris. Yaykasli et al.[10] documented twofold higher expression of the *TIMP-2-418CC* genotype in cases with acne vulgaris.

Furthermore, Gao et al.[16] conducted a study of the Chinese population and found no significant correlation between the TIMP-2-41/C polymorphism and acne vulgaris. Gupta et al.[25] found no evidence of increased risk of acne or atrophic post-acne scars associated with the TIMP-2 nucleotide polymorphism (rs8179090).

Moreover, *TIMP-2* mRNA expression is associated with many skin disorders, including psoriasis,[26] systemic lupus erythematosus,[27] non-melanoma skin cancer,[28] and oral lichen planus.[29] However, the association between *TIMP-2* mRNA expression and the occurrence of acne vulgaris has not been studied to date.

The current study showed a significant difference between patients with acne vulgaris and control subjects, with *TIMP-2* gene expression levels higher in patients than in control subjects.

The results of the present study showed significant associations between mean *TIMP-2* gene expression levels and acne lesions on the chest, NAST classification, and disease duration (years), with higher levels observed in patients with chest lesions, inflammatory acne, and longer disease duration.

The current study supported the use of *TIMP-2* gene expression as a marker for the diagnosis of acne vulgaris, with a cut-off value of ≥ 1.5, demonstrating 93.98% sensitivity and 100.0% specificity. The AUC was 0.996, which was statistically significant.

A significant positive correlation was observed between the mean serum TIMP-2 level and *TIMP-2* gene expression. The *TIMP-2* gene encodes the TIMP-2 protein; therefore, increased expression of the *TIMP-2* gene results in higher levels of its protein product.

In the current study, the mean serum TIMP-2 level was significantly associated with disease severity, GAGS grade, and score. Indeed, a significant positive correlation between *TIMP-2* gene expression and GAGS grade and score was documented.

Both *TIMP-2 gene* expression and serum levels were higher in patients with severe acne, defined by a high GAGS score using lesion type rather than lesion count. This finding can be explained by the likelihood that acne lesions may leave permanent scars, which increases with the depth of the inflammatory process.[30] In line with this finding, Wen et al.[31] revealed that the risk of acne scarring was associated with *TIMP-2* (rs4789932).

Study Limitations

The current study has some limitations. First, MMP-2 levels were not assessed; therefore, the functional relationship between TIMP-2 and MMP-2 could not be directly investigated. Second, the case-control design precludes establishing causal relationships between elevated TIMP-2 levels and acne development or progression. Future longitudinal studies incorporating simultaneous measurement of TIMP-2 and MMP-2 are recommended to clarify the underlying mechanisms.

Conclusion

The present study demonstrated that both serum TIMP-2 levels and *TIMP-2* gene expression are significantly elevated in patients with acne vulgaris compared with healthy individuals. Furthermore, the positive correlations of serum TIMP-2 levels and its gene expression with acne severity scores (GAGS and NAST classification) suggest a probable role for TIMP-2 in the pathogenesis and progression of acne vulgaris. These findings indicate that TIMP-2 may serve as a useful biomarker of disease activity and severity, highlighting its potential utility in the evaluation and management of acne vulgaris. Further studies are warranted to elucidate the underlying mechanisms and explore its potential as a therapeutic target.

Ethics

Ethics Committee Approval: Prior to the initiation of the study, ethical approval was obtained from the Research Ethics Committee, Institutional Review Board, Faculty of Medicine, Menoufia University (approval no: DERMA 27; approval date: 27 October 2022). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Each participant provided written informed consent before the start of the study, which was approved by the local research ethics committee. One of the patients' parents provided consent for the patients under the age of eighteen.

Authorship Contributions

Design: W.S., M.B., Data Collection or Processing: M.A.E-K., Analysis or Interpretation: S.E., S.S.E., Literature Search: M.A.E-K., Writing: S.E., S.S.E.

Footnotes

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

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Original Article

The Silent Sound of Hair Loss: Heat Shock Protein 70 (HSP-70), Hearing Sensitivity, and Alopecia Areata

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Abstract

Aim: This cross-sectional investigation aimed to delineate the role of circulating heat shock protein 70 (HSP-70) in alopecia areata (AA) pathogenesis, to assess its correlation with disease severity, and to evaluate its potential association with auditory function.

Materials and Methods: A cohort comprising 30 AA patients and 30 matched, healthy, AA-free subjects underwent comprehensive assessment. Circulating HSP-70 levels were quantified using enzyme-linked immunosorbent assay, and the Severity of Alopecia Tool (SALT) score was used to objectively assess AA severity. Audiological integrity was evaluated through pure-tone audiometry across standard frequencies. The predictors of AA were identified using multivariate logistic regression.

Results: Revealed a statistically significant elevation of serum HSP-70 in AA patients compared to controls (2.5 ± 0.8 ng/mL vs. 1.3 ± 0.6 ng/mL; $P < 0.001$). Furthermore, AA patients exhibited significantly higher mean auditory thresholds across various frequencies; however, the clinical significance of these differences requires further investigation. Receiver operating characteristic analysis demonstrated robust diagnostic utility for HSP-70, with an area under the curve of 0.847 ($P < 0.001$) and an optimal diagnostic threshold exceeding 1.4 ng/mL. Multivariate analysis indicated that each unit increase in HSP-70 was associated with ninefold higher odds of AA (odds ratio = 9.213, $P < 0.001$). A positive correlation was observed between HSP-70 levels and disease duration (r = 0.504, $P = 0.004$), although no significant associations were found between HSP-70 levels and SALT score or auditory thresholds.

Conclusion: Elevated HSP-70 levels show promise as a biomarker for AA and correlate with disease chronicity. Further research is imperative to elucidate HSP-70's mechanistic contributions to AA pathogenesis and its nuanced relationship with auditory function.

Keywords: Alopecia areata, biomarker, hearing sensitivity, heat shock protein 70, pure-tone audiometry

Introduction

Alopecia areata (AA) is a prevalent immune-triggered disorder with well-defined non-scarring areas of hair loss on different body areas-preferentially scalp and beard- as typical presentations.[1] Nail abnormalities, including pitting and trachyonychia, may also be present.[2]

AA has been associated with various etiological factors, including genetic predisposition, immunological reactions, and oxidative damage. Among these, disturbance of the hair follicular immune privilege is considered a significant pathogenic mechanism, with melanocyte-associated autoantigens serving as the main immunological targets.[3]

Melanocytes are vital for maintaining endocochlear potential, controlling inner hair cell function, and protecting against free radical damage. Similar to hearing loss observed in vitiligo, which may arise from melanocyte depletion, the immune-

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triggered, melanocyte-related pathogenic mechanisms in AA may be associated with sensorineural hearing loss (SNHL). Scant literature comments on a link between AA and hearing loss.[4,5]

Heat shock proteins (HSPs) are a class of proteins that are produced in response to a variety of stimuli, such as heat, toxins, heavy metals, or infections. They play an important role in protecting cells from stress by assisting in the proper packaging of other proteins and are therefore commonly known as molecular chaperones. HSPs accumulate in numerous diseases and malignancies.[6]

Among the various HSP families, heat shock protein 70 (HSP-70) has received particular attention due to its dual role in maintaining cellular homeostasis and modulating immune responses. Intracellularly, depending on their location, HSP-70 fights stress-induced damage and promotes protein production and transfer and inhibits protein folding errors and instability. Extracellularly, or when anchored to the cell surface, HSP-70 plays an important role in activating immunological responses.[6]

This study aims to investigate circulating levels of HSP-70 in patients with AA, to explore its relationship with disease severity, to assess its potential association with audiological abnormalities in these patients, and to generate hypotheses for future research.

Materials and Methods

Design and Population

This cross-sectional study included 60 participants: 30 patients with clinically diagnosed and dermoscopically confirmed AA and 30 matched AA-free controls. The study was conducted over six months, from October 2023 to March 2024. The Benha University Research Ethics Committee approved the protocol (approval number: Ms 17-10-2023, approved on October 17, 2023; final document issued: 29.12.2024), and all subjects provided signed informed consent prior to participation.

Eligibility Criteria

Patients of both genders aged 18 years or older who were clinically diagnosed with AA and had the diagnosis confirmed through dermoscopic examination were included.

Excluded participants were those who had any condition associated with hearing loss from known causes, including acoustic neuroma, central lesions, Meniere's disease, multiple sclerosis, drug or noise exposure, or prior ear surgery. Additional exclusion criteria included the presence of dermatological conditions other than AA; systemic or autoimmune disorders; cardiovascular or cerebral ischemic heart disease; recent use (within the past month) of antibiotics, hormonal medications, compounds containing nitric oxide, or heavy metals; and non-epithelial cancers, such as ovarian, breast, lung, or pancreatic cancer.

Participants were stratified into two equal groups: a patient group comprising individuals diagnosed with AA, and a control group of AA-free volunteers matched for age (P = 0.161) and gender (P = 0.165).

All patients in this study will undergo the following:

History and Clinical Examination

All patients underwent detailed history-taking, including personal information, disease characteristics, and family history of AA; this was followed by a comprehensive clinical examination to exclude other dermatological conditions and to assess the site, number, and size of alopecia patches.

Dermoscopic evaluation of scalp patches was performed using a DermLite® 4 dermoscope (California, USA), and images were documented. AA severity was determined using the Severity of Alopecia Tool (SALT) score,[7] which quantifies hair loss in four scalp regions, with scores measured visually and corroborated by photographic analysis.

Hearing Assessment

Pure-tone audiometry (PTA) was used to assess hearing thresholds in patients and controls. To minimize bias, audiologists were blinded to the group status (AA patient vs. control) during the assessments. This was conducted in a soundproof cabin using a Resonance R37A audiometer (Italy) with frequencies ranging from 250–8000 Hz. Air-conduction thresholds were measured in both ears. Bone conduction audiometry was not performed because the primary aim was to assess overall hearing sensitivity in relation to AA; air conduction thresholds are sufficient for this initial screening. Pure-tone averages were calculated using thresholds at 500, 1000, and 2000 Hz. Hearing loss was defined as a threshold of ≥ 26 dB, categorized as hypoacusis.

Serum HSP-70 Analysis

Venous blood samples were collected from all participants under aseptic conditions and allowed to clot at room temperature for 15–20 minutes. Samples were then centrifuged at 3000 rpm for 20 minutes to separate serum, which was aliquoted into sterile Eppendorf tubes and stored at –70 °C until analysis. Hemolyzed samples were excluded. Serum levels of total HSP-70 were measured using a human HSP-70 enzyme-linked immunosorbent assay kit (Catalogue

No. 201-12-1814; SunRed Biological Technology Co., Ltd., Shanghai, China) according to the manufacturer's instructions in the Clinical and Chemical Pathology Department. This kit measures total HSP-70 (both constitutive and inducible forms).

Sample Size Calculation

Sample size was calculated using G*Power software version 3.1.9.2, based on a previous study by Ghaderi,[8] which investigated serum HSP-70 levels in patients with AA. The study reported a large effect size (d) for differences in HSP-70 between patients with AA and controls. The effect size from Ghaderi[8] was chosen due to its direct relevance to HSP-70 levels in AA patients, providing a comparable basis for our power calculation. The alpha level and statistical power were set at 0.05 and 0.8, respectively.

Statistical Analysis

SPSS version 28 (IBM, Armonk, NY, USA) was employed for statistical analysis. Parametric data were expressed as mean ± standard deviation (SD), non-parametric data as median and interquartile range, and categorical data as frequencies and percentages. HSP-70's diagnostic performance was evaluated using receiver operating characteristic (ROC) analysis, which yielded area under the curve (AUC) values, cut-off points, and diagnostic indices. Multivariate logistic regression analysis was used to identify determinants of alopecia and to estimate odds ratios (ORs) with 95% confidence intervals (CIs). A P-value of < 0.05 was used to define statistical significance.

Results

All AA patients (n = 30) exhibited a sudden onset and a gradual course, with a median disease duration of 18 months, ranging from 5 to 48 months. No patients had nail involvement, a history of medication use, a positive family history, or any associated diseases. Regarding the SALT score, S2 exhibited the highest percentage, 36.7% (n = 11), followed by S1 and S3, each 26.7% (n = 8). S4 had the lowest representation, accounting for only 10.0% (n = 3). Dermoscopic findings revealed that all participants in the study (100%) exhibited yellow dots, black dots, and exclamation mark hairs. The majority (73.3%) showed vellus hair, while 90% displayed broken hair. This high prevalence of characteristic dermoscopic signs likely reflects our stringent inclusion criteria, which focused on patients with active AA and may have introduced selection bias. We acknowledge that this might not fully represent the spectrum of dermoscopic findings across all AA patients.

In the right ear, patients showed significantly higher mean auditory thresholds at 250 Hz (30 ± 6 vs. 22 ± 3, $P < 0.001$), 500 Hz (26 ± 8 vs. 21 ± 4, $P = 0.003$), 1000 Hz (22 ± 3 vs. 20 ± 4, $P = 0.047$), 4000 Hz (25 ± 12 vs. 17 ± 6, $P = 0.002$), and 8000 Hz (25 ± 9 vs. 17 ± 5, $P = 0.002$). In the left ear, significant differences were noted at 250 Hz (27 ± 6 vs. 22 ± 2, $P < 0.001$), 500 Hz (27 ± 7 vs. 20 ± 4, $P < 0.001$), 1000 Hz (22 ± 4 vs. 20 ± 4, $P = 0.029$), 2000 Hz (23 ± 8 vs. 16 ± 5, $P < 0.001$), 4000 Hz (22 ± 7 vs. 17 ± 7, $P = 0.005$), and 8000 Hz (21 ± 7 vs. 18 ± 3, $P = 0.042$). A total of 15 AA patients exhibited auditory thresholds exceeding 26 dB, indicating hypoacusis (Table 1, Figure 1A and B).

Table 1. Auditory thresholds in the studied groups

		Patients (n = 30)	Controls (n = 30)	*P*-value
Right ear				
250 Hz	Mean ± SD	30 ± 6	22 ± 3	**< 0.001***
500 Hz	Mean ± SD	26 ± 8	21 ± 4	**0.003***
1000 Hz	Mean ± SD	22 ± 3	20 ± 4	**0.047***
2000 Hz	Mean ± SD	21 ± 6	19 ± 3	0.106
4000 Hz	Mean ± SD	25 ± 12	17 ± 6	**0.002***
8000 Hz	Mean ± SD	25 ± 9	17 ± 5	**0.002***
Left ear				
250 Hz	Mean ± SD	27 ± 6	22 ± 2	**< 0.001***
500 Hz	Mean ± SD	27 ± 7	20 ± 4	**< 0.001***
1000 Hz	Mean ± SD	22 ± 4	20 ± 4	**0.029***
2000 Hz	Mean ± SD	23 ± 8	16 ± 5	**< 0.001***
4000 Hz	Mean ± SD	22 ± 7	17 ± 7	**0.005***
8000 Hz	Mean ± SD	21 ± 7	18 ± 3	**0.042***

n: Number, SD: Standard deviation, Hz: Hertz, * = Significant P-value at $P < 0.05$

The serum level of HSP-70 was significantly higher in patients (mean ± SD: 2.5 ± 0.8) compared to controls (mean ± SD: 1.3 ± 0.6), with a *P*-value of < 0.001 (Figure 2).

The ROC analysis was performed to evaluate the ability of HSP-70 to predict alopecia. It revealed an AUC of 0.847 (95% CI, 0.739–0.955), indicating good diagnostic performance. The best cut-off point was > 1.4, at which sensitivity, specificity, positive predictive value, and negative predictive value were 83.3%, 90%, 89.3%, and 84.4%, respectively (*P*-value < 0.001) (Figure 3).

The analysis revealed a significant positive correlation between serum levels of HSP-70 and disease duration (r = 0.504, *P* = 0.004). No significant correlations were observed between serum HSP-70 levels and age (*P* = 0.711), SALT score (*P* = 0.618), or right ear frequencies at 250 Hz (*P* = 0.188), 500 Hz (*P* = 0.655), 1000 Hz (*P* = 0.492), 2000 Hz (*P* = 0.456), 4000 Hz (*P* = 0.295), and 8000 Hz (*P* = 0.534). Similarly, no significant associations were found with the left ear frequencies at 250 Hz (*P* = 0.691), 500 Hz (*P* = 0.845), 1000 Hz (*P* = 0.952), 2000 Hz (*P* = 0.130), 4000 Hz (*P* = 0.259), and 8000 Hz (*P* = 0.249) (Table 2, Figure 4).

The SALT score did not show a statistically significant correlation with hearing thresholds at any frequency in either the right or the left ear. For the right ear, the *P*-values were as follows: 250 Hz (*P* = 0.46), 500 Hz (*P* = 0.99), 1000 Hz (*P* = 0.59), 2000 Hz (*P* = 0.231), 4000 Hz (*P* = 0.495), and 8000 Hz (*P* = 0.848). For the left ear, the *P*-values were: 250 Hz (*P* = 0.171), 500 Hz (*P* = 0.409), 1000 Hz (*P* = 0.491), 2000 Hz (*P* = 0.975), 4000 Hz (*P* = 0.981), and 8000 Hz (*P* = 0.196).

A multivariate logistic regression analysis was performed to predict alopecia. It revealed that a one-unit increase in serum HSP-70 was associated with a ninefold increase in the odds of alopecia (OR = 9.213, 95% CI = 3.357–25.282, *P* < 0.001), controlling for age and gender. However, this OR should be interpreted cautiously, as the small sample size may lead to an overestimation of the true effect size. (Table 3).[3]

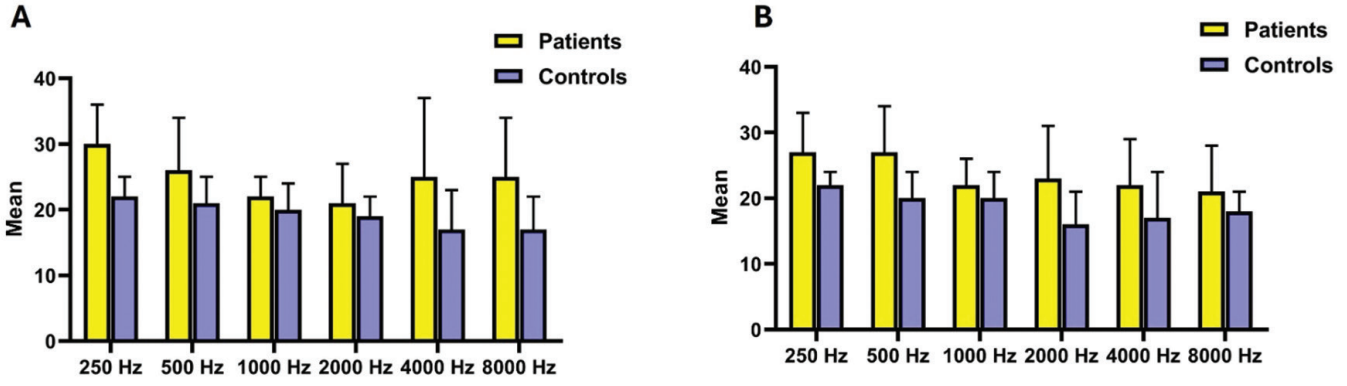

Figure 1. (A) Right and (B) left ear auditory thresholds in the studied groups
Hz: Hertz

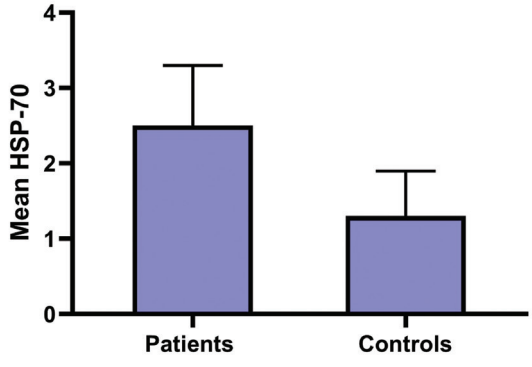

Figure 2. HSP-70 in the studied groups
HSP-70: Heat shock protein 70

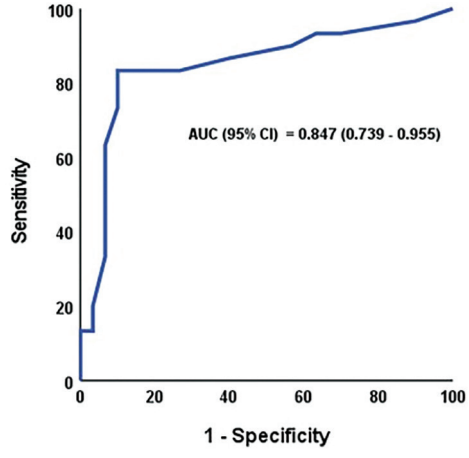

Figure 3. Receiver operating characteristic analysis of heat shock protein 70 to predict alopecia
AUC: Area under the curve, CI: Confidence interval

Table 2. Correlation between serum level of HSP-70 and other parameters

	Serum level of HSP-70	
	r	*P*
Age (years)	-0.071	0.711
Disease duration	0.504	**0.004***
SALT score	-0.095	0.618
Rt 250	-0.247	0.188
Rt 500	0.085	0.655
Rt 1000	0.13	0.492
Rt 2000	-0.141	0.456
Rt 4000	-0.198	0.295
Rt 8000	-0.118	0.534
Lt 250	0.076	0.691
Lt 500	0.037	0.845
Lt 1000	-0.012	0.952
Lt 2000	-0.283	0.13
Lt 4000	-0.213	0.259
Lt 8000	-0.217	0.249

*Significant *P*-value at $P < 0.05$; r: Correlation coefficient, *P*: Probability value, Rt: Right, Lt: Left, HSP-70: Heat shock protein 70, SALT: Severity of Alopecia Tool

Table 3. Multivariate logistic regression analysis to predict alopecia

	OR (95% CI)	*P*-value
Age (years)	0.946 (0.873–1.026)	0.179
Gender	1.949 (0.388–9.801)	0.418
Serum level of HSP-70	9.213 (3.357–25.282)	**< 0.001***

*Significant *P*-value at $P < 0.05$, OR: Odds ratio, CI: Confidence interval, HSP-70: Heat shock protein 70, *P*-value: Probability value

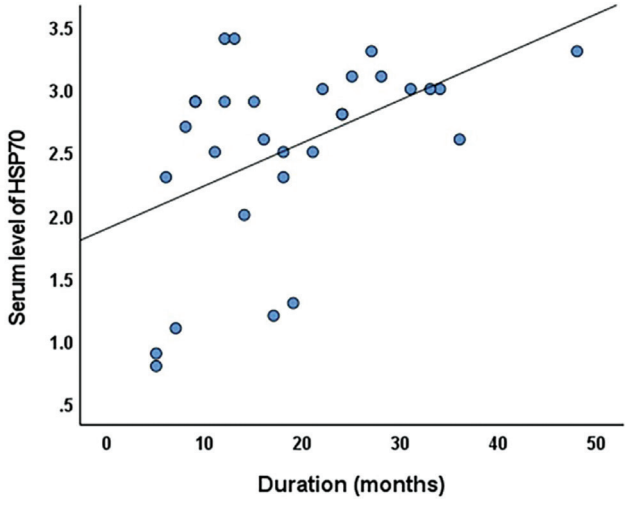

Figure 4. Correlation between HSP-70 and duration
HSP-70: Heat shock protein 70

Discussion

The current study explored the role of circulating HSP-70 in the pathogenesis of AA, its correlation with disease severity, and its potential association with auditory function. Our findings reveal a statistically significant elevation of serum HSP-70 in AA patients compared with healthy controls and significantly higher mean auditory thresholds across various frequencies in these patients. Furthermore, HSP-70 demonstrated robust diagnostic utility for AA, correlating positively with disease duration. These results contribute to the growing body of evidence suggesting a complex interplay among immune responses, stress proteins, and systemic manifestations in autoimmune conditions such as AA. However, given the cross-sectional design, causality cannot be inferred; elevated HSP-70 may simply reflect systemic inflammation, and our findings should be interpreted as hypothesis-generating.

We demonstrated a significant elevation of serum HSP-70 levels in patients with AA compared to healthy controls (2.5 ± 0.8 ng/mL vs. 1.3 ± 0.6 ng/mL; $P < 0.001$). This finding aligns with previous research suggesting the involvement of HSP-70 in autoimmune diseases, including AA.[5,8,9] HSPs are known as molecular chaperones, crucial for maintaining cellular homeostasis and protecting cells from various stressors. However, their role in autoimmune conditions is complex and can be dual-edged; while intracellular HSP-70 protects cells, extracellular or cell surface-anchored HSP-70 can activate immunological responses.[6]

The observed increase in HSP-70 in AA patients could reflect an ongoing cellular stress response within the hair follicles or a systemic immune activation. Given that AA is an immune-mediated disorder characterized by the loss of hair follicle immunological privilege, the elevated HSP-70 might be a compensatory mechanism to mitigate cellular damage or, conversely, contribute to the autoimmune cascade by acting as an autoantigen or an immune stimulator.[3,6] While our study demonstrates a significant association between elevated HSP-70 and AA, further research is needed to determine whether this increase is specific to AA pathogenesis or represents a broader response to systemic stress. Future studies could investigate the correlation between HSP-70 and other specific markers of AA activity or of other autoimmune conditions to better delineate its specificity.

The positive correlation between HSP-70 levels and disease duration ($r = 0.504$, $P = 0.004$) further supports its involvement in the chronicity of AA, suggesting that sustained cellular stress or immune dysregulation might be features of long-standing disease.

These results are consistent with Ghaderi[8] and Elgendy et al.[9], who also reported increased HSP-70 levels in AA

patients. These studies, along with ours, highlight HSP-70 as a potential adjunct biomarker for AA. The robust diagnostic utility demonstrated by ROC analysis (AUC = 0.847, $P < 0.001$) with an optimal diagnostic threshold exceeding 1.4 ng/mL indicates that serum HSP-70 could serve as a valuable tool to aid in the diagnosis of AA, particularly in differentiating it from other forms of hair loss or monitoring disease activity. However, external validation in larger, independent cohorts is mandatory before HSP-70 can be considered for clinical diagnostic use.

Another notable finding of our study is that AA patients exhibited statistically significantly higher mean auditory thresholds across various frequencies than controls. While this suggests a potential link between AA and auditory dysfunction, specifically SNHL, these statistically significant differences do not necessarily indicate clinically significant SNHL for all individuals; mild dB differences may not be clinically meaningful. This association is biologically plausible given the shared embryological origin and immunological characteristics of melanocytes in hair follicles and the inner ear.[4] Melanocytes play a crucial role in maintaining endocochlear potential and protecting against free radical damage in the inner ear.[4,10]

The immune-mediated destruction of melanocytes, a hallmark of AA pathogenesis, could extend to cochlear melanocytes, leading to SNHL. This hypothesis is supported by observations in other autoimmune conditions like vitiligo, where melanocyte depletion is linked to hearing loss.[4] Previous systematic reviews and meta-analyses have also explored the association between AA and SNHL, with some studies indicating a higher prevalence of hearing impairment in AA patients.[4,10,11] Our findings, showing elevated auditory thresholds in both right and left ears across multiple frequencies, further strengthen this proposed connection.

However, our study failed to find a significant correlation between serum HSP-70 levels and auditory thresholds or between SALT score and hearing thresholds. This lack of direct correlation might suggest that, while both AA and auditory dysfunction may share underlying immune-mediated mechanisms involving melanocytes, their specific pathways or the timing of manifestation may differ. For instance, while melanocyte destruction in the scalp leading to hair loss might be a more rapid and acute process, the impact on inner ear melanocytes and subsequent hearing loss could be more insidious and develop over a longer period. It is also possible that HSP-70's role in auditory dysfunction is more indirect or involves different isoforms or cellular compartments not captured by circulating serum levels. Further research, perhaps involving more direct assessment of cochlear function or specific immune markers related to inner ear melanocytes, would be beneficial to fully elucidate this complex relationship.

Study Limitations

Despite these significant findings, our study has several limitations that warrant consideration. First, the restricted sample size (30 AA patients and 30 controls) and single-centre recruitment limit the generalizability of the findings. This small sample size also increases the risk of model overfitting in logistic regression and necessitates external validation of the ROC model. Second, the cross-sectional design precludes the establishment of causality. While we observed associations between elevated HSP-70 and AA, and between AA and auditory dysfunction, we cannot definitively conclude that HSP-70 causes AA or that AA directly causes hearing loss. Longitudinal studies are imperative for understanding the temporal relationships and causal pathways. Furthermore, our patient cohort, characterized by the absence of nail involvement, comorbidities, or a family history of AA, may not fully represent the broad spectrum of the AA population. This is a consequence of our stringent exclusion criteria, designed to minimize confounding factors and focus on the primary research questions. Future studies should aim to include a more heterogeneous AA population to enhance the generalizability of the findings.

Furthermore, while serum HSP-70 levels provide valuable insights, they may not fully capture the localized expression or specific cellular roles of HSP-70 within the hair follicles or inner ear. The absence of assessment of other systemic inflammatory markers (e.g., CRP, ESR) is a limitation, as elevated HSP-70 could reflect systemic inflammation or other unidentified stressors. Future research should include a comprehensive panel of inflammatory markers to better contextualize HSP-70 levels in AA pathogenesis. Future research could also explore tissue-specific HSP-70 expression, different HSP-70 isoforms, and their interactions with various immune cells and pathways involved in AA pathogenesis and auditory function. Advanced audiological assessments beyond PTA, such as otoacoustic emissions or auditory brainstem responses, could provide a more detailed understanding of the cochlear and neural auditory integrity in AA patients.

Investigating genetic polymorphisms related to HSP-70 and their association with AA susceptibility and severity, as well as with hearing loss, could also offer valuable insights.[12]

Finally, the precise mechanistic contributions of HSP-70 to AA pathogenesis and its nuanced relationship with auditory function remain to be fully elucidated. Further experimental studies, including *in vitro* and *in vivo* models, are needed to dissect the molecular mechanisms by which HSP-70 influences immune responses, melanocyte function, and hair follicle integrity in the context of AA. Understanding these mechanisms could pave the way for novel therapeutic targets and interventions for AA and its comorbidities.

Conclusion

Our study provides compelling evidence that elevated circulating HSP-70 levels are a promising diagnostic biomarker for AA and correlate with disease chronicity. We also highlight a significant association between AA and elevated auditory thresholds, suggesting a potential link to SNHL. While further research is warranted to establish causality and elucidate the underlying mechanisms, these findings underscore the systemic nature of AA and the potential for HSP-70 to serve as both a diagnostic marker and therapeutic target.

Ethics

Ethics Committee Approval: The Benha University Research Ethics Committee approved the protocol (approval number: Ms 17-10-2023, approved on October 17, 2023; final document issued: 29.12.2024).

Informed Consent: All subjects provided signed informed consent prior to participation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.G.A., S.E.A., A.O.A.E-G., R.M.A.; Concept: A.M.H., G.M.S.; Design: A.M.H., G.M.S.; Data Collection or Processing: M.G.A-S., S.E.A., G.M.S.; Analysis or Interpretation: A.O.A.E-G., G.M.S.; Literature Search: A.O.A.E-G., R.M.A., G.M.S.; Writing: A.M.H., A.O.A.E-G., R.M.A., G.M.S.

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

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Case Report

Late-Onset, Low-Penetrance NLRP3-Associated Autoinflammatory Disease Presenting with Urticaria-Like Lesions: A CAPS Spectrum Case

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Abstract

Cryopyrin-associated periodic syndromes (CAPSs) are rare autoinflammatory disorders caused by gain-of-function mutations in the *NLRP3* gene, resulting in dysregulated interleukin-1–mediated inflammation. Although traditionally classified into three clinical subtypes according to disease severity and systemic involvement, increasing evidence supports the concept of CAPS as a continuous phenotypic spectrum. Low-penetrance NLRP3 variants may present with milder and atypical phenotypes, creating diagnostic challenges. A 19-year-old male patient presented with a three-month history of recurrent urticaria-like lesions triggered by cold exposure, accompanied by intense pruritus and burning sensation. The lesions appeared on the trunk and extremities, resolved within 24 hours without residual pigmentation, and were not associated with angioedema. The patient denied systemic symptoms such as fever, arthralgia, myalgia, fatigue, or weight loss. Family history was unremarkable. Initially diagnosed with chronic urticaria, he showed no significant response to high-dose second-generation antihistamines. Laboratory investigations during disease flares demonstrated neutrophilia and elevated C-reactive protein and serum amyloid A levels. Skin biopsy revealed superficial and deep perivascular neutrophilic infiltration without evidence of vasculitis. Genetic analysis identified a disease-associated NLRP3 variant, c.592G > A (p.Val198Met), supporting the diagnosis of CAPS. Following initiation of anakinra (100 mg/day), complete remission of cutaneous symptoms was achieved within two months. This case highlights an atypical CAPS presentation characterized by late onset and skin-limited inflammation without systemic manifestations. The findings support a spectrum-based understanding of CAPS and emphasize that isolated cutaneous phenotypes associated with low-penetrance NLRP3 variants should be considered in patients with antihistamine-resistant urticaria-like eruptions accompanied by neutrophilic inflammation and elevated acute-phase reactants.

Keywords: Cryopyrin-associated periodic syndrome, NLRP3, autoinflammatory disease, urticaria-like eruption, interleukin-1

Introduction

Cryopyrin-associated periodic syndromes (CAPS) are a group of rare autoinflammatory disorders caused by gain-of-function mutations in the *NLRP3* gene, leading to dysregulated interleukin-1 (IL-1)–mediated inflammation. Traditionally, CAPS has been classified into three clinical subtypes—familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease—based on age of onset, disease severity, and extent of systemic involvement. However, accumulating evidence indicates that these subtypes represent points along a continuous phenotypic spectrum rather than discrete clinical entities.

Case Report

A 19-year-old male patient presented with a three-month history of recurrent urticaria-like lesions triggered by cold exposure, accompanied by intense pruritus and a burning

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sensation. The patient denied systemic symptoms such as fever, arthralgia, myalgia, fatigue, and weight loss. There was no history of recent infection, drug exposure, or known allergic triggers. The family history was unremarkable. Physical examination during symptomatic periods revealed erythematous, edematous plaques distributed over the trunk and extremities (Figure 1). The lesions appeared and resolved spontaneously within 24 hours without residual pigmentary changes. No accompanying angioedema was reported.

Initially, the patient was thought to have chronic urticaria; however, despite treatment with second-generation antihistamines at up to four times the standard daily dose, he reported no significant improvement in either the frequency or severity of the lesions. Laboratory investigations during disease flares demonstrated neutrophilia and elevated levels of C-reactive protein and serum amyloid A. The combination of unresponsiveness to antihistamines, neutrophilia, and elevated acute-phase reactants raised suspicion of an autoinflammatory disorder rather than chronic spontaneous urticaria, prompting further diagnostic evaluation. A skin biopsy of an active lesion demonstrated no evidence of vasculitis but revealed perivascular neutrophilic infiltration in the superficial and deep dermis, accompanied by a mixed inflammatory infiltrate. Analysis of an autoinflammatory disorders gene panel revealed a heterozygous pathogenic variant in the *NLRP3* gene, c.592G > A (p.Val198Met), classified as Class 2 (possible pathogenicity, 95-99%), supporting the diagnosis of CAPS. Family screening was not performed.

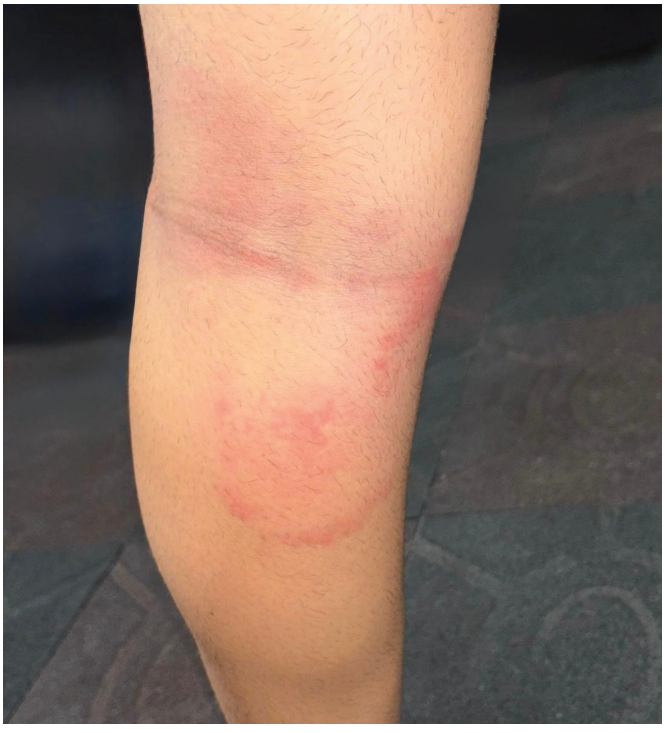

Figure 1. Urticaria-like plaques on the back of the leg

Following the diagnosis, anakinra (100 mg/day subcutaneously), an IL-1 receptor antagonist, was initiated. After two months of treatment, the patient achieved complete resolution of cutaneous symptoms, with no recurrence of urticarial attacks.

Discussion

The present case illustrates an atypical CAPS presentation characterized by delayed disease expression and inflammation confined to the skin, highlighting the diagnostic challenges posed by non-classical phenotypes. Such presentations expose the limitations of rigid subtype-based classifications and support a spectrum-based understanding of CAPS rather than strict categorical definitions.[1-3]

Accumulating clinical and genetic evidence indicates that CAPS represents a continuous phenotypic spectrum. Within this spectrum, low-penetrance NLRP3 variants are frequently associated with milder disease courses, later onset, and restricted organ involvement.[2-4] Patients carrying these variants may lack hallmark systemic inflammatory manifestations, which can delay recognition of CAPS, particularly when cutaneous findings dominate the clinical presentation.[3]

At the molecular level, CAPS is driven by dysregulated activation of the NLRP3 inflammasome, resulting in excessive production of IL-1β, a key mediator of inflammation across the CAPS spectrum.[1,4-6] While robust systemic IL-1 signaling underlies severe CAPS phenotypes, lower-intensity or compartmentalized inflammasome activation may preferentially manifest in the skin. In such cases, IL-1–mediated neutrophilic inflammation can present as recurrent urticaria-like lesions that are poorly responsive to antihistamine therapy, reflecting cytokine-driven rather than mast cell-mediated inflammation.[4,7,8]

Within this framework, the absence of overt systemic inflammatory manifestations should not be interpreted as exclusion from the CAPS spectrum but rather as a consequence of variable genetic penetrance and tissue-specific inflammatory expression.[2-4] The complete and sustained response to IL-1 blockade provides functional confirmation of inflammasome-mediated disease activity and supports classification of this presentation as a skin-limited CAPS phenotype within the broader CAPS spectrum.[5,6]

Conclusion

Taken together, this case supports an expanded conceptualization of CAPS that includes late-onset, skin-limited phenotypes associated with low-penetrance NLRP3

variants, and it highlights the biological plausibility of isolated cutaneous involvement within the CAPS spectrum.

Footnotes

Informed Consent: Written informed consent was obtained from the patient for publication of the clinical images and clinical information included in this article.

Authorship Contributions

Surgical and Medical Practices: M.E.U., Ç.Y., Concept: M.E.U., E.G., Design: M.E.U., E.G., İ.Ü., Data Collection or Processing: M.E.U., E.G., B.Y., Analysis or Interpretation: M.E.U., E.G., Literature Search: E.G., Ç.Y., Writing: M.E.U., E.G.

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Case Report

High-Frequency Electrosurgery for Rhinophyma: A Three-Case Series

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Abstract

Rhinophyma is a progressive dermatologic condition characterized by hypertrophy of sebaceous glands and connective tissue, leading to nasal deformity and significant psychosocial impact. We present three male patients with rhinophyma treated using high-frequency electrosurgery. All patients presented with progressive nasal enlargement causing cosmetic concern, and one case was associated with inflammatory lesions and discharge. High-frequency electrosurgery was performed under local anesthesia using a radiofrequency device, enabling precise tissue debulking with simultaneous coagulation. Postoperative healing was achieved within 2–4 weeks in all patients, with no major complications. At follow-up, all patients demonstrated satisfactory cosmetic outcomes, and only one patient developed minimal scarring that did not affect overall satisfaction. High-frequency electrosurgery provided effective removal of hypertrophic tissue with minimal collateral damage and rapid recovery. These findings suggest that high-frequency electrosurgery appears to be a practical, efficient, and relatively cost-effective treatment option in selected patients with rhinophyma. Further studies with larger patient groups and longer follow-up periods are needed to better define long-term outcomes and recurrence rates.

Keywords: Dermatologic surgical procedures, electrosurgery, radiofrequency, rhinophyma, rosacea

Introduction

Rhinophyma is a disfiguring condition characterized by progressive hypertrophy of the sebaceous glands and connective tissue of the nose and is considered an advanced stage of rosacea.[1] In addition to functional impairment, rhinophyma may cause significant psychosocial distress due to visible facial deformity.[2]

Various treatment options have been described for advanced rhinophyma, including dermabrasion, laser therapy, surgical excision, and electrosurgery.[3] High-frequency electrosurgery enables simultaneous cutting and coagulation with minimal collateral tissue injury and with a low-risk of scarring.[4]

In this study, we report three patients with rhinophyma who were successfully treated with high-frequency electrosurgery. Although high-frequency electrosurgery has previously been described as a treatment modality for rhinophyma, reports detailing procedural parameters, postoperative management, and short-term clinical outcomes remain limited. The present case series aims to contribute additional practical clinical experience regarding the reproducibility, safety, and cosmetic outcomes of this technique.

Case Report

Three male patients with rhinophyma were treated with high-frequency electrosurgery using a Surgitron FFPF EMC RF Energy Source (3.8 MHz; Ellman International, Hicksville, NY, USA) under an infraorbital nerve block and local infiltrative anesthesia. All procedures were performed under local infiltrative anesthesia using 20 mg/mL lidocaine hydrochloride and 0.0125 mg/mL epinephrine (Jetokain®, ADEKA, Türkiye).

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Procedures were performed in the cutting/coagulation mode, using power settings between 2 and 5, according to tissue thickness and intraoperative response. Hypertrophic tissue was gradually debulked in multiple passes until the desired nasal contour was achieved, while preserving the pilosebaceous units to facilitate spontaneous re-epithelialization and maintaining the underlying nasal framework. Tissue removal was performed conservatively to the level of the sebaceous gland units, while preserving the underlying nasal cartilage and contour. Procedure duration ranged from 30 to 45 minutes, and all procedures were performed by the same operator. Hemostasis was achieved using electrocoagulation with a ball electrode.

Postoperative care included daily dressing changes with topical mupirocin ointment for two weeks and oral paracetamol (500 mg twice daily) for one week. Complete epithelialization occurred within 2–4 weeks.

Cosmetic outcomes were evaluated retrospectively based on physician assessment, serial photographic comparison, and patient-reported satisfaction.

A 59-year-old male presented with progressive nasal enlargement of five years' duration and increased nasal discharge over the preceding four months. He denied facial pain, epistaxis, or systemic symptoms and reported a 40-pack-year smoking history.

Dermatological examination revealed a markedly enlarged, bulbous nose with inflammatory lesions and purulent discharge (Figure 1). The patient reported significant psychosocial distress due to the cosmetic deformity.

Topical metronidazole therapy improved pustules and discharge. However, nasal hypertrophy persisted, and high-frequency electrosurgery was performed.

The postoperative course was uneventful (Figure 2). During short-term follow-up, minimal scarring developed at the nasal tip, but it did not require additional treatment or significantly affect cosmetic satisfaction.

A 66-year-old male presented with a 20-year history of progressive enlargement of the nasal tip, causing cosmetic concern. He denied pain, discharge, or nasal obstruction.

Physical examination demonstrated hypertrophy of the distal nasal soft tissues with a characteristic rhinophymatous appearance without ulceration or signs of infection (Figure 3).

Following routine preoperative evaluation, high-frequency electrosurgery was performed using the same technique. The postoperative course was uneventful, with a favorable cosmetic outcome and no complications (Figure 4).

An 80-year-old male presented with progressive enlargement and erythema of the nasal tip, accompanied by acneiform lesions. He reported cosmetic dissatisfaction without pain or nasal obstruction.

His medical history was notable for type 2 diabetes mellitus, treated with metformin, and a rhinophyma surgery performed five years earlier. Dermatological examination revealed nodular thickening of the nasal tip with widened follicular openings and lobulated surface changes consistent with recurrent rhinophyma (Figure 5).

High-frequency electrosurgery was performed using the same technique. Preoperative electrocardiography demonstrated normal sinus rhythm without contraindications to the procedure. The postoperative course was uncomplicated, and a clinically acceptable cosmetic outcome was achieved (Figure 6).

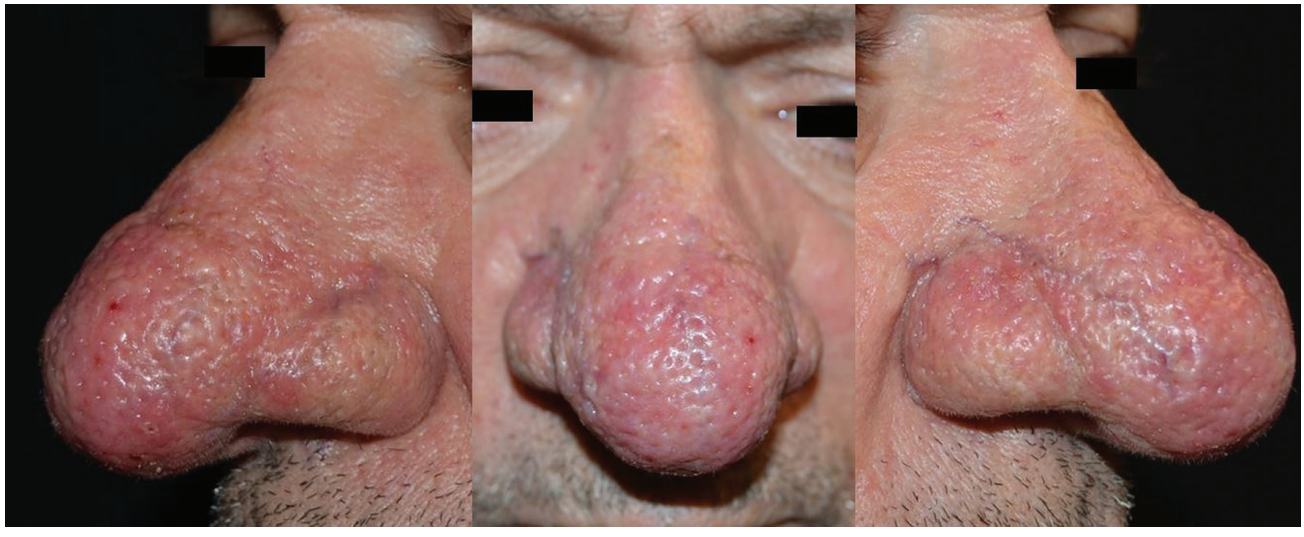

Figure 1. Severe rhinophyma presenting with marked bulbous enlargement of the nose, inflammatory lesions, and purulent discharge before treatment

All patients tolerated the procedure well, and no intraoperative complications were observed. Postoperative care included topical mupirocin therapy and closed dressings during the first two weeks. Complete epithelialization occurred within 2–4 weeks in all patients. At the 3- and 6-month follow-up visits, one patient developed minimal scarring; however, this did not significantly affect cosmetic satisfaction. No other complications were observed, and no recurrence was detected during short-term follow-up.

Discussion

Rhinophyma is a chronic disfiguring condition that may cause significant psychosocial burden and often requires procedural

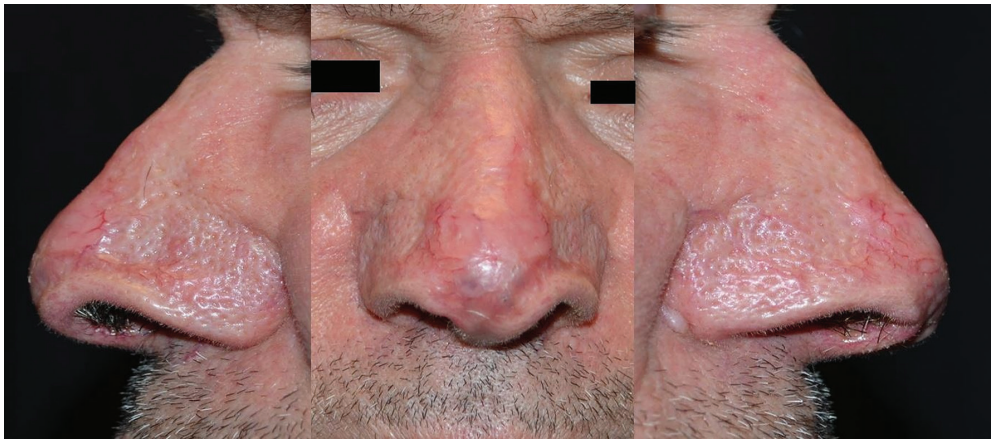

Figure 2. Postoperative appearance demonstrating significant reduction in nasal volume and improved contour following high-frequency electrosurgery

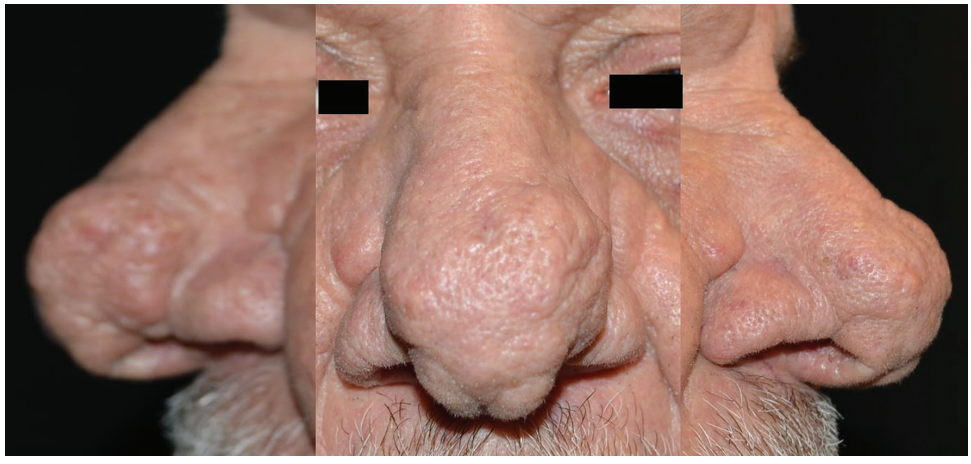

Figure 3. Moderate rhinophyma characterized by hypertrophy of the nasal tip without ulceration or secondary infection

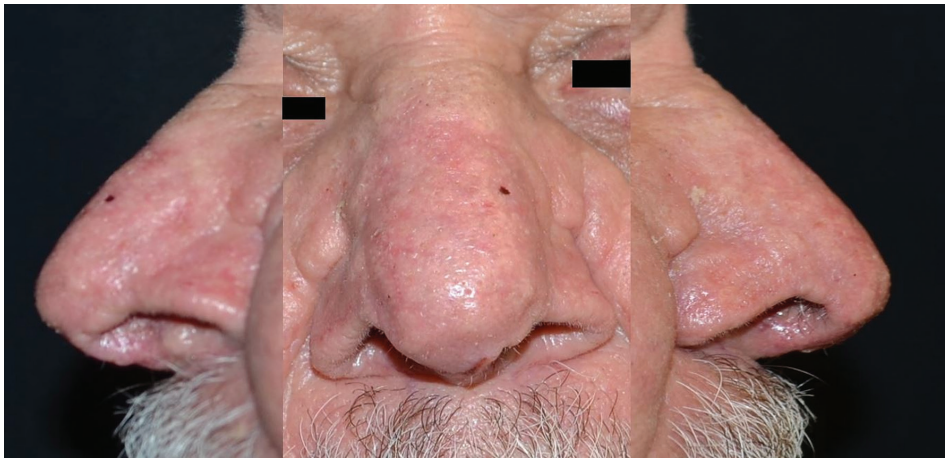

Figure 4. Postoperative result showing favorable cosmetic outcome and restoration of nasal contour

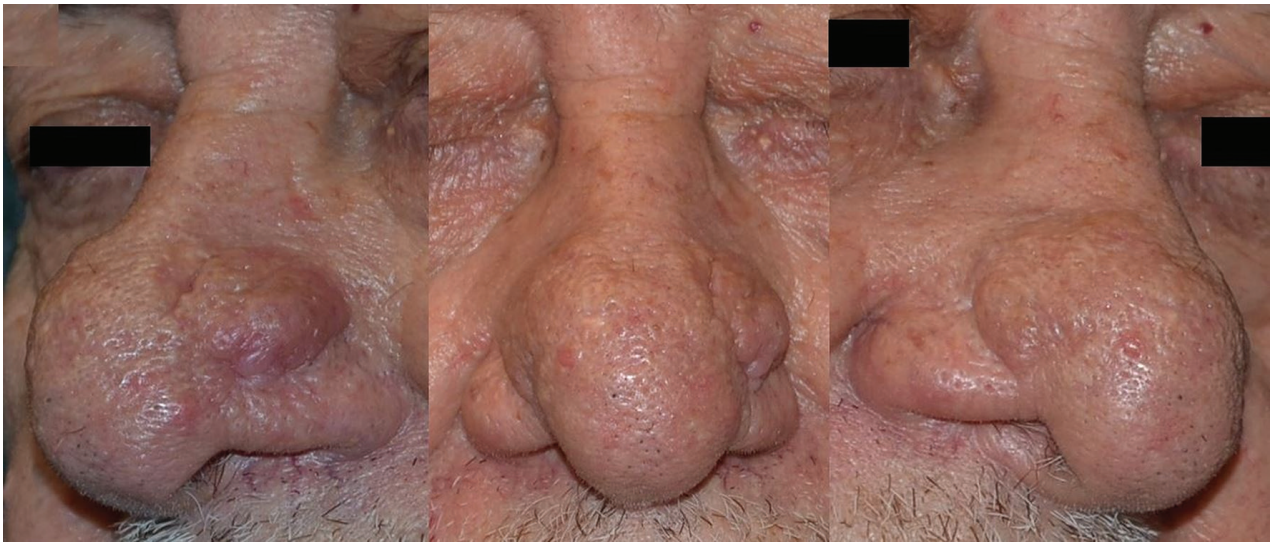

Figure 5. Recurrent rhinophyma with nodular thickening, widened follicular openings, and lobulated surface changes

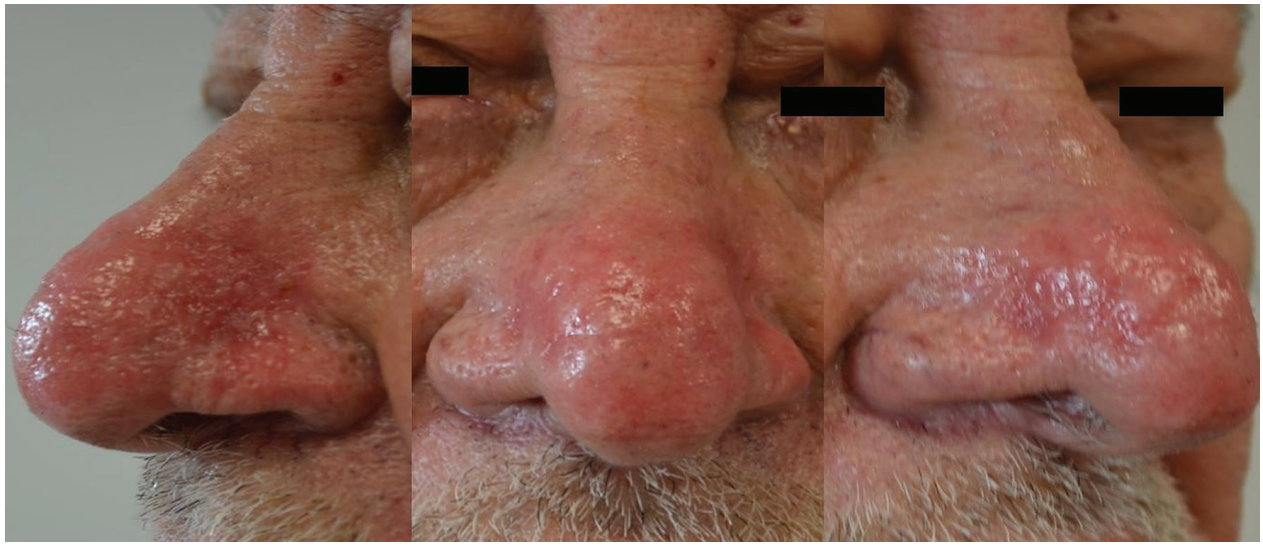

Figure 6. Postoperative appearance showing improved nasal contour after electrosurgical debulking

treatment in advanced stages.[1,2] Various surgical techniques have been described for the treatment of rhinophyma, including scalpel excision, dermabrasion, laser ablation, and high-frequency electrosurgery.[3]

Compared with CO_2 laser therapy, high-frequency electrosurgery may be a more cost-effective and accessible treatment option while providing satisfactory bleeding control and contour restoration.[3] The technique enables simultaneous tissue cutting and coagulation, thereby improving hemostasis, reducing intraoperative bleeding, and promoting rapid wound healing with minimal collateral thermal injury.[4] However, the procedure remains operator-dependent, and excessive tissue removal may result in contour irregularities, scarring, pigmentary alteration, or thermal injury.[4]

Previous studies have reported favorable outcomes with high-frequency electrosurgery for rhinophyma treatment.[5] Consistent with these reports, our patients demonstrated rapid epithelialization and favorable cosmetic outcomes, with minimal complications during short-term follow-up. Cosmetic outcomes were evaluated retrospectively based on physician assessment, serial photographic comparison, and patient-reported satisfaction. One patient developed minimal scarring at the nasal tip that did not significantly affect cosmetic satisfaction, and no recurrence was observed during short-term follow-up.

Another advantage of electrosurgery is its relatively low cost compared with laser-based therapies.[6] Nevertheless, this study has several limitations, including a small sample size; lack of a control group; retrospective, descriptive case-series design;

short follow-up duration; lack of standardized measures of severity and cosmetic outcomes, and lack of histopathological evaluation, because occult malignancy may rarely coexist with rhinophyma.

Conclusion

High-frequency electrosurgery appears to be a practical, efficient, and relatively cost-effective treatment option in selected patients with rhinophyma. Further studies with larger patient groups and longer follow-up periods are needed to better define long-term outcomes and recurrence rates. Prospective studies with standardized outcome measures are needed to further validate these findings.

Footnotes

Informed Consent: Written informed consent was obtained from all patients for publication of the clinical images.

Authorship Contributions

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

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Case Report

Cutaneous Angiosarcoma Mimicking an Inflammatory Scalp Lesion: Diagnostic Insight from Dermoscopy, Tzanck Smear, and Immunohistochemical Analysis

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Abstract

Cutaneous angiosarcoma is a rare and aggressive malignant tumor of vascular endothelial origin that most commonly affects the scalp of elderly individuals and may clinically mimic benign or inflammatory dermatoses, leading to delayed diagnosis. We report the case of an 85-year-old man who presented with a three-month history of a progressively enlarging, painful lesion on the right parietal region of the scalp, which had initially been misdiagnosed as herpes zoster–associated cervical trophic syndrome. Dermatological examination revealed a 13 × 9 cm violaceous plaque with ulceration and yellow crusting. Dermoscopy demonstrated red clods and irregular red-violaceous structureless areas. Cytologic examination using a Tzanck smear showed atypical spindle cells with hyperchromatic nuclei and prominent nucleoli, suggestive of a vascular malignancy. Histopathological evaluation confirmed the diagnosis of cutaneous angiosarcoma, and immunohistochemical staining was positive for ERG, CD31, and CD34 but negative for EMA, CK5/6, HHV8, and BerEP4. Head computed tomography revealed no evidence of metastasis or calvarial invasion. The patient was referred to oncology; however, the patient was referred to oncology; however, systemic chemotherapy was not initiated because of advanced age; surgical excision with consideration of adjuvant radiotherapy was planned. This case highlights that cutaneous angiosarcoma may clinically mimic herpes zoster–related conditions and emphasizes the importance of dermoscopy, cytology, and histopathology in the early diagnosis of atypical scalp lesions.

Keywords: Cutaneous angiosarcoma, dermoscopy, Tzanck smear

Introduction

Angiosarcoma is a rare and aggressive malignant tumor that arises from vascular or lymphatic endothelial cells and is associated with a poor prognosis. Cutaneous angiosarcomas are classified as primary or secondary; primary cutaneous angiosarcomas most frequently occur in elderly men, particularly on sun-exposed regions of the scalp.[1] Owing to its variable clinical presentation, the diagnosis is often delayed or mistaken for other dermatoses.[1-3] Although zosteriform and inflammatory presentations of cutaneous angiosarcoma, as well as its dermoscopic patterns, have previously been described, reports focusing on Tzanck smear findings in primary cutaneous angiosarcoma remain extremely limited. Previous cytological studies of angiosarcoma have mainly described fine-needle aspiration or fluid cytology findings, including pleomorphic epithelioid or spindle cells, hyperchromatic nuclei, intracytoplasmic lumina, and other vasoformative features. Herein, we report a case of cutaneous angiosarcoma that clinically resembled herpes zoster–associated cervical trophic syndrome, highlighting the importance of considering angiosarcoma in the differential diagnosis of atypical cutaneous lesions.

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The present case adds to the literature by demonstrating that bedside Tzanck smear evaluation, when combined with dermoscopy, may provide early cytological clues to angiosarcoma and may help distinguish it from herpes zoster-related lesions before histopathological confirmation.

Case Report

An 85-year-old man presented with a three-month history of a progressively enlarging, painful, erythematous lesion on the right parieto-occipital scalp. He had been misdiagnosed with herpes zoster–associated cervical trophic syndrome. Owing to rapid progression, he was referred to our dermatology clinic. No family history of skin cancer was reported. He had no history of radiotherapy, chronic lymphedema, chronic immunosuppression, or previous malignancy. He also had no known exposure to established environmental carcinogens associated with angiosarcoma, such as vinyl chloride, thorotrast, or arsenic.

Dermatological examination revealed a 13 × 9 cm violaceous plaque with ulceration and yellow crusts (Figure 1A-C). Dermoscopy showed red and purple clods and red, white, and violaceous structureless areas (Figure 1D and E). The Tzanck smear showed atypical spindle and epithelioid cells with hyperchromatic nuclei, prominent nucleoli, poikilokaryosis, and cytoplasmic projections, raising suspicion of a malignant neoplasm, including a vascular tumor (Figure 1F-I). The absence of multinucleated giant cells and acantholytic cells did not support a diagnosis of herpes infection. A definitive diagnosis was established by histopathological examination and immunohistochemical staining, which showed positivity for ERG, CD31, and CD34, whereas EMA, CK5/6, HHV8, and BerEP4 were negative (Figure 2A-E). FLI-1 immunohistochemical staining was not performed in this case. PAS and Alcian blue staining were also performed. Based on these findings, a diagnosis of primary cutaneous angiosarcoma was established. The patient was referred to oncology; however, because of advanced age, chemotherapy was not initiated and surgical excision was planned. Computed tomography of the head revealed no metastases or calvarial invasion. The patient was evaluated by the multidisciplinary oncology team. Because of the patient's advanced age and clinical condition, systemic chemotherapy was not initiated. Surgical excision was planned for localized disease, and adjuvant radiotherapy was considered according to postoperative pathological findings and patient suitability. Written informed consent was obtained from the patient for publication of the clinical images.

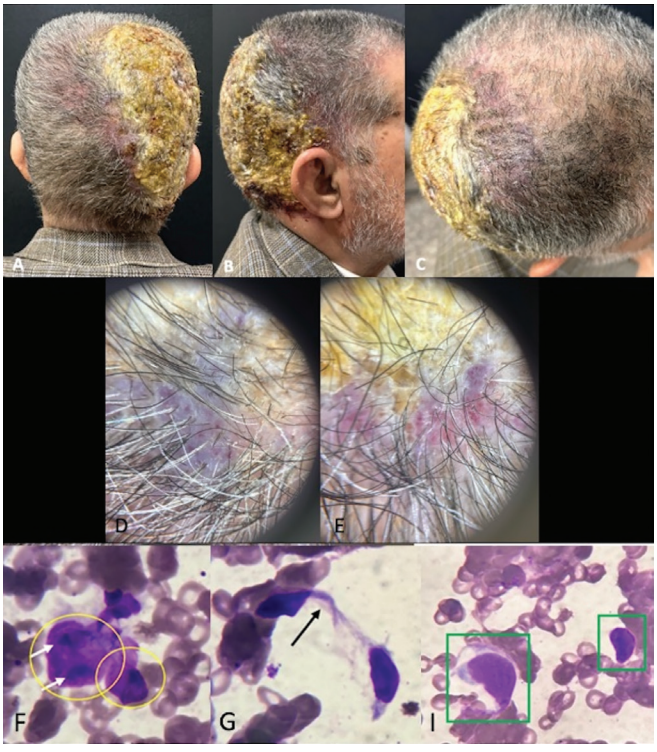

Figure 1. (A–C) Violaceous plaque with ulceration and yellow crusts localized on the right parieto-occipital scalp. (D, E) Dermoscopy: violaceous background with red, purple, and blue structureless areas, white streaks, and yellow clods. (F–I) Diff-Quik-stained Tzanck smear showing pleomorphic epithelioid and spindle cells with prominent nucleoli and cytoplasmic projections, at original magnification ×1000

Discussion

Cutaneous angiosarcoma is an aggressive vascular malignancy that originates from the endothelial cells of blood or lymphatic vessels, has a poor prognosis, and often masquerades as benign or inflammatory dermatoses in its early stages.[1] Cutaneous angiosarcomas may arise as primary tumors, typically affecting the chronically sun-damaged scalp and face of elderly men, or as secondary tumors associated with chronic lymphedema, prior radiotherapy, chronic immunosuppression, and exposure to environmental carcinogens such as vinyl chloride, thorotrast, and arsenic.[1-3] The differential diagnoses of cutaneous angiosarcoma include post-traumatic lesions, infections, inflammatory dermatoses, malignant solid tumors, and cutaneous lymphomas.[1]

Previous reports have shown that scalp angiosarcoma may mimic herpes zoster, facial cellulitis, inflammatory alopecia, infected cysts, or chronic ulcerative/wound-like lesions.[4-8] Similar to these cases, the inflammatory and crusted appearance of the lesion led to an initial herpes zoster–related misdiagnosis in our patient. In this context, dermoscopy and the Tzanck smear were useful adjunctive bedside tools, raising suspicion for a malignant vascular tumor and prompting early biopsy.

In our case, the diagnosis was achieved through the combined use of Tzanck smear, dermoscopy, and histopathology,

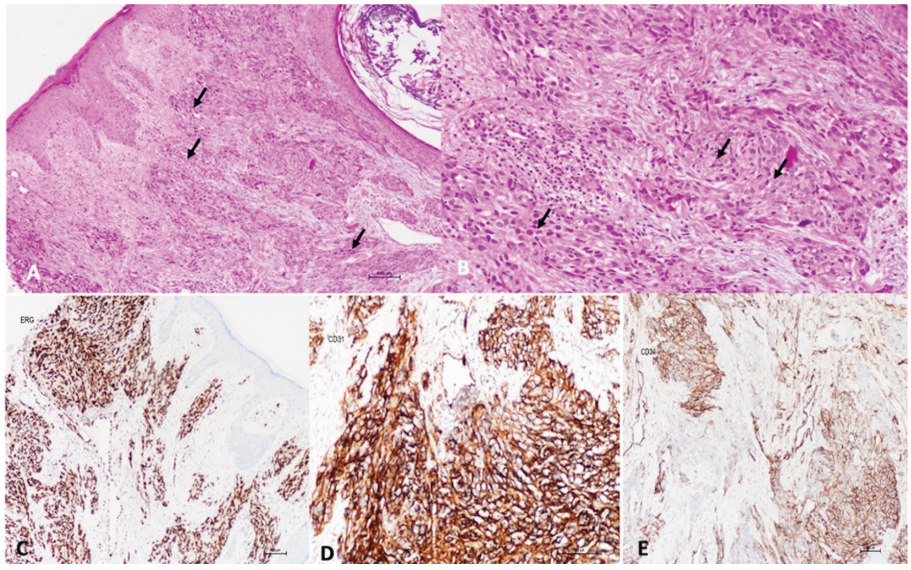

Figure 2. (A) Irregularly shaped vascular structures composed of hyperchromatic, pleomorphic cells (hematoxylin and eosin, 100×). (B) Pleomorphic tumor cells infiltrating the dermis (hematoxylin and eosin, 200×). (C–E) Tumor cells showing positive expression of ERG, CD31, and CD34 (100×, 200× and 100×).

underscoring the importance of multimodal evaluation. Dermoscopy demonstrated irregular, structureless red, purple, and blue areas interlaced with white streaks and yellow clods, while cytologic examination revealed pleomorphic epithelioid clusters with prominent nucleoli, atypical mitoses, and spindle cells.[1,3,9] Definitive confirmation was obtained by histopathology and immunohistochemistry with endothelial markers such as CD31, CD34, FLI-1, and ERG.[1] Optimal management includes wide surgical excision with adjuvant radiotherapy, while systemic treatment may be considered for advanced or unresectable disease.[10]

The novelty of this case lies not merely in the clinical mimicry of an inflammatory or a herpes zoster-related scalp lesion, but also in the bedside demonstration of atypical cytological features on Tzanck smear. While cytological features of angiosarcoma have been reported in fine-needle aspiration and fluid cytology specimens, Tzanck smear findings in primary cutaneous angiosarcoma have rarely been emphasized. Boucher et al.[11] reported the cytological features of angiosarcoma in 14 fine-needle aspiration biopsy specimens and one pleural fluid specimen. In addition, Panwar et al.[12] emphasized that Tzanck smear is an inexpensive and useful bedside diagnostic tool that may aid rapid clinical diagnosis in selected cutaneous lesions. The identification of atypical spindle and epithelioid cells with hyperchromatic nuclei and cytoplasmic projections, together with the absence of multinucleated giant cells, supported early reconsideration of the initial herpes zoster-associated diagnosis and prompted definitive biopsy and immunohistochemical evaluation.

This case highlights the diagnostic value of cytology and dermoscopy, and the necessity of considering angiosarcoma in atypical, persistent cutaneous lesions.

Conclusion

Cutaneous angiosarcoma may mimic inflammatory or infectious dermatoses, leading to diagnostic delay. Cytology and dermoscopy may provide valuable auxiliary clues for early recognition, but histopathology with immunohistochemistry remains the gold standard for diagnosis.

Footnotes

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

Authorship Contributions

Concept: A.D., Data Collection or Processing: P.H., Ö.Ö., G.T., Analysis or Interpretation: P.H., A.K., Literature Search: A.D., Writing: A.K.

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

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Repair of Two Adjacent Surgical Defects with a Single Rotation Flap After Mohs Micrographic Surgery: A Case Report

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Dear Editor,

Basal cell carcinoma (BCC) is the most common type of skin cancer.[1] Mohs micrographic surgery (MMS) is considered the gold standard for the treatment of BCCs with specific features.[1] MMS provides complete margin control while preserving as much healthy tissue as possible, making it particularly useful in cosmetically and functionally critical areas such as the face.[2] Meticulous perioperative planning is essential in the reconstruction of post-MMS defects to optimize outcomes. Thus, several factors must be considered, including defect size, location, and depth; proximity to anatomical boundaries; laxity of surrounding tissues; and the patient's comorbidities.[3] When more than one repair option is available, the simplest technique should be preferred, where cosmesis and functionality are adequately preserved.

A 62-year-old man presented with two adjacent lesions in the left postauricular region (Figure 1a). Histopathology of superior and inferiorly-located lesions was consistent with basosquamous BCC and nodular BCC, respectively. Both tumors were excised using MMS.

The clinical borders of both tumors were delineated using dermoscopy, and 2-mm safety margins were marked. Orientation was performed using the clock-face method, with reference incisions placed at the 12, 3, 6, and 9 o'clock positions (Figure 1b). Excision was performed along the safety margins at a 45° angle, and specimens were transferred to the MMS laboratory without loss of orientation (Figure 1c). After the first MMS stage, both lateral and deep margins of the inferiorly located BCC were negative. Lateral margins of the superiorly located BCC were reported to be negative, while the tumor was observed in the deep margin (Figure 2a-e). After the second stage of MMS, during which the deep margins of the superiorly located tumor were excised down to the supraperiosteal plane, those margins were reported as negative. At completion, two adjacent defects, measuring 21 × 29 mm and 17 × 20 mm, were present (Figure 3b). These two defects were reconstructed with a single rotation flap (Figure 3b and c). At the ninth month of follow-up, a cosmetically acceptable scar was observed (Figure 4). No early- or late-term complications have been observed in our patient.

Small-to-moderate-sized post-MMS defects may be managed by secondary intention healing, primary closure, skin grafting, or local flaps. In the present case, primary closure was not feasible due to significant tension during edge approximation (Figure 3a). Secondary intention healing could be considered because the periosteum at the defect base was preserved and the anatomical location was relatively concealed. However, the patient's comorbidities were expected to adversely affect wound healing; therefore, this option was not pursued.

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Although grafting was technically possible, reconstruction with a local flap was preferred, given its superiority in tissue match in color, thickness, and adnexal characteristics compared with graft tissue, which is often harvested from distant sites and may yield inferior aesthetic results.

When a defect involves more than half of an aesthetic unit, excision of the remaining portion of the unit and reconstruction of the entire unit using a single technique have been recommended. This approach helps to conceal scars along natural borders, achieve better contour matching, and minimize patch-like deformities.[4] While the postauricular region is not a classic facial cosmetic unit, repairing two closely adjacent defects with different methods could have required additional incisions and thereby increased the scar burden. This approach would also create undesirable tension at the wound closure site. Thus, combining two adjacent defects into a single larger defect and reconstructing it with a single approach was favored in our patient.

Linear advancement flaps would provide limited tissue mobility in contrast to transposition and rotation flaps; therefore, their range of movement was thought to be insufficient for adequate defect closure in our case.[5] Similarly, the use of a V–Y advancement flap would be technically challenging due to the relative paucity of subcutaneous adipose tissue in this region.[5,6] Previous studies have reported the reconstruction of retroauricular defects using transposition flaps, such as

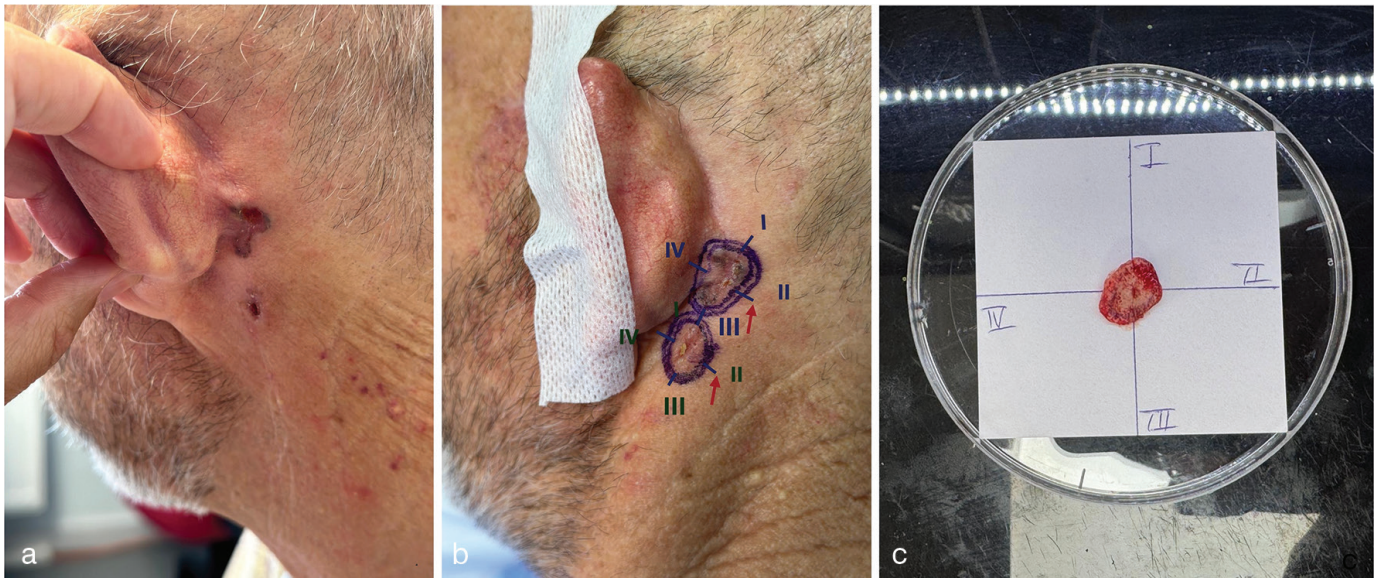

Figure 1. Excision of basal cell carcinoma (BCC) with Mohs micrographic surgery. (a) Two adjacent BCCs located in the postauricular region. (b) Clinical tumor borders and surgical margins, each with a width of 2 mm, are marked. Reference incisions are made at 12, 3, 6, and 9 o'clock for each tumor (red arrows). Excision is performed along the safety margins at 45° (c). The specimen is placed in a Petri dish lined with an orientation guide sheet. Thus, the orientation is preserved during transfer

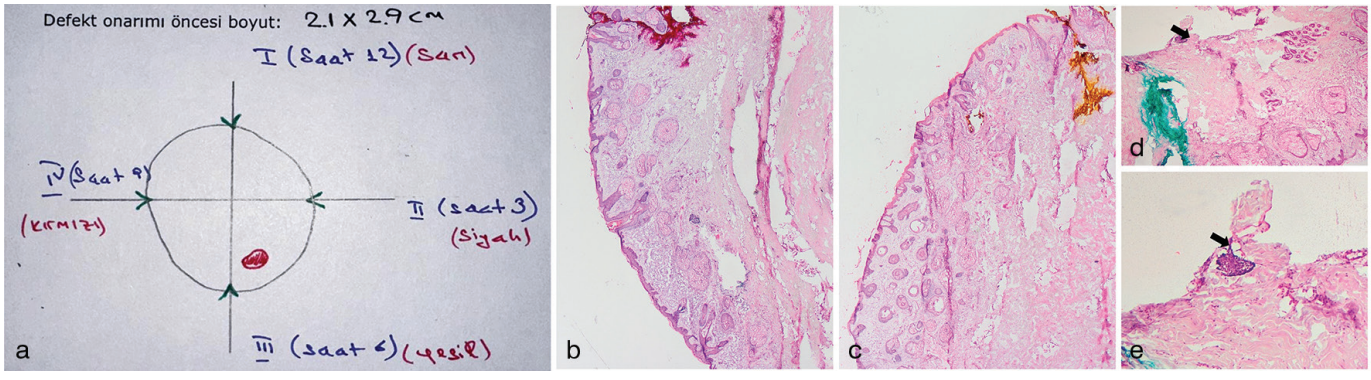

Figure 2. Mohs map and histopathologic examination findings of the superiorly located tumor. (a) Mohs map: as indicated on the Mohs map, the 12 o'clock nick is marked with yellow dye, the 3 o'clock nick with black dye, the 6 o'clock nick with green dye, and the 9 o'clock nick with red dye. The arrow points to the residual tumor, as determined by histopathologic examination. The tumor is continuos in the deep margin (b) 9 o'clock nick (red dye): the lateral and deep surgical margins are negative in the depicted area (c) 12 o'clock nick (yellow dye): the lateral and deep surgical margins are negative in the depicted area (d, e) 6 o'clock nick (green dye): the tumor is present at the deep surgical margin in the location indicated by the arrow. Note: Images corresponding to the 3 o'clock nick are not shown; both the lateral and deep margins in this area were tumor-free

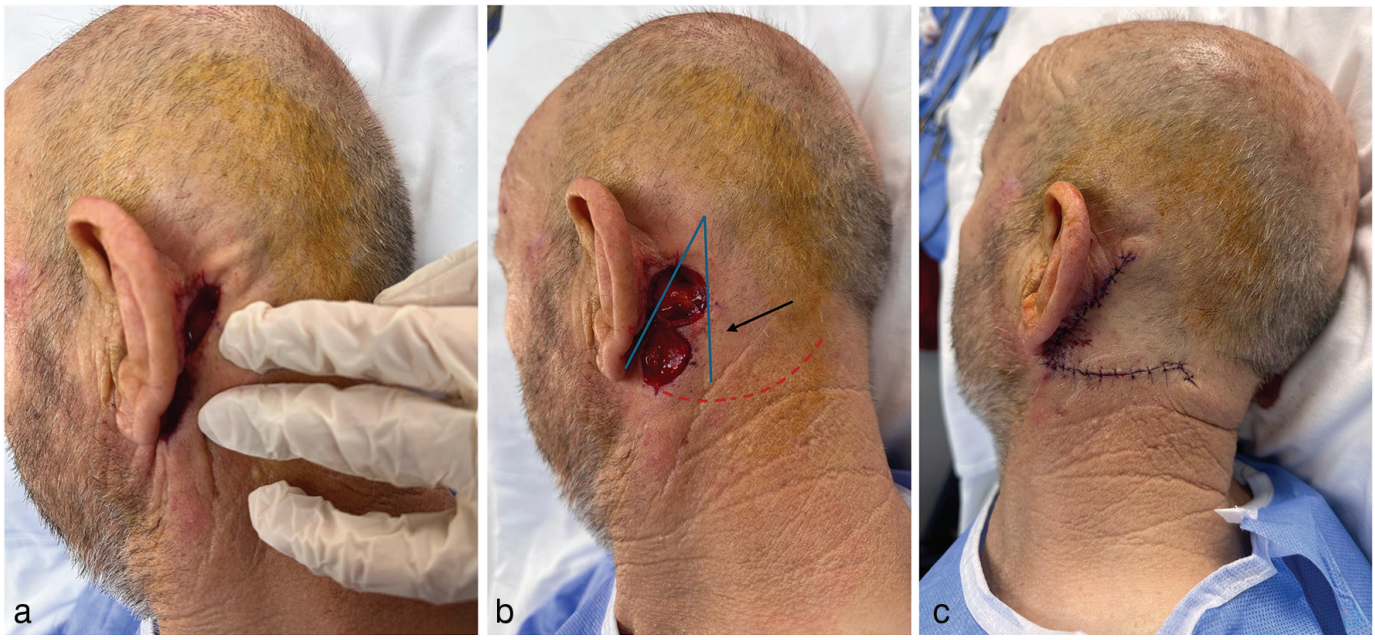

Figure 3. Reconstruction of the surgical defect. (a) Defects cannot be repaired by primary closure due to the excessive tension at the defect closure site (b) design of the rotational flap. The area delineated by the blue triangle will be excised. Note that the defects are located within the planned triangular excision site (c) immediate postoperative appearance after reconstruction with a rotation flap

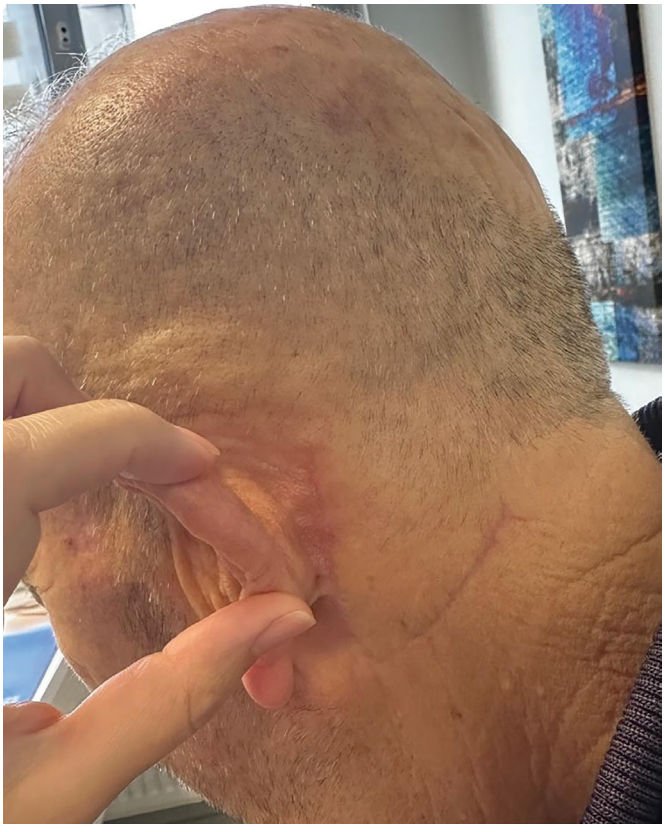

Figure 4. Long-term follow-up outcomes. Cosmetically acceptable scar appearance on the 9th month of follow-up

preauricular transposition and bilobed flap.[7,8] Reconstruction of the final combined defect with a transposition flap was theoretically feasible. Among transposition flaps, the bilobed flap would be preferable. However, it would require an excessively large flap, potentially extending into the cervical region. This approach would also require extensive undermining, thereby increasing the risk of complications. A rhomboid flap would require extension of excisions to the auricle and a significantly larger design to address both defects simultaneously.[9]

Given the proximity to anatomical boundaries (the auricle and hairline) and regional tissue laxity, a rotation flap was considered more advantageous than transposition or advancement flaps. Although reconstruction of postauricular defects using a rotation flap has been previously reported, those cases were single defects.[10] During reconstruction planning, it was observed that the triangular area planned for excision could be positioned within one of the defect sites (Figure 3b). Thus, two adjacent defects could be and were repaired with a single rotational flap. A single-method reconstruction also reduced operative time and improved procedural efficiency.

Converting two adjacent post-MMS defects into a single defect and reconstructing the resulting defect with a single flap may be a practical and efficient approach in selected cases. This approach helps to avoid additional incisions, reduces tension on wound edges, and minimizes scar burden.

Footnotes

Informed Consent: Written informed consent was obtained from the patient.

Authorship Contributions

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

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