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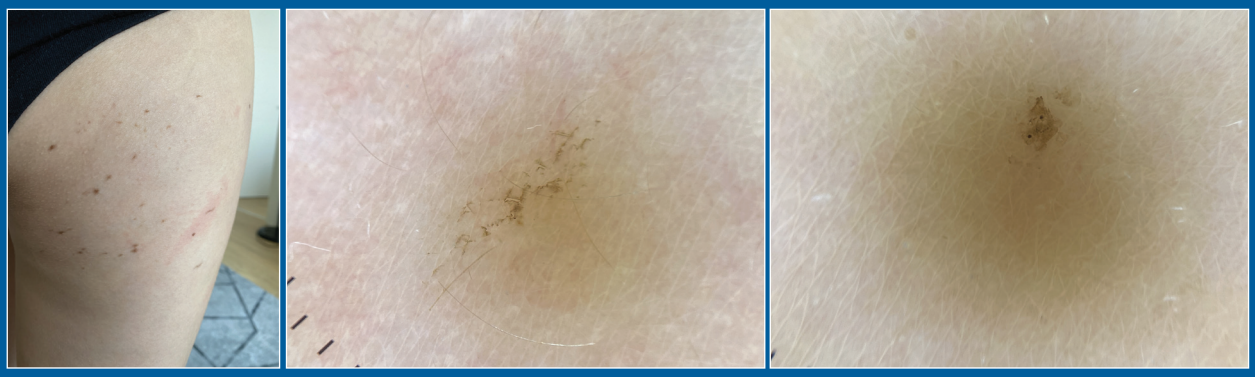

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CONTENTS

Original Article

A Cross-Sectional Study of Mycosis Fungoides Care: Diagnostic Challenges, Therapeutic Accessibility, and Resource-Adapted Solutions

Ece Gökyayla[1], Neslihan Demirel Öğüt[2]

[1]Department of Dermatology and Venereology, Ege University Faculty of Medicine, İzmir, Türkiye
[2]Department of Dermatology and Venereology, Uşak University Faculty of Medicine, Uşak, Türkiye

Abstract

Aim: Mycosis fungoides [(MF) the most common primary cutaneous T-cell lymphoma] is difficult to diagnose early, and treatment access is uneven in middle-income countries; therefore, we aimed to describe current practice, identify barriers, and propose guideline-aligned, resource-adapted solutions.

Materials and Methods: Cross-sectional anonymous online survey of dermatologists (May–June 2025) on diagnostic workflows/access, treatments, and barriers. Analyses were performed using SPSS v23, with descriptive statistics and Spearman's rho correlations. Two-tailed $P < 0.05$ was considered significant.

Results: Among 239 respondents, 61.1% managed MF; 49.3% reported diagnostic uncertainty, and T-cell receptor testing was rarely available. The use of diagnostic algorithms and structured training was inconsistent. Basic topical agents and retinoids were widely available, whereas advanced systemic and device-based options were scarce. Barriers clustered around registration and market availability, workforce constraints, and equipment and maintenance issues. Reported workarounds included evidence-based substitutions, interim symptom-directed therapy, repeat biopsies, and referrals; multidisciplinary tumor boards were underused.

Conclusion: MF care is heterogeneous and resource constrained. A four-component plan — a national diagnostic algorithm with a minimum package and a re-biopsy–consultation–multidisciplinary team loop; targeted capacity building; tiered treatment pathways prioritizing narrow-band ultraviolet B ± retinoids with clear referral thresholds; and system integration via centers of excellence, a national registry, and device uptime programs — may standardize care and improve outcomes.

Keywords: Mycosis fungoides, cutaneous T-cell lymphoma, diagnostic challenges, therapeutic accessibility, resource-adapted solutions

Introduction

Mycosis fungoides (MF) is the most common form of primary cutaneous T-cell lymphoma (CTCL), representing the majority of CTCL cases worldwide.[1] It typically presents as slowly evolving erythematous or mildly pigmented, atrophic patches in sun-protected sites and may progress to infiltrated plaques, tumors, or erythroderma in advanced stages.[1,2] MF displays substantial clinicopathologic heterogeneity, making early diagnosis difficult. Lesions may mimic other dermatoses, such as eczema, psoriasis, or chronic dermatitis, and histopathologic findings are often non-specific.[3,4] In this context, clinicopathological correlation, supported by immunophenotyping and, where available, molecular testing, is essential, and multiple international guidelines recommend a multimodal diagnostic approach. However, real-world

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Address for correspondence: Ece Gökyayla, Department of Dermatology and Venereology, Ege University Faculty of Medicine, İzmir, Türkiye
Email: ecegokyayla@gmail.com
ORCID ID: 0000-0003-0178-6642

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adherence to these recommendations varies widely depending on access to diagnostic resources, specialist expertise, and healthcare infrastructure.

Since accurate diagnosis forms the foundation for disease staging and staging is the principal determinant of treatment selection, these processes are intrinsically linked to ensuring optimal MF care. Early-stage disease is generally approached with skin-directed therapies, while advanced stages often require systemic agents, frequently in combination with skin-directed therapies for symptom control.[5-7] The therapeutic hierarchy outlined in international guidelines is supported by systematic reviews and meta-analyses, which confirm the efficacy of these modalities but also reveal substantial variation in patient outcomes and treatment availability across healthcare systems.[8-10] Such differences are often shaped by disparities in access to advanced diagnostic tools, limitations in the availability of systemic therapies, and inconsistent application of guideline-based protocols, all of which may lead to delays in diagnosis and deviations from evidence-based management.

We hypothesized that significant variability exists in both diagnostic and therapeutic practices for MF, shaped by disparities in resource availability and guideline implementation. To investigate this, we conducted a nationwide, cross-sectional survey among dermatologists in a middle-income country with universal health coverage, aiming to identify current practice patterns, barriers to optimal care, and locally adapted solutions to improve MF management within existing resource constraints.

Materials and Methods

Survey Design

This cross-sectional, questionnaire-based study was conducted between May and June 2025 to evaluate current challenges and potential solutions regarding diagnosis and access to treatments for MF among dermatologists in Türkiye. The survey instrument was developed by the study team. It consisted of qualitative and quantitative items, including open-ended, multiple-choice, and multiple-selection questions. The questionnaire aimed to investigate dermatologists' clinical experience with MF, diagnostic approaches, access to diagnostic modalities (e.g., histopathology, immunohistochemistry, molecular testing), treatment preferences (topical or device-based skin-directed therapies, systemic therapies), and barriers encountered in treatment access (e.g., reimbursement, availability, institutional limitations). Institutions were classified by service scope and technical capacity; rankings were based on technical resources, patient volume, and academic staff, in the following order: University Hospital, Training and Research Hospital, City Hospital, State Hospital, and Private Clinic. The content of the questionnaire is presented in Supplementary Table 1. The final version of the questionnaire was created using Google Forms. A survey link was generated and disseminated to Turkish dermatologists through dermatology-focused professional WhatsApp and Facebook groups on three separate occasions at two-week intervals, to enhance response rates and ensure representative participation.

Participants

The target population comprised dermatologists actively practicing in Türkiye who manage patients with MF in various clinical settings. Informed consent was obtained digitally prior to survey participation. The first page of the online survey included an information section outlining the purpose of the study, data use, and confidentiality. Only participants who provided digital consent could proceed to complete the remaining parts of the questionnaire. Respondents not managing MF patients were included only in descriptive analyses; items requiring direct MF management experience were analyzed within the subgroup actively managing MF.

Statistical Analysis

All responses were collected anonymously. Data were exported to IBM SPSS Statistics version 23 for analysis. Descriptive statistics were used to summarize the data, with categorical variables presented as frequencies and percentages. Correlations between ordinal variables were assessed using Spearman's rank correlation coefficient (rho). All statistical tests were two-tailed, and a P-value < 0.05 was considered statistically significant.

Results

Participant Characteristics

A total of 239 dermatologists participated in the study. Figure 1 shows the distribution of participants by gender, professional experience, institution type, and academic title. Among them, 38.9% (n = 93) did not manage MF patients, most often due to inadequate technical resources (57.0%, n = 53), a preference to refer patients to specialized centers (43.0%, n = 40), no MF patient admissions (32.3%, n = 30), limited clinical experience (10.8%, n = 10), or lack of interest in MF care (7.5%, n = 7).

The remaining 61.1% (n = 146) reported actively managing MF patients. Most followed 0–5 patients annually (35.6%, n = 52), followed by 6–10 patients (22.6%, n = 33), 11–20 patients

(13.7%, n = 20), and > 20 patients (28.1%, n = 41). Patient volume correlated positively with years of clinical experience (Spearman's $\rho = 0.45$, $P < 0.001$). In daily practice, participants primarily referenced European Organisation for Research and Treatment of Cancer (EORTC) guidelines (35.6%, n = 52), National Comprehensive Cancer Network (NCCN) guidelines (30.8%, n = 45), or national experience (21.2%, n = 31), with relatively similar proportions across these three sources.

Diagnostic Approaches, Challenges, and Solutions

Figure 2 summarizes the reported diagnostic modalities. Clinical examination, multiple or repeat biopsies, and basic immunohistochemistry were used by more than 85% of respondents, whereas advanced tests, such as human T-cell lymphotropic virus-1/2 serology and *T-cell receptor* (*TCR*) gene rearrangement, were rarely or never applied.

Diagnostic challenges were common: 49.3% (n = 72) reported diagnostic uncertainty, and 41.1% (n = 60) did not use diagnostic algorithms or were unfamiliar with them. The most frequent obstacles were non-specific histopathology (79.5%, n = 116), atypical presentations (54.8%, n = 80), and clinicopathological discrepancies (51.4%, n = 75). Other reported barriers included pathologist inexperience (48.6%, n = 71) and limited access to advanced molecular techniques (19.2%, n = 28).

When facing such challenges, dermatologists most often performed clinical re-evaluation at follow-up (72.6%, n = 106) or performed repeated biopsies (69.9%, n = 102). Other strategies included symptomatic or topical treatment (49.3%, n = 72), pathology consultation (37.7%, n = 55), multidisciplinary discussion (19.2%, n = 28), and referral to specialized centers (24.7%, n = 36). The specific links between diagnostic barriers and adopted solutions are illustrated in Figure 3.

Therapeutic Accessibility Challenges and Solutions

Treatment accessibility varied by category, as demonstrated in Figure 4. Among topical agents, corticosteroids (99.3%, n = 145), tacrolimus (89.7%, n = 131), pimecrolimus (88.4%, n = 129), and topical bexarotene (82.2%, n = 120) were widely available, while mechlorethamine (2.1%, n = 3) and carmustine (0.7%, n = 1) were rarely or never accessible.

Among participants, 78.5% (n = 117) had an active phototherapy unit; narrowband ultraviolet B was universally available in these centers (100.0%, n = 117), whereas psoralen ultraviolet A (PUVA) (41.9%, n = 49), ultraviolet A1 (17.1%, n = 20), and excimer laser (8.5%, n = 10) were less common. Radiotherapy was accessible to 43.8% (n = 64) of respondents, whereas total skin electron beam therapy (TSEBT) (12.3%, n = 18) and photodynamic therapy (PDT) (5.5%, n = 8) were accessible to only a minority.

Among systemic therapies, acitretin (100.0%, n = 146) and methotrexate (97.9%, n = 143) were almost universally accessible; bexarotene was moderately accessible (50.7%, n = 74); and advanced agents such as brentuximab vedotin (28.1%, n = 41), pegylated interferon alfa-2a (17.1%, n = 25), vorinostat (9.6%, n = 14), and mogamulizumab (5.5%, n = 8) were rarely or never accessible.

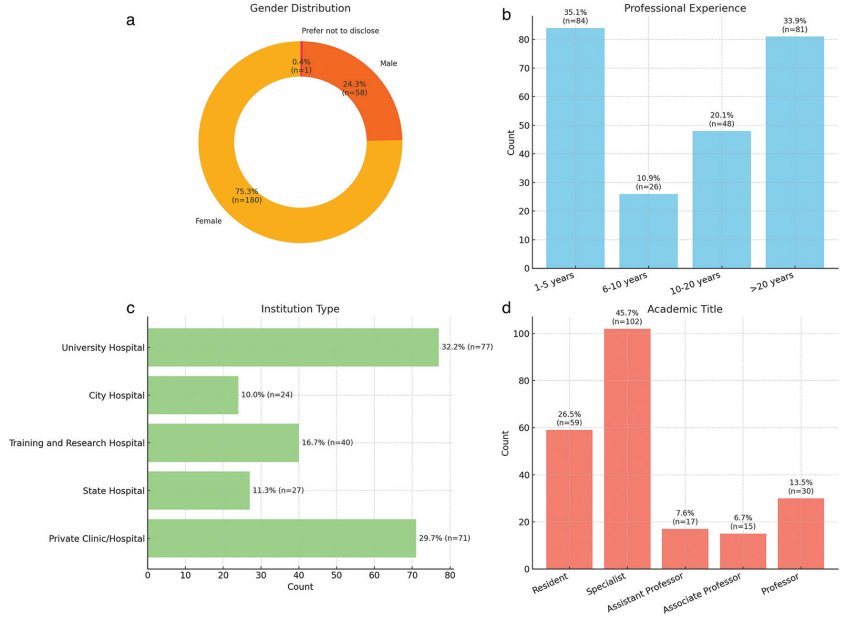

Figure 1. (a) Demographic and (b-d) professional characteristics of participating dermatologists

Reported barriers to access included lack of product registration (80.0%, n = 120), market unavailability (75.0%, n = 112), and limited clinical experience (60.0%, n = 90) for topical agents; lack of personnel (70.0%, n = 100) or device malfunction (65.0%, n = 93) for phototherapy; and lack of knowledge/experience (55.0%, n = 80) or market unavailability (50.0%, n = 73) for systemic treatments.

Accessibility limitations often led dermatologists to use alternative therapies (70.5%, n = 103) or to refer patients to better-equipped centers (57.5%, n = 84), with referral decisions guided by proximity to those centers, academic expertise, and technical capacity. Less common strategies included off-label or non-standardized treatments (6.8%, n = 10), observational management (4.8%, n = 7), and enrollment in clinical research (4.1%, n = 6). Table 1 summarizes selected treatment pathway modifications compared with major international guidelines, indicating whether these reflect guideline-endorsed alternatives, shifts in emphasis, or adaptations primarily driven by local clinical practice.

Discussion

In this study, we evaluated differences in the implementation of diagnostic and therapeutic practices for MF among

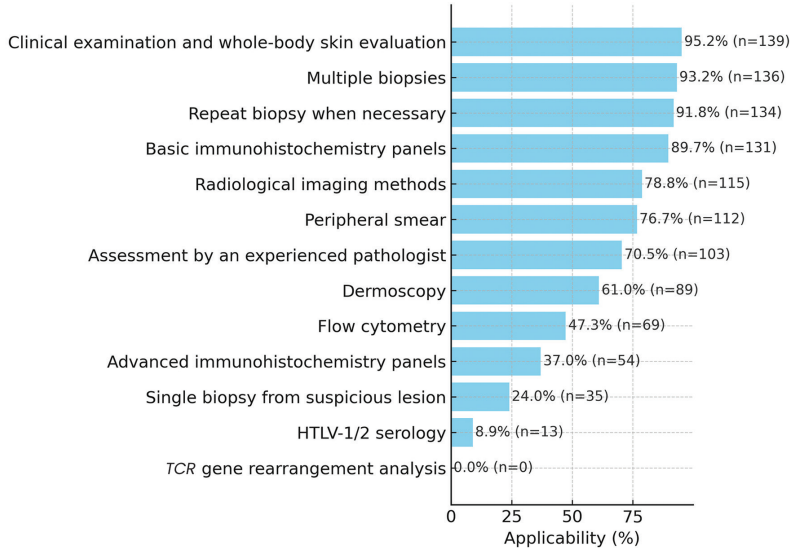

Figure 2. Availability of diagnostic modalities for MF among participating dermatologists
MF: Mycosis fungoides, TCR: T-cell receptor, HTLV-1: Human T-lymphotropic virus type 1, HTLV-2: Human T-lymphotropic virus type 2

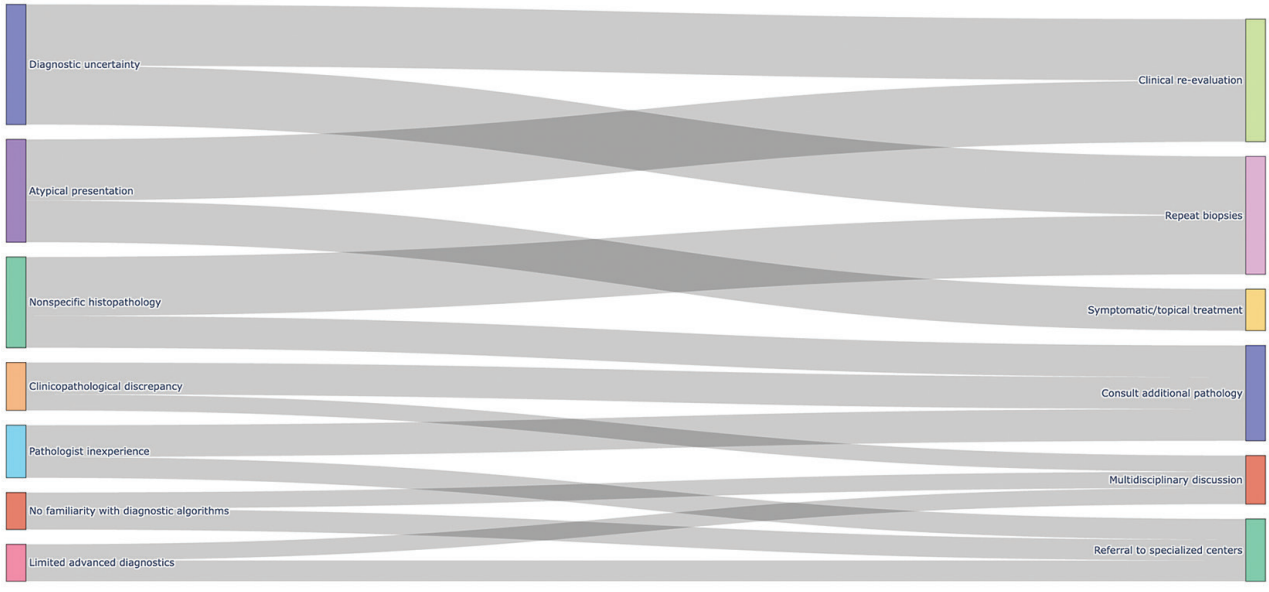

Figure 3. Common diagnostic challenges in MF and corresponding actions taken by participating dermatologists
(For clarity, major diagnostic challenges and corresponding management strategies illustrated in the figure are also summarized in the main text). MF: Mycosis fungoides

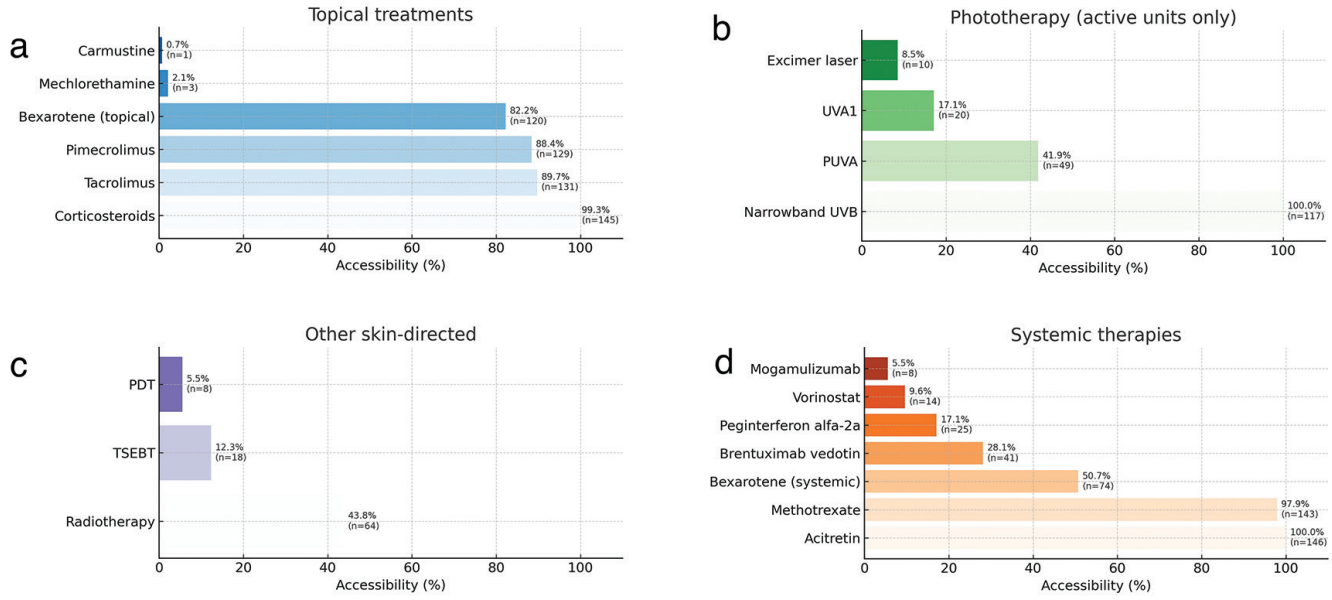

Figure 4. Accessibility of (a) topical treatments, (b) phototherapy modalities, (c) other skin-directed therapies, and (d) systemic therapies for MF among participating dermatologists
MF: Mycosis fungoides, PUVA: Psoralen ultraviolet A, TSEBT: Total skin electron beam therapy, PDT: Photodynamic therapy, UVB: Ultraviyole B

Table 1. Summary of treatment pathway modifications in relation to major international guidelines

	Intervention	Guideline position (EORTC 2023/NCCN 2025/ BAD 2018)	Alignment classification
Skin-directed topical treatments	**Topical tazarotene instead of topical bexarotene**	EORTC 2023: Topical tazarotene is not recommended due to limited evidence and lack of availability; topical bexarotene is not approved in Europe. NCCN 2025: Recommends topical bexarotene; tazarotene is not listed. BAD 2018: Topical bexarotene mentioned; tazarotene absent.	Non-guideline substitution (experience-based)
Skin-directed device based treatments	**Prioritizing nbUVB over PUVA in early stage**	EORTC 2023: PUVA and nbUVB both recommended at same evidence level. NCCN 2025: Lists PUVA and nbUVB without priority. BAD 2018: PUVA preferred in most cases.	Preference shift within guideline options
	Systemic retinoid + nbUVB instead of PUVA	EORTC 2023: PUVA and nbUVB are both recommended at the same level; systemic retinoids can be combined with phototherapy if needed. NCCN 2025: Allows retinoid + phototherapy combinations; no strict preference over PUVA. BAD 2018: PUVA preferred; combination therapy possible but not standard first choice.	Preference shift within guideline options
	Local RT ± systemic treatment for few tumors; TSEBT ± systemic treatment for many tumors	EORTC 2023: Matches this stage-based selection. NCCN 2025: Fully aligned with RT for limited lesions and TSEBT/systemic for widespread. BAD 2018: Similar recommendations.	Full alignment
	For device-based therapy with no alternative: refer to higher-level center		Local practice policy

Table 1. Continued

	Intervention	Guideline position (EORTC 2023/NCCN 2025/ BAD 2018)	Alignment classification
Systemic therapies	**Replacing oral bexarotene with oral acitretin/isotretinoin**	EORTC 2023: Retinoids (acitretin, isotretinoin, bexarotene) all listed; no superiority proven. NCCN 2025: Notes acitretin and isotretinoin as alternatives to bexarotene. BAD 2018: Includes retinoids as systemic options; no strict preference.	Guideline-approved alternative
	Early use of systemic retinoids ± Peg-IFN-α in plaque/ folliculotropic disease	EORTC 2023: Retinoids and Peg-IFN-α are second-line/combination; not mandated early. NCCN 2025: Lists both as systemic options, usually after failure of skin-directed therapy. BAD 2018: Similar sequencing; not first-line in most cases.	Earlier use than standard
	IFN-β instead of IFN-α	EORTC 2023: Peg-IFN-α preferred; IFN- β not listed as option. NCCN 2025: Peg-IFN-α included; no IFN-β mention. BAD 2018: IFN-α recommended; IFN- β absent.	Non-guideline substitution (experience-based)
	Calling vorinostat early if "no response"	EORTC 2023: HDAC inhibitors (vorinostat, romidepsin) not first-line; for refractory/advanced disease. NCCN 2025: HDAC inhibitors listed after multiple prior lines. BAD 2018: Similar to EORTC/NCCN; later-line agents.	Earlier use than standard
	Listing BV/mogamulizumab	EORTC 2023: Strong evidence for both agents in advanced or pretreated disease. NCCN 2025: Recommends BV and mogamulizumab with supporting trial data. BAD 2018: Predates widespread approval; less emphasis.	Guideline-supported (recent agents)
	For systemic therapy with no alternative: refer to higher-level center		Local practice policy

EORTC: European Organisation for Research and Treatment of Cancer, NCCN: National Comprehensive Cancer Network, BAD: British Association of Dermatologists, PUVA: Psoralen ultraviolet A, nbUVB: Narrowband ultraviolet B, RT: Radiotherapy, TSEBT: Total skin electron beam therapy, IFN-α: Interferon alpha, Peg-IFN-α: Pegylated interferon alpha, IFN-β: Interferon beta, HDAC: Histone deacetylase, BV: Brentuximab vedotin

dermatologists and across centers. The results of this nationwide survey revealed substantial variability in MF diagnosis and treatment among dermatologists, with significant gaps in access to advanced diagnostic tools and therapies, frequent use of basic modalities, and adaptations in clinical practice driven by resource limitations, variable local expertise, and the absence of national guidelines.

Almost half of the respondents reported diagnostic uncertainty in MF, primarily due to non-specific histopathology and clinicopathological discrepancies. In early MF lesions, the alignment of atypical lymphocytes along the basal layer of the epidermis, the presence of numerous neoplastic lymphocytes in the epidermis, accompanied by minimal spongiosis, and papillary dermal fibrosis with characteristic wire bundle–like collagen fibers may be absent.[11] Atypical clinical presentations were another important cause of diagnostic difficulties for dermatologists diagnosing MF. The difficulty in considering MF among preliminary clinical diagnoses stems from its ability to mimic a broad spectrum of dermatoses, ranging from common inflammatory conditions such as atopic dermatitis and psoriasis to infectious and granulomatous diseases.[12] Similar diagnostic pitfalls have been described in multiple studies in which both dermatologists and dermatopathologists have faced challenges in differentiating early MF from benign inflammatory dermatoses in the absence of sufficient experience and repeated clinicopathological correlation.[13]

The survey results showed that 40% of dermatologists reported being unfamiliar with diagnostic algorithms. This finding highlights the need for wider implementation of algorithm-based approaches and points to a gap in training. In 2005, the International Society for Cutaneous Lymphomas proposed a diagnostic algorithm to improve the early diagnosis of MF. This algorithm includes four criteria: clinical findings, histopathological features, immunohistochemical results, and

TCR gene rearrangement.[14] Despite its high sensitivity, the algorithm's utility in clinical practice may be limited by its relatively low specificity.[15] The relatively high proportion of participants unfamiliar with diagnostic algorithms underscores a gap in structured diagnostic training, echoing the literature's call for wider implementation of standardized workflows and algorithm-based approaches.[16,17]

Limited access to advanced diagnostic tools, including TCR testing and comprehensive immunohistochemistry panels, represents a major barrier to the implementation of diagnostic algorithms in routine clinical practice, particularly in middle-income healthcare systems. In our study, the absence of *TCR* gene rearrangement testing likely reflects restricted access to specialized molecular laboratories and reimbursement constraints rather than indicating a lack of clinical relevance. This limitation may contribute to persistent diagnostic uncertainty, especially in early-stage disease, and hinder the full application of multimodal diagnostic approaches in real-world settings.

Evidence suggests that targeted investment in diagnostic infrastructure and specialist training can significantly enhance early-stage diagnostic accuracy. These findings strengthen the case for developing a national MF guideline aligned with established frameworks such as EORTC, NCCN, and British Association of Dermatologists guidelines,[5-7] but adapted to local realities using structured approaches.[18]

Treatment accessibility patterns in our data showed frequent use of guideline-consistent substitutions, including replacing oral bexarotene with acitretin or isotretinoin.[5-7] However, other observed modifications, such as early introduction of pegylated interferon or topical tazarotene, lack robust evidence and are largely experience-driven. In several publications, the authors have developed algorithms based on local settings, specified the level of evidence, and clarified stepwise treatment approaches. In these examples, treatment protocols for classic MF have been specifically adapted to local resources and skin phototypes.[19,20]

Prospective, multicenter evaluations are needed to determine the safety and efficacy of these practices. Given the rarity of MF, establishing real-world evidence registries could support the validation and refinement of these adaptations in diverse care settings.[21]

Barriers to device-based therapies, including PUVA, TSEBT, and PDT, were common and often led to referral of patients to higher-capacity centers. This aligns with literature showing that centralization of complex MF care in specialized centers facilitates access to multidisciplinary expertise and advanced technologies, ultimately improving care quality.[22,23] Establishing dedicated MF centers of excellence could address these gaps while also serving as hubs for clinician training, clinical trials, and teledermatology-assisted outreach.

Finally, multidisciplinary management emerged as an underutilized resource in our findings, with only a minority of respondents participating in regular tumor board discussions. Multiple studies confirm that integrated multidisciplinary clinics improve diagnostic accuracy, streamline therapeutic decision-making, and enhance patient outcomes in cutaneous lymphomas.[22,23] Expanding such collaborative models, particularly in resource-constrained environments, could help bridge the gap between guideline recommendations and real-world practice.

Study Limitations

Several limitations should be acknowledged. First, the voluntary, self-administered online survey may have introduced selection bias, as respondents with a particular interest in or experience with MF may have been more likely to participate, potentially limiting the representativeness of the sample. In addition, all data were self-reported, raising the possibility of recall bias and inaccurate estimation of clinical practices, diagnostic capabilities, and treatment accessibility.

Moreover, the cross-sectional design captures practices at a single point in time and does not account for temporal changes in healthcare infrastructure or policy. Institutional characteristics were based solely on participants' reports without external verification. The lack of detailed information on patient outcomes, disease-stage distribution, or survival precludes direct assessment of clinical effectiveness.

Finally, the study was conducted within a middle-income healthcare system. While this context provides valuable insight into resource-limited settings, the generalizability of the findings to high-resource healthcare environments may be limited. In addition, the survey instrument was not formally validated, which should be considered when interpreting the results.

Conclusion

This study highlights substantial variability in diagnostic and therapeutic practices for MF, driven by challenges such as limited access to advanced diagnostic modalities, gaps in structured diagnostic training, and heterogeneous availability of treatments. The findings underscore the need to develop national guidelines aligned with international standards and adapted to local resource settings, to expand the use of standardized diagnostic algorithms, to strengthen specialist training, and to promote centralized, multidisciplinary care models to improve early diagnosis, optimize treatment decisions, and enhance overall patient outcomes.

Ethics

Ethics Committee Approval: Given the anonymous, non-interventional nature of the study, ethics committee approval was deemed unnecessary in accordance with institutional policy and national regulations.

Informed Consent: Informed consent was obtained digitally prior to survey participation.

Authorship Contributions

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

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We declare that artificial intelligence (ChatGPT) was utilized exclusively to enhance linguistic clarity during manuscript preparation, and the final content has been thoroughly reviewed and approved by all authors.

Footnotes

Conflict of Interest: At the time of the peer review and editorial evaluation of this manuscript, the author Ece Gökyayla was not a member of the journal's editorial board and had no involvement in the editorial decision-making process.

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References

1. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol. 2014;70(2):205.e1-16; quiz 221-222.
2. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, Bhagat G, Borges AM, Boyer D, Calaminici M, Chadburn A, Chan JKC, Cheuk W, Chng WJ, Choi JK, Chuang SS, Coupland SE, Czader M, Dave SS, de Jong D, Du MQ, Elenitoba-Johnson KS, Ferry J, Geyer J, Gratzinger D, Guitart J, Gujral S, Harris M, Harrison CJ, Hartmann S, Hochhaus A, Jansen PM, Karube K, Kempf W, Khoury J, Kimura H, Klapper W, Kovach AE, Kumar S, Lazar AJ, Lazzi S, Leoncini L, Leung N, Leventaki V, Li XQ, Lim MS, Liu WP, Louissaint A Jr, Marcogliese A, Medeiros LJ, Michal M, Miranda RN, Mitteldorf C, Montes-Moreno S, Morice W, Nardi V, Naresh KN, Natkunam Y, Ng SB, Oschlies I, Ott G, Parrens M, Pulitzer M, Rajkumar SV, Rawstron AC, Rech K, Rosenwald A, Said J, Sarkozy C, Sayed S, Saygin C, Schuh A, Sewell W, Siebert R, Sohani AR, Tooze R, Traverse-Glehen A, Vega F, Vergier B, Wechalekar AD, Wood B, Xerri L, Xiao W. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748. doi: 10.1038/s41375-022-01620-2. Erratum in: Leukemia. 2023;37(9):1944-1951.
3. Durgadevi S, Srinivas BH, Chandrashekar L, Gochhait D, Sreerekha J, Kar R. Clinicopathological spectrum of cutaneous lymphomas and distinction of early mycosis fungoides from its mimics-a retro-prospective descriptive study from Southern India. Indian Dermatol Online J. 2022;13(6):737-746.
4. Vitiello P, Sagnelli C, Ronchi A, Franco R, Caccavale S, Mottola M, Pastore F, Argenziano G, Creta M, Calogero A, Fiorelli A, Casale B, Sica A. Multidisciplinary approach to the diagnosis and therapy of mycosis fungoides. Healthcare (Basel). 2023;11(4):614.
5. Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, Parry EJ, Mohd Mustapa MF, Exton LS, Kanfer E, Rezvani K, Dearden CE, Morris SL. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. Br J Dermatol. 2019;180(3):496-526.
6. Latzka J, Assaf C, Bagot M, Cozzio A, Dummer R, Guenova E, Gniadecki R, Hodak E, Jonak C, Klemke CD, Knobler R, Morrris S, Nicolay JP, Ortiz-Romero PL, Papadavid E, Pimpinelli N, Quaglino P, Ranki A, Scarisbrick J, Stadler R, Väkevä L, Vermeer MH, Wehkamp U, Whittaker S, Willemze R, Trautinger F. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2023. Eur J Cancer. 2023;195:113343.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Primary Cutaneous Lymphomas (Mycosis Fungoides/Sézary Syndrome). Version 3.2025. Plymouth Meeting (PA): National Comprehensive Cancer Network; 2025. Available from: https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf.
8. Dogra S, Mahajan R. Phototherapy for mycosis fungoides. Indian J Dermatol Venereol Leprol. 2015;81(2):124-135.
9. Stuver R, Geller S. Advances in the treatment of mycoses fungoides and Sézary syndrome: a narrative update in skin-directed therapies and immune-based treatments. Front Immunol. 2023;14:1284045.
10. Şanlı H, Mart HME. Treatment algorithms for mycosis fungoides and Sézary syndrome. Turk J Dermatol. 2025;19(1):41-60.
11. Massone C, Kodama K, Kerl H, Cerroni L. Histopathologic features of early (patch) lesions of mycosis fungoides: a morphologic study on 745 biopsy specimens from 427 patients. Am J Surg Pathol. 2005;29(4):550-560.
12. Lebas E, Collins P, Somja J, Nikkels AF. A comprehensive update of the atypical, rare and mimicking presentations of mycosis fungoides. Dermatol Ther (Heidelb). 2021;11(6):1931-1951.
13. Hodak E, Geskin L, Guenova E, Ortiz-Romero PL, Willemze R, Zheng J, Cowan R, Foss F, Mangas C, Querfeld C. Real-life barriers to diagnosis of early mycosis fungoides: an international expert panel discussion. Am J Clin Dermatol. 2023;24(1):5-14.
14. Pimpinelli N, Olsen EA, Santucci M, Vonderheid E, Haeffner AC, Stevens S, Burg G, Cerroni L, Dreno B, Glusac E, Guitart J, Heald PW, Kempf W, Knobler R, Lessin S, Sander C, Smoller BS, Telang G, Whittaker S, Iwatsuki K, Obitz E, Takigawa M, Turner ML, Wood GS; International Society for Cutaneous Lymphoma. Defining early mycosis fungoides. J Am Acad Dermatol. 2005;53(6):1053-1063.
15. Vandergriff T, Nezafati KA, Susa J, Karai L, Sanguinetti A, Hynan LS, Ambruzs JM, Oliver DH, Pandya AG. Defining early mycosis fungoides: validation of a diagnostic algorithm proposed by the International Society for Cutaneous Lymphomas. J Cutan Pathol. 2015;42(5):318-328.
16. Boh E, Kuraitis D, Jacobson A, Sikes M. Healthcare provider experience in diagnosing and treating cutaneous T-cell lymphoma. Dermatol Ther (Heidelb). 2023;13(3):835-842.
17. Miyashiro D, Sanches JA. Mycosis fungoides and Sézary syndrome: clinical presentation, diagnosis, staging, and therapeutic management. Front Oncol. 2023;13:1141108.
18. Schünemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G, Scholten R, Langendam M, Leeflang MM, Akl EA, Singh JA, Meerpohl J, Hultcrantz M, Bossuyt P, Oxman AD; GRADE Working Group. GRADE Guidelines: 16. GRADE evidence to decision

frameworks for tests in clinical practice and public health. J Clin Epidemiol. 2016;76:89-98.

19. Sanches JA, Cury-Martins J, Abreu RM, Miyashiro D, Pereira J. Mycosis fungoides and Sézary syndrome: focus on the current treatment scenario. An Bras Dermatol. 2021;96(4):458-471.
20. Ibrahim MA, Eltayeb N, Ibrahim MM, Nassar A, Daruish M, El-Zimaity M, El-Lithy M, Mostafa A, El-Afifi A, Abdelbary H, El-Sayed MH. Suggested guidelines for the treatment of mycosis fungoides in countries with limited resources. Dermatol Res Pract. 2023;2023:1360740.
21. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, Robson A, Calonje E, Stefanato CM, Wain EM, Wilkins B, Fields PA, Dean A, Webb K, Scarisbrick J, Morris S, Whittaker SJ. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol. 2010;28(31):4730-4739.
22. Tyler KH, Haverkos BM, Hastings J, Hu E, Philips R, Gru AA, Welliver MX, Mishra A, Wong HK, Porcu P. The role of an integrated multidisciplinary clinic in the management of patients with cutaneous lymphoma. Front Oncol. 2015;5:136.
23. Poligone B, Querfeld C. Management of advanced cutaneous T-cell lymphoma: role of the dermatologist in the multidisciplinary team. Br J Dermatol. 2015;173(4):1081-1083.

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Original Article

Evaluation of Factors Associated with a History of Skin Cancer in Patients with Actinic Keratosis: AKASI as a Clinical Tool for Risk Stratification

Ece Erbağcı, Sema Koç Yıldırım, Neslihan Demirel Öğüt

Department of Dermatology and Venereology, Uşak University Faculty of Medicine, Uşak, Türkiye

Abstract

Aim: We aimed to investigate the clinical, demographic, and laboratory factors associated with a personal history of skin cancer in patients with actinic keratosis (AK), incorporating the actinic keratosis area and severity index (AKASI) and systemic inflammatory markers to identify potential risk factors for malignancy.

Materials and Methods: This single-center, cross-sectional study enrolled 110 patients with AK. Participants were categorized as having a histopathologically confirmed personal history of skin cancer (n = 33) or no personal history of skin cancer (n = 77). Demographic data, clinical characteristics, AKASI scores, and systemic inflammatory indices derived from complete blood counts were collected. Between-group comparisons were performed using appropriate statistical tests.

Results: Patients with a history of skin cancer were significantly older (73.6 ± 12.5 vs. 69.0 ± 9.3 years; $P = 0.036$), had longer AK duration (median, 60 vs. 36 months; $P = 0.003$), and had higher total AKASI scores (median, 5.4 vs. 3.9; $P = 0.044$) than those without a history of skin cancer. Right facial AKASI scores were also significantly higher ($P = 0.035$). Receiver operating characteristic analysis identified a total AKASI cut-off of 3.75, with fair discriminatory performance (area under the curve = 0.621, $P = 0.044$). No significant differences were observed in systemic inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR), derived NLR, platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio, mean platelet volume-to-platelet ratio, systemic immune-inflammation index, and systemic inflammation response index, between groups.

Conclusion: Older age, longer disease duration, and greater AK severity, as measured by AKASI, are associated with a personal history of skin cancer among patients with AK, whereas systemic inflammatory indices are not associated. AKASI may be useful for clinical risk stratification and patient surveillance.

Keywords: Actinic keratosis, actinic keratosis area and severity index, skin cancer

Introduction

Actinic keratosis (AK) is one of the most common dermatological diagnoses encountered in daily clinical practice, particularly among older individuals with significant ultraviolet (UV) radiation exposure. Often considered a hallmark of chronic photodamage, AK represents a spectrum of epidermal keratinocyte dysplasia that may regress, remain stable, or progress to invasive squamous cell carcinoma (SCC).[1,2] Epidemiologically, AK affects up to 60% of the adult population in sun-exposed regions, with prevalence increasing

Address for correspondence: Ece Erbağcı, Department of Dermatology and Venereology, Uşak University Faculty of Medicine, Uşak, Türkiye
Email: ece.erbagci@gmail.com
ORCID ID: 0000-0002-2887-0492

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with age, fair skin phototype, and cumulative sun exposure.[3] The concept of "field cancerization" underscores the idea that AK is not an isolated lesion, but part of a larger area of genetically altered skin at risk of malignant transformation.[4] Consequently, AK serves not only as a precursor to SCC but also as a clinical marker for heightened cutaneous oncologic risk.[5,6]

In daily practice, the burden of AK is often quantified by lesion counting; however, this approach insufficiently captures the extent of field cancerization and severity of individual lesions. To address this, Dirschka et al.[7] proposed the actinic keratosis area and severity index (AKASI), a composite score that incorporates the extent of involvement, lesion distribution, erythema, and thickness across four anatomical regions of the head. Subsequent work confirmed the reproducibility of AKASI and showed that it correlates with physician-based global severity assessments more robustly than total lesion count does.[8] Importantly, higher AKASI scores have been associated with an increased incidence of invasive cutaneous SCC in patients with chronically UV-damaged skin, supporting its use as a quantitative indicator of oncologic risk within the actinic field.[9]

Recent studies have also explored the role of systemic inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) as prognostic factors in cutaneous malignancies, particularly melanoma and non-melanoma skin cancers (NMSC).[10-14] However, data on these markers in the context of AK remain scarce and inconclusive. It remains to be determined whether systemic inflammation contributes meaningfully to the carcinogenic process in early-stage, pre-invasive lesions such as AK.

In this context, our study aimed to investigate the clinical, demographic, and hematologic parameters associated with a personal history of skin cancer among patients diagnosed with AK. By integrating AKASI scoring and systemic inflammatory indices, we sought to evaluate potential predictors of malignancy risk, with the aim of enhancing early identification and clinical management of high-risk individuals.

Materials and Methods

Study Design and Patient Selection

This single-center, cross-sectional study was conducted at the dermatology outpatient clinic of our hospital over a three-month period. Consecutive patients who received a clinical diagnosis of AK were invited to participate during their dermatologic evaluation. Patients who provided written informed consent were enrolled in the study. The exclusion criteria included pediatric patients; individuals with genodermatoses associated with an increased risk of skin cancer (e.g., xeroderma pigmentosum, Gorlin syndrome); individuals with an unclear or unverified history of skin cancer; individuals who did not provide informed consent; and patients with hematological or lymphoproliferative disorders (such as leukemia, lymphoma, or polycythemia vera) that could affect blood count parameters. The study protocol was approved by the Uşak University Non-Interventional Clinical Research Ethics Committee (approval number: 395-395-17, date: 06.06.2024) and was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic information (age and sex), anthropometric measurements [height, weight, and body mass index (BMI)], and smoking status (current, former, or never) were collected for each participant. The presence of systemic immunosuppression, defined as an underlying immunosuppressive condition and/or the use of immunosuppressive medication, was also recorded. The Fitzpatrick skin phototype was determined for all participants. Skin cancer-related clinical data included a personal history of histopathologically confirmed skin cancer [including basal cell carcinoma (BCC), SCC, melanoma, or other skin malignancies] and a family history of skin cancer in first-degree relatives. AK-specific clinical variables included age at AK onset and disease duration (in months), the latter defined as the time elapsed from the patient-reported onset of the first AK lesion to the study enrollment date.

Inflammatory Parameters

Complete blood count (CBC) results were obtained within three months prior to enrollment. Patients without accessible CBC data during this period were excluded from the hematologic analyses. The recorded CBC parameters included white blood cell count (WBC), absolute counts of neutrophils (Neu), lymphocytes (Lym), and monocytes (Mon), hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin (MCH), MCH concentration, red cell distribution width (RDW), platelet count (Plt), mean platelet volume (MPV), plateletcrit, and platelet distribution width. Using these variables, the following systemic inflammatory indices were calculated: (NLR = Neu/Lym), derived NLR [dNLR = Neu/(WBC–Neu)], monocyte-to-lymphocyte ratio (MLR = Mon/Lym), (PLR = Plt/Lym), and MPV-to-platelet ratio (MPR = MPV/Plt). Additionally, more complex composite indices were derived: [SII = (Neu × Plt)/Lym] and systemic inflammation response index [SIRI = (Neu × Mon)/Lym].[11,15]

AKASI Calculation

The clinical severity of AK on the head was assessed using the AKASI. Scoring was performed by the enrolling dermatologist (one of the three study authors) at the time of evaluation. The AKASI system, originally proposed by Dirschka et al.,[7] divides the head into four anatomical regions: the scalp, the forehead, the right facial region, and the left facial region. For each region, four parameters are assessed: percentage of skin area affected, lesion distribution, erythema intensity, and thickness of the most severe lesion. These parameters are graded on predefined ordinal scales. A regional subscore is calculated by multiplying the sum of the component scores by a region-specific coefficient. The total AKASI score is obtained by summing all four regional subscores, yielding a value ranging from 0 (no AK) to 18 (maximum severity).[7-9]

Group Classification

After data collection, patients were categorized into two groups based on their personal history of skin cancer: (i) skin cancer group: patients with histopathologically confirmed skin cancer (current or prior); and (ii) non-skin cancer group: patients without a history of skin cancer. The two groups were compared in terms of demographic and clinical characteristics, AKASI scores, and laboratory parameters, including individual CBC indices and derived inflammatory markers.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). To detect a statistically significant difference between patients with and without a history of skin cancer in the primary outcome (mean total AKASI score) and secondary outcomes (hematologic inflammatory indices), the minimum required sample sizes were estimated as 52 participants for the primary outcome and at least 102 participants for the secondary outcomes, based on a statistical power of 80% and a Type I error rate (α) of 5%. Numerical variables were examined for normality using appropriate graphical methods and tests, and were then summarized as mean ± standard deviation for approximately normally distributed data or as median (interquartile range) for skewed data. Categorical variables were expressed as counts and percentages. Between-group comparisons of continuous variables were performed using independent-samples t-tests or Mann–Whitney U tests, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off values. A two-sided P-value < 0.05 was considered statistically significant.

Results

A total of 110 patients diagnosed with AK were included in the study. Of these, 33 patients (30%) with a personal history of histopathologically confirmed skin cancer were assigned to the skin cancer group, whereas the remaining 77 patients (70%) comprised the non-skin cancer group. Among patients with skin cancer, 13 had a history of SCC, 22 had a history of BCC (4 of whom had histories of both SCC and BCC), and 2 had a history of melanoma. Table 1 summarizes the demographic, clinical, and laboratory features of patients with AK, along with a comparative analysis between those with and without a history of skin cancer.

The mean age of the entire cohort was 70.4 ± 10.5 years and was significantly higher in the skin cancer group than in the non-skin cancer group (73.6 ± 12.5 vs. 69.0 ± 9.3; $P = 0.036$). There were no statistically significant differences between the groups in terms of sex distribution, height, weight, or BMI ($P > 0.05$ for all). Similarly, no significant differences between the groups were observed in smoking status, Fitzpatrick skin phototype distribution, immunosuppression status, or family history of skin cancer ($P > 0.05$ for all comparisons).

Regarding disease characteristics, the mean age at AK onset was comparable between the groups (66.2 ± 12 vs. 65.3 ± 8.6; $P = 0.689$). However, the duration of AK (months) was significantly longer in the skin cancer group [60 (24–108) vs. 36 (12–60); $P = 0.003$]. In terms of disease severity, the median total AKASI score was significantly higher in patients with a history of skin cancer than in those without [5.4 (3.6–6.3) vs. 3.9 (2.7–5.7), $P = 0.044$]. A significant difference was also noted in the right facial AKASI scores [1.8 (1.5–2.1) vs. 1.5 (1.2–1.8); $P = 0.035$], whereas the other regional scores (scalp, forehead, and left face) were comparable between the groups ($P > 0.05$ for all).

ROC analysis was performed to determine the optimal cut-off value of the total AKASI score for predicting a history of skin cancer. The area under the curve (AUC) was 0.621 (95% confidence interval: 0.512–0.731, $P = 0.044$), indicating fair discriminatory ability. The cut-off point of 3.75 yielded the highest Youden index (J = 0.221), corresponding to a sensitivity of 72.7% and a specificity of 49.4%. Therefore, a total AKASI score ≥ 3.75 may serve as a clinically relevant threshold to stratify patients with a possible history of skin cancer.

Table 1. Comparison of demographic and clinical features, AKASI scores, and inflammatory parameters between patients with and without skin cancer

Variables*	Skin cancer group (n = 33, 30%)	Non-skin cancer group (n = 77, 70%)	Total (n = 110, 100%)	*P*
Age (years)	73.6 ± 12.5	69.0 ± 9.3	70.4 ± 10.5	0.036
Sex				
Female	17 (51.5%)	48 (62.3%)	65 (59.1%)	0.3
Male	16 (48.5%)	29 (37.7%)	45 (40.9%)	
Body weight (kg)	70.7 ± 12.4	75.4 ± 14.7	74.0 ± 14.2	0.106
Height (cm)	165 (157–170)	160 (155–170)	160 (155–170)	0.743
BMI (kg/m^2)	26 (23–30)	28.4 (25–31.2)	27.6 (24.7–31.1)	0.092
Smoking status				
Non-smoker	22 (66.7%)	61 (79.2%)	83 (75.5%)	
Current smoker	2 (6.1%)	7 (9.1%)	9 (8.2%)	0.226
Former smoker	9 (27.3%)	9 (11.7%)	18 (16.4%)	
Fitzpatrick skin phototype				
I	1 (3%)	4 (5.2%)	5 (4.5%)	
II	20 (60.6%)	46 (59.7%)	66 (60%)	
III	12 (36.4%)	26 (33.8%)	38 (34.5%)	
IV	0 (0%)	1 (1.3%)	1 (0.9%)	
Light-skinned (types I–II)	21 (63.6%)	50 (64.9%)	71 (64.5%)	
Darker-skinned (types III–IV)	12 (36.4%)	27 (35.1%)	39 (35.5%)	1
Presence of immunosuppression	1 (3%)	3 (3.9%)	4 (3.6%)	1
Positive family history of skin cancer	2 (6.1%)	10 (13%)	12 (10.9%)	0.505
Skin cancer subtype				
SCC	13 (39.4%)	-	13 (11.8%)	
BCC	22 (66.7%)	-	22 (20%)	
Melanoma	2 (6.1%)	-	2 (1.8%)	
Age at AK onset (years)	66.2 ± 12	65.3 ± 8.6	65.6 ± 9.7	0.689
Disease (AK) duration (months)	60 (24–108)	36 (12–60)	36 (12–81)	0.003
AKASI score				
Scalp	0 (0–0)	0 (0–0)	0 (0–0)	0.709
Forehead	1.2 (0–1.8)	1.2 (0–1.5)	1.2 (0–1.8)	0.2
Left face	1.8 (1.2–2.1)	1.5 (1.2–1.8)	1.5 (1.2–2.1)	0.254
Right face	1.8 (1.5–2.1)	1.5 (1.2–1.8)	1.6 (1.2–2.1)	0.035
Total	5.4 (3.6–6.3)	3.9 (2.7–5.7)	4.3 (3.0–6.2)	0.044
Inflammatory parameters				
NLR	2.1 (1.6–3)	2 (1.4–2.6)	2 (1.5–2.7)	0.393
dNLR	1.6 (1.3–2)	1.5 (1.2–1.8)	1.6 (1.2–1.9)	0.389
PLR	111.8 (88.5–152.7)	116.8 (91.6–143.7)	116.3 (91.2–145.2)	0.841
MLR	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.2 (0.2–0.3)	0.163
MPR	0 (0–0.1)	0 (0–0.1)	0 (0–0.1)	0.9
SII	517.8 (363.3–602)	473.3 (342.6–640.2)	483.7 (348.9–633.5)	0.498
SIRI	1 (0.7–1.7)	0.9 (0.5–1.4)	1.0 (0.6–1.5)	0.183

*Data are presented as mean ± SD, median (IQR), or n (%), as appropriate
AK: Actinic keratosis, AKASI: Actinic keratosis area and severity index, BMI: Body mass index, SCC: Squamous cell carcinoma, BCC: Basal cell carcinoma, NLR: Neutrophil-to-lymphocyte ratio, dNLR: Derived neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, MPR: Mean platelet volume-to-platelet count ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, SD: Standard deviation, IQR: Interquartile range

Among the hematologic inflammatory indices, none of the parameters, including NLR, dNLR, PLR, MLR, MPR, SII, and SIRI, showed statistically significant differences between the skin cancer and non-skin cancer groups ($P > 0.05$ for all). These inflammatory indices were also evaluated across skin cancer subtypes (i.e., patients with SCC vs. patients without SCC, patients with BCC vs. patients without BCC, and patients with melanoma vs. patients without melanoma). Similarly, no statistically significant differences were observed between the groups (all $P > 0.05$). In the correlation analysis, neither total nor right facial AKASI scores were significantly associated with systemic inflammatory markers (NLR, PLR, MLR) or composite indices such as SII and SIRI (all $P > 0.05$).

Discussion

In this study, we evaluated the demographic, clinical, and hematological characteristics of patients diagnosed with AK to investigate their associations with a history of skin cancer. Our findings revealed significant differences between patients with and without a history of skin cancer. Patients with a history of skin cancer were older, had longer AK duration, and had higher AKASI scores. These results support the notion that age and cumulative sun exposure are critical factors in the development of skin cancer.[5,6,16] Although hematologic inflammatory parameters were evaluated, no significant differences were observed between groups.

AK is recognized as a precursor to SCC and increasingly viewed as an *in situ* carcinoma because of its potential for malignant transformation. Both AK and SCC exhibit atypical keratinocyte proliferation in the basal and lower spinous layers of the epidermis, with shared molecular alterations such as p53 mutations and UV-signature DNA damage.[17] The annual rate of transformation of AK lesions to SCC ranges from 0.025% to 16%, depending on risk factors.[1] About 60-80% of cutaneous SCCs arise in areas with preexisting AK.[2,18]

Field cancerization highlights that visible AK may reflect broader oncogenic risk in the surrounding skin.[4] AK has been associated with an increased risk of other skin cancers, including BCC and melanoma. In a Swedish cohort study, Guorgis et al.[6] found that AK patients had elevated risks of all major skin cancers, with hazard ratios of 7.7 for SCC, 4.4 for BCC, and 2.7 for melanoma. The highest risk was for SCC, supporting AK as a direct precursor of SCC. In an Australian study, a history of AK was among the top predictors in a melanoma risk model.[19] These findings suggest that AK, especially when severe, predicts SCC risk and indicates photodamage that predisposes to cutaneous malignancies.

Advanced age is a recognized risk factor for cutaneous malignancies due to cumulative UV exposure and age-related decline in immune surveillance.[1] Studies show that longer AK duration and greater extent reflect more severe field cancerization and indicate higher malignant potential.[20,21]

The AKASI has been increasingly utilized to evaluate both the extent and the severity of AK in sun-exposed areas, such as the face and scalp.[7] In our study, patients with a history of skin cancer had significantly higher AKASI scores, suggesting its utility both as a grading tool and as a risk-stratification index for cutaneous malignancies. A multicenter validation study by Pellacani et al.[8] confirmed AKASI's reproducibility and reliability, reporting high intra- and inter-observer consistency (intraclass correlation coefficient > 0.90). They found it superior to total lesion count for assessing disease burden, particularly in cases with confluent erythema and field changes that are common in chronic photodamage. Schmitz et al.[9] showed that AKASI correlates with subclinical field cancerization, with higher scores indicating more extensive keratinocyte dysplasia and UV damage, which are established precursors of SCC and BCC.

Acar and Karaarslan[22] found elevated AKASI scores in patients with previous or current NMSC and proposed a cut-off value of 5.1 to distinguish between patients with and without skin cancer (P = 0.013). Our analysis identified a lower threshold (cut-off = 3.75 for total AKASI) with an AUC of 0.621. These differences may arise from semi-subjective elements in AKASI scoring, such as assessment of erythema and lesion confluence, which can vary between observers despite training. Interobserver variability, differences in clinical experience, and lighting conditions can influence outcomes.[7,8] This necessitates larger studies with standardized protocols to validate thresholds across populations. It should also be noted that these values are calculated based on a history of skin cancer. Prospective studies with long-term follow-up of patients are needed to assess its importance for estimating future risk of skin cancer. Despite these limitations, AKASI remains valuable for evaluating AK severity and field cancerization, potentially enhancing detection strategies and treatment monitoring.

Certain established risk factors, such as systemic immunosuppression and a family history of skin cancer, were not significantly associated with skin cancer in our study population. This divergence may be explained by several factors. Our cohort included a small number of immunosuppressed individuals, limiting statistical power. Previous studies linking immunosuppression to aggressive SCC have often focused on organ transplant recipients or patients with hematologic malignancies, who were underrepresented in our sample.[23] Family history is often underreported in elderly patients, potentially explaining the lack of association.

The role of systemic inflammation in skin cancer development has recently received increased attention. Blood-derived indices have been proposed as biomarkers reflecting tumor-associated immune dysregulation; however, clinical performance varies across studies of melanoma and NMSC, and evidence for precancerous conditions, such as AK, is limited.

In an analysis of United States adults from the National Health and Nutrition Examination Survey, Zhao et al.[11] found that individuals with the highest SII had higher odds of NMSC. Chiu et al.[13] found that higher NLR, PLR, and RDW, and lower lymphocyte-to-monocyte ratio, were associated with worse survival in cutaneous SCC. Maeda et al.[24] showed

that elevated NLR was associated with reduced survival and increased sentinel lymph node positivity. Derebaşınlıoğlu et al.[10] reported higher inflammatory indices in SCC than in BCC and linked higher SII to lymph node metastasis.

Hematologic inflammatory indices from CBC have been linked to melanoma stage and prognosis. In a cohort of 2,721 patients with melanoma, NLR, PLR, and MLR increased with advancing stage, and higher baseline values of these markers were independently associated with poorer melanoma-specific and overall survival.[25] Meta-analyses show that elevated pretreatment NLR is associated with poorer overall and progression-free survival in melanoma.[14,26] For PLR, individual studies suggest prognostic utility, but pooled evidence is inconsistent. One study found PLR independently predicted overall survival,[27] while a meta-analysis showed no significant association with survival outcomes.[28] Composite indices show peripheral blood inflammation indices correlate with advanced cutaneous melanoma,[29] and analyses suggest higher SII associates with increased melanoma odds.[30] However, in advanced melanoma receiving immunotherapy, the pan-immune-inflammation value and SII varied by stage but did not predict response or survival.[31]

The lack of significant associations in our AK cohort may reflect limited statistical power, the presence of many "skin cancer" cases that are prior diagnoses rather than active tumors, and the small number of melanoma cases in our sample, as most supportive data are derived from melanoma cohorts. Cancer-related inflammation varies with tumor stage and condition; different tumors elicit distinct inflammatory responses. AK occurs within a field of cancerization, and localized immune activity may not produce measurable systemic biomarker changes unless invasion or widespread immunosuppression occurs, suggesting the need to study localized and molecular biomarkers for early lesion stratification. Their routine use in AK risk assessment requires larger prospective studies to determine their role in early detection and in predicting progression.

Study Limitations

This study has several limitations. First, the study was a single-center, cross-sectional analysis conducted over a limited period, which limits generalizability and precludes causal inference regarding the associations among AK severity, systemic inflammatory indices, and skin cancer history. AK was diagnosed clinically without histopathological confirmation, potentially introducing diagnostic misclassification. The primary outcome was a personal history of confirmed skin cancer, rather than incident or future cases of cancer; key AK variables (e.g., onset and duration) relied on patient report, thereby introducing recall bias. The statistical power was limited by the modest cohort size (n = 110) and by the small number of patients with prior skin cancer (n = 33), including two cases of melanoma. The inflammatory markers were derived from CBC within three months prior to enrollment and may not reflect inflammation at a time point relevant to carcinogenesis. AK severity was scored by the enrolling dermatologist; despite AKASI's utility, its semi-subjective components may contribute to measurement variability.

Despite its limitations, our study is important, as it is one of the first to evaluate the prognostic relevance of systemic inflammatory indices in AK patients. By incorporating AKASI into the analysis, we found that standardized AK severity scoring for risk stratification.

Conclusion

Collectively, our results suggest that systemic inflammatory indices may have limited practical value for risk assessment in AK, whereas clinical severity measures, such as AKASI, may help identify higher risk patients. Therefore, older patients, those with a longer disease duration, and particularly those with higher AKASI scores may warrant closer surveillance for skin cancer.

Ethics

Ethics Committee Approval: The study protocol was approved by the Uşak University Non-Interventional Clinical Research Ethics Committee (approval number: 395-395-17, date: 06.06.2024) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Patients who provided written informed consent were enrolled in the study.

Footnotes

Authorship Contributions

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

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References

1. Criscione VD, Weinstock MA, Naylor MF, Luque C, Eide MJ, Bingham SF; Department of Veteran Affairs Topical Tretinoin Chemoprevention Trial Group. Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer. 2009;115(11):2523-2530.
2. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet. 1988;1(8589):795-797.
3. George CD, Lee T, Hollestein LM, Asgari MM, Nijsten T. Global epidemiology of actinic keratosis in the general population: a systematic review and meta-analysis. Br J Dermatol. 2024;190(4):465-476.
4. Willenbrink TJ, Ruiz ES, Cornejo CM, Schmults CD, Arron ST, Jambusaria-Pahlajani A. Field cancerization: definition, epidemiology, risk factors, and outcomes. J Am Acad Dermatol. 2020;83(3):709-717.
5. Lee JH, Kim YH, Han KD, Park YM, Lee JY, Park YG, Lee YB. Incidence of actinic keratosis and risk of skin cancer in subjects with actinic keratosis: a population-based cohort study. Acta Derm Venereol. 2018;98(3):382-383.
6. Guorgis G, Anderson CD, Lyth J, Falk M. Actinic keratosis diagnosis and increased risk of developing skin cancer: a 10-year cohort study of 17,651 patients in Sweden. Acta Derm Venereol. 2020;100(8):adv00128.
7. Dirschka T, Pellacani G, Micali G, Malvehy J, Stratigos AJ, Casari A, Schmitz L, Gupta G; Athens AK Study Group. A proposed scoring system for assessing the severity of actinic keratosis on the head: actinic keratosis area and severity index. J Eur Acad Dermatol Venereol. 2017;31(8):1295-1302.
8. Pellacani G, Gupta G, Micali G, Malvehy J, Stratigos AJ, Casari A, Chester J, Kaleci S, Dirschka T. Actinic keratosis area severity index (AKASI): reproducibility study and comparison with total lesion count. Br J Dermatol. 2018;179(3):763-764.
9. Schmitz L, Gambichler T, Gupta G, Stücker M, Dirschka T. Actinic keratosis area and severity index (AKASI) is associated with the incidence of squamous cell carcinoma. J Eur Acad Dermatol Venereol. 2018;32(5):752-756.
10. Derebaşınlıoğlu H, Demir H, Nemmezi Karaca S. The role of inflammatory markers in the differential diagnosis of skin cancers. J Contemp Med. 2022;12(5):761-769.
11. Zhao H, Wu J, Wu Q, Shu P. Systemic immune-inflammation index values are associated with non-melanoma skin cancers: evidence from the National Health and Nutrition Examination Survey 2010-2018. Arch Med Sci. 2024;20(4):1128-1137.
12. Atasever Akkas E, Erdis E, Yucel B. Prognostic value of the systemic immune-inflammation index, systemic inflammation response index, and prognostic nutritional index in head and neck cancer. Eur Arch Otorhinolaryngol. 2023;280(8):3821-3830.
13. Chiu KC-K, Liau J-Y, Chu C-Y, Liao Y-H, Sheen Y-S. Prognostic Value of pretreatment systemic inflammatory markers in cutaneous squamous cell carcinoma: a single-center retrospective study. Dermatol Ther. 2025;2025(1);1-10.
14. Yang Y, Fang H, Cai Z, Xu Q. Prognostic significance of neutrophil-to-lymphocyte ratio in melanoma: a systematic review and meta-analysis. J Surg Oncol. 2025;132(3):456-464.
15. Zhou Q, Su S, You W, Wang T, Ren T, Zhu L. Systemic inflammation response index as a prognostic marker in cancer patients: a systematic review and meta-analysis of 38 cohorts. Dose Response. 2021;19(4):15593258211064744.
16. Khalesi M, Whiteman DC, Doi SA, Clark J, Kimlin MG, Neale RE. Cutaneous markers of photo-damage and risk of basal cell carcinoma of the skin: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2013;22(9):1483-1489.
17. Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis"). J Am Acad Dermatol. 2000;42(1 Pt 2):11-7.
18. Röwert-Huber J, Patel MJ, Forschner T, Ulrich C, Eberle J, Kerl H, Sterry W, Stockfleth E. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. Br J Dermatol. 2007;156 Suppl 3:8-12. Erratum in: Br J Dermatol. 2007;157(2):431.
19. Olsen CM, Green AC, Neale RE, Webb PM, Cicero RA, Jackman LM, O'Brien SM, Perry SL, Ranieri BA, Whiteman DC; QSkin Study. Cohort profile: the QSkin Sun and Health Study. Int J Epidemiol. 2012;41(4):929-929i.
20. Werner RN, Stockfleth E, Connolly SM, Correia O, Erdmann R, Foley P, Gupta AK, Jacobs A, Kerl H, Lim HW, Martin G, Paquet M, Pariser DM, Rosumeck S, Röwert-Huber HJ, Sahota A, Sangueza OP, Shumack S, Sporbeck B, Swanson NA, Torezan L, Nast A; International League of Dermatological Societies; European Dermatology Forum. Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies in cooperation with the European Dermatology Forum - Short version. J Eur Acad Dermatol Venereol. 2015;29(11):2069-2079.
21. Quaedvlieg PJ, Tirsi E, Thissen MR, Krekels GA. Actinic keratosis: how to differentiate the good from the bad ones? Eur J Dermatol. 2006;16(4):335-339.
22. Acar A, Karaarslan I. Comparison of actinic keratosis and severity index with physician global assessment and total lesion count and the ability to predict skin cancer. Dermatol Pract Concept. 2022;12(1):e2022031.
23. Harwood CA, Proby CM, McGregor JM, Sheaff MT, Leigh IM, Cerio R. Clinicopathologic features of skin cancer in organ transplant recipients: a retrospective case-control series. J Am Acad Dermatol. 2006;54(2):290-300.
24. Maeda T, Hiura A, Uehara J, Toyoshima R, Nakagawa T, Yoshino K. Neutrophil-to-lymphocyte ratio is associated with survival and sentinel lymph node positivity in invasive cutaneous squamous cell carcinoma: a retrospective study. J Am Acad Dermatol. 2022;86(3):615-620.
25. Ertekin SS, Mangas C, Riquelme-Mc Loughlin C, Carrera C, Malvehy J, Puig S, Podlipnik S. Prognostic value of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and monocyte-to-lymphocyte ratio in melanoma patients: a cohort study. Acta Derm Venereol. 2024;104:adv27571.
26. Zhan H, Ma JY, Jian QC. Prognostic significance of pretreatment neutrophil-to-lymphocyte ratio in melanoma patients: a meta-analysis. Clin Chim Acta. 2018;484:136-140.
27. Qi Y, Zhang Y, Fu X, Wang A, Yang Y, Shang Y, Gao Q. Platelet-to-lymphocyte ratio in peripheral blood: a novel independent prognostic factor in patients with melanoma. Int Immunopharmacol. 2018;56:143-147.
28. Han SN, Feng SJ, Liu Y. Prognostic and clinicopathological significance of the platelet-to-lymphocyte ratio in melanoma: a meta-analysis involving 2099 patients. Kaohsiung J Med Sci. 2021;37(1):55-62.
29. Di Raimondo C, Fico A, Cicala M, Caposiena Caro RD, Di Domenico P, Lozzi F, Paganini C, Rossi P, Rapanotti C, Galluzzo M, Campione E, Emberti Gialloreti L, Bianchi L. Peripheral blood inflammation indexes correlate with advanced stages in cutaneous melanoma: a single-center retrospective study. Melanoma Res. 2025;35(5):361-365.
30. Tao Q, Wang C, Zeng L, Mao M, Lu Y, Wang C, Liu B. The role of systemic immune inflammation index in predicting melanoma. Front Oncol. 2025;15:1612579.
31. Susok L, Said S, Reinert D, Mansour R, Scheel CH, Becker JC, Gambichler T. The pan-immune-inflammation value and systemic immune-inflammation index in advanced melanoma patients under immunotherapy. J Cancer Res Clin Oncol. 2022;148(11):3103-3108.

Original Article

Discrepancies Between Disease Burden and Digital Search Interest in Dermatology: A Nationwide Google Trends Analysis from Türkiye

Ahmet Uğur Atılan, Niyazi Çetin
Department of Dermatology and Venereology, Pamukkale University Faculty of Medicine, Denizli, Türkiye

Abstract

Aim: To examine the correspondence between the burden of dermatological diseases, measured by disability-adjusted life years (DALYs), and public interest reflected in Google Trends (GTs) search activity in Türkiye, to provide evidence-based contributions for the development of effective public health strategies.

Materials and Methods: DALY estimates for 14 dermatological conditions were obtained from the Global Burden of Disease 2021 database. GTs scores for both medical and lay terms, derived from the Turkish Dermatology Association's patient brochures, were retrieved from January 2021 to May 2025. Relative search volume (RSV) values were normalized to those for acne vulgaris. Associations between DALY burden and search interest were assessed using Spearman's correlation coefficient.

Results: A positive correlation was observed between DALY burden and search interest (Spearman's correlation coefficient $\rho = 0.60$; $P = 0.024$). Acne vulgaris demonstrated a close alignment between the DALY rate (63.37 per 100,000) and the RSV value (76). Conditions with high DALY burden but low visibility included dermatitis (DALY rate = 113.24; RSV value = 8) and psoriasis (DALY rate = 66.6; RSV value = 16). Conversely, pruritus and scabies showed disproportionately high search interest relative to their DALY burden. Malignant melanoma (DALY rate = 18.5; RSV value = 3), squamous cell carcinoma (DALY rate = 14.37; RSV value = 1), and basal cell carcinoma (DALY rate = 0.01; RSV value = 1) had minimal digital visibility despite their clinical importance.

Conclusion: Google search activity captures only part of the epidemiological landscape of dermatological disease in Türkiye. Symptom-driven or highly visible conditions receive substantial attention, while chronic inflammatory diseases and dermatological malignancies remain markedly underrepresented. These discrepancies indicate missed opportunities for targeted awareness and early detection strategies, particularly for skin cancers where timely presentation is essential.

Keywords: Disability-adjusted life years, Google Trends, information seeking behavior, skin diseases, Türkiye/epidemiology

Introduction

Skin diseases constitute a significant public health problem because of their high prevalence and substantial impact on quality of life.[1] The burden of these diseases is typically measured using the disability-adjusted life year (DALY) metric, which combines years of life lost due to premature death with years lived with disability.[2] While DALY burden data provide an objective measure of disease impact, they may not fully reflect public awareness or information-seeking behavior.[3]

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Address for correspondence: Ahmet Uğur Atılan, Department of Dermatology and Venereology, Pamukkale University Faculty of Medicine, Denizli, Türkiye
Email: auatilan@pau.edu.tr
ORCID ID: 0000-0001-9244-1011

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In recent years, digital data sources have emerged as valuable tools for assessing public interest in health-related issues. Digital health data, particularly from Google Trends (GTs), offer new insights into how societies perceive and prioritize health concerns.[4] Previous studies have used search patterns to monitor infectious diseases and public responses during health crises.[5,6] However, little is known about whether the dermatological disease burden aligns with digital search interest, and this relationship has rarely been investigated in countries with high dermatological disease prevalence and rapidly expanding digital health engagement, such as Türkiye.[7] Beyond its national relevance, Türkiye's large and diverse population, positioned at the crossroads of Asia and Europe,[8] makes it a valuable context to generate insights applicable to other regions with similar demographic and digital health dynamics.

Against this background, this study investigates the relationship between DALY rates and GTs search interest for 14 dermatological diseases using 2021 data from Türkiye, aiming to delineate potential concordance or divergence between epidemiological burden and patterns of public information-seeking behavior.

Materials and Methods

Study Design and Data Sources

DALY estimates for dermatological diseases in 2021 were obtained from the Global Burden of Disease (GBD) database for Türkiye.[9] The 14 conditions with the highest DALY rates were included: dermatitis, psoriasis, scabies, non-melanoma skin cancer (squamous cell carcinoma and basal cell carcinoma), malignant melanoma, fungal skin diseases, viral skin diseases, acne vulgaris, alopecia areata, bacterial skin diseases, pruritus, urticaria, and decubitus ulcer.

Search Term Identification and Query Strategy

To capture search behavior consistent with terms used by the public, disease names were complemented with lay expressions identified from patient information brochures published by the Turkish Dermatology Association. Both medical terms and alternative names commonly used in everyday language were employed as search queries (Table 1).[10] Searches were conducted on the GTs platform (https://trends.google.com) using the following parameters: region = Türkiye; time frame = January 1, 2021-May 12, 2025; category = all categories; search type = web search.

The GBD data were restricted to 2021, as this represents the most recent year for which DALY estimates are available. In contrast, GTs data were collected through May 12, 2025, to mitigate potential distortions in search behavior during the coronavirus disease-2019 (COVID-19) pandemic year (2021) and better capture overall search patterns and long-term public interest trends, consistent with prior approaches that compared disease burden with multi-year search data.[11]

Normalization and Data Processing

GT provides relative search volume (RSV) values normalized on a scale from 0 to 100. Because the platform allows comparison of up to five terms at a time, "acne vulgaris," the condition with the highest overall search

Table 1. Turkish search terms used for Google Trends analysis by disease

Disease	Search terms
Acne vulgaris	"akne vulgaris", "sivilce", "akne"
Psoriasis vulgaris	"psoriasis vulgaris", "sedef", "sedef hastalığı", "psoriasis"
Alopecia areata	"alopesi areata", "saç kıran", "sakal kıran"
Urticaria	"ürtiker", "kurdeşen"
Malignant melanoma	"malign melanom", "melanom", "ben kanseri"
Scabies	"scabies", "skabiyez", "uyuz"
Pruritus	"pruritus", "kaşınma", "kaşıntı"
Basal cell carcinoma	"bazal hücreli karsinom", "bazal hücreli kanser", "BCC"
Squamous cell carcinoma	"skuamöz hücreli karsinom", "skuamöz hücreli kanser", "SCC"
Viral skin diseases	"siğil", "uçuk", "Herpes", "molloskum", "molloscum", "zona", "gece yanığı", "6. hastalık", "virüs ve deri"
Bacterial skin diseases	"selülit", "impetigo", "pyoderma", "abse", "çıban", "fronkül", "karbonkül", "eritrezma", "lenfadenit", "bakteri ve deri"
Fungal skin diseases	"tinea", "tırnak mantarı", "deri mantarı", "saç mantarı", "deri ve mantar"
Decubitus ulcer	"dekubit ülseri", "bası yarası", "yatak yarası", "dekubit yarası"
Dermatitis	"dermatit", "egzema", "ekzema", "atopik dermatit", "atopik egzema", "seboreik dermatit", "kontakt dermatit", "allerjik egzema"

Search terms include both English medical terminology and Turkish colloquial terms commonly used by the general population. For each disease category, the term group with the highest search interest was identified and used as the representative search term

interest, was used as the reference term in all queries. RSV values for other conditions were normalized relative to acne to ensure comparability. Weekly RSV data retrieved from multiple GT sessions were merged into a unified dataset, and annual mean RSV values were calculated for subsequent correlation analyses. Within each disease category, the search term with the highest average RSV was selected as representative. Complete lists of all search terms and their corresponding weekly RSV data are provided in Supplementary Table 1.

Comparative Analysis

Normalized annual RSV values were compared with DALY burden estimates for Türkiye in 2021 to evaluate the relationship between public information-seeking behavior and the epidemiological burden of dermatological diseases.

Statistical Analysis

The distribution of normalized RSV and DALY data was first examined for normality using the Shapiro–Wilk test. As the data did not meet the assumptions of normality, non-parametric analyses were performed. Associations between disease-specific DALY rates and mean RSV values were assessed using Spearman's rank correlation coefficient (ρ). Scatterplots of GT-derived mean RSV versus $\log_{10}$-transformed DALY rates were generated to visualize these relationships, and ordinary least squares regression lines ($y = \beta_0 + \beta_1 x$, R^2) were superimposed as visual aids. Rank-discordance scores, calculated as (DALY rank–GT rank), were used to quantify discrepancies between disease burden and public interest. All analyses were conducted in R (version 4.5.1), with statistical significance set at $P < 0.05$.

Ethics Statement

This study was based exclusively on publicly available, de-identified data obtained from the GBD database and GTs platform. No individual-level or sensitive personal information was accessed. Accordingly, the analysis did not require approval from an institutional review board or informed consent from participants.

Results

Disease Burden

According to the GBD 2021 estimates for Türkiye, DALY rates for the 14 dermatological conditions ranged from 0.01 to 113.24 per 100,000 population. Dermatitis had the highest burden (113.24 per 100,000 population), followed by psoriasis (66.60 per 100,000), acne vulgaris (63.37 per 100,000), and urticaria (47.94 per 100,000). Alopecia areata (6.18), decubitus ulcer (4.33), and basal cell carcinoma (0.01) had the lowest burden. The overall mean DALY rate was 30.9 [standard deviation (SD) = 32.0], and the median was 18.7 [interquartile range (IQR) = 37.0] (Table 2).

Search Interest

GTs data from January 2021 to May 2025 yielded RSV values between 1 and 76. Acne vulgaris had the highest RSV (76), followed by viral skin diseases (47), pruritus (38), and

Table 2. Google Trends scores and disability-adjusted life year (DALY) rates for skin diseases in Türkiye

Disease	2021 DALY rate (per 100,000)	95% CI	Google Trends score (0-100)
Acne vulgaris	63.37	38.04-99.70	76
Viral skin diseases	36.82	23.30-55.54	47
Pruritus	11.44	5.58-20.66	38
Scabies	23.86	13.06-39.00	34
Urticaria	47.94	31.84-67.52	24
Psoriasis vulgaris	66.60	48.30-88.52	16
Bacterial skin diseases	7.01	4.97-10.25	12
Dermatitis	113.24	65.46-180.77	8
Fungal skin diseases	18.90	7.71-38.45	7
Alopecia areata	6.18	3.95-8.90	6
Malignant skin melanoma	18.50	8.92-24.86	3
Squamous cell carcinoma	14.37	11.25-19.43	1
Decubitus ulcer	4.33	2.35-5.56	1
Basal cell carcinoma	0.01	0.00-0.01	1

Data are sorted by Google Trends score in descending order. Google Trends scores range from 0 to 100, with higher values indicating greater search interest. CI: Confidence interval

scabies (34). Malignant melanoma (RSV = 3), squamous cell carcinoma (RSV = 1), basal cell carcinoma (RSV = 1), and decubitus ulcer (RSV = 1) had the lowest RSVs. The mean RSV across all conditions was 19.6 (SD 22.1), and the median was 10.0 (IQR: 27.8).

Correlation Between DALY and Search Interest

Spearman's rank correlation coefficient demonstrated a positive association between DALY burden and RSV values ($\rho = 0.60$; $P = 0.024$; 95% confidence interval: 0.10–0.86). Figure 1 presents the distribution of conditions, with $\log_{10}$-transformed DALY rates plotted against mean RSV values. An ordinary least-squares regression line was added for visualization.

Rank-Discordance Analysis

Rank-discordance scores (DALY rank minus RSV rank) quantified the divergence between epidemiological burden and search interest (Figure 2). Conditions with a higher search rank relative to their burden included pruritus (+7), bacterial skin diseases (+4), viral skin diseases (+3), alopecia areata (+2), scabies (+2), and acne vulgaris (+2). Conditions with a lower search rank relative to their burden included dermatitis (–7), psoriasis (–4), malignant melanoma (–3), squamous cell carcinoma (–3), fungal skin diseases (–2), and urticaria (–1). The Decubitus ulcer showed a minimal discrepancy (+1).

Discussion

This study demonstrated a statistically significant positive association between the epidemiological burden of dermatological diseases, measured by DALYs, and public interest as reflected in GTs search volumes in Türkiye ($\rho = 0.60$, $P = 0.024$). Beyond the overall positive correlation, specific patterns emerged when comparing disease burden and search behavior. Acne vulgaris exemplified the "high DALY, high search interest" category, reflecting strong concordance between objective burden and public attention. In contrast, dermatitis and psoriasis, despite being among the leading contributors to DALYs, demonstrated disproportionately low search interest (RSV values of 8 and 16, respectively). Conversely, conditions such as pruritus and scabies displayed relatively higher search volumes compared with their DALY burden, suggesting that symptomatic distress and transmissibility may shape digital health-seeking behavior. Finally, skin malignancies, including malignant melanoma and non-melanoma skin cancers, exhibited moderate-to-high DALYs but minimal search activity, indicating potential gaps in public awareness of oncologic dermatology.

Although dermatitis and psoriasis ranked among the leading contributors to DALYs, their corresponding search interest remained disproportionately low. Dermatitis, with the highest DALY burden among all conditions (113.24 per 100,000), had only a minimal RSV (8), whereas psoriasis, the second-highest DALY contributor (66.6 per 100,000), was similarly underrepresented in public search behavior (RSV = 16). This divergence suggests that despite their substantial

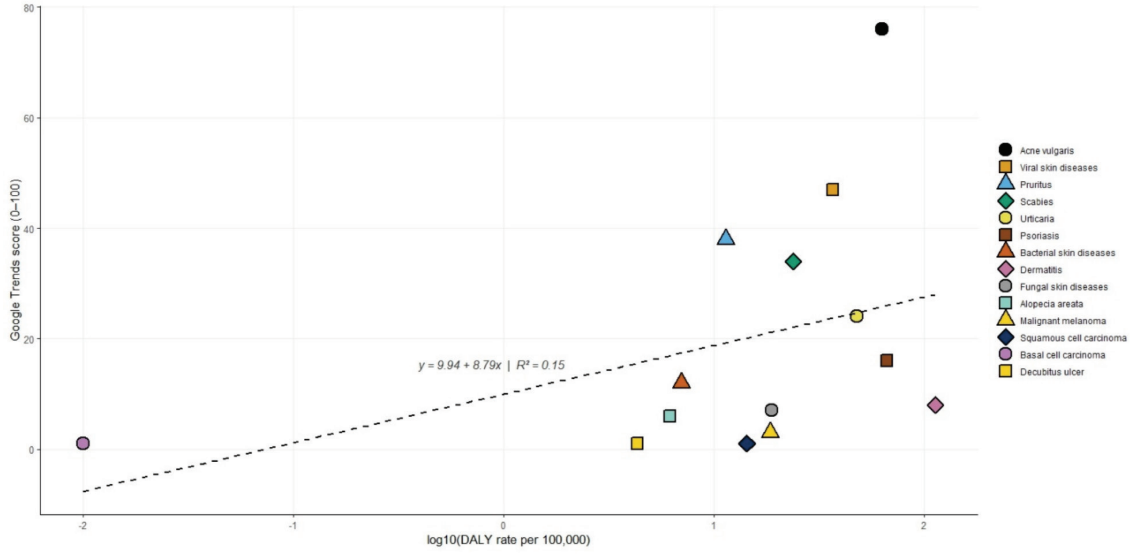

Figure 1. Correlation between disease burden and public search interest for skin diseases. Scatter plot showing the relationship between $\log_{10}$-transformed disability-adjusted life year rates per 100,000 population (x-axis) and Google Trends scores (y-axis, 0-100 scale) for 14 skin diseases in Türkiye. Each point represents a different skin disease as indicated in the legend. The dashed line represents the linear regression fit ($y = 9.94 + 8.79x$, $R^2 = 0.15$), indicating a weak positive correlation between disease burden and public search interest. Notable outliers include acne vulgaris with disproportionately high search interest relative to its disease burden

epidemiological impact, chronic and often normalized skin conditions may elicit limited digital attention, with online engagement tending to peak during treatment decisions or symptomatic flare-ups.[12] International evidence indicates that sustained awareness initiatives, such as World Psoriasis Day and Eczema Awareness Week, can generate measurable increases in online search activity, underscoring the role of advocacy-driven campaigns in amplifying visibility for chronic inflammatory skin diseases.[13-15] In Türkiye, however, comparable large-scale, digitally oriented efforts appear less prominent, which may partly account for the disproportionately low search interest in psoriasis and atopic dermatitis despite their substantial DALY burden.[16] Regional analyses of Google and YouTube activity for these conditions further demonstrate considerable geographic variability, suggesting that local health communication environments substantially shape digital health-seeking behavior.[17] Collectively, these factors may help explain the "high DALY–low RSV" pattern observed in Türkiye.

Skin malignancies, despite their substantial disease burden and associated mortality, exhibit markedly limited digital visibility. Malignant melanoma (DALY rate = 18.5) attracted minimal search interest (RSV value = 3), whereas squamous cell carcinoma (DALY rate = 14.37) and basal cell carcinoma (DALY rate = 0.01) attracted negligible online attention (RSV value = 1 each). This underrepresentation likely stems from the lower overall prevalence of these malignancies than common conditions such as acne, and from the predominance of skin cancers in older age groups, who typically have lower digital engagement and technology use than younger populations.[12,18] Although these demographic and epidemiological factors partially explain the low search volume, the persistently limited digital interest in life-threatening conditions indicates that current digital health strategies fail to effectively reach high-risk groups, reflecting a substantial awareness gap.[4] Such discrepancies underscore a critical void in public health messaging in Türkiye. While international experience, particularly in Australia, demonstrates that sustained digital outreach can drive measurable rises in search activity and early detection,[19] Türkiye currently lacks comparable high-visibility campaigns.[18] Addressing this deficit through targeted, age-sensitive, and digitally integrated strategies could help bridge the gap between clinical reality and public information-seeking behaviors.

Acne vulgaris had the highest GTs score (RSV value = 76), consistent with its DALY rate of 63.37 per 100,000, while viral skin diseases ranked fourth in DALY rate (38.82) but second in search interest (RSV value = 47). Their high visibility likely reflects both prevalence and impact on younger age groups.[12] Yet, elevated digital attention carries risks: for acne, misinformation and reliance on unverified online remedies can drive self-medication and delay professional care;[20] for viral skin diseases, public concern may amplify unfounded fears or promote ineffective treatments.[21] Such behaviors not only increase the risk of poorer outcomes but may also lead to increased economic costs through unnecessary product

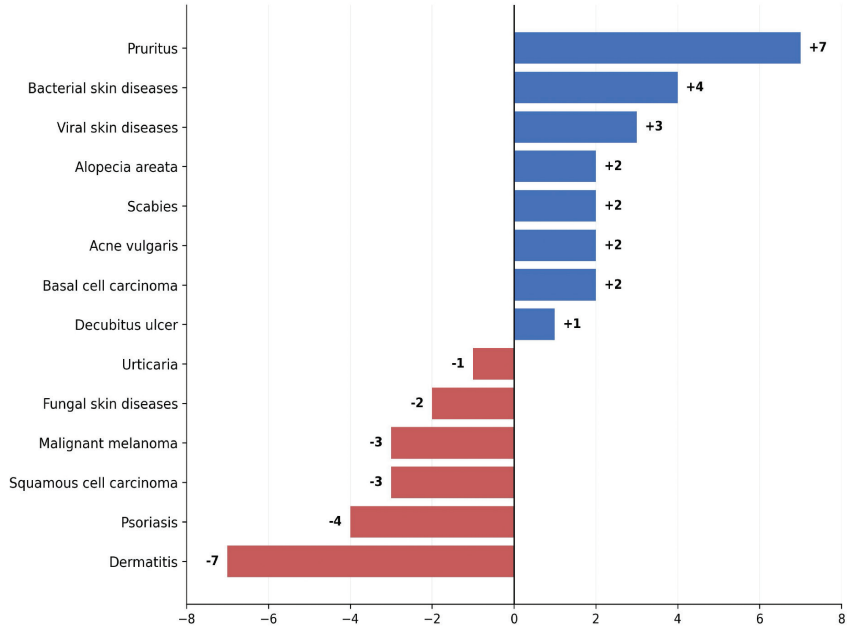

Figure 2. Difference between Google Trends search interest and disease burden for skin diseases in Türkiye. The horizontal axis represents the difference score between normalized Google Trends search interest and disability-adjusted life year burden. Positive values (blue bars) indicate diseases with higher search interest relative to their disease burden (over-represented in public interest), while negative values (red bars) indicate diseases with lower search interest relative to their disease burden (under-represented in public interest)

use and avoidable complications.[22] These findings highlight the need for reliable digital resources and targeted health communication to channel high online engagement into evidence-based care.

Pruritus and scabies, despite relatively low DALY rates (11.44 and 23.86 per 100,000, respectively), attracted disproportionately high levels of public search interest (RSV values of 38 and 34, respectively). This pattern highlights the influence of symptom-driven distress and transmissibility in shaping digital health-seeking behavior. Itch, while not life-threatening, is known to significantly impair quality of life and frequently triggers online information seeking.[23] In Türkiye, the elevated digital prominence of scabies appears to have been further reinforced by recent public health crises. During the COVID-19 pandemic, reduced access to dermatology services and increased household crowding contributed to rising incidence across several regions.[24] Likewise, following the 2023 Kahramanmaraş earthquakes, mass displacement and overcrowded shelters created favorable conditions for outbreaks of contagious skin diseases, including scabies.[25] These factors not only exacerbated the epidemiological burden but also intensified public concern, which likely translated into increased online search activity.

Building upon international evidence and comparative infodemiological patterns, we developed a Türkiye-specific digital dermatology recommendation framework (see Table 3) to guide national strategies for awareness, prevention, and surveillance.[13,19,20,26-30] The findings of this study underscore the potential of digital data to complement traditional epidemiological metrics in dermatology. The divergence observed between burden and search activity for certain conditions highlights the necessity of integrating digital surveillance tools into public health planning. Infodemiological approaches have been increasingly recognized for their ability to identify gaps in awareness, anticipate emerging health concerns, and guide resource allocation. In dermatology, where conditions vary widely in terms of visibility, symptom distress, and public perception, such methods may support more tailored health communication strategies and awareness campaigns, ultimately bridging the gap between epidemiological reality and societal priorities.

Study Limitations

Some limitations of this study should be acknowledged. GTs data reflect relative rather than absolute search volumes and may not capture differences across all demographic groups. In addition, the analysis was restricted to a selected group of dermatological conditions, which may not fully represent the broader spectrum of public interest in skin health. Future research incorporating a wider range of health conditions would be valuable to provide a more comprehensive understanding of digital health-seeking behavior.

Conclusion

The results of this study demonstrate that digital search interest and disease burden are not always proportionally aligned. While certain dermatological conditions with high DALY rates attract substantial public attention online, others remain underrepresented in digital searches despite their clinical significance. Understanding these discrepancies can help guide more effective public health messaging and awareness efforts, ensuring that educational and preventive strategies are not only informed by epidemiological data but also attuned to the patterns of public concern and curiosity.

Table 3. Alignment between disease burden and public search interest in dermatological conditions (Türkiye, 2021–2025)

Disease group	DALY–RSV pattern	Interpretation	Public health action
Chronic inflammatory dermatoses (dermatitis, psoriasis)	High DALY, Low RSV	- Fluctuating course[12] - Low visibility in campaigns[13]	- Develop condition-specific awareness campaigns[13,26] - Expand verified online educational tools[26]
Oncologic dermatology (melanoma, NMSC)	Moderate DALY, Very low RSV	- Low symptom salience[18,19] - Sparse digital campaigns[19]	- Promote early detection via digital tools[19,27] - Strengthen NGO–state outreach models[19,27]
Symptomatic/transmissible diseases (pruritus, scabies)	Low DALY, High RSV	- High symptom burden[23] - Epidemic contexts (e.g., COVID-19, earthquakes)[24,25]	- Monitor RSV for outbreak signals[28,29] - Embed messages into social media channels[28]
High-prevalence, visible skin conditions (acne, viral dermatoses)	High DALY, High RSV	- High youth prevalence[20] - Cosmetic/social concern[20,21]	- Improve digital health literacy[20,30] - Dispel misinformation through verified portals[30]

DALY: Disability-adjusted life year, RSV: Relative search volume, NMSC: Non-melanoma skin cancer, NGO: Non-governmental organization, COVID-19: Coronavirus disease-2019

Ethics

Ethics Committee Approval: This study was based exclusively on publicly available, de-identified data obtained from the Global Burden of Disease database and Google Trends platform. No individual-level or sensitive personal information was accessed.

Informed Consent: Accordingly, the analysis did not require approval from an institutional review board or informed consent from participants.

Footnotes

Authorship Contributions

Concept: A.U.A., Design: A.U.A., N.Ç., Data Collection or Processing: A.U.A., N.Ç., Analysis or Interpretation: A.U.A., N.Ç., Literature Search: A.U.A., N.Ç., Writing: A.U.A., N.Ç.

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References

1. Kantor J. Highlights from JAAD International: July 2025: The global burden of skin disease: insights and interventions. J Am Acad Dermatol. 2025;93(1):41.
2. Huai P, Xing P, Yang Y, Kong Y, Zhang F. Global burden of skin and subcutaneous diseases: an update from the Global Burden of Disease Study 2021. Br J Dermatol. 2025;192(6):1136-1138.
3. Zou Y, Liao K, Traidl S, Buhl T. Burden of inflammatory skin diseases based on GBD data: China vs USA. Acta Derm Venereol. 2025;105:adv43753.
4. Sivesind TE, Szeto MD, Kim W, Dellavalle RP. Google Trends in dermatology: scoping review of the literature. JMIR Dermatol. 2021;4(1):e27712.
5. Mangono T, Smittenaar P, Caplan Y, Huang VS, Sutermaster S, Kemp H, Sgaier SK. Information-seeking patterns during the COVID-19 pandemic across the United States: longitudinal analysis of Google Trends data. J Med Internet Res. 2021;23(5):e22933.
6. Chu AM, Chong ACY, Lai NHT, Tiwari A, So MKP. Enhancing the predictive power of Google Trends data through network analysis: infodemiology study of COVID-19. JMIR Public Health Surveill. 2023;9:e42446.
7. Karadag AS, Kandi B, Sanlı B, Ulusal H, Basusta H, Sener S, Calıka S. Social media use in dermatology in Turkey: challenges and tips for patient health. JMIR Dermatol. 2024;7:e51267.
8. Coban-Akdemir Z, Song X, Ceballos FC, Pehlivan D, Karaca E, Bayram Y, Mitani T, Gambin T, Bozkurt-Yozgatli T, Jhangiani SN, Muzny DM, Lewis RA, Liu P, Boerwinkle E, Hamosh A, Gibbs RA, Sutton VR, Sobreira N, Carvalho CMB, Shaw CA, Posey JE, Valle D, Lupski JR. The impact of the Turkish population variome on the genomic architecture of rare disease traits. Genet Med Open. 2024;2:101830.
9. Institute for Health Metrics and Evaluation (IHME). GBD results tool [Internet]. Seattle (WA): University of Washington; c2025 [updated 2025 May 12; cited 2026 Feb 6]. Available from: http://ghdx.healthdata.org/gbd-results-tool
10. Turkish Society of Dermatology. Patient information brochures [Internet]. Turkey: Turkish Society of Dermatology; c2025 [updated 2025 May 12; cited 2026 Feb 6]. Available from: https://www.dermatoloji.org.tr
11. Whitsitt J, Karimkhani C, Boyers LN, Lott JP, Dellavalle RP. Comparing burden of dermatologic disease to search interest on Google Trends. Dermatol Online J. 2015;21(1):13030/qt5xg811qp.
12. Reinders P, Augustin M, Fleyder A, Otten M. Exploring acceptability, barriers, and facilitators for digital health in dermatology: qualitative focus groups with dermatologists, nurses, and patients. JMIR Dermatol. 2024;7:e57172.
13. Malhotra K, Aggarwal P, Malhotra S, Goyal K. Evaluating the global digital impact of psoriasis action month and world psoriasis day: serial cross-sectional study. JMIR Dermatol. 2023;6:e49399.
14. Andrade LF, Bekhash M, Choragudi S, Gonzalez JM, Valdes R, Yosipovitch G. Impact of a digital atopic dermatitis educational intervention on hispanic patients and family members. J Clin Med. 2023;12(6):2130.
15. Gilbertson A, Ridd MJ, Sutton E, Liddiard L, Clayton J, Roberts A, Chan J, Bhanot A, Wellesley R, Dawson S. Engaging with diverse audiences to raise awareness about childhood eczema: reflections from two community events. Res Involv Engagem. 2021;7(1):6.
16. Özer İ, Yıldırım Dİ. Social awareness about psoriasis: Misconceptions, negative prejudices and discriminatory behavior. Dermatol Ther. 2020;33(6):e14059.
17. Hongler VNS, Navarini A, Brandt O, Goldust M, Mueller SM. Global Trends in YouTube and Google search activity for psoriasis and atopic eczema: detecting geographic hot spots, blind spots and treatment strategies. Dermatol Ther. 2020;33(4):e13510.
18. Uğrlu Z, Işık SA, Balanuye B, Budak E, Elbaş NÖ, Kav S. Awareness of Skin cancer, prevention, and early detection among Turkish university students. Asia Pac J Oncol Nurs. 2016;3(1):93-97.
19. Rasheed N. Melanoma awareness programs and their impact on the life of Australian Queenslanders: a concise analysis. Int J Health Sci (Qassim). 2024;18(1):1-3.
20. Ünal BÜ, Demirbaş A, Erdoğan BG. Social media use as a source of information by acne vulgaris patients. J Cosmet Dermatol. 2024;23(10):3312-3318.
21. Wojtara MS. Use of social media for patient education in dermatology: narrative review. JMIR Dermatol. 2023;6:e42609.
22. Borges do Nascimento IJ, Pizarro AB, Almeida JM, Azzopardi-Muscat N, Gonçalves MA, Björklund M, Novillo-Ortiz D. Infodemics and health misinformation: a systematic review of reviews. Bull World Health Organ. 2022;100(9):544-561.
23. Tizek L, Schielein M, Rüth M, Ständer S, Pereira MP, Eberlein B, Biedermann T, Zink A. Influence of climate on Google internet searches for pruritus across 16 German cities: retrospective analysis. J Med Internet Res. 2019;21(7):e13739.
24. Öztaş Kara R, Solak B, Kara A. Impact of COVID-19 lockdowns and refugee influx on scabies presentations to dermatology outpatient clinics in Turkey. J Infect Dev Ctries. 2024;18(12.1):S337-S343.
25. Beyoğlu MM, Gokler ME. The impact of scabies in tent cities in Kahramanmaraş after the Turkish earthquakes: oral pharmacologic treatment efficacy. PeerJ. 2024;12:e18242.
26. Gudmundsdóttir SL, Ballarini T, Ámundadóttir ML, Mészáros J, Eysteinsdóttir JH, Thorleifsdóttir RH, Hrafnkelsdóttir SK, Bragadóttir HB, Oddsson S, Silverberg JI. Clinical efficacy of a digital intervention for patients with atopic dermatitis: a prospective single-center study. Dermatol Ther (Heidelb). 2022;12(11):2601-2611.
27. Porter E, Rafferty S, Dolan M, McMahon D, Sheikhi A, Field S, Power E. The impact of a novel digital sun protection campaign on sun-related attitudes and behaviours of healthcare workers: a prospective observational study. Skin Health Dis. 2023;4(6):e256.
28. Liscano Y, Anillo Arrieta LA, Montenegro JF, Prieto-Alvarado D, Ordoñez J. Early warning of infectious disease outbreaks using social media and digital data: a scoping review. Int J Environ Res Public Health. 2025;22(7):1104.

29. Ayhan E. Status of the scabies outbreak before, during and after the Covid- 19 pandemic: a single-center hospital-based retrospective evaluation. BMC Infect Dis. 2025;25(1):481.

30. Wan V, Selvakumar R, Zhang Q, Fleming P, Lynde C. The Acne Education Project: an educational initiative to improve acne health literacy and promote help-seeking behavior in young adolescents. Pediatr Dermatol. 2024;41(1):51-57.

Supplementary Table 1: https://d2v96fxpocvxx.cloudfront.net/66b874bd-7aaa-4f61-9199-52f558d61c0d/content-images/5dbb2023-e2aa-42d5-b48c-bfe51b306f9f.pdf

Original Article

Contact Sensitization in Atopic Dermatitis Patients with Refractory Dermatitis

Ali Osman Metintaş[1], Leyla Baykal Selçuk[2], Deniz Aksu Arıca[2], Arzu Ferhatosmanoğlu[2], İbrahim Etem Arıca[2]
[1]Clinic of Dermatology, Ağrı Training and Research Hospital, Ağrı, Türkiye
[2]Department of Dermatology, Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye

Abstract

Aim: Allergic contact dermatitis (ACD) may accompany atopic dermatitis (AD) more frequently than previously recognized. This study aimed to identify concomitant contact sensitization and common allergens in patients with refractory AD.

Materials and Methods: In this prospective single-center study (September 2022–February 2024), 62 AD patients with treatment-resistant or atypically distributed lesions suggestive of contact dermatitis underwent patch testing using the European baseline series. Patch test reactions were evaluated on days 2 and 4 according to International Contact Dermatitis Research Group criteria; reactions graded as + or higher were considered positive. Results were compared with those of 306 non-AD patients who underwent patch testing for suspected ACD during the same period.

Results: The positivity rate for at least one allergen in AD patients was 62.9%, which was significantly higher than that observed in non-AD patients (40.2%). Nickel sulfate was the most frequently identified allergen.

Conclusion: These findings suggest that patients with AD may have increased susceptibility to contact sensitization, and patch testing in recalcitrant cases may help identify potential triggering allergens.

Keywords: Atopic dermatitis, contact sensitization, patch tests

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory disease of the skin that is frequently accompanied by other atopic conditions, including asthma, food allergy, and allergic rhinoconjunctivitis. The relationship between AD and the risk of contact sensitization remains controversial.[1] Early studies suggested a reduced prevalence of contact allergy in AD patients, possibly related to distinct immunological mechanisms.[1] However, impaired epidermal barrier function and prolonged or repeated exposure to topical treatments in AD may facilitate increased percutaneous penetration of irritants and allergens, thereby enhancing the risk of contact sensitization.[2] Clinically, distinguishing AD from concomitant allergic reactions, particularly allergic contact dermatitis (ACD), can be challenging, and both conditions may coexist in the same patient.[1] In this context, patch testing represents a valuable diagnostic tool, especially in AD patients with treatment-resistant disease, atypical lesion distribution, or clinical features suggestive of superimposed contact allergy.[2,3] Accordingly, current recommendations support patch testing in selected AD patients who present with these characteristics. Beyond reporting patch-test positivity rates, the present study aims to clarify the clinical utility of patch testing in AD patients who present with refractory, atypically distributed lesions and to compare their contact-sensitization profiles with those of non-AD patients.

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Address for correspondence: Ali Osman Metintaş, Clinic of Dermatology, Ağrı Training and Research Hospital, Ağrı, Türkiye
Email: osman.metintas@gmail.com
ORCID ID: 0000-0003-3840-7917

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Materials and Methods

A prospective study was conducted at our tertiary referral center between September 1, 2022, and February 29, 2024. The study included AD patients who were suspected of having concomitant ACD. AD was diagnosed according to the Hanifin–Rajka criteria, based on a detailed medical history and a current physical examination. Patients were eligible for inclusion if they presented with treatment-resistant lesions—defined as those that failed to resolve despite adequate topical therapy, or that recurred shortly after treatment discontinuation—or clinical features suggestive of contact dermatitis, including hand eczema, periorbital dermatitis, dermatitis with atypical distribution, adolescent- or adult-onset AD, and nummular dermatitis. Patients younger than eight years of age, pregnant women, individuals receiving active immunosuppressive therapy, patients with ultraviolet exposure within the preceding month, those who had applied topical treatments to the test area within one week prior to testing, and patients with active lesions involving the test area were excluded from the study. Disease severity was assessed using the scoring atopic dermatitis (SCORAD) index.[4] Patients were categorized into two groups according to age: pediatric (< 18 years) and adult (≥ 18 years). All participants underwent patch testing using the 2019 European baseline series, consisting of 30 allergens (chemotechnique diagnostics). Patch tests were applied to the upper back using IQ Ultra™ Chambers and were left in place for 48 hours. Patch test readings were performed on day 2 (D2) and day 4 (D4) by a single physician, following the routine protocol of our clinic and in accordance with the criteria of the International Contact Dermatitis Research Group.[4] Dynamic patch-test evaluation was applied: crescendo and plateau reactions were interpreted as positive, whereas decrescendo reactions were considered irritant and excluded from analysis. Due to limitations related to the study design and patient accessibility, day 7 (D7) readings were not routinely performed. Reactions graded as "+" or higher on D4 were considered positive. During the same period, consecutive patients suspected of ACD who did not have a diagnosis of AD were included as non-AD patients, serving as the control group.

Statistical Analysis

Statistical analyses were performed using SPSS software version 25.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as number and percentage. The normality of the distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Comparisons between two groups were performed using Student's t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test. A P-value < 0.05 was considered statistically significant.

Ethics Committee Approval

Ethical approval was obtained from the Karadeniz Technical University Institutional Ethics Committee (protocol number: 2022/119, date: June 30, 2022; approval number: 24237859-435). Written informed consent was obtained from all participants.

Results

Patch testing was performed on 62 AD patients aged 9–83 years [19 males (30.6%) and 43 females (69.4%); mean age, 31.19 ± 17.97 years]. According to the SCORAD index, 51 patients (82.3%) had mild disease and 11 patients (17.7%) had moderate disease (Table 1). The indications for patch testing in AD patients were: hand eczema (n = 19, 31%); periorbital dermatitis (n = 13, 21%); dermatitis with atypical distribution suggestive of contact dermatitis (n = 10, 16%); dermatitis resistant to standard treatments (n = 9, 14%); adolescent- or adult-onset AD (n = 6, 10%); and nummular dermatitis (n = 5, 8%). At least one positive patch test reaction was observed in 39 AD patients (62.9%). Positivity was detected in 26 of 43 females (60.5%) and 13 of 19 males (68.4%); there was no statistically significant difference between the sexes (P = 0.55). Among patients with positive reactions, 20 (51.3%)

Table 1. Sociodemographic characteristics and comorbidities of atopic dermatitis patients

Age (y), mean (SD)	31.19 (± 17.97)
Gender, n (%)	
Male	19 (30.6%)
Female	43 (69.4%)
Body mass index	24.01 (± 5.30)
SCORAD severity, n (%)	
Mild	51 (82.3%)
Moderate	11 (17.7%)
Treatment history, n (%)	
Topical agents only	39 (62.9%)
Systemic agents combined with topical	23 (37.1%)
Average disease duration (years)	10.89 (± 10.44)
Average number of exacerbations (per year)	5.19 (± 3.75)
Concomitant atopic comorbidity, n (%)	
Allergic rhinitis	18 (29%)
Allergic rhinoconjunctivitis	8 (12.9%)
Asthma	13 (21%)

Data are presented as mean ± standard deviation (SD) for continuous variables and as number (n) and percentage (%) for categorical variables. SCORAD: Scoring atopic dermatitis

reacted to a single allergen, while 19 (48.7%) reacted to two or more allergens, yielding a total of 65 positive reactions. The dynamic pattern analysis of patch test reactions is summarized in Table 2. Patch test positivity was observed in 32 of 51 (62.7%) patients with mild AD and 7 of 11 (63.6%) patients with moderate AD. No statistically significant difference in positivity rates was observed between the two groups (P = 1.000). Patients with severe AD could not be included in the study. The most frequently identified allergens in AD patients were nickel sulfate (n = 19, 30.6%), potassium dichromate (n = 7, 11.3%), fragrance mix I (n = 5, 8.1%), chloromethylisothiazolinone/methylisothiazolinone (n = 5, 8.1%), and textile dyes (n = 4, 6.5%). Of the 62 AD patients, 17 (27.4%) were pediatric patients and 45 (72.6%) were adult patients. At least one patch-test reaction was detected in five of 17 pediatric patients, most commonly nickel sulfate (n = 2; 11.8%). Among adults, 34 of 45 patients had positive reactions; nickel sulfate was again the most frequent allergen (n = 17, 37.8%). Nickel sulfate positivity was significantly higher in adults than children (P = 0.047). Positivity for potassium dichromate was higher in adults (n = 6, 13.3%) than in children (n = 1, 5.9%); however, this difference did not reach statistical significance (P = 0.662) (Table 3).

Table 2. Dynamic pattern analysis of the patch test reactions in 62 atopic dermatitis patients

No.	Patch test allergen	Positive reactions in atopic dermatitis patients n	Crescendo % (n)	Plateau % (n)	Decrescendo n
1	Potassium dichromate	7	71 (5)	29 (2)	2
2	p-Phenylenediamine	3	33 (1)	67 (2)	0
3	Thiuram mix	1	0 (0)	100 (1)	0
4	Neomycin sulfate	1	100 (1)	0 (0)	0
5	Cobalt chloride	3	67 (2)	33 (1)	3
6	Caine mix	0	0 (0)	0 (0)	1
7	Nickel sulfate	19	63 (12)	37 (7)	0
8	2-Hydroxyethyl methacrylate	1	100 (1)	0 (0)	0
9	Colophonium	1	0 (0)	100 (1)	1
10	Paraben mix	0	0 (0)	0 (0)	0
11	N-Isopropyl-N'-phenyl-p-phenylenediamine	1	0 (0)	100 (1)	1
12	Lanolin	1	0 (0)	100 (1)	0
13	Mercapto mix	0	0 (0)	0 (0)	0
14	Epoxy resin	1	100 (1)	0 (0)	1
15	Myroxylon pereirae	2	100 (2)	0 (0)	1
16	4-tert-Butylphenol formaldehyde resin	1	100 (1)	0 (0)	1
17	Mercaptobenzothiazole	0	0 (0)	0 (0)	0
18	Formaldehyde	1	100 (1)	0 (0)	0
19	Fragrance mix I	5	40 (2)	60 (3)	0
20	Sesquiterpene lactone mix	0	0 (0)	0 (0)	0
21	Quaternium-15	1	0 (0)	100 (1)	2
22	Propolis	1	0 (0)	100 (1)	3
23	Methylchloroisothiazolinone and methylisothiazolinone	5	60 (3)	40 (2)	0
24	Budesonide	0	0 (0)	0 (0)	0
25	Tixocortol pivalate	1	100 (1)	0 (0)	0
26	Methyldibromo glutaronitrile	1	100 (1)	0 (0)	4
27	Fragrance mix II	2	50 (1)	50 (1)	1
28	Hydroxylisohexyl 3-cyclohexenecarboxaldehyde	1	100 (1)	0 (0)	1
29	Methylisothiazolinone	1	100 (1)	0 (0)	1
30	Textile dye mix	4	50 (2)	50 (2)	4

Dynamic pattern analysis was performed in atopic dermatitis patients on days 2 and 4. Reaction patterns were categorized as crescendo or plateau. Reactions showing a decrescendo pattern that did not reach a positive reaction grade were considered irritant reactions and were not included as positive reactions. Initial irritant reactions were excluded from the analysis. Data are presented as numbers (n) and percentages (%). The value n represents only the patients with at least one positive reaction to the relevant allergen, not the total number of patients tested

Patch testing was also performed in 306 non-AD patients [122 males (39.9%) and 184 females (60.1%); mean age 33.47 ± 15.58 years]. No significant differences were observed between AD and non-AD groups with respect to age (P = 0.390) or sex distribution (P = 0.225). At least one positive patch test reaction was detected in 123 non-AD patients (40.2%). The overall positivity rate was significantly higher among AD patients than among non-AD patients (62.9% vs. 40.2%; P = 0.001). Nickel sulfate was the only allergen showing a statistically significant difference between the two groups (P = 0.016) (Table 4). Non-AD and AD patients were generally comparable with respect to demographic characteristics.

Patch testing for hand eczema was performed in 201 of 306 non-AD patients and 19 of 62 AD patients. At least one positive reaction was identified in 82 non-AD patients (40.8%) and in 16 AD patients (84.2%), indicating a statistically significant difference between the groups (P < 0.001). In non-AD patients with hand eczema, the most frequent allergens were nickel sulfate (n = 36, 17.9%) and potassium dichromate (n = 10, 5%). Similarly, nickel sulfate (n = 9, 47.4%) and potassium dichromate (n = 4, 21.1%) were the most common allergens among AD patients with hand eczema. Both allergens were significantly more frequent in AD patients than in non-AD patients (P = 0.005 and P = 0.023, respectively) (Table 5).

Table 3. Positivity rates of the two most frequent allergens in patch testing among adult and pediatric AD patients

	Nickel sulfate		Potassium dichromate	
	Number of positive reactions/total number of tests (n/nT, %)	***P*-value**	**Number of positive reactions/total number of tests (n/nT, %)**	***P*-value**
Pediatric group	n = 2/17 (11.8%)	**0.047**	n = 1/17 (5.9%)	0.662
Adult group	n = 17/45 (37.8%)		n = 6/45 (13.3%)	

Comparisons between adult and pediatric AD patients were performed using Fisher's exact test. Data are presented as the number of positive reactions per the total number of tests (n/nT) and as percentages (%). A P-value of < 0.05 was considered statistically significant. AD: Atopic dermatitis

Table 4. European baseline series and patch test positivity rates in AD and non-AD patients

No.	Patch test allergen	Conc. (%)	Positive reactions in AD patients n (% of tested)	Positive reactions in non-AD patients n (% of tested)	*P*-value
1	Potassium dichromate	0.5	7 (11.3%)	13 (4.2%)	0.057
2	p-Phenylenediamine	1.0	3 (4.8%)	7 (2.3%)	0.382
3	Thiuram mix	1.0	1 (1.6%)	8 (2.6%)	1.000
4	Neomycin sulfate	20.0	1 (1.6%)	5 (1.6%)	1.000
5	Cobalt chloride	1.0	3 (4.8 %)	12 (3.9%)	0.725
6	Caine mix	10.0	0 (0.0%)	2 (0.7%)	1.000
7	Nickel sulfate	5.0	19 (30.6%)	53 (17.3%)	**0.016**
8	2-Hydroxyethyl methacrylate	2.0	1 (1.6%)	2 (0.7%)	0.426
9	Colophonium	20.0	1 (1.6%)	5 (1.6%)	1.000
10	Paraben mix	16.0	0 (0.0%)	3 (1.0%)	1.000
11	N-Isopropyl-N'-phenyl-p-phenylenediamine	0.1	1 (1.6%)	1 (0.3%)	0.309
12	Lanolin	30.0	1 (1.6%)	2 (0.7%)	0.426
13	Mercapto mix	2.0	0 (0.0%)	5 (1.6%)	0.594
14	Epoxy resin	1.0	1 (1.6%)	2 (0.7%)	0.426
15	Myroxylon pereirae	25.0	2 (3.2%)	5 (1.6%)	0.335
16	4-tert-Butylphenol formaldehyde resin	1.0	1 (1.6%)	2 (0.7%)	0.426
17	Mercaptobenzothiazole	2.0	0 (0.0%)	4 (1.3%)	1.000
18	Formaldehyde	2.0 aq.	1 (1.6%)	2 (0.7%)	0.426
19	Fragrance mix I	8.0	5 (8.1%)	12 (3.9%)	0.180
20	Sesquiterpene lactone mix	0.1	0 (0.0%)	2 (0.7%)	1.000
21	Quaternium-15	1.0	1 (1.6%)	2 (0.7%)	0.426
22	Propolis	10.0	1 (1.6%)	6 (2.0%)	1.000
23	Methylchloroisothiazolinone and methylisothiazolinone	0.02 aq.	5 (8.1%)	9 (2.9%)	0.068

Table 4. Continued

No.	Patch test allergen	Conc. (%)	Positive reactions in AD patients n (% of tested)	Positive reactions in non-AD patients n (% of tested)	*P*-value
24	Budesonide	0.01	0 (0.0%)	0 (0.0%)	N/A
25	Tixocortol pivalate	0.1	1 (1.6%)	0 (0.0%)	0.168
26	Methyldibromo glutaronitrile	0.5	1 (1.6%)	4 (1.3%)	1.000
27	Fragrance mix II	14.0	2 (3.2%)	9 (2.9%)	1.000
28	Hydroxylisohexyl 3-cyclohexenecarboxaldehyde	5.0	1 (1.6%)	1 (0.3%)	0.309
29	Methylisothiazolinone	0.2 aq.	1 (1.6%)	7 (2.3%)	1.000
30	Textile dye mix	6.6	4 (6.5%)	12 (3.9%)	0.324

The substances are listed according to their order in the series. The vehicle was petrolatum unless otherwise indicated. Comparisons of patch test positivity rates between patients with and without AD were performed using Fisher's exact test. Data are presented as the number and percentage of patients with positive reactions. A *P*-value < 0.05 was considered statistically significant, and such values were indicated in bold. N/A: Not applicable, Conc.: Concentration, AD: Atopic dermatitis

Table 5. Comparison of the four most frequent allergens between AD and non-AD patients with hand eczema

	AD patients	Non-AD patients	*P*-value
	Number of positive reactions/total number of tests (n/nT, %)	Number of positive reactions/total number of tests (n/nT, %)	
Nickel sulfate	9/19 (47.4%)	36/201 (17.9%)	**0.005**
Potassium dichromate	4/19 (21.1%)	10/201 (5%)	**0.023**
Fragrance mix I	2/19 (10.5%)	7/201 (3.5%)	0.177
Textile dye mix	2/19 (10.5%)	7/201 (3.5%)	0.177

Comparisons between groups were performed using the chi-square test or Fisher's exact test, as appropriate. A *P*-value such values were indicated in bold was considered statistically significant. AD: Atopic dermatitis

Discussion

Our findings indicate that contact allergy represents an important comorbidity in AD patients, supporting the use of patch testing in this population. While some studies[5-7] have focused exclusively on pediatric AD patients, others[8-11] have included patients across all age groups. Although ACD can develop at any age, it is more frequently observed in adults.[12] Patch testing is performed less frequently in pediatric patients,[13] possibly due to the higher prevalence of AD during childhood and the clinical difficulty in distinguishing AD from ACD.[14] The predominance of adult patients in our cohort may be explained by these factors. ACD is generally more common among females in the general population. Although AD is slightly more prevalent in males during childhood, it becomes more common in females after puberty.[15] Previous studies have shown that most patients referred for patch testing, regardless of AD status, are female.[5,8-11,16,17] A similar sex distribution was observed in our study. Consistent with the findings of Ibekwe et al.,[4] we did not observe a significant association between sex and contact sensitization. However, some studies[5] have reported higher positivity rates in females. This difference may be explained by the higher frequency of patch test referrals among female patients.

The predominance of patients with mild disease in our study may be explained by the general indication for patch testing in patients with localized lesions. The absence of severe cases may be related to difficulties in achieving drug-free intervals required for patch testing, the need for symptom control, and the frequent use of active immunosuppressive therapy in this patient group. Although direct comparisons are limited by different disease-severity scoring systems in the literature, some studies have included patients with severe AD.[4-6]

Within the limits of our study population, AD severity (restricted to mild and moderate disease) was not associated with patch test positivity ($P = 1.000$). While some studies[4,5,17] have reported similar findings, others[6] have demonstrated higher positivity rates with increasing disease severity. These discrepancies may be related to differences in study populations, allergen series, and methodological approaches.

Higher rates of positive patch test reactions are expected among selected patient populations than in the general population. In our study, patch-test positivity was significantly higher among patients with AD than among those without AD. However, the literature reports inconsistent findings. Peng et al.[9] reported positivity rates of 78.4% in AD patients and

66.8% in non-AD patients; Malajian and Belsito[11] reported 71.7% and 64.5%, respectively. Large retrospective studies have also demonstrated a higher prevalence of contact allergy among patients with AD.[7,8,18] Conversely, some studies[10,19] have reported lower sensitization rates in AD patients, whereas others[20] have demonstrated similar prevalence rates of contact allergy between AD and non-AD patients. The relatively high positivity rate observed in our cohort may be related to the inclusion of patients with treatment-resistant or recurrent disease and possible exposure to multiple allergens. The use of the European baseline series, which includes a broad range of allergens, as well as the relatively higher mean age of our study population—which may increase cumulative allergen exposure—may also have contributed to these findings.

Numerous studies have evaluated contact sensitization or ACD in pediatric patients with or without AD. Due to heterogeneity in study populations, age groups, methodologies, and patch test series, the reported findings vary considerably. Nevertheless, the overall trend suggests higher patch test positivity rates among children with AD. The most frequently reported allergens include metals—particularly nickel sulfate—as well as fragrances and preservatives.[4-7,14] In our study, the contact sensitization rate among pediatric AD patients was 29.4%, and the allergen profile was consistent with previous reports. However, the relatively small sample size and the inclusion of patients with treatment-resistant disease may limit the generalizability of our findings.

Comparison of patch test results in AD patients with suspected ACD is challenging due to heterogeneity in sample size, demographic characteristics, disease severity, diagnostic criteria, allergen series, and methodological approaches. Several studies have reported common allergens in patients with AD: Peng et al.[9] identified nickel sulfate (33.3%), cobalt chloride (19.6%), and methylisothiazolinone (22.5%) as the most frequent allergens, whereas Choi et al.[10] reported nickel sulfate (26.4%), cobalt chloride (24.5%), and potassium dichromate (9.4%). A Japanese study identified nickel and topical medications as common allergens in treatment-resistant AD.[21] Trimeche et al.[17] reported textile dyes (24.7%), nickel (20.2%), cobalt (12.7%), and chloromethylisothiazolinone/methylisothiazolinone (8.5%) as prevalent allergens. In another study involving 48 patients with treatment-resistant AD, the most frequent allergens were bichromate (27%), nickel (27%), wool alcohol (24%), and cocamidopropyl betaine (24%).[22] The impaired skin barrier in AD facilitates allergen penetration. This process may be further exacerbated by filaggrin mutations, which reduce the skin's chelating capacity and may increase susceptibility to metal sensitization.[23] Nickel represents a notable exception among contact allergens, as sensitization rates may be comparable in AD and non-AD patients or even higher among AD patients.[2] This has been attributed to a relatively Th17-skewed immune response, characterized by attenuated Th1 activity, in AD patients exposed to nickel.[2] Consistent with previous literature and our findings, metals—particularly nickel—remain the most frequently identified allergens, which likely reflects widespread daily exposure.

Frequent topical exposure represents another important risk factor for contact sensitization in these patients.[20] Fragrances, formaldehyde-releasing preservatives, and topical antibiotics are well-recognized sensitizers.[23] In the general population, fragrance sensitization rates range from 0.7% to 2.6%,[24] whereas higher rates have been reported in selected patient populations. Among patients referred for suspected ACD, the North American Contact Dermatitis Group reported fragrance allergy rates (including fragrance mix I, fragrance mix II, and balsam of Peru) ranging from 5.3% to 11.3%.[25] In our study, sensitization rates were 8.1% for fragrance mix I and 3.2% for both fragrance mix II and balsam of Peru. These rates were higher than those reported in the general population but lower than those observed in selected patient cohorts. Increased use by AD patients of personal care products, cleaning agents, and herbal topical preparations containing fragrances —often due to impaired skin barrier function—may contribute to greater exposure. Conversely, some patients who are aware of fragrance sensitivity may preferentially use fragrance-free products, which could partially explain the lower rates compared with selected populations.

Although patients with AD are considered at increased risk of Group A corticosteroid allergy,[26] only one patient (1.6%) in our study demonstrated a positive reaction to tixocortol-21-pivalate; no reactions to budesonide were observed. Previous studies have reported significantly higher rates of budesonide sensitization in AD patients compared with non-AD patients.[10] However, some studies have reported lower rates of budesonide sensitization among AD patients, possibly reflecting differences in patterns of topical treatment exposure.[20] The relatively low sensitization rate observed in our study may be related to the absence of an extended corticosteroid series, the possibility of missed late reactions due to final readings performed on day 4, and the local preference for prescribing corticosteroids from Groups C and D for treatment-resistant patients. These findings highlight the importance of performing more comprehensive corticosteroid testing, including late patch test readings,[27] to improve the detection of corticosteroid sensitization in AD.

Among the tested allergens, only nickel sulfate showed a statistically significant difference in positivity between AD and non-AD patients in our study. Malajian and Belsito[11] reported higher positivity rates for nickel sulfate, cobalt chloride, potassium dichromate, and fragrance mix I in AD patients; these differences were statistically significant for

all allergens except fragrance mix I. Similarly, Peng et al.[9] found significantly higher positivity rates for nickel sulfate and cobalt chloride in AD patients. The frequent detection of metal allergens—particularly nickel sulfate—in AD patients is consistent with previous literature. However, Qian et al.[8] reported a higher prevalence of ACD related to cosmetics, topical medications, and dyes in AD patients, and observed an inverse association with metal allergens. Furthermore, a large-scale review[28] reported lower nickel sensitization rates in AD patients than in non-AD patients and found no positive correlation between AD and nickel sensitization. Similarly, a study conducted in Singapore reported that nickel was the most frequent allergen in both AD and non-AD patients, with no statistically significant difference in sensitization rates between the two groups.[20] These discrepancies may be explained by differences in study methodologies, patient populations, and allergen series used.

In our study, positivity to nickel sulfate was significantly higher in adult AD patients than in pediatric AD patients, likely reflecting greater cumulative exposure. Although only a limited number of studies have directly compared these age groups, Boonstra et al.[22] similarly reported higher rates of nickel sensitization in adult patients.

The lack of additional clinically meaningful information derived from dynamic patch test evaluation in AD patients should be considered a strength of the study, as it helps define the practical limits of this approach beyond standard readings.

To the best of our knowledge, studies specifically addressing allergen profiles and patch test positivity in patients with hand eczema and a history of AD remain limited. Most available studies have focused on patch-test results in patients with hand eczema, regardless of AD status. In our study, patch test positivity in AD patients presenting with hand eczema (84.2%) was markedly higher than in the overall AD population (62.9%) and in non-AD patients with hand eczema (40.8%). These findings suggest increased susceptibility to contact sensitization in this subgroup. A recent large multicenter study conducted in a Chinese population also demonstrated that AD in patients with hand eczema was associated with altered contact sensitization patterns, further supporting the clinical importance of evaluating contact allergy in this subgroup.[29] Previous studies have also reported high sensitization rates in patients with hand eczema.[30] Nickel sulfate, which was frequently detected in our study and in previous reports, remains a major allergen across age groups.

Study Limitations

Conducting the study in a tertiary referral center limited long-term follow-up, thereby preventing assessment of clinical compliance, confirmation of ACD diagnosis, and evaluation of rates of clinical relevance. However, patients were advised to avoid allergens that yielded positive test results and were clinically relevant based on their clinical history. The absence of D7 readings, due to study design and logistical constraints—particularly as many patients were referred from remote areas—may have resulted in missed delayed-type hypersensitivity reactions, especially to corticosteroids. Additional limitations include the relatively small sample size and single-center design, which may limit generalizability. However, because our center is a tertiary referral center that receives complex, treatment-resistant cases from surrounding provinces, our cohort provides clinically meaningful data for this patient subgroup. Furthermore, the use of a single allergen panel for patch testing may not fully capture sensitization to less common allergens. Although non-AD patients were matched for age and sex, complete matching for all potential confounding variables was not feasible, which may have affected the strength of intergroup comparisons.

Conclusion

Our findings indicate that contact sensitization rates are higher in AD patients than in the general population. Patch testing appears to be particularly valuable for identifying contact sensitization, particularly to metal allergens, in patients with treatment-resistant or recurrent disease. The low rate of corticosteroid sensitization observed in this study warrants further investigation using an expanded patch test series. Larger-scale prospective studies are required to optimize the management of AD and to further elucidate the relationship between contact sensitization and ACD.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Karadeniz Technical University Institutional Ethics Committee (protocol number: 2022/119, date: June 30, 2022; approval number: 24237859-435).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: L.B.S., A.F., İ.E.A., D.A.A., Design: L.B.S., A.F., İ.E.A., D.A.A., Data Collection or Processing: A.O.M., Analysis or Interpretation: L.B.S., A.F., İ.E.A., D.A.A., Literature Search: A.O.M., L.B.S., Writing: A.O.M., L.B.S.

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References

1. Yüksel T, Nørreslet LB, Thyssen JP. Allergic contact dermatitis in patients with atopic dermatitis. Curr Dermatol Rep. 2021;10(3):67-76.
2. Zhang J, Li G, Guo Q, Yang Y, Yang J, Feng X, Yao Z. Allergens in atopic dermatitis. Clin Rev Allergy Immunol. 2025;68(1):11.
3. Bonamonte D, Foti C, Vestita M, Ranieri LD, Angelini G. Nummular eczema and contact allergy: a retrospective study. Dermatitis. 2012;23(4):153-157.
4. Ibekwe P, Ekop E, Out T, Bassi P, Ukonu BA. Patch tests in children with active atopic dermatitis: a prospective study and review of the significance of European baseline series to the African region. Current Allergy & Clinical Immunology. 2023;36(2):100-105.
5. Cattani CAS, Oppermann K, Perazzoli S, Guarda NH, Baréa P, Bonamigo RR. Sensitizing agents found in children and adolescents with recalcitrant atopic dermatitis: a cross-sectional study with a pediatric battery. An Bras Dermatol. 2022;97(3):307-314.
6. Handa S, Bhattacharjee R, Thakur V, De D, Mahajan R. Contact hypersensitivity to Indian standard patch test series correlates with disease severity among children with atopic dermatitis. Indian J Dermatol Venereol Leprol. 2023;90(1):46-51.
7. Barwari L, Rustemeyer T, Franken SM, Ipenburg NA. Patch test results in a Dutch paediatric population with suspected contact allergy: a retrospective cohort study. Contact Dermatitis. 2023;88(2):120-128.
8. Qian MF, Li S, Honari G, Sarin KY, Chen JK. Prevalence of allergic contact dermatitis following patch testing in patients with atopic dermatitis: a retrospective United States claims-based study. J Am Acad Dermatol. 2023;88(6):1388-1390.
9. Peng F, Schwartz RA, Chen Z, Zhang JZ. High prevalence of contact hypersensitivity to metals and preservatives in Chinese patients with atopic dermatitis. Chin Med J (Engl). 2019;132(23):2881-2882.
10. Choi YJ, Byun JY, Choi YW, Roh JY, Choi HY. Analysis of positive patch test allergens in allergic contact dermatitis patients with atopic dermatitis. Ann Dermatol. 2023;35(4):303-312.
11. Malajian D, Belsito DV. Cutaneous delayed-type hypersensitivity in patients with atopic dermatitis. J Am Acad Dermatol. 2013;69(2):232-237.
12. Ramírez-Marín HA, Silverberg JI. Differences between pediatric and adult atopic dermatitis. Pediatr Dermatol. 2022;39(3):345-353.
13. Silverberg JI, Hou A, Warshaw EM, DeKoven JG, Maibach HI, Belsito DV, Zug KA, Taylor JS, Sasseville D, Dunnick CA, Houle MC, Atwater AR, Reeder MJ, DeLeo VA, Pratt MD, Fowler JF Jr, Zirwas MJ, Marks JG Jr. Age-related differences in patch testing results among children: analysis of North American Contact Dermatitis Group Data, 2001-2018. J Am Acad Dermatol. 2022;86(4):818-826.
14. Johnson H, Aquino MR, Snyder A, Collis RW, Franca K, Goldenberg A, Sui JY, Eichenfield DZ, Kozy BJ, Chen JK, Shope C, Goldminz AM, Yu J. Prevalence of allergic contact dermatitis in children with and without atopic dermatitis: a multicenter retrospective case-control study. J Am Acad Dermatol. 2023;89(5):1007-1014.
15. Johansson EK, Bergström A, Kull I, Melén E, Jonsson M, Lundin S, Wahlgren CF, Ballardini N. Prevalence and characteristics of atopic dermatitis among young adult females and males-report from the Swedish population-based study BAMSE. J Eur Acad Dermatol Venereol. 2022;36(5):698-704.
16. Warshaw EM, Buonomo M, DeKoven JG, Pratt MD, Reeder MJ, Silverberg JI, Belsito DV, Maibach HI, Atwater AR, Houle MC, Taylor JS, Zug KA, DeLeo VA, Dunnick CA. Importance of supplemental patch testing beyond a screening series for patients with dermatitis: the North American Contact Dermatitis Group Experience. JAMA Dermatol. 2021;157(12):1456-1465.
17. Trimeche K, Lahouel I, Belhadjali H, Salah NB, Youssef M, Zili J. Contact allergy in atopic dermatitis: a prospective study on prevalence, incriminated allergens and clinical insights. Contact Dermatitis. 2024;90(5):514-519.
18. Németh D, Pónyai G. Contact allergy in the elderly: a study of 600 patients. Life (Basel). 2022;12(8):1228.
19. Zafrir Y, Trattner A, Hodak E, Eldar O, Lapidoth M, Ben Amitai D. Patch testing in Israeli children with suspected allergic contact dermatitis: a retrospective study and literature review. Pediatr Dermatol. 2018;35(1):76-86.
20. Wee C, Tan CH, Zhao X, Yew YW, Goon A. Pattern of contact sensitization in patients with and without atopic dermatitis in an Asian dermatology center. Contact Dermatitis. 2022;86(5):398-403.
21. Tamagawa-Mineoka R, Masuda K, Ueda S, Nakamura N, Hotta E, Hattori J, Minamiyama R, Yamazaki A, Katoh N. Contact sensitivity in patients with recalcitrant atopic dermatitis. J Dermatol. 2015;42(7):720-722.
22. Boonstra M, Rustemeyer T, Middelkamp-Hup MA. Both children and adult patients with difficult-to-treat atopic dermatitis have high prevalences of concomitant allergic contact dermatitis and are frequently polysensitized. J Eur Acad Dermatol Venereol. 2018;32(9):1554-1561.
23. George S, Yu J. Patch testing in atopic children: is there a difference? Curr Dermatol Rep. 2023;12(4):1-6.
24. Reeder MJ. Allergic contact dermatitis to fragrances. Dermatol Clin. 2020;38(3):371-377.
25. DeKoven JG, Warshaw EM, Zug KA, Maibach HI, Belsito DV, Sasseville D, Taylor JS, Fowler JF Jr, Mathias CGT, Marks JG, Pratt MD, Zirwas MJ, DeLeo VA. North American contact dermatitis group patch test results: 2015-2016. Dermatitis. 2018;29(6):297-309.
26. Vatti RR, Ali F, Teuber S, Chang C, Gershwin ME. Hypersensitivity reactions to corticosteroids. Clin Rev Allergy Immunol. 2014;47(1):26-37.
27. Svendsen SV, Mortz CG. The benefit of late patch test readings in corticosteroid allergy. Contact Dermatitis. 2022;87(5):466-468.
28. Hamann CR, Hamann D, Egeberg A, Johansen JD, Silverberg J, Thyssen JP. Association between atopic dermatitis and contact sensitization: a systematic review and meta-analysis. J Am Acad Dermatol. 2017;77(1):70-78.
29. Zhang J, Yu Y, Zhao P, Yuan L, Wang X, Gu J, Hao F, Wang G, Lu Q, Li H, Zheng J, Zhang F, Lai W, Jin H, Liu X, Sun Q, Guo Q, Chen L, Ding Y, Kang X, Li J, Li Y, Liu Y, Lv C, Mei S, Song Z, Wang J, Xiao T, Yang W, Yao X, Zou Y, Liang Y, Yang B. Clinical characteristics of hand eczema and its association with atopic dermatitis in the Chinese population: a multicenter cross-sectional study. J Invest Dermatol. 2025;145(12):3089-3099.e7.
30. Suzuki NM, Hafner MFS, Lazzarini R, Duarte IAG, Veasey JV. Patch tests and hand eczema: retrospective study in 173 patients and literature review. An Bras Dermatol. 2023;98(3):339-346.

Original Article

Evaluation of Serum Zonulin Levels in Patients with Recurrent Aphthous Stomatitis

Gülsün Hazan Tabak[1], Ayşen Karaduman[1], Burçin Şener[2]
[1]Department of Dermatology, Hacettepe University Faculty of Medicine, Ankara, Türkiye
[2]Department of Clinical Microbiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye

Abstract

Aim: Recurrent aphthous stomatitis (RAS) is an inflammatory disease of the oral mucosa. Recently, it has been emphasized that an impaired intestinal barrier is involved in the development of inflammatory diseases. Zonulin, which reversibly increases intestinal permeability, may be involved in this process. We aimed to reveal the potential effect of intestinal permeability on the etiopathogenesis of RAS by measuring serum levels of zonulin.

Materials and Methods: This prospective case-control study included patients aged 18 to 65 years who were diagnosed with RAS, and a healthy control group. Serum zonulin levels in the groups were evaluated using the enzyme-linked immunosorbent assay.

Results: A total of 78 individuals were included: 27 diagnosed with RAS who had active ulcers, 25 diagnosed with RAS without ulcers, and 26 healthy controls. In the patient groups, serum zonulin levels were significantly higher than that in the healthy control group (127.32 ± 61.52 ng/mL, 121.04 ± 62.88 ng/mL, 89.22 ± 49.51 ng/mL, respectively; $P < 0.05$).

Conclusion: This study has demonstrated that serum zonulin levels are increased in patients with RAS. Increased serum zonulin levels suggest that leaky gut may be an etiological factor in the pathophysiology of RAS. The limitations of our study are the lack of prior research on the topic and the limited sample size.

Keywords: Aphthous ulcer, intestinal barrier function, microbiota, mouth mucosa, permeability

Introduction

Recurrent aphthous stomatitis (RAS), or RAS, is a chronic inflammatory disease characterized by painful, round ulcers of the non-keratinized oral mucosa that can cause difficulties in eating, swallowing, and speaking. Generally, RAS ulcers are covered by a pseudomembrane and surrounded by an erythematous halo.[1] RAS is slightly more common in children and adults of higher socioeconomic status and affects approximately 20% of the general population at any time.[2] Several factors have been proposed as possible causative agents. Trauma, psychosocial stress, hematinic deficiencies, microbial factors, and allergies to dietary ingredients are possible causal agents of RAS in genetically susceptible individuals.[3,4] Although the etiopathogenesis of the disease remains unclear, autoimmunity has been associated with RAS.[5,6]

Alterations in intestinal barrier integrity and subsequent impairment of gut permeability have been implicated in various chronic inflammatory diseases, such as celiac disease, inflammatory bowel disease, irritable bowel syndrome, non-alcoholic fatty liver disease, type 1 and type 2 diabetes, obesity, and depression.[7] Leaky gut increases antigen trafficking by allowing toxins, antigens, and bacteria

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Address for correspondence: Gülsün Hazan Tabak, Department of Dermatology, Hacettepe University Faculty of Medicine, Ankara, Türkiye
Email: gulsunhazan@gmail.com
ORCID ID: 0000-0003-1553-5190

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to enter the bloodstream. The combination of immune dysregulation and environmental factors can trigger the onset of autoimmune disease in genetically susceptible individuals.[8] Intestinal permeability and integrity can be measured in many ways, such as urinary excretion of marker molecules including monosaccharides, disaccharides, and chromium-51 EDTA (51Cr-EDTA), serum or fecal zonulin levels, and cell-culture models.[8,9] Upregulation of zonulin, a putative physiological modulator of intestinal tract integrity, causes intestinal hyperpermeability and an uncontrolled influx of dietary and microbial antigens.[7,10] Zonulin is the precursor of haptoglobin-2, and serum zonulin levels can be readily measured by enzyme-linked immunosorbent assay (ELISA).[11]

In our study, we aimed to investigate the potential effect of intestinal permeability on the etiopathogenesis of RAS by measuring serum levels of zonulin.

Materials and Methods

Study Participants

The present prospective case-control study, conducted between November 2021 and January 2022, included patients aged 18–65 years who were diagnosed clinically with RAS and had no chronic systemic or dermatologic disease; RAS patients were divided into two groups according to the presence or absence of an active aphthous ulcer, and a healthy control group without any chronic systemic or dermatologic disease was also included. The minimum sample size was calculated by power analysis to be 19 participants per group, and 75 participants, planned to be grouped as follows, were included in the study.

Group IA: 25 Patients with clinically diagnosed RAS with an active oral ulcer.

Group IB: 25 Patients with clinically diagnosed RAS but without an active oral ulcer.

The healthy control group: A control group of 25 healthy participants without chronic skin disease.

Patients with a 3-year or longer history of regularly recurring episodes of oral aphthous ulceration and at least three ulcers per year for the previous 12 months were included, while those with a history of systemic disease in which oral ulceration may be a feature (such as Behçet's syndrome, coeliac disease, Crohn's disease, or ulcerative colitis); those receiving concurrent systemic steroids, immunomodulatory drugs, or cytotoxic medications; those who used systemic antibiotics, probiotics, or prebiotics in the last 3 months; those on a current specific diet (vegan, vegetarian, or gluten-free); those with previous gastrointestinal tract surgery; those with malignancy; and those who were pregnant were excluded.

Age, gender, smoking status, duration of breastfeeding, mode of delivery, disease duration, age of onset, and attacks per year were recorded. Disease duration, age at onset, and attacks per year were referred to as the "activity parameters of RAS".

Blood Sample Collection and Laboratory Analysis

Ethical approval for the study was obtained from the Hacettepe University Ethics Committee (approval number: 2021/10-50, date: 04.05.2021). After obtaining written informed consent, blood samples were collected from each participant. One gel vacuum biochemistry tube of blood was collected from each participant. Following coagulation for 45-60 min at room temperature, the serum was separated by cold centrifugation (+4 °C) at 4000 rpm for 10 minutes and then stored at -80 °C until analysis. Serum zonulin level was quantified using a commercial kit (Catalog No. E-EL-H5560, Elabscience) employing a sandwich ELISA with a 3-fold dilution. The measurement range of the kit was 0.78-50 ng/mL, and the sensitivity was 0.47 ng/mL. Serum zonulin values outside the detection range were calculated using a continuous parabolic equation whose R-squared value was closest to 1 in Excel.

Also, hemoglobin, serum ferritin, serum vitamin B12, and serum folate levels were measured in each patient. The normal values accepted for hemoglobin were > 12 g/dL for women and > 13 g/dL for men; serum ferritin, > 9 µg for women and > 18 µg/L for men; serum B12, > 200 ng/L; and folate, 3 µg/L.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences, version 20.0, for Windows. Continuous variables were expressed as mean [± standard deviation (SD)], ordinal variables as median (interquartile range), and as numbers and percentages for categorical variables. The normality of the numerical variables was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Independent two-group comparisons for numerical that are normally distributed were performed using independent samples t-test, and one-way ANOVA was used for comparisons of more than two groups. For numerical data that were not normally distributed, the Mann–Whitney U test and the Kruskal–Wallis H test were used. If the conditions for the "chi-square" test were met, the "chi-square" test statistic was used to analyze the categorical variables; otherwise, "Fisher's exact test" was used. Correlation analysis between the two numeric variables was performed using a Pearson or Spearman test, depending on data normality. The "paired samples statistics" or "Wilcoxon" test was used for binary comparisons between dependent

groups. For all analyses, a *P*-value < 0.05 was considered statistically significant, and 95% confidence intervals were reported.

Results

Study Participants

A total of 78 participants, comprising 27 patients with RAS and an active oral ulcer (6 females, 21 males; group IA), 25 patients with RAS without an active oral ulcer (4 females, 21 males; group IB), and 26 healthy controls (6 females, 20 males) were enrolled in the study. In the active oral ulcer group, 15 (56%) patients had only minor aphthae, and 7 (26%) patients had only major aphthae. The remaining 5 patients had both types of oral aphthae. In both patient groups, no history of herpetiform aphthae was reported, and no active herpetiform lesions were observed. The mean age was 36 ± 11.8 (mean ± SD) and 36 ± 13.2 years, respectively, for the patient groups and 33.4 ± 9.4 years for the control group. There were no significant differences between the groups in age and gender ($P = 0.798$ and $P = 0.792$, respectively) (Table 1).

Three patients in group IA, seven in group IB, and nine participants in the control group were current smokers; there was no significant difference in smoking habits between the groups ($P = 0.120$). Other descriptive features of RAS patients are shown in Table 2.

In groups IA and IB, twelve (23.1%) patients were delivered by Caesarean section and 40 (76.9%) by normal vaginal delivery. Four participants in the control group (15.4%) were delivered by Caesarean section and 22 (84.6%) by normal vaginal delivery. There was no difference in mode of delivery between the groups ($P = 0.428$). The proportion of patients who received breast milk for less than six months was higher in the control group [6 patients (11.5%) in the patient group; 4 patients (15.6%) in the control group]. However, there was no significant difference in the duration of breast milk intake between the groups ($P = 0.486$).

Hematinic Deficiencies in RAS Patients and Healthy Controls

Blood hemoglobin levels were below normal in 2 patients (7.4%) in group IA, 3 patients (12%) in group IB, and 3 patients (11.5%) in the control group ($P = 0.809$). Ferritin levels were below normal in 5 patients (18.5%) in group IA, 6 patients (24%) in group IB, and 5 patients (19.2%) in the control group ($P = 0.870$). Vitamin B12 levels were below normal in group IA (12 patients, 44.4%), group IB (5 patients, 20%), and the control group (10 participants, 18.5%) ($P = 0.159$). Serum folic acid levels were within normal limits in all participants.

Serum Zonulin Levels in RAS Patients and Healthy Controls

The serum zonulin levels of groups IA and IB were found to be significantly higher compared to that in the control group (127.3 ± 61.5 ng/mL, 121 ± 62.9 ng/mL, and 89.2 ± 49.5 ng/mL, respectively; $P = 0.017$ and $P = 0.049$, respectively) (Figure 1). In contrast, there was no significant difference between groups IA and IB ($P = 0.718$).

Table 1. Age and gender of the study participants

	Age (years) Mean ± SD (min-max)	Gender n (%)	
		Female	Male
Group IA	36 ± 11.8 (21-63)	21 (77.8%)	6 (22.2%)
Group IB	36 ± 13.2 (19-61)	21 (84%)	4 (16%)
Control group	33.4 ± 9.4 (20-56)	20 (76.9%)	6 (23.1%)
***P*-value**	0.798	0.792	

SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Descriptive features of RAS patients

	All patients (n = 52)	Group IA (n = 27)	Group IB (n = 25)	*P*-value
Disease duration (years) median (IQR)	15 (10-25)	15 (10-25)	19 (10-27.5)	0.600
Age of onset (years) median (IQR)	15 (10-22)	16 (9-27)	15 (10-19.5)	0.653
Attacks/per year median (IQR)	7 (4-12)	10 (4-15)	6 (4-10)	0.106

IQR: Interquartile range, RAS: Recurrent aphthous stomatitis

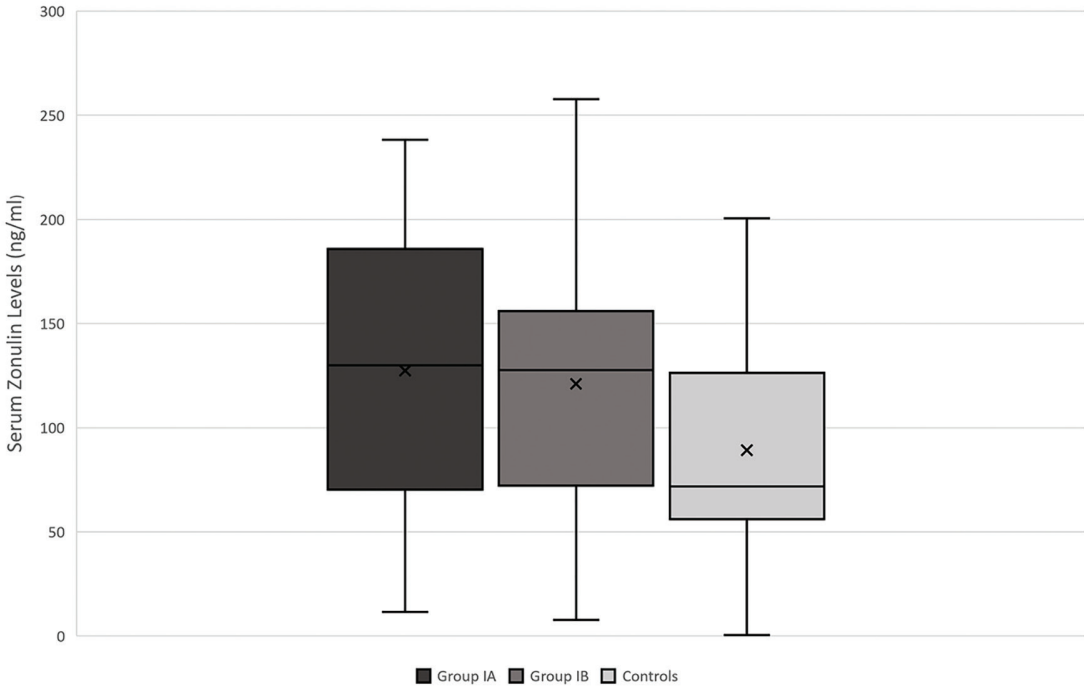

Figure 1. Serum levels of zonulin were significantly higher in the patient groups compared with the healthy controls ($P = 0.046$)

Age (rs = -0.028, $P = 0.805$), smoking status ($P = 0.141$), disease duration (rs = -0.108, $P = 0.444$), age of onset (rs = 0.141, $P = 0.320$), and attacks/per year (rs = 0.061, $P = 0.670$) were not correlated with serum zonulin levels. The results show a significant difference in the serum zonulin levels of females and males, with values of 125.4 ± 61.5 ng/mL and 63.1 ± 58 ng/mL, respectively ($P < 0.001$).

While the mode of delivery and duration of breast milk intake separately did not have an effect on the serum zonulin levels ($P = 0.128$ and $P = 0.830$, respectively), the serum zonulin levels of those who were delivered by vaginal delivery and received breast milk for longer than 6 months were significantly lower than that of those who were delivered by Caesarean section and received breast milk for less than 6 months (101.7 ± 58.8 ng/mL and 154.5 ± 56.6 ng/mL, respectively; $P = 0.045$).

Discussion

Our findings demonstrated that serum zonulin levels were significantly increased in patients with RAS compared with healthy controls, supporting the hypothesis that impaired gut barrier function may be involved in the pathogenesis of RAS.

The tightly packed single-cell-thick epithelial layer of the intestinal mucosa serves an essential role as a "gatekeeper" against large microbial communities and potentially harmful antigens in the lumen. Zonulin, the physiological modulator of intercellular tight junction competence, has been the subject of numerous clinical studies because it may play a role in the pathogenesis of many chronic inflammatory diseases, including celiac disease, type I diabetes, ankylosing spondylitis, and inflammatory bowel disease, due to its triggering effect on the immune response.[12-14]

Celiac disease is a gluten-sensitive autoimmune enteropathy accompanied by progressive mucosal damage. Lammers et al.[15] conducted an *in vitro* physiological study and identified that gliadin binds to chemokine receptor CXCR3 on intestinal epithelial cells and consequently permits aberrant passage of the possible antigens from the lumen to the mucosa by releasing of zonulin. Drago et al.[16] found that intestinal exposure to gliadin leads to intestinal hyperpermeability in both individuals with and without celiac disease but revealed that the patients with celiac disease exhibit an exaggerated and persistent intestinal zonulin releasing.

Sapone et al.[17] reported that patients with type I diabetes and their first-degree relatives without celiac disease have significantly higher serum zonulin levels compared to age and sex-matched healthy controls and detected that participants' serum zonulin levels have a positive correlation with intestinal permeability by using lactulose/mannitol urine test.

RAS is one of several chronic, inflammatory, ulcerative diseases of the oral mucosa. Susceptibility to RAS is determined by various DNA polymorphisms, particularly those related to alterations in cytokine metabolism; these cytokines [e.g., interleukin (IL)-1, IL-2, IL-10, IL-12, interferon-γ, and tumor necrosis factor-α] elicit abnormal antigen-presenting

cell function and T-cell activity, and susceptibility is modified by environmental factors.[18-21] Manthiram et al.[22] proposed to define RAS as the mildest form of Behçet's spectrum disorders due to the similarities within pathogenesis and genetic architecture. Fresko et al.[23] demonstrated intestinal hyperpermeability in patients with Behçet's disease without known gastrointestinal manifestations by the determination of 51Cr-EDTA excretion rate. Increased intestinal permeability in Behçet's disease, independent of gastrointestinal tract involvement, was demonstrated by a sugar absorption test in another study.[24] We found that serum zonulin levels were significantly higher in the patient groups, consistent with other studies in several chronic inflammatory disorders. To our knowledge, the present study is the first to investigate the role of intestinal hyperpermeability in patients with RAS.

Our study showed significant differences in serum zonulin levels between females and males. Sex-based immunological differences contribute to variations in the incidence of autoimmune diseases. It is now well established that 80% of autoimmune diseases occur in females, which is compatible with our results. The biallelic overexpression of pseudoautosomal immunomodulatory genes on the X chromosome in females and the effects of sex hormones on innate and adaptive immunity could explain females' susceptibility to autoimmune diseases.[25,26]

The mode of delivery and diet during infancy (breast milk or formula) play a major role in shaping the healthy gut microbiota that supports intestinal integrity by maintaining its structure and function.[27] We demonstrated that vaginal delivery and receiving breast milk for more than 6 months positively affect intestinal permeability.

Sapone et al.[17] demonstrated that serum zonulin levels don't correlate with indicators of glycemic control such as hemoglobin A1c, serum glucose levels, and the age at diagnosis of type 1 diabetes. On the contrary, Szymanska et al.[28] revealed that elevation in fecal zonulin is associated with Crohn disease activity, and significantly correlate with fecal calprotectin level. Singh et al.[29] observed a correlation between serum zonulin levels and diarrhea severity in patients with diarrhea-predominant irritable bowel syndrome. We did not find a correlation between serum zonulin levels and RAS activity parameters.

Study Limitations

The primary limitation of this study was the small sample size. Although this did not prevent achieving statistically significant results, a larger sample size in future studies will provide more robust evidence regarding the relationship between intestinal hyperpermeability and the activity parameters of RAS.

Conclusion

In this study, serum zonulin levels in patients with RAS were significantly higher than those in the control group. The results of the study suggest that leaky gut may play a role in the etiopathogenesis of RAS. Given the paucity of published findings, our findings should prompt further investigations into the role of zonulin in the development of RAS.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Hacettepe University Ethics Committee (approval number: 2021/10-50, date: 04.05.2021).

Informed Consent: After obtaining written informed consent, blood samples were collected from each participant.

Authorship Contributions

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

Footnotes

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

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References

1. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. J Am Dent Assoc. 2003;134(2):200-207.
2. Natah SS, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Häyrinen-Immonen R. Recurrent aphthous ulcers today: a review of the growing knowledge. Int J Oral Maxillofac Surg. 2004;33(3):221-234.
3. Lau CB, Smith GP. Recurrent aphthous stomatitis: a comprehensive review and recommendations on therapeutic options. Dermatol Ther. 2022;35(6):e15500.
4. Slebioda Z, Szponar E, Kowalska A. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review. Arch Immunol Ther Exp (Warsz). 2014;62(3):205-215.
5. Lee YC, Jeong SJ, Eun YG, Song R, Oh IH. Risk of autoimmune diseases in recurrent aphthous ulcer patients: a nationwide population study. Oral Dis. 2021;27(6):1443-1450.
6. Lin KC, Tsai LL, Ko EC, Sheng-Po Yuan K, Wu SY. Comorbidity profiles among patients with recurrent aphthous stomatitis: a case-control study. J Formos Med Assoc. 2019;118(3):664-670.
7. Fasano A. All disease begins in the (leaky) gut: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. F1000Res. 2020;9:F1000 Faculty Rev-69.

8. Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke JD, Serino M, Tilg H, Watson A, Wells JM. Intestinal permeability–a new target for disease prevention and therapy. BMC Gastroenterol. 2014;14:189.
9. Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. Gut. 2019;68(8):1516-1526.
10. Sturgeon C, Fasano A. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases. Tissue Barriers. 2016;4(4):e1251384.
11. Fasano A. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. Physiol Rev. 2011;91(1):151-175.
12. Ciccia F, Guggino G, Rizzo A, Alessandro R, Luchetti MM, Milling S, Saieva L, Cypers H, Stampone T, Di Benedetto P, Gabrielli A, Fasano A, Elewaut D, Triolo G. Dysbiosis and zonulin upregulation alter gut epithelial and vascular barriers in patients with ankylosing spondylitis. Ann Rheum Dis. 2017;76(6):1123-1132.
13. Wood Heickman LK, DeBoer MD, Fasano A. Zonulin as a potential putative biomarker of risk for shared type 1 diabetes and celiac disease autoimmunity. Diabetes Metab Res Rev. 2020;36(5):e3309.
14. Vanuytsel T, Vermeire S, Cleynen I. The role of Haptoglobin and its related protein, Zonulin, in inflammatory bowel disease. Tissue Barriers. 2013;1(5):e27321.
15. Lammers KM, Lu R, Brownley J, Lu B, Gerard C, Thomas K, Rallabhandi P, Shea-Donohue T, Tamiz A, Alkan S, Netzel-Arnett S, Antalis T, Vogel SN, Fasano A. Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. Gastroenterology. 2008;135(1):194-204.e3.
16. Drago S, El Asmar R, Di Pierro M, Grazia Clemente M, Tripathi A, Sapone A, Thakar M, Iacono G, Carroccio A, D'Agate C, Not T, Zampini L, Catassi C, Fasano A. Gliadin, zonulin and gut permeability: effects on celiac and non-celiac intestinal mucosa and intestinal cell lines. Scand J Gastroenterol. 2006;41(4):408-419.
17. Sapone A, de Magistris L, Pietzak M, Clemente MG, Tripathi A, Cucca F, Lampis R, Kryszak D, Cartenì M, Generoso M, Iafusco D, Prisco F, Laghi F, Riegler G, Carratu R, Counts D, Fasano A. Zonulin upregulation is associated with increased gut permeability in subjects with type 1 diabetes and their relatives. Diabetes. 2006;55(5):1443-1449.
18. Chen L, Ke Z, Zhou Z, Jiang X, Zhao Y, Zhang J. Associations of IL-1, 6, and 10 Gene polymorphisms with susceptibility to recurrent aphthous stomatitis: insights from a meta-analysis. Genet Test Mol Biomarkers. 2018;22(4):237-245.
19. Bhosale SS, Rajput BS, Takkar H, Bhagat SV, Vagger RM, Shaikh MIK. Establishment of role of IL-2, IL-10 and IL-12 in patients with recurrent aphthous stomatitis-a clinical study. J Contemp Dent Pract. 2018;19(10):1242-1245.
20. Najafi S, Yousefi H, Mohammadzadeh M, Bidoki AZ, Farhadi E, Rezaei N. Interleukin-2, interferon-gamma gene polymorphisms in recurrent aphthous stomatitis. Prague Med Rep. 2017;118(2-3):81-86.
21. Dalghous AM, Freysdottir J, Fortune F. Expression of cytokines, chemokines, and chemokine receptors in oral ulcers of patients with Behcet's disease (BD) and recurrent aphthous stomatitis is Th1-associated, although Th2-association is also observed in patients with BD. Scand J Rheumatol. 2006;35(6):472-475.
22. Manthiram K, Preite S, Dedeoglu F, Demir S, Ozen S, Edwards KM, Lapidus S, Katz AE; Genomic Ascertainment Cohort; Feder HM Jr, Lawton M, Licameli GR, Wright PF, Le J, Barron KS, Ombrello AK, Barham B, Romeo T, Jones A, Srinivasalu H, Mudd PA, DeBiasi RL, Gül A, Marshall GS, Jones OY, Chandrasekharappa SC, Stepanovskiy Y, Ferguson PJ, Schwartzberg PL, Remmers EF, Kastner DL. Common genetic susceptibility loci link PFAPA syndrome, Behçet's disease, and recurrent aphthous stomatitis. Proc Natl Acad Sci U S A. 2020;117(25):14405-14411.
23. Fresko I, Hamuryudan V, Demir M, Hizli N, Sayman H, Melikoğlu M, Tunç R, Yurdakul S, Yazici H. Intestinal permeability in Behçet's syndrome. Ann Rheum Dis. 2001;60(1):65-66.
24. Koc B, Aymelek S, Sonmez A, Yilmaz MI, Kocar H. Increased sucrose permeability in Behçet's disease. Rheumatol Int. 2004;24(6):347-350.
25. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16(10):626-638.
26. Raza HA, Sen P, Bhatti OA, Gupta L. Sex hormones, autoimmunity and gender disparity in COVID-19. Rheumatol Int. 2021;41(8):1375-1386.
27. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. World J Gastroenterol. 2015;21(29):8787-8803.
28. Szymanska E, Wierzbicka A, Dadalski M, Kierkus J. Fecal zonulin as a noninvasive biomarker of intestinal permeability in pediatric patients with inflammatory bowel diseases-correlation with disease activity and fecal calprotectin. J Clin Med. 2021;10(17):3905.
29. Singh P, Silvester J, Chen X, Xu H, Sawhney V, Rangan V, Iturrino J, Nee J, Duerksen DR, Lembo A. Serum zonulin is elevated in IBS and correlates with stool frequency in IBS-D. United European Gastroenterol J. 2019;7(5):709-715.

Case Report

Cydnidae (Burrowing Bug) Pigmentation in a Non-Acral Site: Clinical and Dermoscopic Features

Şule Yıldız Sağcan Tercan, Göksu Dalgıç Demirtaş, Mustafa Turhan Şahin
Department of Dermatology and Venereology, Manisa Celal Bayar University Faculty of Medicine, Manisa, Türkiye

Abstract

Cydnidae can cause transient cutaneous pigmentation through defensive secretions. We report a case of 24-year-old woman who presented with sudden-onset asymptomatic brownish-black macules on the gluteal region following seaside exposure. The lesions were non-blanching and resistant to cleansing; dermoscopy revealed brown dots and irregular linear structures with superficial light-brown amorphous pigmentation. The pigmentation resolved spontaneously within one week, consistent with pigmentation caused by burrowing bugs. Awareness of this rare, self-limiting condition at atypical sites may prevent unnecessary diagnostic procedures.

Keywords: Burrowing bug, cydnidae pigmentation, dermoscopy, hemiptera, skin pigmentation

Introduction

Cydnidae, in the order Hemiptera, possess morphological adaptations for digging and release an odorous defensive secretion that can cause pigmented macules on human skin, especially during the rainy season.[1-3] Burrowing bug–induced pigmentation has been increasingly recognized through recent case reports; however, it remains an uncommon and likely underreported arthropod-related dermatosis. The condition typically presents with sudden-onset, asymptomatic brown to dark brown macules that may resemble lentigines or exogenous pigmentation.[4,5] Most cases involve exposed acral areas, consistent with the natural habitat of these soil-dwelling insects and with their increased activity during the wet or monsoon seasons.[4,6] Dermoscopic findings, such as superficial shiny brown globules, clods, and irregular streak-like structures with a characteristic "stuck-on" appearance, provide additional diagnostic support.[6] Recognition of these diverse presentations is essential to avoid misdiagnosis and unnecessary interventions.

Herein, we report an unusual case involving an uncommon body site.

Case Report

An otherwise healthy 24-year-old female presented with sudden-onset, asymptomatic, multiple tiny brown spots on the left gluteal region (Figure 1), which had developed one week prior to presentation. Lesion onset was observed following a stay at the seaside during summer vacation. There was no history of preceding trauma, drug use, or exposure to chemicals. On examination, multiple discrete, irregularly shaped, brownish-black macules with streaky ends, measuring 2–6 mm in diameter, and resembling lentigines, were observed on the left gluteal region (Figure 1). Other mucocutaneous sites were not involved.

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Address for correspondence: Şule Yıldız Sağcan Tercan, Department of Dermatology and Venereology, Manisa Celal Bayar University Faculty of Medicine, Manisa, Türkiye
Email: sule9635sagcan@gmail.com
ORCID ID: 0009-0002-4539-0383

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The patient stated that there had been no changes in the color or texture of the lesions from their initial appearance to the time of the current assessment. The macules were non-blanching upon pressure and remained unaffected when attempts were made to remove them using alcohol, soap, or water. Dermoscopic examination demonstrated irregular, superficial light-brown amorphous pigmentation accompanied by linear streaks and focal dark-brown dots, consistent with pigment deposition limited to the stratum corneum (Figure 2). No insect was identified at the time of presentation. The lesions resolved spontaneously within one week without any intervention. Given the patient's history, clinical presentation, dermoscopic features, and self-limiting course, a presumptive diagnosis of Cydnidae (burrowing bug) pigmentation was made.

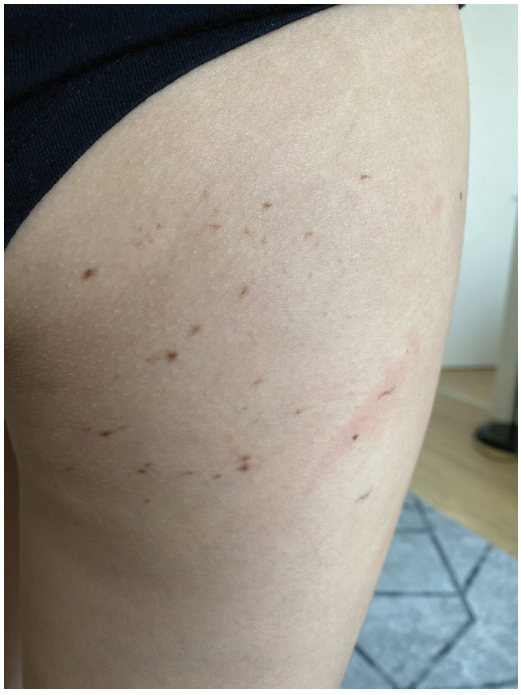

Figure 1. Multiple discrete, irregularly shaped brownish-black macules with streaky ends, measuring 2-6 mm in diameter, resembling lentigines were observed on the left gluteal region

Discussion

Cydnidae, also known as burrowing bugs, belong to the order Hemiptera and are characterized by morphological adaptations that facilitate digging. These insects burrow into the soil to feed on plants and are therefore encountered less frequently.[1] The odorous secretion released from specialized glands serves as a defense mechanism; however, upon contact with human skin, it can induce pigmented macules. Patients, particularly during the rainy season, present with the sudden onset of asymptomatic pigmented spots.[2,3] The lesions typically resolve spontaneously within 1–2 weeks without the need for treatment.[4] Similar to other arthropod-induced pigmentation, these lesions predominantly affect acral areas; however, rare non-acral involvement, such as the abdomen, back, and chest, has been described in isolated reports.[2,3] Our case differs from previously published cases in demonstrating isolated gluteal involvement following seaside exposure, further expanding the anatomical spectrum of this condition. Lesions range from oval to irregular in shape, measuring from pinpoint to a few millimeters in diameter. They may appear as isolated spots or grouped formations with streaky, tapering ends, and usually develop within minutes of contact with the insect's fluid following accidental crushing. They closely resemble lentigines, particularly on exposed areas.[4] Acral melanoma, melanocytic nevi, petechiae, and exogenous pigmentation from chemical exposure can be excluded based on the patient's history.[5]

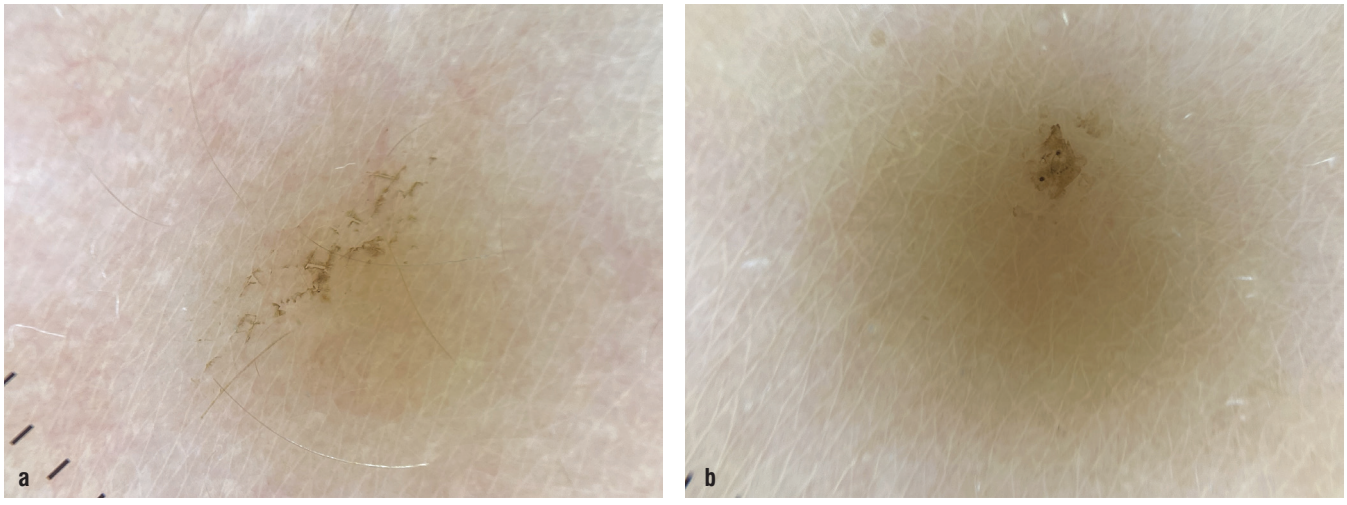

Figure 2. Dermoscopic examination showing (a) superficial structureless brown pigmentation with irregular linear streaks and (b) irregular, superficially located light brown amorphous pigmentation with focal dark brown dots (polarized, 10x)

In the present case, the diagnosis was based on clinical morphology, dermoscopic features, and spontaneous resolution, as no insect specimen was available for identification. This represents a limitation; however, the characteristic presentation and clinical course strongly support the diagnosis.

Awareness of this rare and benign condition is crucial to avoid unnecessary biopsies, laboratory investigations, and patient anxiety, particularly when lesions occur at atypical sites.[6]

Conclusion

This case report emphasizes that pigmentation caused by Cydnidae (burrowing bugs) may present in non-acral regions, warrants consideration in the differential diagnosis, and necessitates dermoscopic assessment.

Footnotes

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

Authorship Contributions

Concept: Ş.Y.S.T., G.D.D., M.T.Ş., Design: Ş.Y.S.T., G.D.D., M.T.Ş., Data Collection or Processing: Ş.Y.S.T., G.D.D., M.T.Ş., Analysis or Interpretation: Ş.Y.S.T., G.D.D., M.T.Ş., Literature Search: Ş.Y.S.T., G.D.D., M.T.Ş., Writing: Ş.Y.S.T., G.D.D., M.T.Ş.

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

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References

1. Chakraborty S, Sil A, Panigrahi A. Burrowing bug pigmentation. Infection. 2021;49(6):1363-1364.
2. Amrani A, Das A. Cydnidae pigmentation: unusual location on the abdomen and back. Br J Dermatol. 2021;184(4):e125.
3. Bhanja DB, Sil A, Chandra A, Chakraborty U. Atypical presentation of burrowing bug pigmentation involving a non-acral site. BMJ Case Rep. 2021;14(2):e241792.
4. Batrani M, Kaur A, Kubba A, Ramam M. A curious case of vanishing pigmented spots resembling lentigines. Indian J Dermatopathol Diagn Dermatol. 2019;6(1):42-44.
5. Malhotra AK, Lis JA, Ramam M. Cydnidae (burrowing bug) pigmentation: a novel arthropod dermatosis. JAMA Dermatol. 2015;151(2):232-233.
6. Dhiman A, Chauhan P, Daroach M. Cydnidae bug pigmentation mimicking dermatitis artefacta. Indian J Dermatol Venereol Leprol. 2023;90(1):136.

Case Report

Missed Pathology Follow-Up Leading to Delayed Melanoma Diagnosis

Handan Merve Erol Mart, Muhammet Talha Saraç, Bengü Nisa Akay
Department of Dermatology, Ankara University Faculty of Medicine, Ankara, Türkiye

Abstract

Missed pathology follow-up is a preventable cause of delayed melanoma diagnosis and can be compounded by cognitive biases. We report two cases in which failure to review pathology results led to delayed recognition of nodular melanoma. Both cases highlight the interplay between system failures and anchoring bias. Strengthening result verification processes, incorporating electronic alerts for unreviewed reports indicating malignancy, and promoting patient access to results are essential to preventing similar diagnostic delays.

Keywords: Delayed diagnosis, malignant melanoma, metastasis, vitiligo-like depigmentation

Introduction

Cognitive errors remain an important contributor to delayed melanoma diagnosis. Failure to verify or follow-up on pathology results, combined with anchoring to benign or trauma-related explanations, can delay recognition of malignancy. We present two cases illustrating unfavourable outcomes resulting from missed pathology follow-up for nodular melanoma.

The authors obtained consent from all patients for the publication of recognizable photographs, with the understanding that these photographs may be publicly available.

Case Report

Case 1: A 72-year-old man underwent excision of a nodular subcutaneous lesion on his left shoulder in 2020. Pathology was reported as nodular melanoma (Breslow thickness 5.5 mm, Clark level IV, 10 mitoses/mm², and ulceration), corresponding to pT4b disease. Neither regression nor evidence of lymphovascular or perineural invasion was identified. Immunohistochemical (IHC) analysis showed diffuse positivity for S-100 and HMB-45. The Ki-67 proliferation index was elevated, but the patient never received the report. He remained asymptomatic for five years until he presented with newly developed vitiligo-like depigmented macules on his face and an approximately 5-cm firm mass in his left axilla (Figure 1a). Positron emission tomography/computed tomography (PET/CT) demonstrated metabolically active metastatic involvement of the left axillary lymph nodes, without evidence of distant metastasis. The patient underwent surgical excision of the involved nodal mass and was subsequently referred for oncologic management and close multidisciplinary follow-up.

Case 2: A 29-year-old man presented in 2023 with a bleeding lesion on his right forearm following minor trauma. It was clinically interpreted as a pyogenic granuloma by a plastic surgeon and was completely excised. Pathology was reported

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Address for correspondence: Handan Merve Erol Mart, Department of Dermatology, Ankara University Faculty Medicine, Ankara, Türkiye
Email: handanmerveerol@gmail.com
ORCID ID: 0000-0003-3409-8985

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as nodular malignant melanoma (Breslow thickness 5 mm; Clark level IV; 5 mitoses/mm²; no ulceration; no regression; no evidence of lymphovascular or perineural invasion), corresponding to pT4a disease. IHC analysis demonstrated strong diffuse positivity for HMB-45, SOX10, and PRAME. The Ki-67 proliferation index was 20%. It was uploaded to the national e-health system but never reviewed by either the clinician or the patient. Two years later, halo nevi and patchy beard leukotrichia developed, prompting dermatologic reassessment (Figure 1b). Review of the national health records at that time revealed the prior malignant pathology. PET/CT showed no metastatic disease; therefore, no additional treatment was administered. The patient has been followed at 3-month intervals for one year, with no evidence of local recurrence, regional or distant metastases, or a new primary melanoma.

Discussion

Both cases highlight critical diagnostic vulnerabilities arising from failures in pathology follow-up and cognitive biases. In the first case, the unreviewed melanoma report is a classic example of a high-impact error at the system–communication interface in which the absence of structured verification ultimately delayed oncologic evaluation and may have influenced prognosis. In the second case, specifically anchoring bias, the premature acceptance of a trauma-related benign explanation hindered reconsideration of melanoma and demonstrated how immune-mediated depigmentation can serve as a delayed but crucial clinical clue to an overlooked melanoma diagnosis.[1-3]

A shared underlying issue in both cases was the absence of direct, mandatory communication and confirmation of pathology results. Complete reliance on electronic systems, without concurrent clinician and patient verification, allowed critical malignant diagnoses to go unnoticed. Cognitive contributors included premature closure and failure to consider alternative diagnoses once an initially benign interpretation was accepted.

To prevent recurrence of similar errors, structured communication and verification pathways must be prioritized.[4,5] The proposed patient safety interventions can be operationalized within three complementary domains. First, closed-loop verification systems should require the responsible clinician to acknowledge pathology reports and to document appropriate follow-up actions (e.g., referral, repeat excision, or surveillance). Second, high-risk results, such as malignant melanoma, should be automatically triaged and escalated within electronic health record systems, triggering alerts to clinicians and designated oversight teams when reports remain unreviewed. Third, patient-facing access to pathology results through national e-health platforms, combined with targeted patient education on the importance of result review and follow-up, may provide an additional safeguard against missed diagnoses.

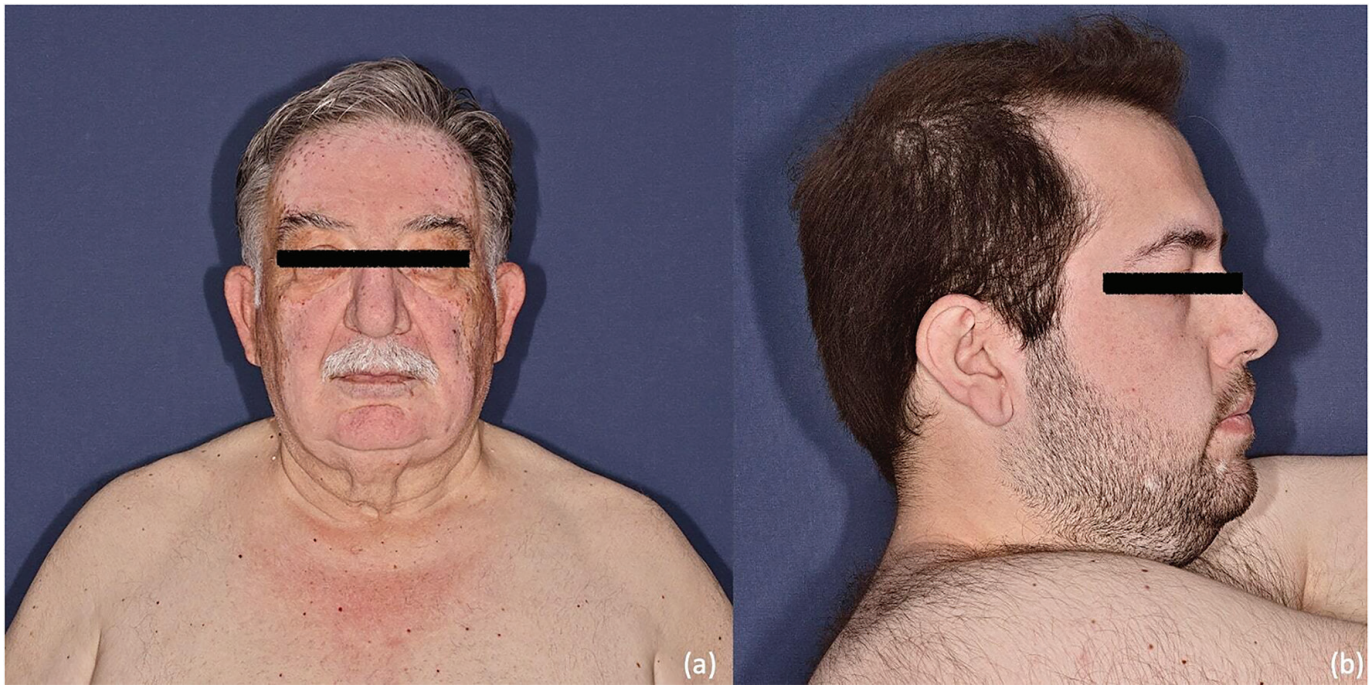

Figure 1. Clinical presentations of the patients. (a) Vitiligo-like depigmented macules on the face of Case 1, five years after excision of a nodular melanoma on the left shoulder. (b) Patchy beard leukotrichia in Case 2, two years after excision of a forearm lesion initially misdiagnosed as pyogenic granuloma

Conclusion

These cases exemplify how overlooked diagnostic data and anchoring bias can delay melanoma recognition. Reinforcing communication loops among pathologists, clinicians, and patients is essential to prevent the recurrence of such errors and to enhance patient safety. Strengthening national digital health infrastructures with automated alert systems for unreviewed malignant reports, mandatory acknowledgment mechanisms, and seamless interoperability between pathology and clinical databases can minimize communication gaps and ensure timely diagnostic follow-up.

Footnotes

Informed Consent: The authors obtained consent from all patients for the publication of recognizable photographs, with the understanding that these photographs may be publicly available.

Authorship Contributions

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

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

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

References

1. González R, Torres-López E. Immunological basis of melanoma-associated vitiligo-like depigmentation. Actas Dermosifiliogr. 2014;105(2):122-127.
2. Kiecker F, Hofmann M, Sterry W, Trefzer U. Vitiligo-like depigmentation as a presenting sign of metastatic melanoma. J Eur Acad Dermatol Venereol. 2006;20(9):1135-1137.
3. Cho EA, Lee MA, Kang H, Lee SD, Kim HO, Park YM. Vitiligo-like depigmentation associated with metastatic melanoma of an unknown origin. Ann Dermatol. 2009;21(2):178-181.
4. Wright B, Lennox A, Graber ML, Bragge P. Closing the loop on test results to reduce communication failures: a rapid review of evidence, practice and patient perspectives. BMC Health Serv Res. 2020;20(1):897.
5. El-Kareh R, Hasan O, Schiff GD. Use of health information technology to reduce diagnostic errors. BMJ Qual Saf. 2013;22 Suppl 2(Suppl 2):ii40-ii51.

Case Report

Benign Melanosis of the Nipple and Areola During Pregnancy: A Case Report

Munise Daye[1], Şükran Dallıgül[1], Fahriye Kılınç[2], Aylin Okçu Heper[3]
[1]Department of Dermatology, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye
[2]Department of Pathology, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye
[3]Department of Pathology, Ankara University Faculty of Medicine, Ankara, Türkiye

Abstract

Benign melanosis of the nipple and areola is a rare pigmentary disorder that may clinically mimic malignant melanoma and pigmented Paget's disease, particularly during pregnancy. We report a 30-year-old woman at 28 weeks' gestation who presented with bilaterally asymmetric, heterogeneously hyperpigmented macules on the nipples and areolae. Dermoscopy revealed a prominent and regular pigment network with heterogeneous light- and dark-brown coloration. Multiple punch biopsies were performed to exclude melanoma *in situ*. Histopathological examination showed irregular acanthosis and increased basal layer pigmentation without melanocytic atypia. Immunohistochemical staining demonstrated scattered MART-1– and HMB-45–positive melanocytes without an increase in number, supporting the diagnosis of benign melanosis of the nipple and areola. The coexistence of vitiligo represents a rare and noteworthy feature of this case. This report emphasizes the importance of histopathological evaluation in differentiating benign melanosis from malignant pigmented lesions in pregnant patients.

Keywords: Benign melanosis of the nipple and areola, pregnancy, vitiligo, melanoma *in situ*, dermoscopic features, areolar pigmentation

Introduction

Benign melanosis of the nipple and areola is a rare pigmentary disorder characterized by increased basal layer pigmentation without significant melanocytic proliferation.[1] Most reported cases occur in women of reproductive age, including pregnant patients.[1-5] These observations suggest that hormonal changes during pregnancy may play a role in the development of this entity. Due to its irregular borders, asymmetry, and heterogeneous hyperpigmentation, benign melanosis of the nipple and areola may clinically mimic malignant melanoma of the nipple. Therefore, dermoscopic and histopathological evaluations are essential for accurate differentiation.[2] In this report, we present a case of benign melanosis of the nipple and areola that developed during pregnancy, with the aim of contributing to the limited literature on this uncommon condition.

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Case Report

A 30-year-old woman at 28 weeks' gestation presented with dark discoloration of both nipples that had developed during the third trimester. Seventeen years earlier, she developed hypopigmented areas on the chin, right areola, and lumbar region; at that time she was diagnosed with vitiligo and treated with topical pimecrolimus. The newly developed hyperpigmentation predominantly appeared on the previously depigmented areolar regions. Dermatological examination revealed asymmetrical, irregularly bordered macules with heterogeneous hyperpigmentation in light- and dark-brown tones on both areolas, more pronounced on the right (Figure 1).

Dermoscopy revealed a prominent and regular pigment network with heterogeneous light- and dark-brown coloration

Address for correspondence: Şükran Dallıgül, Department of Dermatology, Necmettin Erbakan University Faculty of Medicine, Konya, Türkiye
Email: drsukranbalci1994@gmail.com
ORCID ID: 0009-0009-5710-4162

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(Figure 2). Considering the differential diagnosis between melanoma *in situ* and benign melanosis of the nipple and areola, multiple punch biopsies (4 mm) were obtained from clinically and dermoscopically heterogeneous areas, including three from the right areola and one from the left areola, to adequately assess asymmetric, heterogeneous pigmentation. Histopathological evaluation demonstrated irregular acanthosis, confluence of the lower ends of the rete ridges, and irregular brown pigmentation of the basal layer (Figure 3). Immunohistochemical staining revealed scattered MART-1– and HMB-45–positive melanocytes in the basal layer, without clustering or a significant increase in number (Figure 4). No cytologic atypia, mitotic activity, or pagetoid spread were observed. Fine superficial hyperkeratosis was present. Additional findings included Ki-67 positivity limited to the basal epidermal layer, cytokeratin 5/6 positivity in surface epithelial cells, sparse cytokeratin 7 positivity, and negative p16 staining. Overall, these findings were consistent with benign melanosis of the nipple and areola; melanoma *in situ* was excluded. The patient was placed under clinical follow-up.

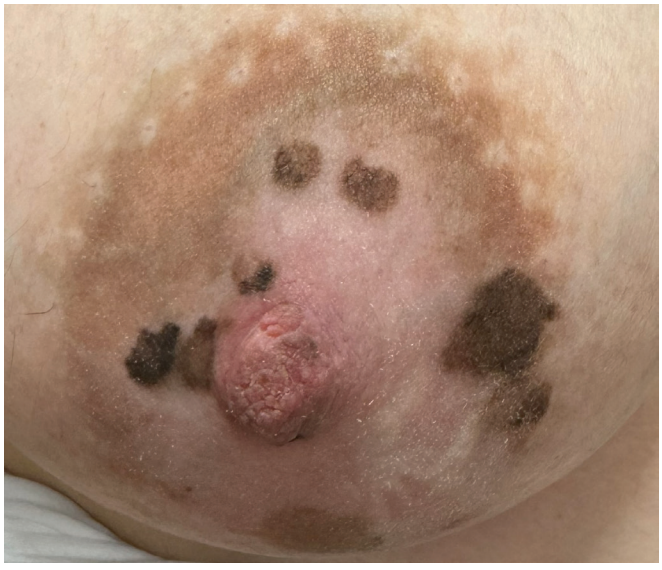

Figure 1. Asymmetric, irregularly bordered, heterogeneously hyperpigmented macules, light to dark brown in color are observed on the areola

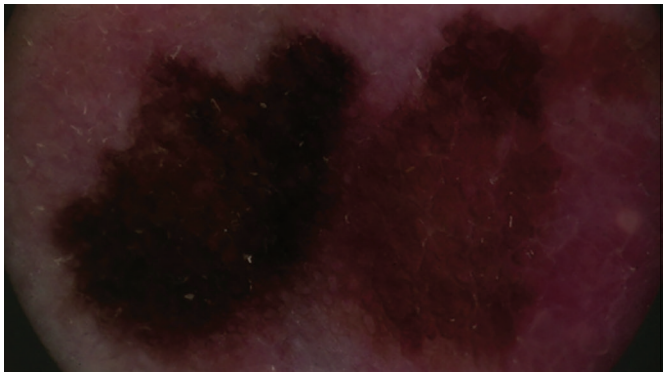

Figure 2. Dermoscopic image showing a prominent and regular pigment network with heterogeneous light and dark brown coloration

Written informed consent was obtained from the patient for publication of clinical data and images. According to institutional regulations, ethical committee approval was not required for this single case report.

Discussion

Approximately 20 cases of benign melanosis of the nipple and areola have been reported in the literature to date. The largest case series reported by Isbary et al.[3] included five patients identified at a single center over a 26-month period, suggesting that this condition may be underrecognized rather than truly rare. Most reported cases involve women of reproductive age and pregnant patients; moreover, a case of

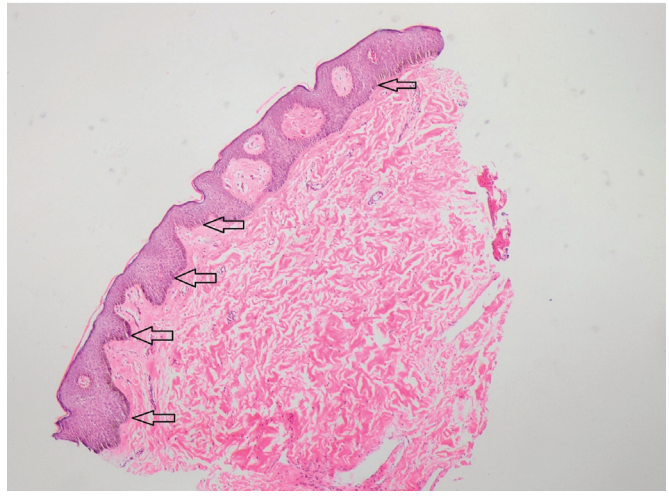

Figure 3. Histologic sections of the skin biopsy show irregular acanthosis in the epidermis, confluence of the lower ends of the rete ridges, and increased brown pigmentation in the basal layer (arrows), (hematoxylin and eosin stain, x40)

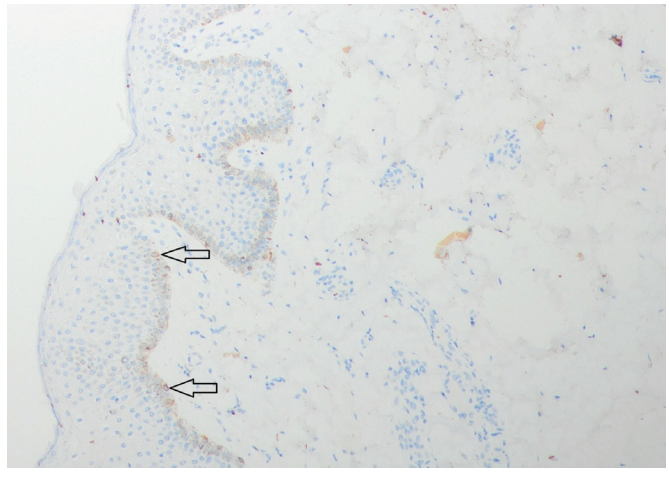

Figure 4. MART-1 staining demonstrates scattered melanocytes in the basal layer without a noticeable increase in number (arrows), (MART-1 immunostaining, x100)

benign melanosis of the nipple and areola has been described in a 7-year-old girl with early thelarche. Taken together, these observations support a potential role for hormonal stimulation in the pathogenesis of this entity.[1-6]

Benign melanosis of the nipple and areola is frequently confused clinically with malignant melanoma and pigmented Paget's disease. The absence of an atypical pigment network and blue-white veil, features typical of melanoma, and the lack of perifocal erythema, commonly associated with pigmented Paget's disease, may aid dermoscopic distinction.[7] Because benign melanosis of the nipple and areola may closely resemble melanoma *in situ* on dermoscopic examination, histopathological confirmation remains essential. In the present case, the absence of melanocytic atypia and the lack of a significant increase in MART-1– and HMB-45–positive melanocytes ruled out melanoma *in situ*.

Additionally, the patient's history of vitiligo and the development of pigmented islands within previously depigmented areolar areas are noteworthy. Only three cases of coexistence of vitiligo and benign melanosis of the nipple and areola during pregnancy have been reported in the literature.[3-5] This rare coexistence represents a distinctive feature of the present case and suggests that pregnancy-related hormonal alterations may induce localized pigmentary changes in patients with vitiligo, thereby contributing to the development of benign melanosis of the nipple and areola.

Conclusion

In conclusion, benign melanosis of the nipple and areola may clinically mimic malignant pigmented lesions, posing a diagnostic challenge. The limited number of reported cases contributes to its perceived rarity in the literature. Given the scarcity of experience and available data, particularly regarding its coexistence with vitiligo, we present this case to expand the current body of knowledge and emphasize the importance of accurate clinicopathological correlation.

Footnotes

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

Authorship Contributions

Surgical and Medical Practices: M.D., Ş.D., F.K., A.O.H., Concept: M.D., Ş.D., F.K., A.O.H., Design: M.D., Ş.D., F.K., A.O.H., Data Collection or Processing: M.D., Ş.D., F.K., A.O.H., Analysis or Interpretation: M.D., Ş.D., F.K., A.O.H., Literature Search: M.D., Ş.D., F.K., A.O.H., Writing: M.D., Ş.D., F.K., A.O.H.

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

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References

1. Chaima K, Mariem A, Khadija S, Rim K, Emna B, Tahya B, Hamida T. Unilateral hyperpigmented lesion of the breast. Clin Case Rep. 2023;11(4):e7132.
2. Blum A, Metzler G, Caroli U. Melanosis of the areola in dermoscopy. J Am Acad Dermatol. 2004;51(4):664-665.
3. Isbary G, Coras-Stepanek B, Dyall-Smith D, Guther S, Tillmann A, Stolz W. Five patients with melanosis of the nipple and areola clinically mimicking melanoma. J Eur Acad Dermatol Venereol. 2014;28(9):1251-1254.
4. Dhami RK, Sankaran A, Jr MH. Melanosis with coincident vitiligo of the areola. Pigment Int. 2024;11(1):62-63.
5. Huerta-Brogeras M, Garrido-Ríos A, Borbujo J, Tardío JC. Unilateral hyperpigmented lesion of the breast in a young woman. Melanosis of the areola and nipple. JAMA Dermatol. 2013;149(3):357-363.
6. Frangos JE, Amini AE, Schmidt B, Ganske IM. Brief report: areolar melanosis in a girl with precocious puberty. Pediatr Dermatol. 2023;40(5):877–878.
7. Tosti G, Salvini C, Barisani A, Vaccari S. In situ melanoma of the nipple and areola: a dermoscopic report in two new cases. Dermatol Pract Concept. 2021;11(2):e2021001.

Illegal and Original Toxin Discrimination with the Help of Wood's Light

Mustafa Şen, Aslan Yürekli, Gülşen Akoğlu, Anıl Çağrı Tuna
Department of Dermatology, University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Ankara, Türkiye

Dear Editor,

In recent years, the field of aesthetic medicine has experienced a significant increase in demand for minimally invasive cosmetic procedures. Botulinum toxin injections have become particularly prominent due to their effectiveness in treating dynamic wrinkles, hyperhidrosis, and neuromuscular conditions. However, parallel to this rise, there has been a concerning increase in illegally imported and unapproved toxin-containing products. These counterfeit formulations, often produced without standardized manufacturing protocols or adequate oversight, pose serious risks to patient safety and clinical practice.

One of the main drivers of illegal toxin use is financial motivation. Because licensed botulinum toxin products are costly and strictly regulated, smuggled products are sometimes used to reduce expenses. These toxins are often processed from unauthorized raw materials and distributed without quality control, making dose standardization and safety monitoring impossible. This increases the risk of adverse events, including botulism, a rare but potentially life-threatening condition.[1] Recent real-world data further highlight this risk, as a 2024 report from the United States documented multiple cases of serious illness following administration of presumed counterfeit botulinum toxin in nonmedical settings.[2] Consequently, distinguishing authentic toxin products from counterfeit ones has become a critical clinical responsibility. Among toxins used illicitly, abobotulinumtoxinA is one of the most frequently counterfeited formulations. Counterfeit packaging and vial designs often closely resemble genuine products, making visual differentiation challenging even for experienced clinicians. Therefore, practical methods to support authenticity verification are needed.

In this context, Wood's light examination represents a simple and accessible tool. Wood's light emits long-wave ultraviolet radiation at approximately 365 nm and is widely used in dermatology for diagnostic purposes. When Wood's light is applied to toxin packaging, a key distinguishing feature can be observed: authentic abobotulinumtoxinA products display a bright, reflective hologram, whereas counterfeit products lack this fluorescence (Figure 1).

In the present study, 156 abobotulinumtoxinA vials were examined, comprising 78 authentic and 78 counterfeit vials. All vials were independently assessed under Wood's light, and findings were consistent across assessments. Original products uniformly demonstrated a bright holographic reflection, whereas none of the counterfeit vials exhibited fluorescence, indicating reproducible differentiation between original and counterfeit products.

Wood's light is readily available in most dermatology and aesthetic clinics, and the examination requires only a few seconds. Incorporation of this step into routine practice may strengthen product authentication, reduce complications, and enhance patient confidence.

Manufacturer documentation supports hologram-based security features as authenticity markers. Official prescribing information for abobotulinumtoxinA (DYSPORT®) states

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Address for correspondence: Aslan Yürekli, Department of Dermatology, University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Ankara, Türkiye
Email: aslanyurekli03@hotmail.com **ORCID ID:** 0000-0003-2812-2133

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that the outer carton contains a unique hologram and advises clinicians not to use the product if the hologram is absent.[3] Similarly, FDA-approved labeling for onabotulinumtoxinA (BOTOX®) specifies a holographic film on the vial label as an anti-counterfeiting measure.[4] These features are manufacturer-defined and brand-specific rather than universal. Hologram technology is widely used as a high-security anti-counterfeiting method in banknotes, official documents, and luxury goods. Nevertheless, Wood's light examination should be considered a supportive screening tool rather than a definitive validation method. False-negative results may occur because of packaging damage or lighting conditions, whereas false-positive results are theoretically possible if counterfeit products imitate holographic elements. A limitation of this evaluation is its focus on a single formulation. AbobotulinumtoxinA was selected because it is the botulinum toxin product most commonly counterfeited, both globally and in our country. Broader generalization to other formulations should be approached with caution. Clinicians also bear ethical and legal responsibility for obtaining toxin products exclusively from authorized supply chains. In many countries, including ours, distribution is regulated through traceability systems such as global location number–based identification. Products obtained outside these systems pose legal, professional, and patient-safety risks and should be reported to the relevant authorities or the manufacturers.

Figure 1. Image of the original and illegal product under Wood light. Note the shining hologram on the original product on the left

Differentiation between original and counterfeit botulinum toxin products is a medical necessity. Wood's lamp examination is a fast, inexpensive, and practical adjunctive method that can enhance clinical safety when used in conjunction with regulatory compliance and manufacturer verification.

Footnotes

Authorship Contributions

Concept: M.Ş., A.Y., G.A., Design: M.Ş., A.Y., G.A., Data Collection or Processing: A.Y., A.Ç.T., Analysis or Interpretation: A.Y., G.A., Literature Search: M.Ş., A.Y., A.Ç.T., Writing: M.Ş., A.Y., G.A., A.Ç.T.

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References

1. Chen Z, Chen ZY, Liu WH, Li GS. Botulism due to cosmetic injection of botulinum toxin: five-year experience. Plast Reconstr Surg. 2021;148(2):335e-337e.
2. Thomas CM, McElroy R, Yackley J, Fill MA, Goonewardene D, Mackley C, Roth E, Ackelsberg J, Slavinski S, Habrun C, Hodge B, Rush C, Brown CM, Waltenburg MA, Bertling LH, McGorty M, Johnson R, Schaffner W, Jones TF, Dunn JR. Notes from the field: Illnesses after administration of presumed counterfeit botulinum toxin in non-medical settings - Tennessee and New York City, March 2024. MMWR Morb Mortal Wkly Rep. 2024;73(27):609-611.
3. Ipsen Biopharmaceuticals, Inc. DYSPORT® (abobotulinumtoxinA) prescribing information. Available from: https://www.dysportusa.com/PI
4. Allergan, Inc. BOTOX® (onabotulinumtoxinA) FDA-approved labeling. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103000s5232lbl.pdf