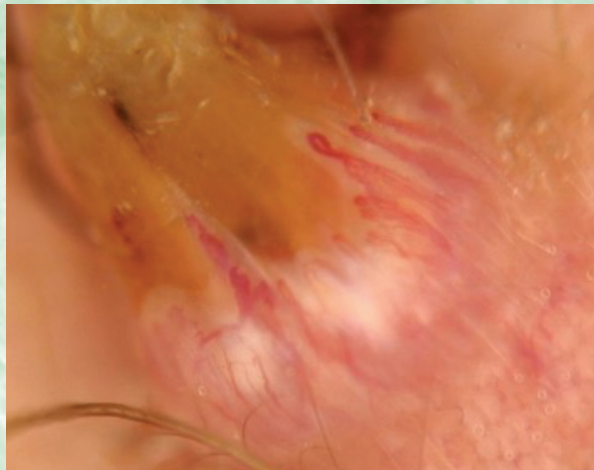
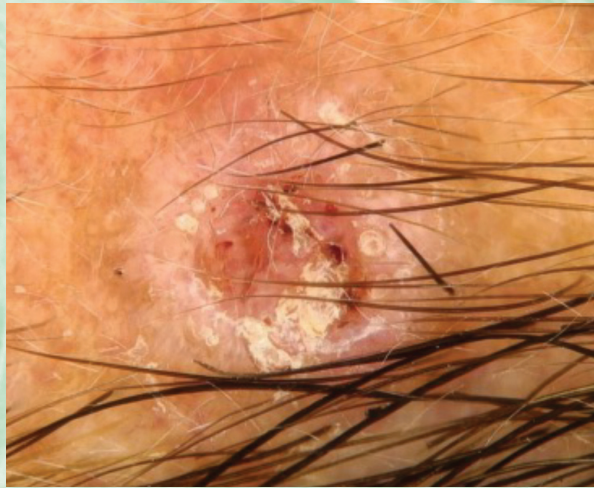


Anais Brasileiros de Dermatologia

VOLUME 100 ■ NUMBER 4 ■ 2025

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Evaluation of dermoscopic findings in patients with cutaneous squamous cell carcinoma according to histopathological subtype and lesion morphology
Ürün M, et al.



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- ❑ Pre- and post-analytical guidelines for the microscopic diagnosis of melanoma: recommendations from the Brazilian Society of Pathology
- ❑ Precision medicine and Treat-to-Target approach in atopic dermatitis: enhancing personalized care and outcomes
- ❑ Latin American consensus on tapering of biological therapy in psoriasis
- ❑ Mycoplasma-Induced Rash and Mucositis (MIRM) mimicking herpetic stomatitis

Volume 100. Number 4. July/August 2025

CONTENTS

Editorial

- Anais Brasileiros de Dermatologia – Impact Factor and CiteScore for 2024..... 501168
Sílvia Alencar Marques, Ana Maria Ferreira Roselino, Hiram Laranjeira de Almeida Junior, Luciana Patrícia Fernandes Abbade

Continuing Medical Education

- Pre and post-analytical guidelines for the microscopic diagnosis of melanoma: recommendations from the Brazilian Society of Pathology..... 501139
José Cândido Caldeira Xavier-Júnior, Karina Munhoz de Paula Alves Coelho, Mariana Petaccia de Macedo, Rute Facchini Lellis, Nathanael de Freitas Pinheiro Junior and Robledo Fonseca Rocha, Dermatopathology Committee of the Brazilian Society of Pathology

Original Article

- Analysis of the clinical and epidemiological profile of leprosy in Brazil and major regions..... 501127
Alicia de Siqueira Sczmanski, Lucas Pazin, Thiago Mamoru Sakae and Josete Mazon
- Dermatological manifestations in patients with gastrointestinal malignancies: a focus on early diagnosis and patient comfort..... 501128
Burcu Aydemir Demirci, Deniz Aksu Arica, Leyla Baykal Selcuk, Evren Fidan, Ali Guner, Savas Yayli and Ibrahim Etem Arica
- Evaluation of dermoscopic findings in patients with cutaneous squamous cell carcinoma according to histopathological subtype and lesion morphology..... 101091
Mustafa Ürün, Yıldız Gürsel Ürün, Ömer Faruk Elmas and Nuray Can
- Influence of sentinel lymph node biopsy on the prognosis of acral melanoma patients..... 501129
Thiago Francischetto, Ana Clara Falcão, Adson Santos Neves, Ana Beatriz Lira, Robson Freitas de Moura, Thiago Souza Oliveira Freitas de Moura, Juvandy Antonio Inacio Santos, André Bacellar Costa Lima, Marco Antonio Oliveira Lessa, Jussamara Britos Santos, Alexandre Farias de Albuquerque and Vaner Paulo da Silva Fonseca Pinheiro
- Long-term outcome of juvenile dermatomyositis associated with lipodystrophy: experience of a University hospital..... 501130
Igor Kapetanović, Mirjana Gajić-Veljić, Branka Bonač i-Nikolić and Miloš Nikolić
- Predictors of PASI90 response in patients with psoriasis treated with treated with interleukin inhibitors: observational cohort study 501132
Burhan Engin, Yusuf Demir, Sera Nur Yucesoy and Tumay Ak
- Prevalence of reactive allergens in contact patch testing studies using the Brazilian standard battery: a systematic review 501126
Ana Laura Andrade Bueno, Nathalia Hoffmann Guarda Aguzzoli and Renan Rangel Bonamigo

Pruritus in atopic dermatitis: a cross-sectional study of adult patients from a tertiary university hospital in São Paulo, Brazil..... 101093
Georgia Biazus Soares, Raquel Leão Orfali, Beatriz Lacerda Averbach, Qai Ven Yap, Gil Yosipovitch and Valeria Aoki

White piedra: fungal extracellular matrix formation and its importance in pathogenesis. An ultrastructural study..... 501140
Hiram Larangeira de Almeida Jr., Thales de Moura Assis, Eduardo Camargo Faria and Viviane Mazo Fávero Gimenes

Review

Inflammasome pathways in atopic dermatitis: insights into inflammatory mechanisms and therapeutic targets..... 501136
Yasmim Álefe Leuzzi Ramos, Anna Julia Pietrobon, Franciane Mouradian Emidio Teixeira, Valeria Aoki, Maria Notomi Sato and Raquel Leão Orfali

Precision medicine and Treat-to-Target approach in atopic dermatitis: enhancing personalized care and outcomes.. 501135
Dan Hartmann, Catalina Retamal and Fernando Valenzuela

Special Article

Latin American consensus on tapering of biological therapy in psoriasis 501134
Angela María Londoño-García, Juan Raúl Castro-Ayarza, Manuel Darío Franco Franco, Cesar Fernando González Ardila, Gabriel Magariños, Enrique Salvador Rivas Zaldivar, Susan Martínez, Linda Ibatá, Julieth Carolina Castillo, Paola Jimena Cárdenas Rojas, Evelyn Giuliana Castro Vargas, Claudia Romina Contreras, Claudia de la Cruz Fernández, Andrés Chavarriaga Restrepo, Cristina Mariela Echeverría, André Vicente Esteves de Carvalho, Benjamín Hidalgo Matlock, Enrique Loayza, Matías Rafael Maskin, Ricardo Romiti and Fernando Valenzuela

Letter - Research

Botryomycosis: series of cases diagnosed between 2000 and 2023 in the Dermatology division of a tertiary hospital..... 501144
Nicole de Souza Aranha, João Avancini, Caroline Heleno Chagas de Carvalho, Walter Belda Júnior and Marcello Menta Simonsen Nico

Translation, cultural adaptation and validation of the Brazilian version of the Alopecia Areata Quality of Life Index (AA-QLI-BRA)..... 501146
Paula Rosa Coutinho Goulart Borges Mariotoni, Leonardo Spagnol Abraham, Daniel Fernandes Melo, Rodrigo Pirmez, Leopoldo Duailibe Nogueira Santos, Paulo Müller Ramos and Hélio Amante Miot

Use of imiquimod in 21 patients with molluscum contagiosum: better results in specific areas..... 501142
John Verrinder Veasey, Bruna Cavaleiro de Macedo Souza, Rebeca Naomi Shida and Guilherme Camargo Julio Valinoto

Using ChatGPT 4.0 for diagnosis in Dermatology: performance analysis in clinical cases from Anais Brasileiros de Dermatologia 501143
Matheus Alves Pacheco and Athos Paulo Santos Martini

Letter - Clinical

Adult T-cell lymphoma/leukemia following infective dermatitis in an adult with HTLV-1 infection: a case report..... 501151
Denis Miyashiro, Tatiane Assone, Augusto César Penalva de Oliveira, Sabri Saeed Mohammed Ahmed Al-Sanabani, José Antonio Sanches and Jorge Casseb

Exuberant terra firma-forme dermatosis in an elderly patient 501131
Marinna Sampaio Campos, Loanda Oliveira Fukuma, Juliana Carvalho Delgado, Paulo Ricardo Criado, Karla Calaça Kabbach Prigenzi and Sandra Lopes Mattos e Dinato

FGF22 heterozygous and FGFR2 mosaic mutations in Munro acne nevus: a case study..... 501141
Jiachen Sun, Yimeng Wang, Lihua Zhang, Chunlei Zhang and Chuan Ma

Intravenous immunoglobulin in the treatment of scleromyxedema associated with monoclonal gammopathy 501149
Amanda Cochlar Medeiros Perrella, Alexandre Michalany, Mário Cezar Pires and Cassio Oliveira Lima

Lymphangiectasia and genital lymphedema secondary to metastatic Crohn's 501150
Nelly Marlene Román Mendoza, María Dolores Caro Gutiérrez, José Javier Mateos Rico, Alberto Alegre Bailo, Lourdes Estrada Muñoz and Francisco Javier Vicente Martín

Lymphocytic thrombophilic arteritis, an infrequent cause of livedo reticularis - Case report	501148
<i>Dominga Peirano, Maria Luz Hubner-Garretón, Martha Fernandez and Andrés Figueroa</i>	
Mycoplasma-Induced Rash and Mucositis (MIRM) mimicking herpetic stomatitis	501138
<i>Sara Becerril-Andrés, Adolfo Alejandro Cabanillas-Cabral and Gloria Baeza-Hernández</i>	
Optical super-high magnification dermoscopy versus standard dermoscopy in basal cell carcinoma	501152
<i>Izadora Moreira do Amaral, Elisa Scanduzzi Maciel, Daniela Surjan Milheti, Camila Arai Seque, Milvia Maria Simões e Silva Enokihara and Sérgio Henrique Hirata</i>	
Primary extramedullary plasmacytoma: a rare case presentation	501137
<i>Pedro Barbosa, Clara de Diego, Javier Anaya and Corina Busso</i>	
Rare case of lymphomatoid papulosis type E.....	501133
<i>Máté Attila Bognár, Csaba Gyömörei and Zsuzsanna Lengyel</i>	

Letter - Tropical/Infectious and parasitic dermatology

Epidemiological profile of anogenital lesions in 4,029 consultations at a Sexually Transmitted Infections Clinic in São Paulo, Brazil	501145
<i>Julia Aires Thomaz Maya, Kaique Arriel, Laura Stamato de Figueiredo and John Verrinder Veasey</i>	

Letter - Therapy

Acneiform rash secondary to trametinib in two patients with neurofibromatosis.....	501158
<i>Macarena Nougues, Luciana Laura Tirelli, Paula Carolina Luna, Darío Macas Ordoñez and Margarita Larralde</i>	
Oxcarbazepine induced systemic lupus erythematosus: a clinical challenge	501154
<i>Eduardo López Vera, Elisabeth Gómez Moyano, María Ayala Blanca and María Salas Cassinello</i>	
Paradoxical psoriasiform alopecia secondary to secukinumab: a case report.....	501155
<i>Inés Segovia Rodríguez, María Castillo Gutiérrez, Fernando Pinedo-Moraleda and Beatriz Aranegui Arteaga</i>	
Stabilization of a recalcitrant and aggressive necrobiotic xanthogranuloma with tofacitinib.....	501159
<i>Miguel Mansilla-Polo, Carlos Abril-Pérez, Daniel Martín-Torregrosa and Rafael Botella-Estrada</i>	
Successful intravenous immunoglobulin therapy in paraneoplastic pemphigus associated with hepatocellular carcinoma	501153
<i>José Ramos, Cláudia Afonso, Ângela Roda and Cristina Fonseca</i>	
Successful repigmentation with ritlecitinib and combined home-based phototherapy in an intractable case of generalized vitiligo	501157
<i>Xiu-Kun Sun and Ai-E Xu</i>	
Use of ustekinumab in the treatment of severe psoriasis in a liver transplant recipient	501156
<i>Tiago Almeida Santos Costa, Juliana Schinzari Palo and Renata Ferreira Magalhães</i>	



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EDITORIAL

Anais Brasileiros de Dermatologia – Impact Factor and CiteScore for 2024[☆]



Dear Colleagues,

Recently, on June 18, 2025, the Journal of Citation Reports released the metrics for 2024 of the 96 audited journals in Dermatology and related specialties. The various metrics calculated are intended to show the performance of the journals and define, even if this is not an explicit intention, and there may be biases, their ranking in their respective areas of activity or specialty. And once again, we are happy to be able to communicate to the national and international dermatology community the progress of the Impact Factor (IF), and items contributing to the composition of the IF and CiteScore of the *Anais Brasileiros de Dermatologia* (ABD). It is important to emphasize that we understand this as a collective achievement, the result of the efforts of the body of Scientific and Technical Editors, the contributions of countless Authors, and the quality of the voluntary work of the Reviewers. Although the metrics are somewhat distinct in their calculation methodologies, the different metrics allow several inferences and are indicative of paths to be maintained and others to be corrected and improved.

The IF of ABD for 2024 increased to 3.6; one point above the IF for 2023.¹ This progress places us in 18th place among the 96 evaluated international journals, therefore in the first quartile - Q1, and in the 3rd place among Brazilian medical journals. Resulting from practically constant growth since the indexing of ABD in PubMed/Medline in 2009, considering the values of its first IF = 0.337 (2010). The CiteScore, which uses methodology and databases from different source journals, also increased, albeit from a modest 0.1 to 2.5. It is obvious that these advances, particularly in the IF, are very welcome, but they do not satisfy or content us, since the

vigor and productivity of Ibero-Latin American dermatology qualify us for positions of greater prominence. Anyhow, such results justify the celebrations of ABD on its centenary.

The metrics and auxiliary data provided allow Editors to identify areas or subjects with the greatest impact and repercussion and, consequently, to expand, as much as possible, the space allocated to such topics. Likewise, to identify subjects or topics with less or no repercussion and impact. The ABD has historically been a journal with multiple subjects and of interest to readers, as it prioritizes the most classic clinical dermatology, allocating space to aesthetic and surgical dermatology, and also to tropical and infectious dermatology and dermatopathology. And, it uses the "Letters" resource with fewer words and figures, to expand the allocated space to portray the indisputable wealth of the clinical and therapeutic universe in dermatology.²⁻⁶

The numbers reported above suggest that we are on the right track: a journal with multiple sections, robust in its emphasis on clinical dermatology in its broadest sense, and that remains demanding in the intellectual, visual, and editorial quality of the articles. However, we want to go further, and in 2025, the ABD will start publishing 35 articles per issue, or 15% more, as an essential initiative to avoid a backlog of approved articles awaiting publication. Furthermore, what we believe to be of great importance in terms of increasing the visibility and equalization of articles: starting with volume 101 (1), the ABD will be published exclusively in English, both online and in print, without changing its historic and century-old name.⁷ Therefore, starting in September 2025, all articles will have to be submitted in English.

We will continue to count on the financial support and infrastructure of the Brazilian Society of Dermatology and on the quality of the Authors and Reviewers who honor us with their work, observations, and dissemination.

We would like to give our thanks to all of you.

[☆] Study conducted at the Department of Infectology, Dermatology, Diagnostic Imaging and Radiotherapy, Universidade Estadual Paulista, Botucatu, SP, Brazil.

Financial support

None declared.

Authors' contributions

Silvio Alencar Marques: Approval of the final version of the manuscript; drafting and editing of the manuscript.

Ana Maria Roselino: Approval of the final version of the manuscript; drafting and editing of the manuscript.

Hiram Larangeira de Almeida Junior: Approval of the final version of the manuscript; drafting and editing of the manuscript.

Luciana P. Fernandes Abbade: Approval of the final version of the manuscript; drafting and editing of the manuscript.

Conflicts of interest

None declared.

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CONTINUING MEDICAL EDUCATION

Pre and post-analytical guidelines for the microscopic diagnosis of melanoma: recommendations from the Brazilian Society of Pathology[☆]



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Received 11 December 2024; accepted 27 January 2025

Available online 3 July 2025

KEYWORDS

Dermatology;
Guideline;
Melanoma;
Microscopy;
Pathology

Abstract The guidelines project of the Brazilian Society of Pathology aims to disseminate recommendations for pathologists, surgeons, and clinicians, based on solid data from the literature and through adaptations of international guidelines to the reality of Brazilian physicians. This article is the result of the efforts of a group of pathologists, members of the Dermatopathology Committee of the Brazilian Society of Pathology, focused on melanocytic diseases, who, through topics, established pertinent recommendations for clinicians and surgeons for the accurate diagnosis of melanocytic lesions suspected of melanoma. This article aims to clarify the best way to perform excision in cases of suspected melanocytic lesions, as well as the pre-analytical care

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related to the material, how to interpret the anatomopathological report, and the situations in which immunohistochemical and molecular studies can be auxiliary tools for diagnosis and/or therapy.

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Introduction

According to data from the Global Cancer Observatory (GLOBOCAN), in 2022, 331,647 new cases and 58,645 deaths from cutaneous melanoma were identified¹; the primary skin tumor is the most lethal and there is a tendency for increased mortality from this neoplasm in the elderly Brazilian population.² Moreover, national data, in agreement with the international literature, indicate an increase in the incidence of melanoma cases in a time series,^{3,4} with stability of histological subtypes that show early invasive behavior, which corresponds to a considerable fraction of specific mortality.³ Patients with clinically suspicious pigmented skin lesions should preferably undergo (whenever possible) surgical excision (excisional biopsy),⁵ since the diagnosis remains anatomopathological, despite all the advances in molecular pathology and *in-vivo* imaging tools regarding the knowledge of these neoplasms.⁶ As is also the case with most malignant neoplasms in other sites, an accurate early diagnosis of cutaneous melanoma is associated with a better prognosis.^{7,8} In addition, the creation of standardized protocols for collection, preparation, analysis, and structured reports is essential for the correct monitoring of these patients⁹ and to ensure the integrity of the material for possible complementary studies (immunohistochemical and molecular ones), when applicable.

It is worth noting that this guideline was developed by the Brazilian Society of Pathology (SBP, *Sociedade Brasileira de Patologia*), which created a working group of experts in the area to evaluate the literature, Brazilian legislation, classic books, and international recommendations to propose a protocol oriented to the reality of health care in the country. These recommendations will be published in two articles, with similar and complementary content. The present article was written with a focus on clinicians and surgeons, while another article, aimed at pathologists, will be published in the journal *Surgical and Experimental Pathology*, of SBP. The present article aims to clarify the best way to perform excision in cases of suspicious melanocytic lesions, as well as the pre-analytical care with the material, how to interpret the anatomopathological report, and the situations in which immunohistochemical and molecular studies can be auxiliary tools for diagnosis. Table 1 shows the list of all recommendations in this article.

Surgical procedure

Providing an appropriate biopsy and a pertinent clinical history is essential for the diagnosis and accurate prognosis of melanoma.⁵ In cases of lesions suspected of melanoma, an excisional biopsy with exiguous free margins should be the preferred approach. Occasionally, an incisional biopsy may

be considered the first approach in very large lesions or in lesions located in regions of aesthetic or functional interest. Shaving biopsy is expressly contraindicated because it may add difficulties to the histopathological diagnosis and, in the future, compromise the correct determination of the Breslow index (thickness).¹⁰⁻¹² The use of the Mohs surgery technique is not validated for the approach to melanocytic lesions and may also compromise the accurate diagnosis of these lesions.¹³

After the procedure, the biopsy/surgical specimen must be immediately submerged in a clean, transparent, wide-mouthed, well-sealed, and accurately identified container containing buffered formalin (10% buffered formaldehyde) in a volume approximately 10 to 20 times the size of the specimen (Fig. 1). The ideal fixation time may vary between six and 72 hours. It is expressly contraindicated to send specimens/biopsies in other media such as petroleum jelly, alcohol, or saline solution. All of these measures are important to maintain the morphological integrity of the tissue, as well as the proteins and genetic material of the tumor cells; potential future targets of immunohistochemical and molecular studies, respectively.¹¹ To ensure that the formalin used is buffered, direct communication with the person in charge of the hospital unit or with the partner pathology laboratory is suggested. To prevent excessive fixation of the materials, the ideal is not to perform surgical excision (excisional biopsy) on the eve of holidays, or even in the late afternoon on Fridays, if the partner laboratory does not have processing hours on Saturday. Avoid performing surgical excision in an institution/clinic that does not have agile flow logistics for sending samples for processing and analysis to prevent long periods of exposure to formalin and material overfixation. It is important to highlight the impossibility of processing and diagnosing skin lesions on the same day as the lesion is removed since the minimum time for fixation and histological processing must be taken into account. It is also essential that only one excision specimen be placed in each container to allow correct lesion identification with the final histopathological diagnosis.

Handling of the surgical specimen after removal must be careful to prevent causing crushing artifacts.¹⁴ The use of electrocautery should be cautious, since, if excessive, it may impair the assessment of the lesion edges.¹⁵

Recommendation 1: In cases of suspected melanoma, excisional biopsy with exiguous margins (1-3 mm) should be the preferred approach.

Recommendation 2: After removal, the biopsy/surgical specimen should be immediately submerged in an appropriate container containing buffered formalin (10% buffered formaldehyde) in a volume approximately 10 to 20 times the sample size.

Table 1 Summary of recommendations.

Recommendation 1	In the case of suspected melanoma, excisional biopsy with exigous margins (1–3 mm) should be the preferred approach.
Recommendation 2	After removal, the biopsy/surgical specimen should be immediately submerged in an appropriate container containing buffered formalin (10% buffered formaldehyde) in a volume approximately 10 to 20 times the sample size.
Recommendation 3	Clinical information, especially patient age and sex, as well as lesion location and size, are essential data for the accurate microscopic diagnosis of melanocytic lesions.
Recommendation 4	Whenever possible, include all the material sent in case of lesions suspected of melanoma. Clinicians and surgeons are advised to verify whether this recommendation was followed by carefully reading the macroscopy section of the anatomopathological report.
Recommendation 5	Immunohistochemical studies are not essential for the microscopic diagnosis of melanoma, being reserved for selected cases, indicated by the pathologist in the report, often through comments and notes.
Recommendation 6	Perioperative examination is contraindicated for both diagnosis and margin evaluation of melanocytic lesions.
Recommendation 7	Perioperative examination is contraindicated for sentinel lymph node evaluation in cases of cutaneous melanoma.
Recommendation 8	Molecular testing to detect mutations in the <i>BRAF</i> gene is recommended in the scenario of patients with high-risk stage 2, 3 and 4 melanoma, using a sample with adequate neoplastic representation and a molecular technique duly validated by the laboratory.

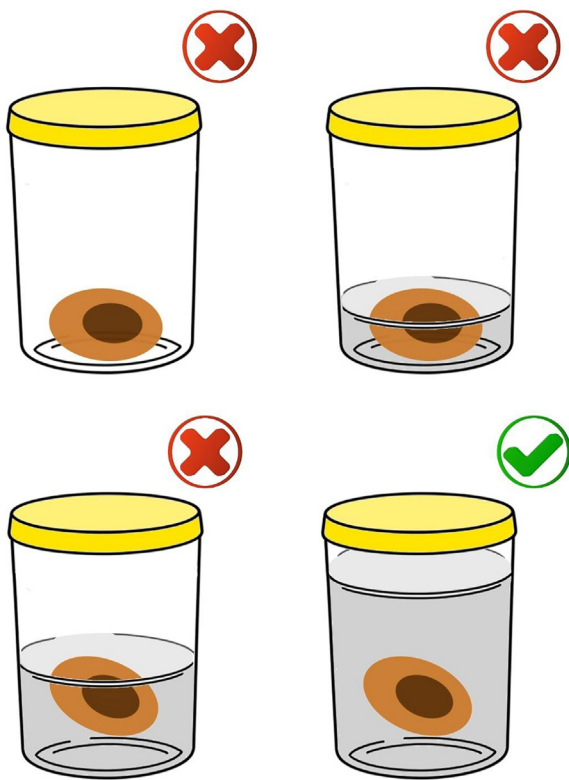


Figure 1 The correct way to store the specimen is using a volume of 10% buffered formalin greater than 10–20 times the volume of the specimen (bottom right image). It is not acceptable to send the material without formalin, in a volume that does not cover the specimen in its entirety or in a volume slightly greater than the volume of the specimen.

Request for anatomopathological examination

In the absence of a specific request form from the laboratory, the request may be performed using a prescription

form containing the physician's identification, date and minimum patient identification information (always consider at least three parameters, for example, full name, date of birth and CPF (Brazilian/Cadastro de Pessoa Física) or other identification document).¹⁶

It is essential to send the clinical history and dermatological description of the lesion (Fig. 2), its evolution, results of complementary exams and diagnostic hypotheses, as they are part of the prerequisites for a full report and may influence the diagnostic decision in the case of melanocytic lesions. Sex, location of the lesion and patient age are the minimum data for microscopic analysis without which a conclusive and adequate diagnosis is at risk.^{8,17,18}

Among the most relevant data for the analysis of a melanocytic lesion are: a) Age: Age range affects the interpretation of microscopic findings. For example, the same microscopic findings that would lead to the diagnosis of acral melanoma in an elderly patient may not characterize malignancy in a pediatric patient. b) Location: Benign melanocytic lesions located in so-called "special sites" (e.g., scalp, genitalia, breast line, auricle, and flexural regions) may present microscopic and dermoscopic findings simulating malignancy that would not be admissible in other anatomical locations. c) Clinical description of the lesion: ABCDE rule (asymmetry, borders, color, diameter, and evolution), as well as any other relevant information (e.g., increase in size, changes in characteristics, occurrence of trauma, results of previous biopsies, appearance of ulceration, mainly). d) Clinical history: Pregnancy,¹⁹ personal and family history of melanoma and dysplastic nevi. e) Other tests: Description of dermatoscopy and, if applicable, other complementary tests (e.g., confocal microscopy and germline genetic testing)^{6,20,21} (Figs. 3 and 4).

Recommendation 3: Clinical information, especially patient age and sex, as well as lesion location and size, are essential data for the accurate microscopic diagnosis of melanocytic lesions.

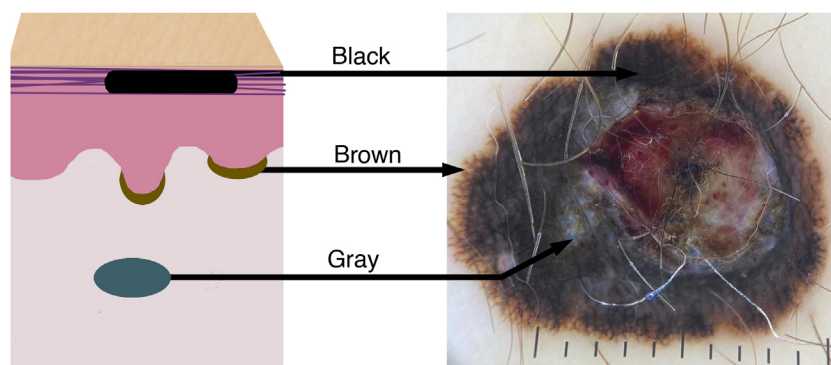


Figure 2 Color variation in melanocytic lesions reflects the location of the melanin pigment in the skin. The schematic drawing shows the correspondence of the colors/tones of melanoma in the dermoscopic examination according to the melanin deposit: black in the stratum corneum, brown in the basal layer of the epidermis, and bluish/gray in the dermis.

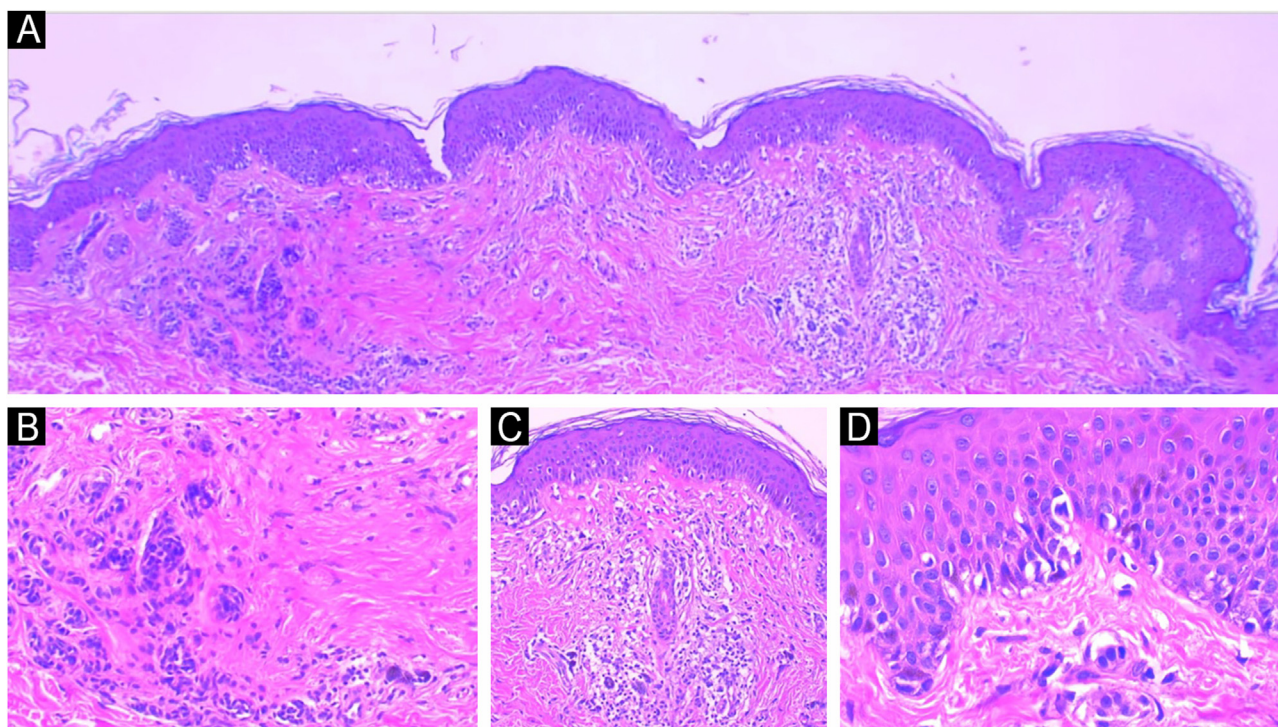


Figure 3 Traumatized nevi are a good example of the need for clinical-pathological correlation. See the panoramic image of a nevus on the thigh of a 44-year-old female patient. The remaining nevus can be seen on the left, the central fibrosis and the dermal inflammatory infiltrate with melanophages on the right (A) Hematoxylin & eosin $\times 40$. In detail, the remaining intradermal nevus and the fibrosis parallel to the direction of the epidermis, Hematoxylin & eosin $\times 200$ (B). In detail, the inflammatory infiltrate with melanophages, Hematoxylin & eosin $\times 200$ (C). Presence of atypical proliferated junctional melanocytes, a common finding in traumatized melanocytic lesions, Hematoxylin & eosin $\times 400$.

Pre-analytical laboratory evaluation

The macroscopic description consists of measuring the skin fragment received and a direct but detailed description of the identified lesion (Fig. 5). Every anatomopathological report includes the macroscopic description, which is usually found just below the clinical information. This allows correlation with data from the surgical specimen sent. Ideally, the specimen should be included in its entirety. In cases of very large and clearly advanced lesions (e.g. amputation products with evident bone infiltration), detailed sampling

may be an option. To verify whether all the material has been included, one should simply read the statement at the end of the macroscopy. It is also possible to verify in the macroscopic description how many paraffin blocks resulted from the material inclusion, which must be identified.

See below, for instance, the macroscopic description of melanoma, in which it is highlighted that all the material was submitted to microscopic analysis, how many blocks were generated from the specimen (five blocks), and how many fragments were placed in each block (blocks 1 and 2 contain six fragments and the other blocks contain one fragment

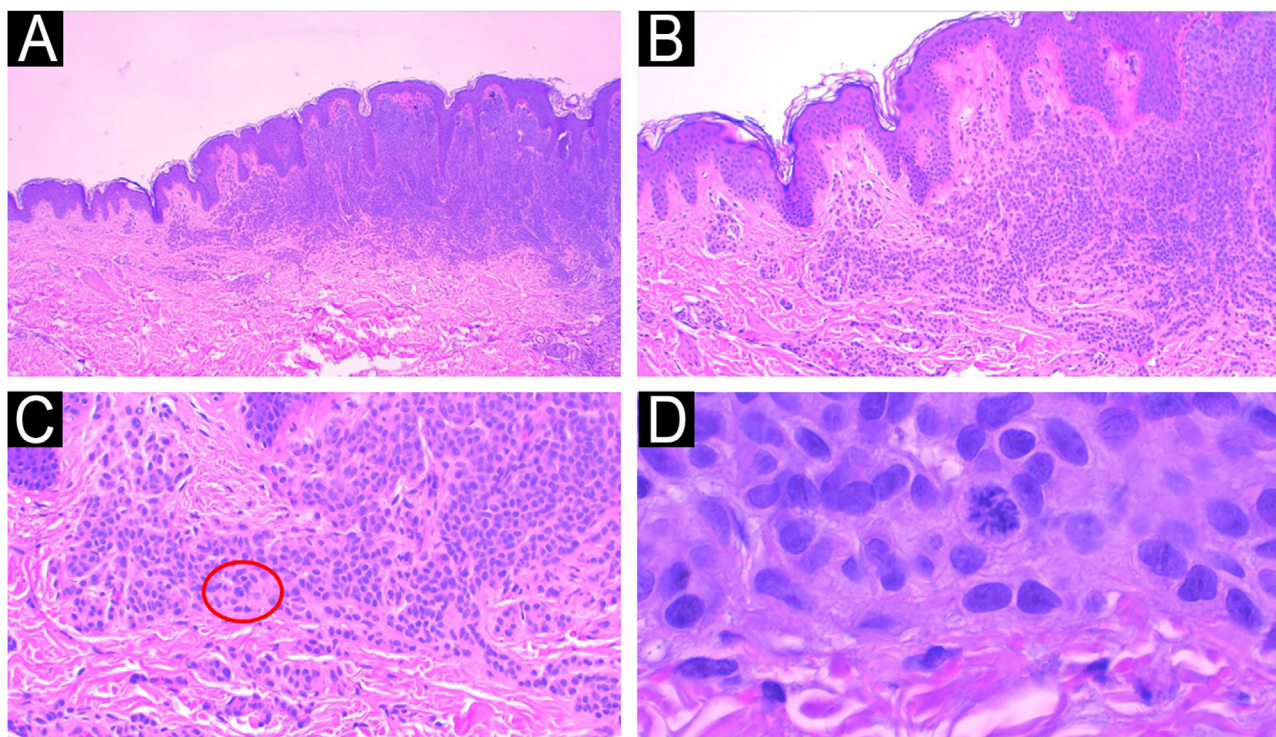


Figure 4 Another example of the importance of anatomical-clinical correlation: intradermal melanocytic nevus removed for aesthetic purposes from a 14-year-old female patient. Panoramic view of the intradermal nevus (A), Hematoxylin & eosin $\times 40$. Melanocytes arranged in nests with maturation to depth (B) Hematoxylin & eosin $\times 100$ and no signs of atypia (C) Hematoxylin & eosin $\times 200$. The presence of atypical deep mitosis in the center of the image, which does not change the diagnosis, Hematoxylin & eosin $\times 1000$.

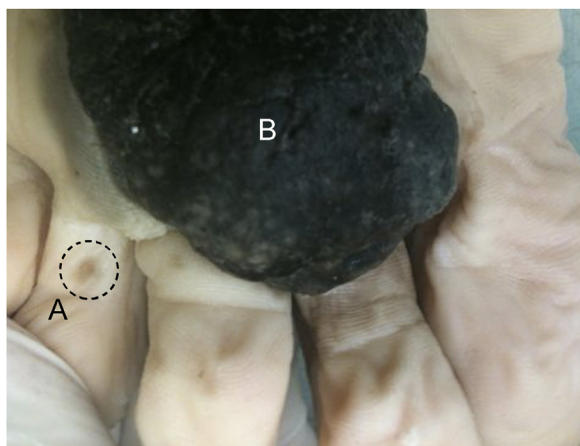


Figure 5 Macroscopic image of acral melanoma with a small discontinuous lesion (A) and a large tumor component (B). The identification of satellites/microsatellites/cutaneous metastases influences staging and can occur through detailed macroscopic examination.

each): "Approximately circular skin fragment measuring $3.0 \times 2.5 \times 0.8$ cm showing, in the center, a brownish pigmented lesion with irregular borders, with blackened areas measuring 1.8×1.2 cm and 0.2 cm from the closest margin.

All the material was submitted for histological analysis. Legend: 1: Extremity (6F); 2: Extremity (6F); 3: Central portion (1F); 4: Central portion (1F); 5: Central portion (1F)".

Recommendation 4: Whenever possible, include all the material in case of lesions suspected of melanoma. Clinicians and surgeons are advised to verify whether this recommendation was followed by carefully reading the macroscopy section of the anatomopathological report.

Microscopy

Following current international recommendations,^{10,11} the melanoma excision report should contain the following parameters: histological type; Breslow index (maximum tumor thickness) measured in millimeters, considering only one decimal place (after the period) and drawing a straight line between the deepest tumor cell and the most superficial cell of the granulosa layer; presence/absence of ulceration; mitotic index in the "hot spot" with the mitosis count per 1 mm^2 area; angiolymphatic invasion; perineural invasion; presence/absence of satellitosis; presence/absence of associated nevus; surgical margin status and anatomopathological staging (Figs. 6–8). Margin widening is part of melanoma treatment regardless of staging, so it is not necessary to measure the tumor distance in relation to the margin. The main parameters for melanoma staging are the Breslow index and the presence of ulceration, which define cutaneous melanoma staging.^{10,11} A recent Brazilian study also demonstrated a significant association between these two parameters and the result of the sentinel lymph node and patient survival with invasive cutaneous melanoma.²² The following items: Clark level, growth phase,

MELANOMA PATHOLOGY REPORT TEMPLATE

GENERAL DATA

Patient's name: [Patient's full name]

Mother's name: [Mother's full name]

Date of birth:

Age:

Identification document: [ID, CPF(Brazilian/Cadastro de Pessoa Física, or other identification number)]

Clinical history: [Summary of relevant clinical history]

Biopsy location: [Exact location where the sample was taken]

Dermatological and lesion description:

Diagnostic hypotheses and pertinent information: [Hypotheses raised and relevant information]

MACROSCOPY

Macroscopic description: [Detailed description of the surgical specimen with the naked eye]

Number of samples: [Number of specimens/containers received]

Biopsy location: [Exact location where the sample was taken]

Dimensions: [Precise dimensions of the specimens and identified lesions, including the distance from the margins]

MICROSCOPY/DIAGNOSIS:*

- CUTANEOUS MELANOMA (indicate whether "*in situ*" or invasive)

Histological type:

Growth phase:

Breslow: (written with only one decimal place - round up if greater than or equal to 0.5, and down if less than 0.5)

Nível de Clark: = Clark level:

Ulceration:

Mitotic index: (measure the number of mitoses per 1 mm². Identify the area with the highest number of mitoses ("hot spot") and, using X400 magnification, count in adjacent fields until completing an area of 1 mm²)

Angiolymphatic invasion:

Perineural invasion:

Peritumoral inflammatory infiltrate:

Intratumoral inflammatory infiltrate:

Regression:

Satellitosis:

Associated nevus:

Other findings:

Circumferential surgical margins:

Deep surgical margin:

Anatomopathological staging (AJCC; 2018):

NOTES:

Recommendations for complementary tests (immunohistochemical or molecular), if necessary for diagnostic clarification.

*Structured microscopic description for melanoma cases.

Figure 6 Example of a structured report. It is important to note that some cases do not require notes and services have the autonomy to adapt the structure by inverting the order or merging, for example, microscopy with diagnosis.

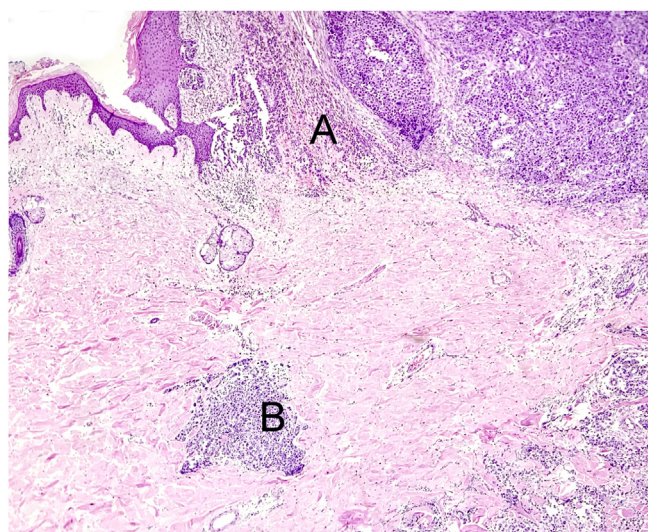


Figure 7 The histological section (Hematoxylin & eosin ×40) shows the primary melanoma in vertical growth (A) and microsatellite (B) in the dermis. The microsatellite is characterized by discontinuous tumor proliferation, adjacent to the main tumor, permeated by normal tissue, without findings of inflammatory infiltrate or fibrosis that could suggest tumor regression.

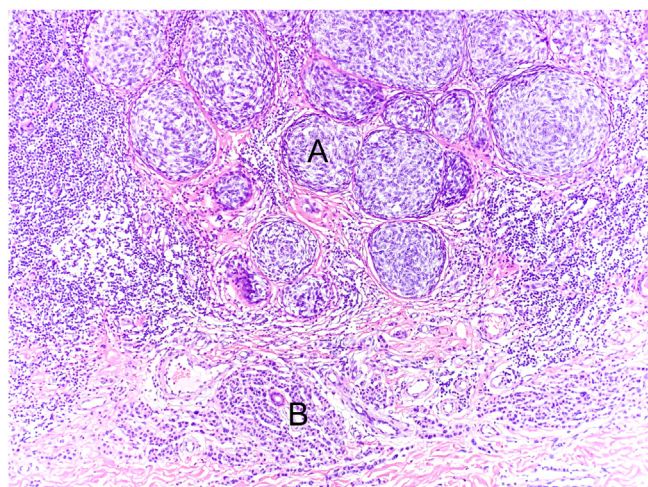


Figure 8 The histological section (Hematoxylin & eosin ×40) shows melanoma (A) associated with intradermal melanocytic nevus (B). The melanoma is characterized by nests of atypical melanocytic cells without signs of maturation and exhibiting moderate nuclear pleomorphism (A). Below (B) small melanocytic cells can be observed, scattered throughout the dermis, exhibiting scarce cytoplasm and no cytological atypia.

presence/absence of peri- and intratumor inflammatory infiltrate and presence/absence of regression have been losing value in recent years, and are no longer mandatory in the report.¹¹

Ulceration is defined by the combination of the following microscopic findings: complete loss of epidermis (including the absence of stratum corneum and basement membrane); evidence of reactive changes (e.g., presence of fibrinoleukocyte infiltrate); and thinning/effacement or reactive hyperplasia of the adjacent epidermis in the absence of

recent trauma or surgical procedure.¹¹ If the ulceration is secondary to a prior biopsy, it should not be reported and/or considered for staging purposes.^{10,11} Unlike invasive melanomas, the presence of ulceration does not alter the staging of cases of melanoma "*in situ*".^{10,11} Furthermore, it is suggested that ulceration extent is a more accurate predictor of survival than the simple presence of ulceration in cases of invasive cutaneous melanomas.^{23,24}

Considering the latest editions of the World Health Organization classification of skin tumors, the histological subtype definition was redefined considering the carcinogenesis pathways and the most frequently mutated genes in each histological subtype. In general terms, the four most common subtypes (superficial spreading, lentigo malignant melanoma, acral and nodular) were redivided into: melanoma associated with chronic sun exposure/high cumulative sun damage (which includes cases of lentigo malignant melanoma and some cases of nodular melanomas), melanoma associated with intermittent sun exposure/low cumulative sun damage (which includes cases of superficial spreading melanoma and some cases of nodular melanomas) and acral melanomas for which the relationship with sun exposure is not yet clear. Some less common types, such as the Spitz melanoma group, may require molecular confirmation for correct diagnosis.⁶

Regarding the evaluation of the lymphocytic inflammatory infiltrate, it can be classified as absent, present but not active ("non-brisk"), or active ("brisk"). To be considered active, the presence of lymphocytes among the tumor cells is not necessary, since the inflammatory cells may only be on the lesion periphery (border). Although it is an optional item in the report, the prognostic value of lymphocytes permeating or infiltrating melanoma cells remains under discussion.^{25,26}

Aiming at performing the anatomopathological diagnosis of melanocytic lesions in diagnostic categories based on risk stratification, rather than on the classic histological diagnosis, the system that receives the English name "The Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx)" was created in 2014.²⁷ Version 2.0 of this system was published in 2023, which shows four diagnostic classes: class I for lesions with a very low risk of progression to invasive melanoma (e.g., dysplastic nevi with low-grade cytological atypia), class II for lesions with a low risk of progression to invasive melanoma (e.g., dysplastic nevi with high-grade cytological atypia and melanoma "*in situ*"), class III for lesions with a low risk of metastasis (e.g., melanoma stage pT1a) and class IV for lesions with a moderate to high risk of metastasis (e.g., melanomas stage $\geq$ pT1b).⁹ It is believed this classification system would increase diagnostic agreement between services, reducing academic discussions that are not relevant to patient monitoring but are often not understood by the lay public. To cite an example, it would be the differentiation between melanoma "*in situ*" and dysplastic nevus with high-grade cytological atypia since both lesions would be classified as class II of MPATH-Dx⁹ and patients would have to undergo surgical margin expansion. Categorization according to the classes of this system remains optional and scarcely used in the medical community in the studied country. Some barriers to the use of this system would be the establishment of a conduct that is seen with a more comprehensive view of

the patient and not only based on histopathological findings, as well as the indication of more aggressive conduct by the system, such as margin extension in Spitz nevi and cellular blue nevi, for example.⁹

Immunohistochemistry

It is a misconception to think that every case of melanocytic lesion should be submitted to immunohistochemical study. Therefore, the use of such technique is indicated for: I) Lineage confirmation in cases of poorly differentiated melanomas; II) Cell proliferation index assessment (Ki-67); III) Research of markers related to specific molecular alterations (ALK, ROS, BAP1, BRAF, NTRK, and p16).⁶ It is worth noting, however, that there is currently no single, validated, known, and long-standing marker to differentiate benign and malignant melanocytic lesions. Furthermore, the results of immunohistochemical markers should always be interpreted together with histopathological findings.

For highly pigmented lesions, special techniques can be used: the use of magenta chromogen in the immunohistochemical reaction (preferred method), counterstaining with Giemsa, and depigmentation with hydrogen peroxide are some of the options.^{28,29} It is important to note that depigmentation with hydrogen peroxide must be performed very carefully because there is a high risk of damaging the material, making the reaction unfeasible.

For cases that are difficult to interpret, some melanocytic markers are very sensitive (e.g., MITF, SOX10 and S100) and specific (e.g., MART1); they are used to detect cell density and neoplastic growth patterns when it is not possible to do that with Hematoxylin & eosin staining (due to coexisting inflammation, artifact, etc.). In desmoplastic melanomas, the most sensitive antibody is the one that detects the S-100 protein.⁶ HMB-45 (Human Melanoma Black-45) is a valuable marker for the differential diagnosis between nevus and melanoma since cell maturation is identified through a change in color gradient in benign lesions, which is stronger in the upper portions and negative in the deep portion. HMB-45 is also useful in differentiating between nevus and subcortical metastases in sentinel lymph node evaluation.³⁰ Careful analysis should also be performed for the p16 protein, encoded by the CDKN2a tumor suppressor gene, which acts by slowing cell division through cell cycle progression inhibition. Loss of p16 nuclear expression assessed in immunohistochemistry is associated with significantly increased tumor cell proliferation, which may indicate a more aggressive tumor.³⁰

The Ki-67 antibody marks any cell that is not at rest (G0 phase of the cell cycle), that is, it is positive in all cells in the G1, S, G2 phases, and in mitosis. Therefore, it is not a specific marker for melanocytes. In cases with dense inflammatory infiltrate, double staining of MART-1 using the magenta chromogen (cytoplasmic staining) and diaminobenzidine for Ki-67 (nuclear staining) is a useful tool if there is interpretive doubt. It is also noteworthy that nevi in adult patients generally do not show mitoses and exhibit low cell proliferation characterized by rare Ki-67-positive cells and no positive cells in the deep portion of the lesion. To date, there is no cutoff number for the percentage of Ki-

67-positive cells that differentiates benign from malignant melanocytic lesions considering this marker alone.^{20,31}

The PRAME antibody (PRAME-Preferentially expressed Antigen in MELanoma) is a recent and more efficient marker for differentiating nevi from melanomas, with preferential staining in melanoma in relation to benign lesions. However, it is a marker whose positivity does not overlap with morphological findings since there is no defined pattern in doubtful cases that are difficult to interpret diagnostically (intensity and extent of staining).³² In addition, there is more than one clone of this antibody on the market, making it difficult to draw conclusions regarding the experience of different services and published articles.

Recommendation 5: Immunohistochemical studies are not essential for the microscopic diagnosis of melanoma, being reserved for selected cases, indicated by the pathologist in the report, often through comments and notes.

Perioperative examination

The frozen section examination is one of the types of perioperative examination and consists of the microscopic analysis of a specimen during the patient's surgery. It is an indicated and fundamental tool in the management of different clinical scenarios, providing valuable information to the surgeon, such as the diagnosis of malignancy or the presence of neoplasia in a margin, allowing therapeutic conduct to be taken during the surgical procedure.³³ Briefly, it consists in submitting a representative tissue fragment to freezing, allowing it to be cut very thinly, with subsequent staining. In this examination, a limited microscopic visualization is performed, allowing a preliminary (not definitive) diagnosis during the surgical procedure. However, in the scenario of melanocytic lesions, freezing a tumor suspected of melanoma is not appropriate and may put the patient's accurate diagnosis at risk.¹¹

Below are some reasons: I) The act of freezing the material generates artifacts in the tissue that impairs morphology. Melanocytic lesions that are difficult to interpret often require serial sections for accurate evaluation, and correct microscopic interpretation is not possible due to the less clear visualization provided by the frozen material. II) It is not possible to accurately evaluate cytological atypia in frozen sections.³⁴ III) Melanomas often have unclear limits and may present with "skip lesions"³⁵, preventing margin evaluation in these cases. IV) Even in histological sections after adequate fixation, it may be difficult to microscopically differentiate melanocytic proliferation secondary to solar damage from lentigo maligna, and this differentiation cannot be properly performed in the histological evaluation of the frozen section.³⁵ V) Additionally, the freezing process may damage the material and even impair subsequent immunohistochemical evaluation.

Considering that perioperative examination is contraindicated, any type of frozen section examination, including Mohs micrographic surgery, to define margins or diagnose a primary melanocytic lesion of the skin has to be avoided. The gold standard for evaluating surgical margins is the microscopic examination of slides stained with Hematoxylin & eosin, after correct fixation and histological processing. Performing a perioperative immunohistochemical study is not a

validated technique and is not recommended. Freezing a tumor suspected of melanoma is not appropriate and may jeopardize the patient's diagnosis.⁸

Recommendation 6: Perioperative examination is contraindicated for both diagnosis and margin evaluation of melanocytic lesions.

Sentinel lymph node

The treatment of melanoma is a rapidly evolving field, and the role of the sentinel lymph node has been debated in certain clinical settings but remains an important tool for disease staging and prognosis. Therefore, appropriate handling, macroscopy, and microscopic evaluation of the sentinel lymph node are mandatory to guide appropriate care for the melanoma patient. Frozen section examination of the sentinel lymph node is also contraindicated because the manipulation required to perform the perioperative examination may reduce the procedure sensitivity.^{11,36}

For melanoma examination, careful handling of the sentinel lymph node is recommended to avoid damage to the lymph node capsule. The lymph node should be measured, sectioned, and submitted in its entirety for histological processing and subsequent microscopic evaluation by a pathologist.

Several parameters have been reported for the microscopic evaluation of tumor burden in the sentinel lymph node of a patient with melanoma, including microanatomic location, largest deposit axis, tumor depth, surface area and surface area ratio, volume, size, and cell count.³⁷ The minimum report should include both dimensions of the deposit and the presence of extranodal extension.

If more than one lymph node is sent for analysis, both lymph nodes should be analyzed and their identification and description should be kept separate.

Recommendation 7: Perioperative examination is contraindicated for sentinel lymph node evaluation in cases of cutaneous melanoma.

Molecular assessment

The molecular tests currently applied in the routine of patients with melanoma can be divided into germline and somatic.

The main germline molecular alterations related to the risk of developing melanoma are alterations in the *CDKN2a*, *CDK4*, *MC1R*, *BAP1*, *TERT*, *MITF*, *PTEN* genes. In general, the suspected patient is one with a personal and/or family history of melanoma, multiple melanomas, and cancers in the family such as pancreatic, kidney, breast, uveal, mesothelioma and astrocytoma. It is recommended that the investigation be conducted together with an oncologist/geneticist for correct counseling and additional decisions on testing the individual/family.

Somatic alterations, that is, present in neoplastic cells only, can be divided into two large groups: those for therapeutic decision-making purposes (predictive) and alterations that may be useful for diagnostic purposes.

Testing for mutations involving codon 600 of the *BRAF* gene is necessary to establish therapeutic decisions in patients with stage 3 and 4 melanoma. Its role in high-risk

stage II has been increasing. The presence of this mutation can be tested using different techniques, including immunohistochemical studies using the VE1 antibody clone, and techniques such as PCR and Next Generation Sequencing (NGS). The sample to be tested is a sample from histological processing, paraffin-embedded and representative of the tumor, which may be from the primary lesion or metastasis. The sample must be evaluated by a pathologist to ensure that it represents a sufficient quantity of tumor cells for testing. The molecular test success depends directly on the quality of the genetic material of the lesion in the paraffin block, which depends, among other factors, on how the sample was fixed and packaged.

There are many tests described in the literature with potential diagnostic usefulness for melanocytic lesions, in defining whether a lesion is benign or malignant. Among the tests, there are gene expression tests, tests that evaluate losses and gains in genomic regions such as Fluorescent In-Situ Hybridization (FISH) and Comparative Genomic Hybridization (CGH) tests. None of these tests alone, to date, is indicated for use to define between benign and malignant lesions. A thorough morphological analysis supported by solid clinical-pathological correlation remains, to date, the main tool in the diagnosis of melanocytic lesions. The NGS test, by identifying molecular alterations characteristic of any of the nine distinct molecular pathways of melanocytic lesions, can help in the diagnostic definition of these lesions.

Recommendation 8: Molecular testing to detect mutations in the *BRAF* gene is recommended in the scenario of patients with high-risk stage II, III and IV melanoma, using a sample with adequate neoplastic representation and a molecular technique duly validated by the laboratory.

Conclusions

For an accurate melanoma diagnosis, a close clinical-pathological correlation is essential. Excisional biopsy with exigous margins (1-3 mm) is the preferred approach, and the specimen should be immediately submerged in buffered formalin, and the fixation time should not exceed 72 hours. Diagnosis continues to be made through complete inclusion of the lesions and evaluation using Hematoxylin & eosin staining. Complementary studies (immunohistochemical and molecular) are only applied to a small percentage of cases. The perioperative examination is expressly contraindicated for the diagnosis or margin evaluation of suspicious melanocytic lesions, as well as for the evaluation of the sentinel lymph node in cases of cutaneous melanomas.

Financial support

Novartis company funded an in-person meeting of specialist pathologists, without any type of interference in the content of this study.

Authors' contributions

José Cândido Caldeira Xavier Junior: Design and planning of the study; collection of data, or analysis and interpre-

tation of data; drafting and editing of the manuscript or critical review of important intellectual content; effective participation in research orientation; critical review of the literature; approval of the final version of the manuscript.

Karina Munhoz de Paula Alves Coelho: Design and planning of the study; collection of data, or analysis and interpretation of data; drafting and editing of the manuscript and critical review of important intellectual content; critical review of the literature; approval of the final version of the manuscript.

Mariana Petaccia de Macedo: Design and planning of the study; collection of data; drafting and editing of the manuscript, collection, analysis and interpretation of data; critical review of the literature; approval of the final version of the manuscript.

Rute Facchini Lellis: Design and planning of the study; drafting and editing of the manuscript and critical review of important intellectual content; graphic design; approval of the final version of the manuscript.

Nathanael de Freitas Pinheiro Junior: Design and planning of the study; critical review of important intellectual content; approval of the final version of the manuscript.

Robledo Fonseca Rocha: Design and planning of the study; critical review of important intellectual content; critical review of the literature; approval of the final version of the manuscript.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Analysis of the clinical and epidemiological profile of leprosy in Brazil and major regions[☆]



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Received 27 June 2024; accepted 24 September 2024

Available online 18 June 2025

KEYWORDS

Leprosy;
Leprosy/epidemiology;
Neglected diseases;
Neglected diseases/epidemiology

Abstract

Background: Leprosy is an infectious disease, endemic to Brazil, associated with poor living conditions. Although curable, it is a neglected disease, posing a serious public health problem. The literature lacks comprehensive and recent analyses of the pathology.

Objectives: The study aims to describe and analyze the clinical-epidemiological profile of leprosy patients in large Brazilian regions and compare it with regional sociodemographic indicators.

Methods: This is an ecological, descriptive, and analytical observational study, carried out through the collection of secondary data from the Disease Notification Information System from 2014 to 2019, the 2010 census, and population estimates from the Brazilian Institute of Geography and Statistics.

Results: A total of 215,155 new cases were reported and the annual detection rate was maintained in four Brazilian regions, with only the South showing a significant decrease. The highest rate was observed in the Midwest and the lowest in the South. The predominant profile was male, age range between 60 and 79 years old, literate, and black and brown ethnicity. There was a predominance of the borderline cases, multibacillary form, more than five skin lesions, and zero grade of disability at diagnosis. Bacilloscopy was not performed in 42.8% of the cases and cure was the outcome in 77%.

Study limitations: The use of secondary data and the time interval analyzed are restricted by the data source platform and the COVID-19 pandemic.

Conclusions: This shows a perpetuated public health problem, mainly in the North, Northeast, and Midwest regions, associated with socioeconomic indicators and has a clinical-epidemiological profile that favors the bacillus transmission.

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<https://doi.org/10.1016/j.abd.2025.501127>

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Introduction

Leprosy is characterized as an infectious-contagious disease caused by *Mycobacterium leprae* (*M. leprae*), known as Hansen's bacillus, and *Mycobacterium lepromatosis* (*M. lepromatosis*). It is one of the oldest diseases known to humanity, with reports dating back over 3,000 years. The etiological agent was first described in 1873 by Norwegian physician Gerhard Armauer Hansen.¹

The parasite is an acid-fast, obligate intracellular bacillus, which multiplies slowly and does not proliferate *in vitro*, making it difficult to obtain scientific knowledge about it.² Despite its low pathogenicity, the bacillus is highly infective,³ has an affinity for skin cells and peripheral nerves, and its multiplication time is slow, lasting 11 to 16 days.³ It is estimated that the disease incubation period lasts an average of five years.² The infection is mainly transmitted by untreated sick individuals with a high bacillary load, who excrete the bacillus through the upper airways, which also act as a gateway for susceptible individuals. Transmission occurs through direct contact between individuals and is facilitated by the coexistence of susceptible individuals with untreated patients. The hematogenous route is the mechanism of dissemination to the skin, nerves, mucous membranes and other tissues.² Susceptibility to the bacteria has a strong genetic influence so family members of individuals with leprosy are more likely to become ill.

It manifests itself through marked dermatoneurological signs and symptoms such as skin and peripheral nerve lesions. There are four clinical forms described: indeterminate, tuberculoid, lepromatous, and borderline, with the latter being subdivided into borderline-tuberculoid, borderline-borderline, and borderline-lepromatous. There is also the primary or pure form of neural leprosy, which does not show skin lesions and, although it is not listed as a specific clinical form in the pathology notification form, represents up to 10% of all cases.³ The disease is severe, and the infected individual may develop various degrees of physical disabilities and deformities, often irreversible ones, which lead to several problems in the social, professional, and psychological spheres.³ However, since the disease has well-defined peculiarities, diagnosis is simple in most cases: it is made through anamnesis and physical examination with or without the aid of a bacilloscopy test² and a correct and early diagnosis allows the cure and interruption of the disease transmission chain. Treatment is effective and available through the Brazilian Unified Health System.²

It is a disease almost exclusive to the developing world, associated with poor socioeconomic conditions, poverty, and lack of access to adequate housing, food, health and education.² It is classified as a neglected disease that affects areas of Asia, Africa and Latin America,⁴ and three countries account for approximately 80% of cases: India (56.6%), Brazil (13.8%) and Indonesia (8.6%). Leprosy is an endemic disease in Brazil, a public health problem that needs to be overcome. The country is responsible for more than 90% of new cases of infection in the entire region of the Americas. As part of the National List of Compulsory

Notification of Diseases, Injuries and Public Health Events (MS/GM Consolidation Ordinance Number 4, of September 28, 2017), 215,155 new cases were diagnosed between 2014 and 2019.^{5,6}

Given Brazil's position in terms of prevalence in the global panorama, it is clear that studies with current data need to be carried out, seeking to outline the current clinical and epidemiological profile of leprosy. As the disease incidence has a positive association with socioeconomic factors,⁷ it is essential to correlate epidemiology to the social indicators of each region, since the country has continental dimensions, divided into areas with different climatic and social conditions.

Thus, this study sought to compare the clinical-epidemiological profile of leprosy in different regions of Brazil, according to sex, age group, skin color or race and illiteracy; to analyze the distribution of leprosy in the five Brazilian regions and to correlate the annual detection rate of leprosy with socioeconomic indicators of the regions.

Methods

Study design and area

This is an observational, ecological, descriptive and analytical study, using secondary data collection. The research population consisted of new cases of leprosy diagnosed and registered on the SINAN platform using the TABNET tool from 2014 to 2019. This interval was delimited in view of the update of SINAN and TABNET in 2014, which aimed to improve data quality, so that previous data are subject to inaccuracy, and due to the distortions caused by the COVID-19 Pandemic regarding the number of new cases in 2020 and 2021.

Data source and variables

In this study, data from patients residing in Brazil whose new diagnosis was registered on SINAN and TABNET from 2014 to 2019 were used for the temporal analysis. All cases that did not contain data of interest for the research were excluded.

Data collection was carried out virtually, on the SINAN website on the page "Indicators and Basic Data on Leprosy in Brazilian Municipalities" – <http://indicadoreshanseniaze.aids.gov.br>, where data from SINAN, the Ministry of Health (MoH) and the Health Surveillance Secretariat (SVS, *Secretaria de Vigilância em Saúde*) can be found, and on the DATASUS website, through the TABNET page "Leprosy Cases – Since 2001 (SINAN)" – <http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinannet/cnv/hanswbr.def>. Then, the five Brazilian regions and the variables of interest were selected: sex of the individual, age group, skin color or race, illiteracy, clinical form, operational classification, bacilloscopy, skin lesions, type of outcome, grade of disability and year of diagnosis.

The population and socioeconomic data for each region were obtained from the most recent complete

Table 1 Annual detection rate of new cases of leprosy per 100,000 inhabitants. Brazil and Regions, 2014–2019.

Year/Region	Brazil	North	Northeast	Southeast	South	Midwest
2014	18.76	41.76	29.07	6.39	4.48	50.73
2015	17.59	37.98	27.66	5.99	4.45	46.99
2016	15.78	36.72	24.32	5.59	3.8	40.03
2017	17.04	38.57	27.15	5.56	3.7	44.69
2018	17.94	42.2	26.83	5.54	3.63	53.95
2019	17.85	40.51	26.7	5.68	3.76	54.05
Mean	17.49	39.62	26.95	5.79	3.97	48.41
AI	-0.007	-0.004	-0.014	-0.023	-0.032	0.021
β	-0.119	0.201	-0.397	-0.782	-0.849	0.406
p-value	0.823	0.703	0.436	0.066	0.032	0.425

Fonte: IBGE – DATASUS, adapted by the authors, 2023.

AI, Annual Increase; β , Beta Index.

national census available, currently from 2010, found on the Brazilian Institute of Geography and Statistics (IBGE, *Instituto Brasileiro de Geografia e Estatística*) 2010 Census website – <https://censo2010.ibge.gov.br>, and also from the most recent National Household Sample Survey (PNAD, *Pesquisa Nacional por Amostra de Domicílio*), also found on the IBGE website – <https://www.ibge.gov.br/estatisticas/sociais/populacao/9127-pesquisa-nacional-por-amostra-de-domicilios.html?&t=resultados>.

The data were transformed into an annual detection rate of new cases for the total cases and an average detection rate between 2014 and 2019 for the analyzed variables, all calculated per 100,000 inhabitants, for Brazil and its Major Regions.

Annual detection rate

$$= (\text{Number of New Cases} / \text{Total Resident Population}) \times 100,000 \quad (1)$$

It is noteworthy the impossibility of calculating the average detection rate of new cases according to skin color or race in the “unknown/white” classification due to the lack of data for this population in the Census.

Statistical analysis

The data were organized using Google Sheets, and the distribution of variables was obtained in absolute values and proportions (%). The case frequency was transformed into an annual and average detection rate, according to the variables of interest in the study, to compare the incidence between each macro-region and Brazil. The Relative Risk (RR) was calculated for the variables sex, race and illiteracy according to the detection rates.

The statistical analysis was performed using the IBM SPSS software, version 23.0 (SPSS 23.0®). Temporal trends were analyzed using the average annual variation of each category, annual increase rate, linear regression (beta coefficient) and Spearman’s correlation coefficient. The investigation of an association between the variables was performed using linear regression and Spearman’s correlation. Bivariate analysis with calculation of R^2 (correlation

coefficient) was used for the results of the temporal series. Values of $p < 0.05$ were considered statistically significant.

$$\text{Annual increase rate} = (\text{Current Year Value}$$

$$- \text{Previous Year Value}) / (\text{Previous Year Value}) \times 100 \quad (2)$$

Results

Brazil is the fifth most populous country in the world, with an estimated population of 204,860,101 inhabitants (inhab) according to a survey carried out in 2015 by the Brazilian Institute of Geography and Statistics (IBGE) and has an average Human Development Index (HDI) of 0.724, according to the latest data from the Institute of Applied Economic Research, calculated in 2010. The country is divided into five major regions. The North Region has an estimated population of 17,523,777, and an average HDI of 0.667. The Northeast Region has an estimated population of 56,640,710 and the lowest average HDI in the country - 0.663. The South Region has an estimated population of 29,290,154 and an average HDI of 0.754. The Southeast Region, the most populous and most developed one, has an estimated population of 85,916,158 and an average HDI of 0.766. The Midwest Region has the smallest population among the regions, estimated at 15,489,302, and an average HDI of 0.757.

In the period from 2014 to 2019, a total of 215,155 new cases of leprosy were reported in Brazil (Table 1), with 41,666 cases in the North, 91,623 in the Northeast, 44,988 in the Midwest, 29,855 in the Southeast and 6,976 in the South. The highest annual detection rate of new cases nationwide occurred in 2018 with 17.94/100,000 inhabitants, and the lowest in 2016, at 15.78/100,000 inhabitants.

Table 1 shows the annual detection rate of newly reported cases of leprosy per year during the studied period. There was a slight decline in the detection rate in the Brazilian population from 18.76/100,000 inhab. in 2014 to 17.85/100,000 inhab. In 2019, with a negative Annual Increase (AI) of -0.7%, without statistical significance. Clear differences were observed in the distribution of annual detection rates between the regions of the country, with hyperendemic rates in the Midwest, very high rates in the

Table 2 Average detection rate ($\times 100,000$) of leprosy according to sex, race, age group and illiteracy. Brazil and Regions, 2014–2019.

Variable/Region	Brazil	North	Northeast	Southeast	South	Midwest
Sex						
Male	20.73	47.73	31.23	6.70	4.74	55.39
Female	14.86	31.79	23.21	4.69	2.88	42.60
Race						
White	9.01	25.14	15.72	4.48	3.45	36.97
Black and Brown	22.88	41.60	28.53	6.50	4.98	53.16
Yellow	41.58	337.78	158.72	5.37	54.28	70.94
Indigenous	20.54	25.30	20.79	5.90	3.33	105.83
Age range						
0 to 14 years	4.28	11.60	7.88	1.04	0.24	6.17
15–39 years	13.75	34.06	21.01	4.08	2.41	36.28
40–59 years	25.22	58.97	40.01	11.62	5.79	74.66
60–79 years	28.14	70.14	53.64	10.04	8.21	77.47
80 or older	18.15	46.67	35.50	5.76	4.88	45.08
Illiteracy						
Unknown/white	3.82	7.11	7.16	1.45	0.75	7.91
No (> 15 years)	20.71	48.92	32.87	6.74	5.15	66.53
Yes (> 15 years)	28.62	56.83	28.06	11.97	10.23	80.67

Source: IBGE and DATASUS, adapted by the authors, 2023.

North and Northeast, and average rates in the Southeast and South. The highest rate observed in the period was 54.05 in 2019 in the Midwest; in contrast, the lowest rate was 3.63 in 2018 in the South. The Midwest was the only region to show a positive AI (2.1%), which shows an average increase. Next, the North (AI -0.4%), Northeast (AI -1.4%), Southeast (AI -2.3%) and, finally, the South (AI -3.2%) with the lowest rate found and a significant decrease in the detection rate ($p=0.032$). The other regions showed a trend towards indicator stability ($p>0.05$).

In Spearman's correlation analysis between the variables "year" and "new cases in Brazil", which was used to calculate the annual detection rate, a negative correlation (-0.086) was observed without statistical significance ($p>0.05$). The bivariate analysis with the calculation of R^2 (correlation coefficient=0.014) for the same two variables also showed no statistical significance. Thus, the correlations demonstrate that the rates remained stable throughout the period.

Regarding the epidemiological characteristics (Table 2), it was observed that the majority of reported cases were male (56.59%), with a relative risk almost 40% higher than females (RR = 1.39; Confidence Interval [95% CI: 1.29–1.48]; $p<0.00001$). The most affected age group was 40–59 years old, with 62,876 total cases, while the highest detection rate was observed between 60 and 79 years old, with a rate of 28.14/100,000 inhabitants. The main ethnicity is black and brown (71.98%), followed by white (23.24%) and a minority of Asians (1.16%). Regarding the level of schooling, the detection rate in Brazil was higher among illiterate individuals, comprehending 8.99% of the infected population, with a rate of 28.62/100,000 inhabitants, comprising a risk almost 40% higher than that of literate individuals (RR = 1.38; 95% CI: 1.29–1.45; $p<0.0001$).

Regarding the clinical characteristics and progression of the disease (Table 3), it is observed that the borderline

form (48.48%) is the most common, followed by the lepromatous form (17.59%), with the remaining cases being divided between the indeterminate and tuberculoid forms. The multibacillary operational classification is the most prevalent (75.75%) and incident - 79.55 per 100,000 inhabitants. Regarding bacilloscopy, it was not performed or ignored in 42.80% of cases, 31.48% were negative and 25.72% were positive. As for the dermatological lesions, 36.63% of the patients had more than five skin lesions affected by mycobacteria, with a rate of 38.47 per 100,000 inhabitants; 29.56% had between two and five lesions and 21.41% had only one lesion, corresponding to rates of 31.05 and 22.48, respectively. The absence of lesions (0 reported) and unreported lesions (99 reported) accounted for 12.40% of cases.

The majority of the outcomes comprised a cure for the disease (Table 3), with this amount being estimated at 77.34%. Other types of outcomes comprised transfers in 8.56% of the cases and a rate of 8.99; abandonments in 6.70% of the cases and a rate of 7.03; blank in 4.09% of the cases and a rate of 4.3. The occurrences of death and diagnostic error characterized the minority, 1.66% of the cases each, with average rates of 1.74. The grades of physical disability found in 54.81%, 24.53% and 8.40% of the patients at the time of diagnosis were respectively grade 0, 1 and 2, and 12.27% of the cases did not have an assessed grade of disability.

Discussion

This study aimed to analyze the detection, temporal trend, clinical and epidemiological profile, and performance of social indicators of leprosy in Brazil and its regions. The World Health Organization (WHO) stipulated the elimination of the disease, with a target of less than 1 case per 10,000 inhabitants by 2020.⁸ Despite the slight overall drop in the detection rate in the studied population, only the

Table 3 Characteristics of the clinical presentation and leprosy outcome. Brazil, 2014–2019.

Variable	Frequency (n=215155)	%	Rate (×100000)
Clinical Form			
Indeterminate	25.909	12.04%	12.65
Tuberculoid	27.633	12.84%	13.49
Borderline	104.300	48.48%	50.91
Lepromatous	37.851	17.59%	18.48
Not classified/unknown	19.462	9.05%	9.5
Operational Classification			
Paucibacilar	51.870	24.11%	25.32
Multibacilar	162.971	75.75%	79.55
Bacilloscopy			
Positive	55.337	25.72%	27.01
Negative	67.729	31.48%	33.06
Not performed/unknown	92.089	42.80%	44.95
Skin Lesions			
Informed 0 or 99	26.675	12.40%	13.02
Single lesion	46.056	21.41%	22.48
2 to 5 lesions	63.606	29.56%	31.05
> 5 lesions	78.818	36.63%	38.47
Type of outcome			
Cure	166.396	77.34%	81.22
Transferred	18.417	8.56%	8.99
Death	3.552	1.65%	1.73
Abandonment	14.407	6.70%	7.03
Diagnostic error	3.582	1.66%	1.75
Not filled out	8.801	4.09%	4.3
Grade of disability			
Grade zero	117.917	54.81%	57.56
Grade I	52.779	24.53%	25.76
Grade II	18.067	8.40%	8.82
Not assessed/unknown	26.392	12.27%	12.88

Source: IBGE and DATASUS, adapted by the authors, 2023.

South and Southeast regions reached the target, even though Brazil proposed the elimination of leprosy as a public health problem three decades ago.⁹

The parameters of the indicators for monitoring progress and elimination of leprosy by the MoH classify the endemicity situation according to the detection rate of new cases as: hyperendemic $\geq 40/100,000$ inhab.; very high $20\text{--}39.99/100,000$ inhab.; high $10\text{--}19.99/100,000$ inhab.; medium $2\text{--}9.99/100,000$ inhab.; and low $< 2/100,000$ inhab.¹⁰ Thus, one can list the regions from highest to lowest endemicity, starting with the Midwest, classified as hyperendemic with an average detection rate of $48.41/100,000$ inhab., followed by the North and Northeast, classified as very high, with 39.62 and $26.95/100,000$ inhab., respectively, the Southeast with $5.79/100,000$ inhab. and the South with $3.97/100,000$ inhab., both regions with average parameters.

The high rates found in the Midwest, North and Northeast regions are due to the difficulty in controlling the disease and late detection of cases,⁴ proven by the main indicator of late diagnosis, physical disability grade II at the time of diagnosis. Of the 18,067 cases diagnosed with this grade, 37.5% occurred in the Northeast region. These results were also found in previous studies.^{11,12} In addition, these regions have the lowest Human Development Indexes (HDI) and the

worst variables related to sanitation (proportion of residents in households with rudimentary septic tanks and proportion of residents in households supplied with well water), metrics that show worse living conditions, which are associated with higher disease rates.¹³ Furthermore, the states that comprise the so-called Legal Amazon, an area at risk for leprosy due to the type of land occupation and indexes of living conditions, are all from these regions.¹¹

The highest average annual detection rates of new cases of leprosy per 100,000 inhabitants were 48.41 in the Midwest and 39.62 in the North regions, representing figures that are, respectively, 2.77 and 2.26 times higher than the national average for the period. These regions have been considered risk areas for decades¹¹ and have been targets of internal migration since 1970, encouraged by the Brazilian government with agricultural modernization and highway construction.¹⁴ Combined with the overload and lack of infrastructure, leprosy began to gain strength in these regions. The lowest average annual detection rates were found in the South (3.97) and Southeast (5.79) regions, well below the national average of 17.49 cases per 100,000 inhabitants. This finding shows continuity with older studies, whose results also pointed to these peculiarities.^{11,12} The relationship between the disease and socioeconomic conditions is unquestionable. Brazilian studies have already

demonstrated a significant relationship between low HDI and the disease in different regions of the country.^{13,15} Thus, as expected, the two most developed Brazilian regions had the lowest rates. However, it is necessary to add indicators such as higher temperature and humidity, greater presence of bacilliferous patients in endemic regions, and genetic susceptibility to factors associated with high disease rates.^{16,17} The regions with the highest rates are the least developed ones, with more fragile urban spaces, population agglomeration, and greater economic vulnerability. Thus, the national situation provides exposure, contamination and persistence of the condition, and also conceives autochthonous and imported cases.⁴

There was a predominance of males, presumably justified by the fact that men are more exposed to risky environments, have greater social contact, and take less care of their health than women, a phenomenon that was observed in other studies on leprosy in Brazil.^{18–20} Genetic susceptibility and hormonal interference in the immune response to the bacillus are also factors that are investigated.²¹

There was a predominance of cases in individuals with black skin color, including blacks and browns, in all age ranges analyzed, in agreement with other studies.^{21,22} It is believed that these groups are more affected due to the historical process of social inequality.²² The highest detection rate occurred in the Asian ethnic group, 41.58/100,000 inhabitants, showing a higher risk than other ethnic groups. There is no data in the international literature to support this prevalence; therefore, in the present study, the low self-declaration of yellow skin color in the Census is suggested as the probable cause. The Indigenous population has very high rates, which can be linked to the environment, genetics and lifestyle of this population.²³ It is worth noting the small number of studies focused on this group, is a detrimental scenario for this population, given the significant rates and the fact that the lack of robust analysis delays possible interventions.

Regarding the age range defined by the study, the 40–59 age range had the highest number of cases in total; however, the highest detection rate occurred between the 60–79 years range throughout the country. These data infer that individuals diagnosed with leprosy are part of the economically active population and, as this is a limiting and disabling disease, it can cause harm to the economy. It is also worth noting that the population at greatest risk is the elderly, as shown by the detection rate, which is linked to the long incubation period and the natural decline of the immune system.^{21,24} It is also important to mention that cases in children under 15 years of age are related to at least one confirmed case in the family, with possible pediatric contamination occurring within the family itself due to failure to combat the chain of transmission. It is noteworthy that there is greater difficulty in diagnosis in childhood, culminating in possible disease complications, decreased school performance, and development of the individual due to physical and social impairment.⁴ The detection of leprosy in children under 15 years of age is an indicator of continued transmission of the bacillus,²⁵ whose tendency has been decreasing in the regions, being a national trend and therefore indicating a tendency for a decrease in the disease incidence throughout Brazil.

Most affected individuals in raw numbers were literate and the highest detection rate was among illiterate people, a reality in most regions. This discrepancy was even greater in the more developed South and Southeast regions, where the illiteracy rate was approximately twice that of the literate population. Considering that, according to IBGE, only 6.6% of the Brazilian population is illiterate,²⁶ the number of illiterate people affected is alarming. This makes them a population at risk, with low levels of schooling and illiteracy being unfavorable social determinants regarding the transmission of Hansen's bacillus and the progression to disabling forms of the disease, as they make it difficult to recognize the clinical manifestations and understand treatment guidelines.^{7,19,20,24,27}

During the analyzed period, the borderline form predominated, accounting for almost half of all cases, followed by the lepromatous form, accounting for 17.59% of the total. These forms were also shown to be dominant in some studies carried out in the North and Midwest regions.^{24,28} Other references indicate the tuberculoid form as the most common, especially in regions where the disease is endemic.²⁹ Thus, in Brazil, it can be inferred that the predominant clinical form varies according to the location and its characteristics of endemicity and transmission.

The multibacillary operational classification represented the vast majority of cases (75.75%), in agreement with several studies.^{24,28,30} This finding, combined with the progressive increase in the percentage of multibacillary cases in Brazil since 2010, is especially relevant since individuals classified as multibacillary are important sources of contagion for the community and maintenance of the epidemiological chain.²

Of the total number of cases reported throughout Brazil during the period, only 57.2% underwent bacilloscopy, with 45% of the tests being positive, indicating a higher risk of disease transmission.

Regarding skin lesions, 36.63% of the reported cases consisted of patients with more than five lesions; 29.56% had two to five lesions, and 21.41% had a single lesion. This pattern was also found in other studies.^{19,29} The absence of skin lesions and unreported lesions are combined as a single piece of information in the database, equivalent to 12.40%. This association compromises the accuracy of pure neural leprosy frequency, given the impossibility of measuring the absence of skin involvement alone.

The vast majority evolved to cure, which means that these patients correctly completed the polychemotherapy treatment recommended by the Ministry of Health,² with a percentage of 77.34%. Other studies have also shown a high proportion of cured patients in Santa Catarina and Bahia, to the detriment of low death rates.^{19,31} A significant percentage of abandonment (6.7%) stands out, which may be related to the long treatment duration, lack of knowledge about the disease and its progression, skepticism regarding the cure, lack of encouragement, social stigma, leprosy reactions, and also the distance between the patient's residence and the health service.³² These patients must be rescued in such a way as to break the transmission chain, resistance to polychemotherapy, and the emergence of physical disabilities.²

Most individuals with leprosy did not have sequelae at diagnosis, classified as having grade zero physical disabili-

ity. This proportion was also present in studies conducted in hyperendemic regions, with very high and medium endemicity,^{19,29–31} demonstrating a common distribution throughout the country, with some exceptions that indicate grade I as the most frequent.^{24,33} Approximately 33% of the evaluated cases had grade I or grade II disability at diagnosis, respectively occurring with decreased sensitivity or muscle strength in the hands, feet and/or eyes for grade I patients and visible physical deformities or blindness for grade II patients.² These grades confirm the duration of disease progression, with grade II being evidence of late diagnosis.

The current study had some limitations inherent to its nature. Firstly, the use of secondary data may characterize inconsistencies due to the fact that the notifications were filled out by health professionals who possibly did not receive training or standardized guidelines for filling out the notification forms. Incomplete and “unknown/white” data, especially regarding the items’ race/skin color and level of schooling, hinder the epidemiology study. Another issue was the time period assessed, since the data source platform was changed and only has more complete and reliable data from the initial year chosen for the research. It is worth noting that TABNET is a database with continuous updates and may show differences in relation to epidemiological bulletins that have closed data. Additionally, the study could not last longer due to the social isolation imposed by the COVID-19 pandemic, which generated underdiagnosis in the years following its outbreak.

Conclusion

It can therefore be inferred that leprosy remains a public health problem in Brazil, as evidenced by the maintenance of disease rates in four of the five major regions, with a decrease being observed only in the South region during the studied period. The high rates in the North, Northeast, and Midwest regions pose a risk to the population due to the perpetuated endemicity. Regarding socioeconomic indicators, it was observed that they follow the same trend as described in the literature, with a higher incidence in places with lower HDI, worse living conditions, and type of land occupation.

The results found in the study indicate the need to expand leprosy control measures and intervention strategies at the national level, focusing on the regions with higher endemicity. The National Strategy for Combating Leprosy should be strengthened; the disease and its complications should be addressed and stigma and discrimination should be fought. Based on the analyzed data, it is suggested that emphasis be placed on actions aimed at socioeconomic groups included in the risk profile and that special attention be paid to early diagnosis through the active search for cases aiming at treatment and reduction of transmissibility.

Financial support

None declared.

Authors’ contributions

Alícia de Siqueira Sczmanski: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; effective participation in research orientation; critical review of the literature; critical review of the manuscript.

Lucas Pazin: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; effective participation in research orientation; critical review of the literature; critical review of the manuscript.

Thiago Mamoru Sakae: Statistical analysis; approval of the final version of the manuscript; collection, analysis and interpretation of data; effective participation in research orientation; critical review of the manuscript.

Josete Mazon: Approval of the final version of the manuscript; design and planning of the study; effective participation in research orientation; critical review of the manuscript.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Dermatological manifestations in patients with gastrointestinal malignancies: a focus on early diagnosis and patient comfort[☆]



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Received 16 April 2024; accepted 17 June 2024

Available online 18 June 2025

KEYWORDS

Acanthosis nigricans;
Dermatology;
Gastrointestinal
neoplasms;
Keratoses;
Seborrheic;
Paraneoplastic
syndromes

Abstract

Background: The increasing prevalence of gastrointestinal (GI) malignancies highlights the critical need for a better understanding of associated dermatological manifestations to improve early diagnosis and patient management.

Objectives: This study aims to catalog the dermatological findings in patients with GI malignancies, emphasizing the implications for early diagnosis, and management.

Methods: The authors conducted a comprehensive whole-body dermatologic examination on 150 patients diagnosed with GI malignancies. Data on sociodemographic factors, lifestyle habits, comorbid conditions, and malignancy characteristics were meticulously collected.

Results: The cohort comprised 96 males (64%) and 54 females (36%), with a mean age of 62.47 (SD ± 10.7) years. The most prevalent primary malignancy was colonic (32.7%), with a mean disease duration of 12.72 (SD ± 20.5) months. Xerosis (dry skin) was the most frequent dermatological condition, affecting 92% of patients. The itching was reported by 31.3% of patients. Eruptive seborrheic keratosis (20.7%) and acanthosis nigricans (10.7%) were the most common paraneoplastic dermatoses observed. Both conditions were more common in patients with BMIs above 28.5, and seborrheic keratosis was seen more often in men. Dry skin, itching, paraneoplastic dermatoses, and skin infections were significantly more prevalent in patients older than the mean age of 62 years.

[☆] Study conducted at the Karadeniz Technical University, Faculty of Medicine, Trabzon, Turkey.

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Study limitations: The cross-sectional design of the present study limits causal inference. Longitudinal studies are needed to explore the temporal dynamics between dermatological manifestations and GI malignancy progression.

Conclusions: Dermatologic symptoms including pruritus, xerosis, seborrheic keratosis, and acanthosis nigricans should be considered potential indicators of underlying malignancy. Routine dermatological screening is essential for comprehensive patient care.

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Introduction

The global incidence of gastrointestinal (GI) malignancies is on the rise, presenting increasing challenges to healthcare systems worldwide.¹ Patients suffering from these malignancies constitute a particularly vulnerable group, facing not only the primary effects of the cancer and its systemic repercussions but also the adverse effects associated with various treatment modalities. Dermatological manifestations are emerging as significant both for their potential in early cancer detection and for their influence on patient quality of life.^{2,3}

Dermatological complications in these patients may include paraneoplastic skin conditions, which could act as early indicators of underlying malignancy, as well as a spectrum of skin disorders that are often exacerbated by immunosuppression and adverse reactions to medications.^{3–6} The increased prevalence of skin conditions in this patient population offers dermatologists a crucial role in the multidisciplinary approach to managing individuals with GI malignancies, highlighting the importance of dermatological assessment in this context.

This study explores dermatological manifestations in patients with gastrointestinal (GI) malignancies with two main objectives: enhancing early cancer detection and improving management of skin conditions. By examining these correlations, the authors aim to advance early diagnosis and comprehensive treatment of GI cancers, thereby improving patient outcomes and quality of life.

Methods

This cross-sectional study was conducted in collaboration with the Departments of Dermatology, Medical Oncology, and General Surgery at the Faculty of Medicine, Karadeniz Technical University. The study included a cohort of patients who presented to the respective outpatient clinics over a one-year period from April 2021 to April 2022.

A total of 150 patients with a confirmed clinical and histopathological diagnosis of gastrointestinal system malignancy were enrolled in the study. Inclusion criteria were a definitive diagnosis of GI malignancy, while exclusion criteria included patients without a confirmed histopathological diagnosis and those who declined to participate in the study.

Sociodemographic data (age, sex, occupation, education level), lifestyle habits (smoking status, alcohol consumption), comorbidities, and detailed information related to the primary malignancy (type, stage, duration of illness) were meticulously recorded for each patient. A standardized data collection form was utilized to ensure the consistency

and reliability of the gathered information. All participants underwent a comprehensive whole-body dermatological examination upon their initial visit. The examination was performed by experienced dermatologists in accordance with established protocols to identify both general dermatological conditions and specific paraneoplastic skin findings. The dermatological findings were meticulously documented using a standardized reporting form to facilitate subsequent data analysis.

The study was approved by the Institutional Review Board (IRB) of Karadeniz Technical University Faculty of Medicine. All procedures performed in the study adhered to the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical methods

Data analysis was conducted using the SPSS statistical software package, version 23.0. During the statistical evaluation, quantitative data were expressed as mean $\pm$ Standard Deviation (SD), while categorical data were presented as frequencies and percentages (%). The normality of distribution for the quantitative data was assessed using the Kolmogorov-Smirnov test. For data following a normal distribution, comparisons between two means were performed using the Student's *t*-test or the Z-test, as appropriate. The Mann-Whitney *U* test was employed for comparisons of data not conforming to a normal distribution. Categorical data were compared using the Chi-Square test. Correlations between parameters were examined using Pearson's or Spearman's correlation analysis depending on the distribution type. The level of significance was set at a *p*-value of less than 0.05 (*p* < 0.05).

Results

In this study, the authors included a total of 150 patients diagnosed with GI malignancies, of which 96 (64%) were male, and 54 (36%) were female. The mean age was 62.47 years with a standard deviation of 10.7 years. The Fitzpatrick skin types of the patients varied, with type 3 being the most common at 42.7%, followed by type 4 (29.3%), type 2 (26.7%), and type 5 (1.3%). The average Body Mass Index (BMI) was 25.86 with a standard deviation of 5.7.

The primary malignancies observed were predominantly colon (32.7%), stomach (32%), and rectum (16.7%). Adenocarcinoma was the most frequent histological subtype,

Table 1 The sociodemographic and clinical characteristics of the study population.

Age, mean ($\pm$)	62.47 ($\pm$ 10.7)
Sex, n(%)	
Male	96 (64%)
Female	54 (36%)
Body Mass Index (BMI) ($\pm$ SD)	25.86 ($\pm$ 5.7)
Habits, n (%)	
Smoker	11 (7.3%)
Alcohol consumption	2 (1.3%)
Comorbidities, n (%)	
Hypertension	58 (38.7%)
Diabetes mellitus	33 (22%)
Cardiovascular disease	38 (25.3%)
Hyperlipidemia	23 (15.3%)
Malignancy subtype, n (%)	
Oral cavity	1 (0.7%)
Esophagus	5 (3.3%)
Stomach	48 (32%)
Small intestine	1 (0.7%)
Colon	49 (32.7%)
Rectum	25 (16.7%)
Pancreas	14 (9.3%)
Gallbladder	2 (1.3%)
Liver	5 (3.3%)
Disease duration, (mean $\pm$ SD), month	12.72 ($\pm$ 20.5)

accounting for 93.3% of cases. The mean duration of the disease was 12.72 months ($\pm$ 20.5 months), calculated from the initial diagnosis to the inclusion in the study. A majority of the patients (80.7%) presented with advanced disease (stages 3 and 4), and 56.7% were undergoing chemotherapy at the time of evaluation. Sociodemographic and clinical characteristics are summarized in [Table 1](#).

The most prevalent dermatological condition observed in this study was xerosis (dry skin), affecting 92% of the patients. A higher incidence of dry skin was noted particularly in patients older than the mean age of 62 years, and this finding was statistically significant ($p=0.014$). Pruritus (itching) was reported by 31.3% of the cohort, occurring more frequently among those diagnosed with colorectal and gastric adenocarcinomas. However, when comparing the incidence of pruritus across different types of malignancies, no statistically significant difference was found. Additionally, pruritus was more commonly experienced by patients above the mean age, with this correlation reaching statistical significance ($p=0.007$).

Eruptive seborrheic keratosis (20.7%) and acanthosis nigricans (10.7%) were the most frequent paraneoplastic skin manifestations. Both conditions were more common in patients with Body Mass Index (BMI) values above 28.5 ($p=0.04$ and $p<0.001$, respectively), and seborrheic keratosis was seen more often in men and those over the age of 62 ($p=0.01$ and $p=0.003$, respectively). 37.5% of patients with acanthosis nigricans had concurrent diabetes.

The distribution of seborrheic keratosis and acanthosis nigricans among the patients was characterized by their anatomical location and frequency. Seborrheic keratosis was predominantly located on the trunk (48.4% of patients), fol-

lowed by the head and neck region (41.9%). A total of 45.2% of patients exhibited between 50 and 100 lesions. Acanthosis nigricans showed a predilection for the inguinal area, with 35.3% of affected patients reporting it in this region. The neck was the next most common site (29.4%), followed by the axilla (23.5%). In some cases, patients showed manifestations in both axillary and inguinal regions (11.8%).

Acquired ichthyosis was found in 5.3% of the patient cohort, with a temporal association with malignancy diagnosis. Among these patients, stomach adenocarcinoma was the most common underlying malignancy (five patients), followed by esophageal squamous cell carcinoma, colon adenocarcinoma, and pancreatic adenocarcinoma, with one patient each.

Acquired hypertrichosis lanuginosa was observed in 4% of patients, with colon adenocarcinoma being identified in 50% of these cases. Other malignancies associated with hypertrichosis lanuginosa included esophageal squamous cell carcinoma, hepatocellular carcinoma, and gastric adenocarcinoma, each comprising 16.7% of cases. This condition was significantly more frequent in female patients ($p=0.023$).

[Table 2](#) details the statistical analysis of dermatological findings in relation to age, sex, BMI, and malignancy type.

Dermatological assessment of facial conditions in this cohort indicated that rosacea was the predominant diagnosis, affecting 38.7% of the patients. Within this subset, 93.1% were classified as having the erythematotelangiectatic subtype of rosacea. The most frequently associated malignancy among patients with rosacea was colorectal adenocarcinoma, accounting for 48.3% of cases. Seborrheic dermatitis was identified in 6.7% of the patient population. Of those with seborrheic dermatitis, a significant majority (80%) were diagnosed with colorectal adenocarcinoma.

Upon examination of the patient cohort for premalignant and malignant skin neoplasms, the authors identified multiple actinic keratoses (defined as more than 10 lesions) in 3.3% of patients. In addition, Bowen's disease and basal cell carcinoma were each detected in 0.7% of the patient population.

Additional dermatological findings in our patient cohort were as follows: multiple acrochordons, with a presentation of more than ten lesions, were observed in 6% of patients. A considerable prevalence of cherry angiomas, also characterized by more than ten lesions, was noted in 21.3% of the patients. Palmar telangiectasias were identified in 4% of the cohort. Conditions with a prevalence of 2.7% included trichostasis spinulosa and keratosis pilaris. Additionally, 2% of patients were found to have decubitus ulcers, and 0.7% presented with post-zoster granulomatous dermatitis.

In terms of infectious dermatological conditions within our patient cohort, the following prevalences were observed: tinea unguium was the most common, affecting 68.7% of patients, followed closely by tinea pedis at 62%. Tinea cruris was present in 4% of patients. Oral candidiasis was diagnosed in 34.7% of patients, indicating a significant incidence of this opportunistic infection. Pityriasis versicolor was identified in 2% of the cohort, while scabies were less common, and found in 0.7% of patients. Herpes zoster was noted in 6.7% of patients; it was documented approximately two years prior to the diagnosis of malignancy in eight patients (5.3%), following the diagnosis in one patient,

Table 2 Statistical analysis of dermatological findings by age, gender, body mass index, and type of malignancy.

	Seborrheic keratosis. n (%)	p-value	Acanthosis nigricans. n (%)	p-value	Acquired ichthyosis. n (%)	p-value	Acquired hypertrichosis lanuginosa. n (%)	p-value
Age		0.003		0.310		0.160		0.090
<62	8 (10.8)		6 (8.1)		2 (2.7)		5 (4)	
>62	23 (30.3)		10 (13.2)		6 (7.9)		1 (1.3)	
Sex		0.010		0.890		0.150		0.014
Female	5 (9.3)		6 (11.1)		1 (1.8)		5 (9.2)	
Male	26 (27.1)		10 (10.4)		7 (7.3)		1 (1)	
Body Mass Index		0.039		<0.001		0.120		0.920
<25.8	20 (27.8)		1 (1.4)		6 (8.3)		3 (4.2)	
>25.8	11 (14.1)		15 (19.2)		2 (2.6)		3 (3.8)	
Malignancy type		0.460		0.250		0.084		0.550
Gastric	8 (16.7)		3 (6.2)		5 (10.4)		1 (2.1)	
Colorectal	15 (20.3)		11 (14.9)		1 (1.3)		3 (4.1)	
Other	8 (28.6)		2 (7.1)		2 (7.1)		2 (7.1)	

and one patient presented with an active infection during the examination.

The most prevalent hair-related finding was androgenetic alopecia, affecting 58.7% of the patient population. This was followed by chemotherapy-associated anagen effluvium, which was observed in 21.3% of the patients.

Within the assessment of nail disorders in our patient cohort, excluding tinea unguium, longitudinal ridging emerged as the predominant condition, affecting 20.7% of patients. Additional nail abnormalities observed included brittle nails (onychoschizia) in 9.3% of the patients, leukonychia in 6.7%, Mees' lines in 6%, Muehrcke's lines in 3.3%, splinter hemorrhages in 4%, and Beau's lines in 0.7% of the cohort.

In terms of oral mucosal health, oral candidiasis was notably present in 34.7% of patients, reflecting a significant concern for oral health in this population. Additional findings were atrophic glossitis in 7.3%, fissured tongue (lingua plicata) in 2.7%, geographic tongue (benign migratory glossitis) in 2%, black hairy tongue also in 2%, and oral aphthous ulcers in 0.7% of the patients.

When analyzing the data based on age and gender, it was observed that certain dermatological conditions were significantly more prevalent in patients older than 62 years. These conditions included paraneoplastic dermatoses, cherry angiomas, rosacea, onychomycosis, tinea pedis, and herpes zoster, with p-values of 0.008, 0.007, 0.027, 0.006, 0.003, and 0.050, respectively. Additionally, seborrheic dermatitis and tinea pedis were found to be more common in female patients, with p-values of 0.014 and 0.023, respectively.

Discussion

The present study contributes to the growing body of literature on the association between malignancies and dermatologic manifestations, particularly in patients with GI cancers. This correlation has intrigued clinicians for decades, yet the lack of prospective epidemiological studies has hindered a comprehensive understanding. By cataloging skin findings in our cohort, the authors aimed to

enhance clinical awareness and provide a reference for future research.

Itching and malignancy

Pruritus, commonly known as itching, has been increasingly recognized as a symptom that may signal the presence of systemic diseases, including cancer.⁷ A substantial study by Larson Valerie A. et al. Analyzed 16,925 patients experiencing pruritus and found that 17.1% had malignancies, with a notable association with cancers of the liver, gallbladder, biliary tract, hematopoietic system, and skin.⁸ In a similar vein, Kılıç et al. researched 700 patients with solid organ and hematological malignancies, noting that 13% had generalized pruritus together with other skin conditions. Upon investigating the skin findings in patients diagnosed with internal malignancies within the last month, the most frequent conditions identified were tinea pedis/onychomycosis, followed by xerosis (dry skin), and pruritus. These conditions were predominantly observed in patients with hematological malignancies, accounting for 68.96% of cases.⁹ These findings align with these observations, noting a higher prevalence of itching (31.7%) in our cohort, predominantly among colorectal adenocarcinoma patients. This suggests that pruritus may be an important clinical indicator for underlying malignancies, deserving of more rigorous investigation.

Dermatologic findings and their implications

Seborrheic keratoses have been speculated to be potential markers of internal malignancies, particularly in conjunction with acanthosis nigricans. In a study by Fink AM et al., 42% of 150 patients with internal organ malignancies were found to have seborrheic keratoses, with a significant proportion of these patients (62) having gastrointestinal cancers.¹⁰ The lesions predominantly appeared on the trunk (72.5%) and were least common on the head (5.6%).

These findings indicate a lower occurrence rate of seborrheic keratoses (20.7%) compared to Fink AM et al., yet

with a similar distribution, primarily on the trunk. A majority of patients in the present study (90.4%) exhibited a high count of seborrheic keratoses (over 50 lesions), a significant observation given the sparse literature documenting the correlation between the number and placement of these lesions and malignancy.

While the literature lacks comprehensive data on the average age, number, gender distribution, and direct correlation of seborrheic keratosis with BMI, the present study found a higher prevalence of these lesions among patients with a BMI greater than 25, suggesting a noteworthy link that merits further exploration.

These insights enhance our understanding of seborrheic keratosis in the context of internal malignancies and propose that factors like lesion count and BMI might play more critical roles than previously thought. Further research is necessary to elucidate these connections and assess the potential of seborrheic keratoses as indicators of underlying malignancies.

Acanthosis nigricans, known for its links to metabolic issues like obesity, diabetes, and metabolic syndrome, show a highly variable prevalence in literature, ranging from 4.5% to 74%.¹¹⁻¹⁴ This variance may result from different study populations, diagnostic criteria, or associated metabolic conditions.

In comparison to existing studies, our findings indicate a lower prevalence of acanthosis nigricans (10.7%). Bahadursingh S. et al. reported a 52.7% prevalence among 311 patients with type 2 diabetes,¹³ in our cohort, and only 37.5% of patients with acanthosis nigricans had concurrent diabetes. Similarly, the study by Garcia-Hidalgo L. et al.¹⁴ detected acanthosis nigricans in 29.4% of 156 obese patients, a rate that is notably greater than the 19.2% found in our study of a similar patient population. These disparities could be influenced by ethnic diversity, obesity severity, glycemic control, and diagnostic sensitivity, emphasizing the complex dynamics between acanthosis nigricans and metabolic health.

The present study also detailed the anatomical distribution, most frequently noting the inguinal region, which aligns with the condition's tendency to appear in skin folds. This observation points to a need for further detailed studies on its topography across different demographics.

Moreover, while Brown J. et al.¹² found a strong association between malignant acanthosis nigricans and gastric carcinoma (55% of cases), our findings indicate a higher link with colorectal cancer (68.7%), followed by gastric adenocarcinoma (18.7%). These discrepancies may be influenced by genetic, environmental, or dietary factors and regional cancer prevalence. The present data, alongside Brown J. et al.'s, underscores the potential of acanthosis nigricans as a paraneoplastic marker, particularly for detecting early gastrointestinal cancers.

These results also corroborate the literature on the association between acquired ichthyosis and gastric adenocarcinoma, with the majority of our cases linked to this type of cancer, reinforcing the observations made by Pérez R. et al. and Saldana M. et al.^{15,16} This recurrent link in the literature and our study suggests that when acquired ichthyosis is diagnosed, especially in the absence of other typical causes, a thorough evaluation for gastric adenocarcinoma should be considered.

The relationship between hypertrichosis lanuginosa and malignancy is similarly intriguing. A review of case reports indicated that out of 64 patients with acquired hypertrichosis lanuginosa, colorectal adenocarcinoma was present in 17 patients and pancreatic adenocarcinoma was noted in one patient.¹⁷ This pattern of association is mirrored in our study, where 50% of patients with acquired hypertrichosis lanuginosa were found to have colon adenocarcinoma. The consistent association between certain rare dermatologic conditions and specific gastrointestinal malignancies, as observed in our study and supported by literature, suggests a significant, non-random connection with diagnostic implications.

Although the exact mechanisms of these associations remain unclear, the uniformity of findings across studies indicates a biological interaction that deserves further exploration. The present research supports the potential of these dermatologic conditions as markers for gastrointestinal cancers. Clinicians should be aware of these links to enable timely evaluation and management of possible underlying malignancies, potentially improving patient outcomes through early diagnosis.

In clinical examinations, the authors observed that 21.3% of our patients exhibited a widespread presentation of cherry angiomas, with more than 10 lesions each. Factors such as chemical exposure and immunosuppression caused by medications like cyclosporine have been reported to potentially induce or predispose individuals to develop cherry angiomas.¹⁸ According to Corazza et al., cherry angiomas were found in 15.5% of patients with melanoma and 14.4% of patients with non-melanoma skin malignancies, showing a statistically significant association.¹⁸ While previous studies have noted a higher incidence of widespread cherry angiomas in older individuals, males, and those with immunosuppression,^{18,19} these findings particularly highlight a significant prevalence in older patients. Further research is needed to determine if widespread cherry angiomas could act as an indicator of malignancy, especially in relation to non-cutaneous malignancies.

Infections and gastrointestinal malignancies

The present study highlights a significant incidence of fungal pathologies, notably tinea pedis/onychomycosis and oral candidiasis, among individuals with gastrointestinal neoplasms. Notably, the prevalence of onychomycosis in this study group significantly exceeds the global average of approximately 5.5%,²⁰ possibly due to factors such as age, sociodemographic variables, reduced self-care, and immunosuppression related to malignancy.

Comparatively, while Perea et al. reported a community prevalence of tinea pedis at 2.9%,²¹ these findings indicate a much higher prevalence of 62% within our cohort, suggesting a marked increase among our subjects. However, the prevalence of tinea cruris in the present study was about 4%, which is consistent with general population rates.

For pityriasis versicolor, our observed incidence rate of 2% in patients with malignancy aligns with the broader range of 0.8% to 5% reported in the literature.^{22,23}

Regarding oral candidiasis, which is known to occur in 20% to 40% of individuals undergoing chemotherapy,²⁴⁻²⁶ this

study found a similar incidence rate of 34.7%. These findings emphasize the increased risk of infectious complications in immunocompromised patients and highlight the need for effective prophylactic and therapeutic strategies to manage fungal infections in this vulnerable group.

Herpes zoster was observed in 6.7% of patients in this study, a rate higher than the general community incidence of 4.8% but lower than the 11.7% prevalence among cancer patients, indicating potential variability influenced by cancer types.²⁷ Ongoing research, including a meta-analysis showing a relative risk of 1.42 (95% CI: 1.18, 1.71) for cancer development within one year after a herpes zoster episode, suggests a possible link between herpes zoster and subsequent cancer development.²⁸ Furthermore, 5.3% of patients experienced herpes zoster two years prior to their cancer diagnosis, highlighting its potential role as an early indicator of undiagnosed malignancy and emphasizing the need for vigilant clinical assessment in these patients.

Hair findings

Androgenetic alopecia emerged as the most common hair-related finding in the present study, aligning with its known prevalence in the general population. Anagen effluvium, a rapid and diffuse hair loss triggered by chemotherapy, was another focus of our research. Typically developing within days to weeks after starting cytotoxic treatment, anagen effluvium affects about 65% of patients undergoing chemotherapy, highlighting its significant impact.²⁹

Interestingly, this study recorded a lower incidence of anagen effluvium at 25.9%, much less than the commonly reported rate. This notable difference can be attributed to several factors, including the type and dosage of chemotherapeutic agents, the variety of cancers treated, differences in chemotherapy regimens, genetic predispositions, and the use of newer, targeted therapies that tend to have different side effect profiles.

This discrepancy emphasizes the need to consider individual factors in the management and counseling of chemotherapy patients. It shows that while anagen effluvium is a major concern, its severity and likelihood can vary significantly among individuals.

Further studies are needed to better understand the predictors of anagen effluvium and to devise effective strategies to alleviate this distressing side effect. The present research provides additional insights into the frequency and characteristics of anagen effluvium in a specific patient group, potentially aiding in the development of preventive and therapeutic approaches to improve patient quality of life during chemotherapy.

Conclusion

In conclusion, this study underscores the critical role of dermatological manifestations as potential indicators of gastrointestinal (GI) malignancies, emphasizing the importance of early cancer detection and improved management of skin conditions. By highlighting the correlation between dermatologic symptoms such as pruritus, xerosis, seborrheic keratosis, and acanthosis nigricans, and underlying malignancies, these findings advocate for routine dermatological

screening as an integral part of comprehensive patient care. This approach aims to advance early diagnosis and enhance the overall treatment and quality of life for patients with GI cancers, reinforcing the necessity of dermatological assessment in oncology protocols.

Financial support

None declared.

Authors' contributions

Burcu Aydemir Demirci: Concept; design; supervising; financing and equipment; data collection and entry; analysis and interpretation; literature search; writing.

Deniz Aksu Arica: Concept; design; supervising; financing and equipment; data collection and entry; analysis and interpretation; literature search; writing; critical review.

Leyla Baykal Selcuk: Financing and equipment; data collection and entry; analysis and interpretation; literature search; critical review.

Evren Fidan: Supervising; financing and equipment; data collection and entry; analysis and interpretation.

Ali Güner: Concept; design; supervising; financing and equipment; data collection and entry; analysis and interpretation; writing; critical review.

Savaş Yaylı: Supervising.

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Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Evaluation of dermoscopic findings in patients with cutaneous squamous cell carcinoma according to histopathological subtype and lesion morphology*



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Received 21 July 2024; accepted 23 September 2024

Available online 13 February 2025

KEYWORDS

Bowen's disease;
Carcinoma, squamous cell;
Dermoscopy;
Keratoacanthoma

Abstract

Background: Cutaneous squamous cell carcinoma (cSCC) includes in situ cSCC (Bowen's disease [BD]) and invasive cSCC. By contrast, keratoacanthoma (KA) is a well-differentiated cSCC with self-resolving tendencies. Dermoscopy aids in monitoring vascular and keratin pattern changes to diagnose and track cSCC invasion.

Objectives: To examine dermoscopic findings of cSCC according to histopathological differentiation and clinical morphological characteristics.

Methods: Clinical and dermoscopic images of 118 cSCCs were retrospectively examined.

Results: Compared to other cSCC subtypes, BD more frequently presented with pigmentation ($p = 0.028$) and a clustered ($p = 0.042$) or serpiginous ($p = 0.006$) vascular arrangement. Central keratin plugs were more common in well-differentiated invasive cSCCs ($p = 0.021$), while white circles surrounding follicles ($p < 0.001$), ulceration/bleeding ($p = 0.001$), and red background ($p = 0.004$) were observed more in poorly differentiated invasive cSCCs. Central keratin plugs (87.5%) and branched vascular arrangements (75%) were observed in patients with nodular KA, with both statistically more frequent than in invasive cSCC ($p < 0.001$, $p = 0.040$, respectively). White halos surrounding vessels ($p = 0.004$) and a clustered vessel arrangement ($p = 0.037$) were more common in nodular invasive cSCC compared to nodular KA.

Study limitations: The number of examined lesions in the subgroups was relatively small.

Conclusions: Dermoscopy aids in distinguishing well-differentiated invasive cSCC from poorly differentiated invasive cSCC, distinguishing nodular KA from nodular invasive cSCC, and diagnosing BD. Further studies are needed to identify dermoscopic findings that can distinguish moderately differentiated invasive cSCC from other invasive cSCCs.

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Introduction

Cutaneous squamous cell carcinoma (cSCC) accounts for 20%–30% of non-melanoma skin malignancies.¹ cSCC encompasses a broad spectrum of clinical entities that vary in terms of cellular atypia and dysplasia and range from precursor lesions to *in situ* cSCC and invasive cSCC.² There are three main subtypes of cSCC: Bowen's disease (BD), keratoacanthoma (KA), and invasive cSCC.³

Dermoscopic findings of BD (i.e., *in situ* SCC) include a pink or pigmented background accompanied by clustered glomerular vessels and dotted vessels, yellow-white squams, and erosion.⁴ KA shares common clinical and histopathological features with well-differentiated cSCC.⁵ KA very rarely transforms to invasive cSCC and thus its accurate diagnosis prevents overtreatment.⁶

Invasive cSCC has specific dermoscopic signs related to its differentiation and depth of invasion.⁷ The dermoscopic structures seen in cSCC can be summarized as follows: 1) Keratin/central keratin, 2) Vascular structures, 3) Ulceration, and 4) White structureless areas.⁸ As invasive cSCC differentiates further, the keratin structures disappear, a polymorphic pattern of linear vessels covers the lesion, and ulceration develops.⁹ Histopathological differentiation is an important risk factor in cSCC tumor aggressiveness and recurrence risk.^{3,10} Early differential diagnosis of the variants of cSCC is especially important considering the metastatic potential of invasive cSCC.¹¹

This present study aimed to examine the distribution of dermoscopic findings in cases of invasive cSCC with different histopathological differentiation, as well as compare dermoscopic findings according to different morphological characteristics in cSCC patients and evaluate the dermoscopic findings of patients presenting with nodular invasive cSCC compared to those of patients with KA. The authors also aimed to further contribute to the literature by reviewing the dermoscopic findings of BD.

Methods

Statement of ethics

The study was approved by the Non-interventional Clinical Research Ethics Committee of the Trakya University Faculty of Medicine (2023/479).

Patients

This retrospective cross-sectional study examined the records of 118 patients from January 2019 to July 2024 at the Trakya University dermatological and venereal diseases outpatient clinic. The study included patients who had a histopathological diagnosis of invasive cSCC, BD, or KA following complete surgical excision of the tumor, who had high-quality macroscopic and dermoscopic photographs, and who had sociodemographic and clinical data available''.

The patients' sociodemographic characteristics (age, gender, past history of SCC, Fitzpatrick phototype), clinical characteristics (presence of multiple actinic keratoses at diagnosis, lesion duration, lesion location, whether in

sun-exposed or sun-protected area),¹² and histopathological diagnosis (well-differentiated cSCC, moderately differentiated cSCC, poorly differentiated cSCC, BD, or KA) were recorded by a member of the research team (M.Ü). The same researcher evaluated macroscopic images for lesion morphology (erythematous papule/plaque, hyperkeratotic papule/plaque, hyperkeratotic nodule, tumor, ulcerated papule/plaque, and ulcerated nodule) and classified the lesions as flat or elevated after evaluating their clinical features. Macroscopic photographs were collected from the clinic's image dataset. Patients who had invasive cSCC and KA with nodular morphology were evaluated in separate subgroups. As ulceration is morphologically rare in KA, ulcerated nodular lesions were not evaluated. The histopathological classification has been revised according to the diagnostic criteria set by the WHO in 2024 (N.C).¹³

Dermoscopy

Dermoscopic images were obtained using 20× lenses and a dermoscopy system based on the FotoFinder platform (FotoFinder Systems GmbH, Germany). All images were obtained by contact dermoscopy with alcohol gel or ultrasound gel in patients with highly elevated lesions. Evaluation of dermoscopic images was performed independently by two researchers (Y.G.Ü & Ö.F.E) who were both blinded to the patient's clinical information and histopathological diagnoses. Dermoscopic images were retrieved from the database of the digital video dermoscopy system at the clinic.

Using the parameters specified by Sgouros et al. and Rosendahl et al.,^{3,8} the dermoscopic images were evaluated under the following main headings: 1) Features of keratinization (scales, central keratin plug, white halos surrounding vessels, white circles, white clods, white lines, white clods/dots, white structureless areas, and rosettes) (Figs. 1 and 2) 2) Epidermal and dermal losses (ulceration/bleeding, erosion, and blood spots), and 3) Background color (white, pink, red, or mixed). In addition, vessels were classified in more detail according to 1) Vascular pattern (monomorphous, polymorphous, no clear vascular pattern), 2) Vascular structures (dots, clods, linear) (Figs. 3 and 4), and 3) Vascular arrangement (random, clustered, serpiginous, linear, centered, radial, reticular, branched) (Figs. 5 and 6). Linear vascular structures were evaluated as straight, looped, curved, serpentine, helical, or coiled (Figs. 3 and 4).¹⁴ The dermoscopic terms used are based on the study by Kittler et al.¹⁵

Statistical analysis

The data obtained from the study were analyzed using the IBM SPSS Statistics Version 21 package program. Frequency, percentage, mean, and standard deviation were used as descriptive statistical methods in the data analysis. The concordance of the dermoscopic findings identified by the two physicians was evaluated using Cohen's Kappa statistic. The dermoscopic findings showed high intra-rater agreement and were compared with histopathological findings using chi-square and Fisher exact tests. A p-value below 0.05 was considered statistically significant.

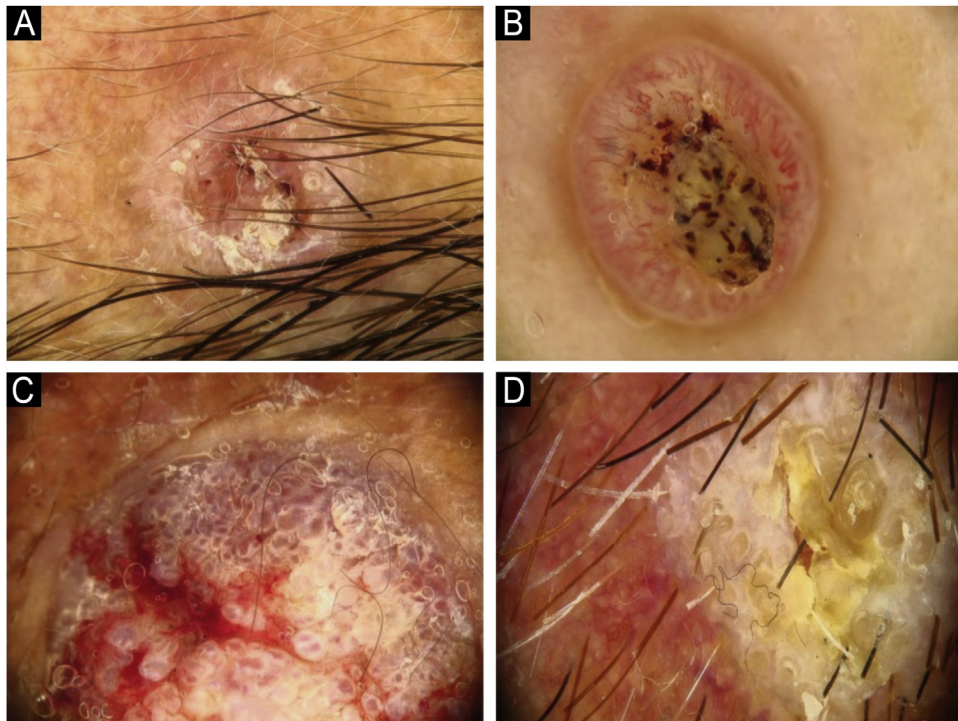


Fig. 1 Features of keratinization dermoscopically in cutaneous squamous cell skin cancer: (A) Keratin crust/scale, (B) Central keratin plug, (C) White halos surrounding vessels, (D) White circles surrounding follicles.

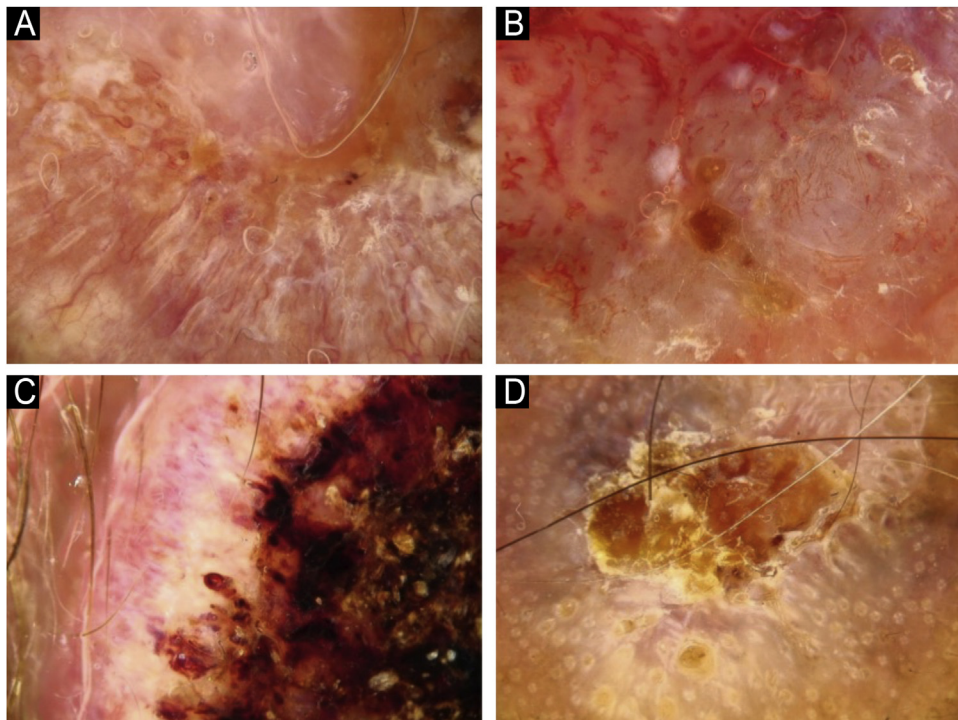


Fig. 2 Features of keratinization dermoscopically in cutaneous squamous cell skin cancer: (A) White lines, (B) White clod/dots, (C) White structureless areas, (D) Rosettes.

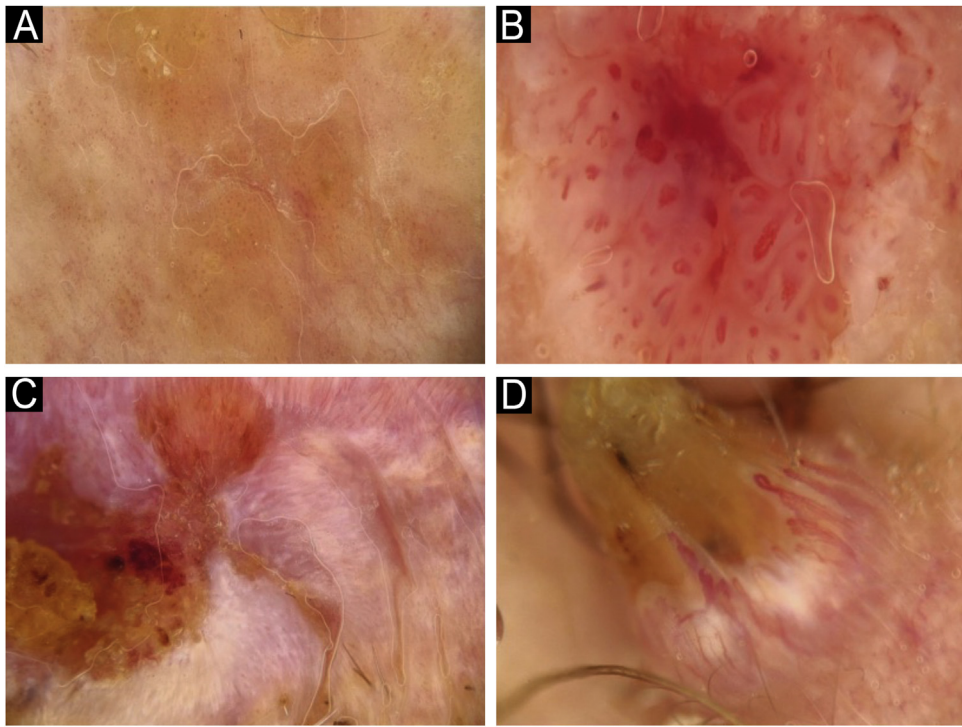


Fig. 3 Vascular structures in cutaneous squamous cell carcinoma: (A) Dots, (B) Clods, (C) Linear straight, (D) Linear looped.

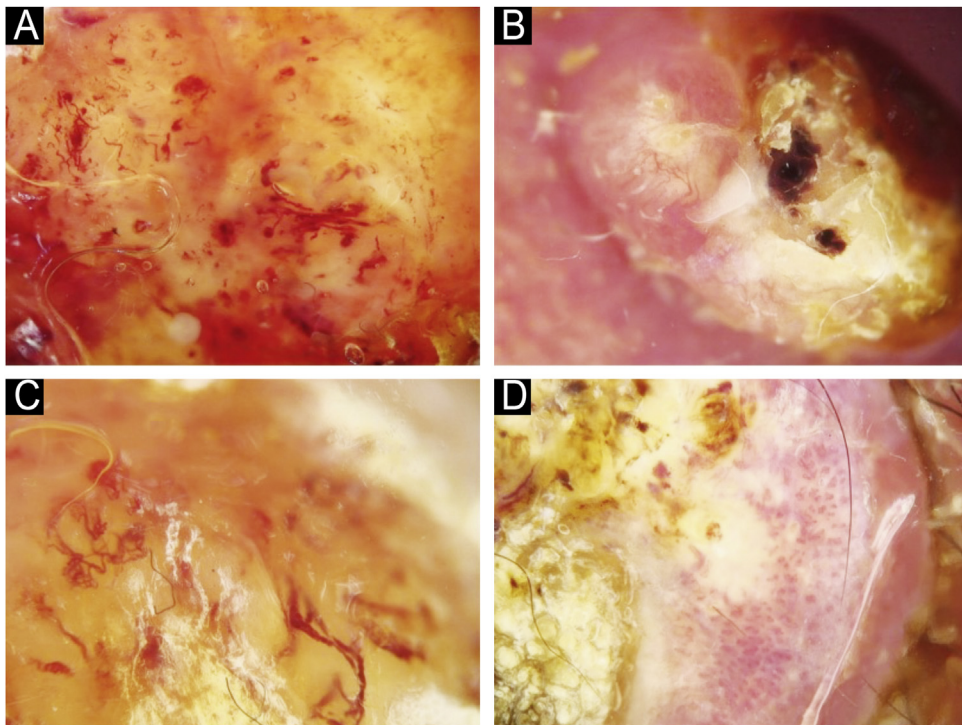


Fig. 4 Vascular structures in cutaneous squamous cell carcinoma: (A) Linear curved, (B) Linear serpentine, (C) Linear helical, (D) Linear coiled.

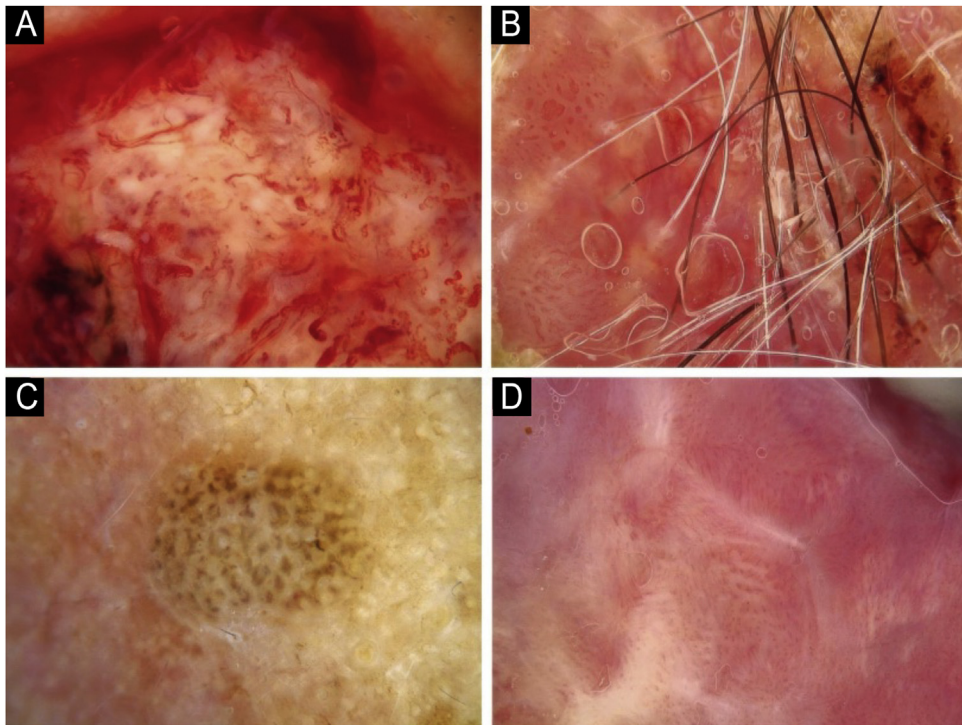


Fig. 5 Vascular arrangement in dermoscopy: (A) Random, (B) Clustered, (C) Serpiginous, (D) Linear.

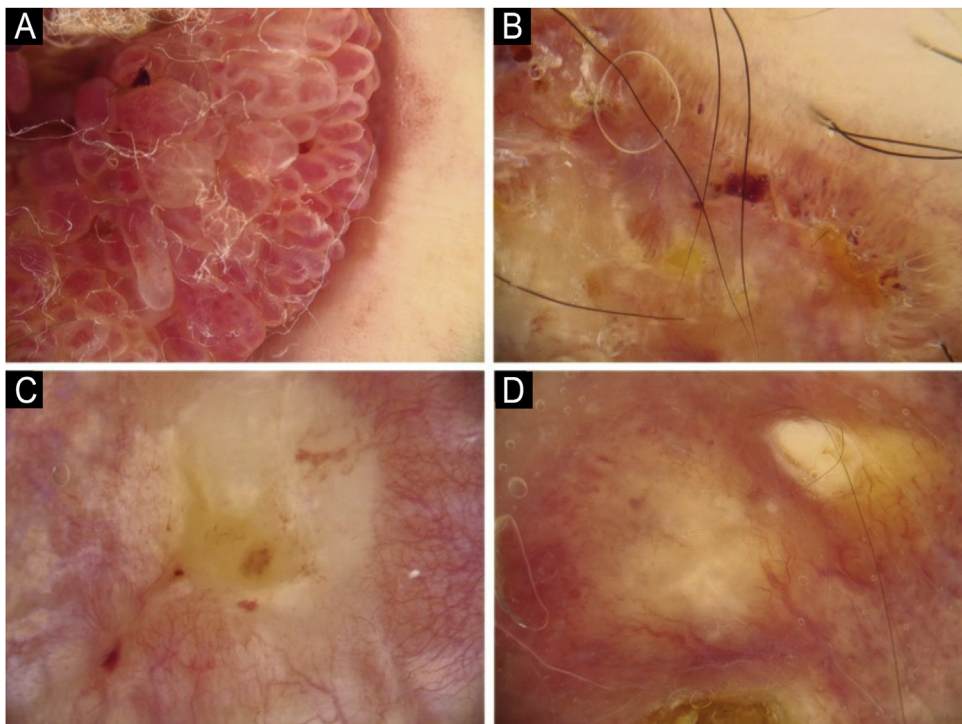


Fig. 6 Vascular arrangement in dermoscopy: (A) Centered, (B) Radial, (C) Reticular, (D) Branched.

Table 1 Demographic and clinical characteristics and histopathologic diagnoses of patients with cutaneous squamous cell carcinoma.

	n = 118
Age (years), mean $\pm$ SD (range)	69.05 $\pm$ 11.92 (42–90)
Gender, n (%)	
Male	79 (66.9)
Female	39 (33.1)
Lesion duration (months), mean $\pm$ SD (range)	14.78 $\pm$ 29.53 (1–240)
Past history of SCC, n (%)	21 (17.8)
Multiple actinic keratosis ^a , n (%)	45 (38.1)
Fitzpatrick phototype, n (%)	
II	49 (41.5)
III	56 (47.5)
IV	13 (11.0)
Location, n (%)	
Head and neck	102 (86.4)
Upper limbs	10 (8.5)
Trunk	4 (3.4)
Lower limbs	2 (1.7)
Lesion site, n (%) ^b	
Sun-exposed	106 (89.8)
Sun-protected	12 (10.2)
Histopathological subtype, n (%)	
Well-differentiated cSCC	50 (42.4)
Moderately differentiated cSCC	19 (16.1)
Poorly differentiated cSCC	16 (13.6)
Bowen's disease	10 (8.5)
Keratoacanthoma	23 (19.4)

cSCC, cutaneous Squamous Cell Carcinoma.

^a Patients with multiple actinic keratosis diagnosed clinically and dermoscopically at the time of cutaneous SCC diagnosis.

^b According to the study by Morelló-Vicente et al.¹²

Results

Demographic and clinical characteristics of the patients

The mean age of the patients was 69.05 $\pm$ 11.92 years, and the male-to-female ratio was 2:1. Most of the lesions were located in the head and neck region (n = 102, 86.4%). Multiple actinic keratosis lesions were detected in 38.1% (n = 45) of the patients at the time of diagnosis. The histopathological classification was well-differentiated cSCC in 50 patients (42.2%), moderately differentiated cSCC in 19 patients (16.1%), poorly differentiated cSCC in 16 patients (13.6%), BD in 10 patients (8.5%), and KA in 23 patients (19.5%) (Table 1).

When the distribution of morphological features determined by clinical image analysis was examined according to histopathologic subtype, the authors observed that well-differentiated cSCC most commonly presented with hyperkeratotic papules/plaques (n = 29, 58%), poorly differentiated cSCC with ulcerated papules/plaques and nodules (n = 6, 37.5%), BD with erythematous papules/plaques (n = 8,

80%), and KA with hyperkeratotic nodules (n = 16, 69.5%) (See Supplementary Table S1).

Dermoscopic features

There was complete agreement between the two physicians' evaluations for the parameters of dermoscopic pigmentation, absent vessels, ulceration/bleeding, erosion, blood spots, and pink background color ($\kappa = 1.000$; $p < 0.001$). There was also high agreement for all other dermoscopic features ($p < 0.001$ for all parameters except linear vascular arrangement, $p = 0.003$) (See Supplementary Table S2).

The most common dermoscopic findings in cSCC included keratin crust/scale (78.9%), linear serpentine vascular structures (74.5%), random vascular arrangement (67.7%), white clod/dots (66.1%), white structureless areas (65.2%), and blood spots (63.5%) (Supplementary Table S3). The distribution of dermoscopic findings in invasive cSCC, BD, and KA is shown in Table 2. Dermoscopic pigmentation was more common in BD patients than in invasive cSCC and KA patients ($p = 0.028$). Linear serpentine vascular structures were detected more frequently in invasive cSCC and BD than in KA ($p = 0.028$). The linear coiled vascular arrangement was most common in BD ($p = 0.032$). Clustered and serpiginous vascular arrangements were also detected more frequently in BD than in invasive cSCC and KA ($p = 0.042$ and $p = 0.006$, respectively). Central keratin plug was detected more in KA than in invasive cSCC and BD ($p < 0.001$). White structureless areas were less common in BD patients than in invasive cSCC and KA patients ($p = 0.039$). The dermoscopic finding of ulceration/bleeding was most common in invasive cSCC but was not observed in any patients with BD ($p < 0.001$).

The comparison of dermoscopic findings according to invasive cSCC histopathologic differentiation is shown in Table 3. Central keratin plug was more common in patients with well-differentiated cSCC than in patients with moderately and poorly differentiated cSCC ($p = 0.021$). White circles surrounding follicles, ulceration/bleeding, and red background color were significantly more common dermoscopic findings in poorly differentiated cSCC than other histopathological subtypes of invasive cSCC ($p < 0.001$, $p = 0.001$, and $p = 0.004$, respectively).

Based on macroscopic images and clinical features, 20.3% of the lesions were flat. When dermoscopic features were compared between flat and elevated cSCC lesions, the authors found that dermoscopic pigmentation and ulceration/bleeding were prominent in flat lesions ($p < 0.001$, $p = 0.004$, respectively), while central keratin plug was more common in elevated lesions ($p < 0.001$) (Supplementary Table S4).

The dermoscopic characteristics of 14 invasive cSCC and 16 KA patients with nodular morphology are compared in Table 4. The most common dermoscopic findings in nodular lesions were scales (n = 21, 70%), central keratin plug (n = 20, 66.7%), and white structureless areas (n = 18, 60%). Central keratins plug and branched vascular arrangement were observed in 87.5% and 75% of patients with KA, which was statistically more frequent than in invasive cSCC ($p \leq 0.001$, $p = 0.040$, respectively). Dermoscopic findings of white halos surrounding the vessels and clustered vessel arrangement were statistically more common in invasive nodular cSCC

Table 2 The distribution of dermoscopic findings in invasive cutaneous squamous cell carcinoma (cSCC), Bowen's disease, and keratoacanthoma.

Dermoscopic Findings	Invasive cSCC (n = 85) n (%)	Bowen's disease (n = 10) n (%)	Keratoacanthoma (n = 23) n (%)	Fisher ^a n (%)	p-value ^a n (%)
Dermoscopic pigmentation	4 (4.8)	3 (30.0)	1 (4.3)	6.486	0.028
Vascular pattern					
Absent	12 (14.1)	1 (10.0)	8 (34.7)	2.232	0.345
Monomorphous	31 (36.5)	5 (50.0)	7 (30.5)	1.418	0.481
Polymorphous	42 (49.4)	4 (40.0)	8 (34.8)	1.693	0.416
Vascular structures					
Dots					
Clods	46 (54.1)	8 (80.0)	12 (52.2)	2.408	0.293
Linear straight	23 (27.1)	3 (30.0)	5 (21.7)	0.421	0.885
Linear looped	30 (35.3)	2 (20.0)	5 (21.7)	1.959	0.409
Linear curved	51 (60.0)	5 (50.0)	8 (34.8)	4.699	0.097
Linear serpentine	30 (35.3)	1 (10.0)	4 (17.4)	4.437	0.119
Linear helical	68 (80.0)	8 (80.0)	12 (52.2)	6.929	0.028
Linear coiled	34 (40.0)	7 (70.0)	5 (21.7)	6.791	0.032
Vascular arrangement					
Random	58 (68.2)	7 (70.0)	15 (65.2)	0.180	0.946
Clustered	15 (16.5)	4 (40.0)	1 (4.3)	6.049	0.042
Serpiginous	5 (5.9)	4 (40.0)	2 (8.7)	8.772	0.006
Linear	9 (10.6)	- (0.0)	2 (8.7)	0.467	0.891
Centered	4 (4.7)	1 (10.0)	1 (10.0)	1.649	0.509
Radial	32 (37.6)	1 (10.0)	4 (17.4)	3.033	0.221
Reticular	6 (7.1)	- (0.0)	- (0.0)	1.412	0.486
Branched	29 (34.1)	- (0.0)	12 (52.1)	5.425	0.065
Features of keratinization					
Keratin crust/scale	65 (76.4)	7 (70.0)	21 (91.4)	0.851	0.676
Central keratin plug	29 (34.1)	1 (10.0)	18 (78.5)	18.557	<0.001
White halos surrounding vessels	24 (28.2)	3 (30.0)	6 (26.1)	0.163	1.000
White circles surrounding follicles	27 (31.8)	2 (20.0)	5 (21.7)	1.271	0.153
White lines	36 (42.4)	2 (20.0)	8 (34.8)	1.995	0.423
White clod/dots	60 (70.6)	5 (50.0)	13 (56.5)	2.984	0.246
White structureless areas	60 (70.6)	3 (30.0)	14 (60.9)	6.404	0.039
Rosettes	19 (22.4)	- (0.0)	3 (13.0)	2.600	0.294
Ulceration/bleeding	34 (40.0)	- (0.0)	2 (8.7)	13.801	<0.001
Erosion	24 (28.2)	3 (30.0)	2 (8.7)	3.519	0.165
Blood spots	58 (68.2)	4 (40.0)	13 (56.5)	3.239	0.205
Background color					
White	20 (23.6)	2 (20.0)	12 (47.8)	4.780	0.096
Pink	10 (11.7)	2 (20.0)	2 (8.7)	1.098	0.648
Red	10 (11.7)	2 (20.0)	1 (4.3)	1.993	0.317
Mixed	45 (53.0)	4 (40.0)	8 (34.8)	1.744	0.444

^a Fisher's exact test and Pearson's Chi-Square test. Statistically significant results ($p < 0.05$) shown in bold.

compared to nodular KA ($p = 0.004$ and $p = 0.037$, respectively).

Discussion

The sociodemographic and clinical characteristics of these patients were consistent with previous studies indicating that most cSCC patients are older and male, and lesions are most commonly located in the head and neck region.^{16,17} The incidence of actinic keratosis increases with age, and this increase is higher in the 70-year age range.¹⁸ Multiple

actinic keratosis is one of the risk factors for the development of invasive cSCC.¹⁹ In a study, the number of multiple actinic keratoses accompanying invasive cSCC was reported as 11.5%.¹⁷ This rate was found to be higher in the present study. This may be related to the average age in this study being 69.05 and patients being regularly followed up for actinic keratosis and cSCC.

In different studies, dermoscopic pigmentation in cSCCs is reported to vary between 0.01% and 25%.²⁰ Its prevalence was found to be higher (5.5%) in pigmented BD.²¹ In the present study, this rate was found to be 6.7% and it was most commonly observed in BD. When evaluating dermo-

Table 3 The distribution of dermoscopic findings in invasive cutaneous squamous cell carcinoma according to histopathologic differentiation.

Dermoscopic Findings	Well differentiated (n = 50)	Moderately differentiated (n = 19)	Poorly differentiated (n = 16)	Fisher ^a	p-value ^a
	n (%)	n (%)	n (%)	n (%)	n (%)
Dermoscopic pigmentation	2 (4.0)	1 (5.3)	1 (6.2)	4.250	0.111
Vascular pattern					
Absent	8 (4.0)	3 (15.8)	1 (6.2)	0.309	0.947
Monomorphous	20 (40.0)	5 (26.3)	4 (25.0)	1.293	0.534
Polymorphous	22 (44.0)	11 (57.9)	11 (68.8)	2.710	0.582
Vascular structures					
Dots	25 (50.0)	11 (57.9)	10 (62.5)	0.905	0.630
Clods	9 (18.0)	7 (36.8)	7 (43.8)	5.342	0.058
Linear straight	13 (26.0)	10 (52.6)	7 (43.8)	4.906	0.079
Linear looped	29 (58.0)	11 (57.9)	11 (68.8)	0.633	0.786
Linear curved	14 (28.0)	9 (47.4)	7 (43.8)	2.879	0.250
Linear serpentine	37 (74.0)	16 (84.2)	15 (93.8)	2.925	0.247
Linear helical	8 (16.0)	4 (21.1)	4 (25.0)	0.963	0.688
Linear coiled	16 (32.0)	16 (47.4)	9 (56.3)	3.537	0.181
Vascular arrangement					
Random	31 (62.0)	15 (78.9)	12 (75.0)	2.241	0.324
Clustered	5 (10.0)	6 (31.6)	3 (18.8)	4.647	0.086
Serpiginous	4 (8.0)	- (0.0)	1 (6.3)	1.295	0.698
Linear	4 (8.0)	2 (10.5)	3 (18.8)	1.706	0.427
Centered	2 (4.0)	1 (5.3)	1 (6.3)	0.733	1.000
Radial	22 (44.0)	5 (26.3)	5 (31.3)	2.071	0.352
Reticular	3 (6.0)	2 (10.5)	1 (6.3)	0.783	0.840
Branched	15 (30.0)	9 (47.4)	5 (31.3)	1.921	0.437
Features of keratinization					
Keratin crust/scale	42 (84.0)	13 (68.5)	10 (62.5)	1.749	0.449
Central keratin plug	23 (46.0)	4 (21.1)	2 (12.5)	7.709	0.021
White halos surrounding vessels	14 (28.0)	6 (31.6)	4 (25.0)	0.252	0.893
White circles surrounding follicles	9 (18.0)	6 (31.6)	12 (75.0)	18.170	<0.001
White lines	25 (50.0)	7 (36.8)	4 (25.0)	3.301	0.187
White clod/dots	35 (68.0)	15 (78.9)	10 (62.5)	2.373	0.294
White structureless areas	39 (78.0)	11 (57.9)	10 (62.5)	3.422	0.193
Rosettes	14 (28.0)	3 (15.8)	2 (12.5)	1.968	0.365
Ulceration/bleeding	15 (30.0)	6 (31.6)	13 (81.2)	13.587	0.001
Erosion	14 (28.0)	8 (42.1)	2 (12.5)	3.642	0.173
Blood spots	32 (64.0)	14 (73.7)	12 (75.0)	0.917	0.685
Background color					
White	14 (28.0)	5 (26.3)	1 (6.25)	1.505	0.535
Pink	6 (12.0)	3 (15.8)	1 (6.25)	0.752	0.808
Red	3 (6.0)	1 (5.3)	6 (37.5)	9.580	0.004
Mixed	27 (54.0)	10 (52.6)	8 (50.0)	0.142	1.000

^a Fisher's exact test and Pearson's Chi-Square test. Statistically significant results (p < 0.05) shown in bold.

scopic findings, it should be kept in mind that pigmentation may rarely be seen in KA and invasive cSCC.

Among the dermoscopic findings of cSCC, the most common is linear irregular vessels.^{3,16} If linear vessels have more than one turn, it is referred to as a serpentine vessel.^{14,15} The linear irregular vessel structure is also known as a serpentine vessel.^{22,23} In a study by Lallas et al., the dermoscopic findings of invasive cSCC included radial linear irregular and dotted vessels.¹⁶ Although the studies use different nomenclatures of dermoscopic terms, the dermoscopic features of serpentine and dotted vessels should be

considered in the diagnosis of cSCC, consistent with the literature.

Rosendahl et al. determined that the vessel arrangement in KA and invasive cSCC was most frequently random, i.e., nonspecific.⁸ In the present study, a similar distribution was observed in subtypes other than BD. Several studies have demonstrated glomerular vessels and a clustered vascular arrangement to be important findings in the dermoscopic diagnosis of BD.^{3,9} As a result, glomerular vessels and clustered vascular arrangement help to differentiate from KA and invasive cSCC when diagnosing BD.

Table 4 Distribution of dermoscopic findings in patients with nodular invasive squamous cell carcinoma and nodular keratoacanthoma.

Dermoscopic Findings	Nodular invasive cSCC (n = 14) n (%)	Nodular KA (n = 16) n (%)	Total n (%)	p-value ^a
Dermoscopic pigmentation	- (0.0)	- (0.0)	- (0.0)	-
Vascular pattern				
Absent	3 (21.4)	3 (18.8)	6 (20.0)	0.919
Monomorphous	5 (35.7)	7 (43.7)	12 (40.0)	0.709
Polymorphous	6 (42.9)	6 (37.5)	12 (40.0)	0.765
Vascular structures				
Dots	7 (50.0)	8 (50.0)	15 (50.0)	1.000
Clods	3 (21.4)	2 (12.5)	5 (16.7)	0.642
Linear straight	3 (21.4)	3 (18.8)	6 (20.0)	1.000
Linear looped	8 (58.1)	7 (43.8)	15 (50.0)	0.464
Linear curved	4 (28.6)	3 (18.8)	7 (23.3)	0.675
Linear serpentine	9 (64.3)	9 (56.2)	18 (60.0)	0.654
Linear helical	3 (21.4)	1 (6.2)	4 (13.3)	0.315
Linear coiled	5 (35.7)	4 (25.0)	9 (30.0)	0.694
Vascular arrangement				
Random	8 (57.1)	8 (50.0)	16 (53.3)	0.696
Clustered	4 (28.6)	- (0.0)	4 (13.3)	0.037
Serpiginous	- (0.0)	- (0.0)	- (-)	-
Linear	- (0.0)	- (0.0)	- (-)	-
Centered	3 (21.4)	1 (6.2)	4 (13.3)	1.000
Radial	6 (42.9)	5 (31.2)	11 (36.7)	0.510
Reticular	2 (14.3)	- (0.0)	2 (6.7)	0.209
Branched	5 (35.7)	12 (75)	17 (56.7)	0.040
Features of keratinization				
Keratin crust/scale	10 (71.4)	11 (68.8)	21 (70.0)	1.000
Central keratin plug	6 (42.8)	14 (87.5)	20 (66.7)	<0.001
White halos surrounding vessels	10 (71.4)	3 (18.8)	13 (43.3)	0.004
White circles surrounding follicles	7 (50.0)	4 (25.0)	11 (36.7)	0.156
White lines	5 (35.7)	4 (25.0)	9 (30.0)	0.694
White clod/dots	9 (64.3)	7 (43.8)	16 (53.3)	0.261
White structureless areas	9 (64.3)	9 (56.3)	18 (60.0)	0.654
Rosettes	6 (42.8)	3 (18.8)	9 (30.0)	0.236
Ulceration/bleeding	- (0.0)	- (0.0)	- (0.0)	-
Erosion	1 (7.1)	1 (6.3)	2 (6.7)	1.000
Blood spots	6 (42.9)	7 (43.8)	13 (43.3)	0.961
Background color				
White	7 (50.0)	9 (56.2)	16 (53.3)	0.696
Pink	2 (14.3)	1 (6.2)	3 (10.0)	0.586
Red	1 (7.1)	1 (6.2)	2 (6.7)	1.000
Mixed	4 (28.6)	5 (31.2)	9 (30.0)	1.000

cSCC, Cutaneous Squamous Cell Carcinoma; KA, Keratoacanthoma.

^a Fisher's exact test and Pearson's Chi-Square test. Statistically significant results ($p < 0.05$) shown in bold.

Well-differentiated invasive cSCCs show an exophytic growth pattern and are present with white structures accompanied by squam on dermoscopy.^{16,23} Sgouros et al. detected the dermoscopic finding of white perifollicular openings more frequently in well-differentiated invasive cSCC.³ Manfredini et al. reported that the dermoscopic finding of white structureless areas was more common in well-differentiated invasive cSCC.²⁴ In a study conducted in 2024, it was determined that dermoscopic findings such as centrally distributed keratin, white circles, and whitish perivascular halo were more commonly observed

in well-differentiated invasive cSCC compared to non-well-differentiated invasive cSCC.²⁵

Lallas et al. emphasized that a central distribution of scales or keratin on dermoscopic images was a negative predictor of the diagnosis of poorly differentiated invasive cSCC.¹⁶ In this study, dermoscopic findings of the central keratin plug, keratin crust/scale, and white structureless areas were seen more frequently in well-differentiated invasive cSCCs.

Poorly differentiated cSCC presents clinically as a flat lesion and dermoscopically as red in color, often with abnor-

mal vascular structures.^{16,24} In a study, it is emphasized that the dermoscopic finding of arborizing vessels is important in the diagnosis of poorly differentiated invasive cSCCs. In this study, invasive cSCCs were examined in two groups: well-differentiated and non-well-differentiated.²⁵ Both this study and the study by Sgouros et al.³ examined invasive cSCC across three different histopathological subtypes. No difference was found between these 3 different histopathological subtypes in terms of dermoscopic findings of vascular structures. Among the patients with poorly differentiated cSCC in the present study, ulceration was detected clinically in 75%, and ulceration/bleeding and red background color were more common dermoscopically. The authors believe that further research is needed on this subject.

In the literature, the dermoscopic findings of white circles surrounding follicles and white halos surrounding vessels are not used separately but referred to collectively as white circles.^{16,22} However, Papageorgiou et al. examined these two dermoscopic findings separately and emphasized that white circles surrounding follicles supported a diagnosis of poorly differentiated invasive cSCC.²⁴ The findings of our study support this. In the same study, white halos surrounding vessels were determined to be an important dermoscopic finding for early invasive cSCC. In the present study, white halos surrounding vessels were most frequently detected in well-differentiated cSCC and were important in differentiating nodular invasive cSCC from KA.

The presence of keratin on dermoscopy has high sensitivity in the differentiation of invasive cSCC and KA from cutaneous basal cell carcinoma, one of the other non-melanocytic skin cancers.⁸ However, the positive predictive value of this dermoscopic finding decreases to 50% when distinguishing cSCC and KA from BD. In the present study, among the dermoscopic signs of keratinization, white circles and white structureless areas were less common in patients with BD. As in this study and the study by Rosendahl et al., the dermoscopic findings of white circles and white structureless areas are supportive of cSCC and KA when differentiating from BD.⁸

In their study, Sgouros et al. emphasized that dermoscopic erosion was mostly seen in patients with BD, while ulceration was mostly seen in patients with invasive cSCC.³ In this study, ulcerations were not seen in any of the patients with BD, whereas erosion was detected more frequently than invasive cSCC and KA. When evaluated together with the literature, these findings stand out as important in the dermoscopic differentiation of BD.

Dermoscopic findings seen in KA include a white background, central keratin plug, and linear irregular or hairpin vessels.^{3,6} The literature emphasizes the similarity of dermoscopic findings in KA and invasive cSCC.^{8,26} The most common dermoscopic finding is keratin crust/scale, observed in 100% of KAs and 90% of invasive cSCC.²³ The dermoscopic findings of keratin crust/scale and white background were most commonly observed in KA in the present study, consistent with the literature. However, the central keratin plug is seen significantly more in KA than in the other subtypes. As this study supports, the central keratin plug is important in the diagnosis of KA.

The most common morphological presentation of KA is nodular lesions with well-defined margins and central hyper-

keratotic plugs.⁵ In the present study, 69.5% of KA patients presented with nodular lesions. Nodular and ulcerated lesions are morphologies seen in invasive cSCC.³ Dermoscopic differentiation of KA and invasive cSCC is important in patients presenting with similar morphology. Lin et al. argued that the central keratin plug was important in distinguishing KA from nodular cSCC.²³ The present findings also support this. In the same study, glomerular vascular structures were reported to be the most common vascular structures in nodular cSCC, while no difference in vascular structures or vascular arrangement was found between cSCC and KA. In the study by Pyne et al.,²⁷ the branching vessel structure was found to be more common in KA than in invasive cSCC. No comments have been made about lesion morphologies in this study. In the present study, branched vascular arrangement was seen more frequently in patients with nodular KA. In the dermoscopic diagnosis of nodular KA, the presence of central keratin plug and branched vascular arrangement structures should be considered.

Limitations of this study are its retrospective design, the relatively small number of examined lesions in the subgroups, and evaluation of the clinical morphology of the lesions based solely on clinical images, without palpation.

Conclusions

In this study, specific dermoscopic findings were obtained for the differential diagnosis of BD and nodular KA. However, specific dermoscopic findings were not detected for moderately differentiated invasive cSCC.

The accuracy of the proposed dermoscopic criteria cannot be generalized as a result of the present study, but it will assist clinicians in this regard due to the limited number of studies in the literature.

Authors' contributions

Mustafa Ürün: Approval of the final version of the manuscript; study conception, design, and planning; collection, analysis, and data interpretation; writing; critical literature review and critical review of the manuscript.

Yıldız Gürsel Ürün: Approval of the final version of the manuscript; study conception, design, and planning; data interpretation; critical review of the manuscript.

Ömer Faruk Elmas: Approval of the final version of the manuscript; analysis, and data interpretation; critical literature review.

Nuray Can: Approval of the final version of the manuscript; analysis, and data interpretation; writing; critical literature review.

Financial support

None declared.

Appendix A. Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.abd.2024.09.005>.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Influence of sentinel lymph node biopsy on the prognosis of acral melanoma patients[☆]



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Received 11 June 2024; accepted 31 August 2024

Available online 18 June 2025

KEYWORDS

Biopsy;
Melanoma;
Prognosis;
Sentinel lymph node

Abstract

Background: Sentinel lymph node (SLN) biopsy in melanoma patients has an important role in staging, prognosis assessment, and treatment definition. Few studies have evaluated its role in the Acral Melanoma (AM) subtype.

Objective: To evaluate the results of SLN biopsy in 79 patients with acral melanoma treated at a single oncological center and compare them with the data described in the literature.

Methods: Between January 2016 and December 2022, the authors analyzed all patients with AM who underwent SLN biopsy in a single institute. The authors analyzed the epidemiological, clinical and histopathological data. Overall Survival (OS) and Disease-Free Survival (DFS) curves were estimated using the Kaplan-Meier method. Multivariate analyses were conducted using the Cox regression model.

Results: During the period, the authors analyzed 79 cases. The mean age was 60 years and median thickness was 4.5 mm and 67.1% had ulceration. SLN was positive in 27 patients (34.2%). The estimated OS and DFS were 67.7% and 45.2%. OS was better in the negative SLN group compared to the positive SLN group (70.9% vs. 53.2%), but without statistical significance ($p = 0.08$). Estimated DFS for positive SLN was associated with a significantly worse prognosis ($33.8 \times 46.7\%$, $p = 0.001$).

[☆] Study conducted at the Santa Casa de Misericórdia da Bahia, Hospital Santa Izabel, Salvador, BA, Brazil.

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Study limitations: The retrospective nature of the study and the limited number of patients.
Conclusions: The present study has significant implications for determining prognosis. Patients with AM and positive SLN had a worst prognosis compared to those with negative SLN.
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Introduction

Acral lentiginous melanoma is a rare subtype that accounts for 1% to 3% of melanoma cases, primarily affecting the acral skin of the palm, nails, and, especially, the sole of the foot. It is not directly related to sun exposure and is the most common subtype among individuals of African and Asian descent.^{1–3} In Brazil, it has a higher incidence than the global average, attributed to the racial diversity of the population. Some studies suggest that acral melanoma is associated with an unfavorable prognosis when compared to other subtypes.^{3–5} This may be partly explained by diagnoses at more advanced stages. However, some Asian studies do not confirm these findings and suggest a better prognosis.^{6–8}

Despite its rarity and specific characteristics, the treatment of acral melanoma follows the same principles as other subtypes. Sentinel lymph node (SLN) biopsy is currently recommended for patients with intermediate-thickness melanomas and has been widely used with low morbidity.^{9–11} Since the publication of The Second Multicenter Selective Lymphadenectomy Trial (MSLTII) and Dermatologic Cooperative Oncology Group Trial (DECOG), patients with a positive SLN have been spared of complete lymph node dissection, and with the introduction of new effective treatments, the role of SLN biopsy has been questioned.^{12,13} However, its role has proven important in prognosis assessment, staging melanoma more accurately, and defining complementary treatment strategies. Its therapeutic role is still under debate, but data from MSLTI suggest an improvement in prognosis in patients with thick melanoma and better local control with a reduction in nodal recurrence in patients undergoing SLN biopsy.^{14,15}

When analyzing major prospective studies, the majority of patients had the superficial spreading subtype, located on the trunk and extremities, while a smaller number had the acral subtype.^{12–15} Most studies on acral melanoma are retrospective, involving a limited number of patients, and have been conducted in Asia.^{7,8,16–22}

Due to the lack of data on the use of SLN biopsy in this subgroup of patients and the high proportion of patients with this subtype in Brazil, it is essential to obtain more information about the use of SLN biopsy in this group. Therefore, the aim of this study is to evaluate the results of SLN biopsy in 79 patients with acral melanoma treated at a single oncological center and compare them with the data described in the literature.

Methods

Patient selection

Between January 2016 and December 2022, a retrospective cohort of 79 patients with acral melanoma consecutively

submitted to SLN biopsy and lymphatic mapping at a single institution was analyzed. The inclusion criteria were patients with confirmed histological diagnosis of acral cutaneous melanoma, absence of lymph node enlargement and Breslow greater than 1 mm or presence of ulceration, Clark IV or V. There were no limits regarding gender, age or skin color.

SLN biopsy and lymphatic mapping

SLN biopsy and lymphatic mapping were performed by the same team of surgeons. Dynamic lymphoscintigraphy was performed on the morning before surgery with an intradermal injection of 1 mCi ⁹⁹Tc-m-phytate. Vital blue dye was injected subdermally around the primary melanoma or biopsy site at the time of surgery. SLNs were localized with a handheld gamma probe intraoperatively, and by visual inspection for blue dye. In vivo and ex vivo counts of the radiolabeled lymph nodes were obtained and compared with nodal bed counts before and after removal. All “hot” and “stained” lymph nodes were considered as SLNs and excised.

Pathological assessment and treatment choices

SLNs were not evaluated during perioperative time. The SLNs were processed in the pathology laboratory, stained with Hematoxylin and Eosin (H&E) and with the immunohistochemical markers HMB 45, Melan A, and S100. Complete lymph node dissection was initially scheduled in all positive cases. After the publication of MSLT II e DECOG, a conservative approach was offered to positive SLNs patients.

The micromorphometric classification adopted was based on maximum diameter. Invasion depth from the capsule was also evaluated. Metastatic deposits identified in the SLNs had their larger diameter measured using an optical microscope with an ocular micrometer. The largest value defined the SLN's tumor burden. If multiple positive SLNs were present, the largest maximum diameter in any of the SLNs was considered. The number of metastatic deposits in each SLN was also evaluated.

Data collection

Data were retrospectively collected from the Hospital's medical records and electronic databases. Postoperative follow-up was performed in the melanoma outpatient clinic and consisted of a clinical examination every 3-months and chest radiography every 6-months. Other examinations were performed according to the patient's needs. The patient's current status was classified as alive without evidence of dis-

ease, alive with disease, dead from disease, or dead from other causes.

Outcomes and statistical analysis

The statistical analyses were performed using the Statistical Package for Social Sciences (Version 18.0; SPSS Inc., Chicago, IL, USA). The Chi-Square test was used to evaluate relationships between categorical variables. Disease-free survival (DFS) and overall survival (OS) were calculated from the date of SLN biopsy to date of first recurrence or death, respectively, censored at the date of last contact if there were no events.

Univariate estimations of survival were performed by the Kaplan-Meier method and compared by using the log-rank test. Multivariate analysis was performed with the Cox proportional-hazards regression model including variables with statistical significance on univariate analysis; p-value of less than 0.05 was considered statistically significant. The study was approved by the Committee on Human Research Publications and Ethics of Santa Izabel Hospital.

Results

Demographic and preoperative characteristics

In this study, 79 patients diagnosed with acral melanoma underwent SLN biopsy from 2016 to 2022. The median age was 60-years, ranging from 20- to 92-years, with a slight male predominance (51%). 83.5% were classified as black or mixed-race, and 63.3% had comorbidities. 17.7% of patients had a family history of cancer, with 5.1% having a family history of melanoma, and only 1 patient (1.3%) had a previous diagnosis of melanoma (Table 1).

The diagnosis was mainly made through incisional biopsy (49.4%) or excisional biopsy (46.8%) followed by unknown (2.5) and punch biopsy (1.3). The preferred location was the sole of the foot (62%), followed by subungueal hand (15.2%), subungueal foot (13.9%) and palmar (8.9%).

Operative outcomes

All patients underwent surgical resection with curative intent, and amputation was necessary in 19% of patients. The intraoperative surgical margin was greater than 1 cm in 72.1%. All patients had a clinically negative lymph node chain and underwent SLN biopsy. In 100% of cases, patent blue dye was used, and only 2 cases (2.5%) did not undergo preoperative lymphoscintigraphy.

The median number of identified sentinel lymph nodes was 1.75, ranging from 1 to 6, with 82.2% having 1 or 2 sentinel lymph nodes. The preferred drainage chain was the inguinal in 72.2% of the cases. In the anatomopathologic study of the surgical specimen, the Clark level was above III in 87.3%, ulceration was present in 67.1%, regression in 7.6%, and satellitosis in 15.2%. The median Breslow thickness was 4.5 mm, ranging from 0 to 25 mm (Table 2).

Sentinel lymph nodes were positive in 27 patients (34.2%). Additionally, 17 patients (21.5%) underwent complete lymphadenectomy of the drainage chain. Among these

Table 1 Clinical and histopathological characteristics.

	Sample (n = 79)
Gender	
Male	40 (50.67)
Female	39 (49.4)
Mean age	60.4 (±15.36)
Comorbidities	
Yes	29 (36.7)
No	50 (63.3)
Skin Colour	
White	12 (15.2)
Nonwhite	67 (84.8)
Previous melanoma	
Yes	1 (1.3)
No	78 (98.7)
Anatomical site	
Plantar	49 (62.0)
Palmar	7 (8.9)
Subungueal hand	12 (15.2)
Subungueal foot	11 (13.9)
Diagnostic modality	
Incisional biopsy	39 (49.4)
Excisional biopsy	37 (46.8)
Punch biopsy	1 (1.3)
Unknown	2 (2.5)
pT Stage, n (%)	
Tis	2 (2.5)
T1a	1 (1.3)
T1b	8 (10.1)
T2a	9 (11.4)
T2b	7 (8.9)
T3a	5 (6.3)
T3b	14 (17.7)
	5 (6.3)

patients, 14 (82.3%) had lymphadenectomy due to a positive SLN, 2 (11.8%) had lymphadenectomy due to nodal recurrence after negative SLN biopsy, and 1 (5.9%) had lymphadenectomy due to nodal recurrence after conservative treatment with a positive SLN. The median number of lymph nodes dissected was 7.7 (ranging from 4 to 12), and the median number of positive lymph nodes was 1.5 (ranging from 0 to 6).

Analyzing the 27 patients with positive sentinel lymph nodes, 14 (51.8%) underwent elective lymphadenectomy. Among these patients, only 4 (28.6%) had no other positive lymph nodes besides the SLN. In 13 patients with positive SLN (48.2%), a conservative approach was chosen, and only 1 had a nodal recurrence and underwent therapeutic lymphadenectomy. The size of the tumor deposit was described in only 8 patients and the median of the largest diameter was 2.4 mm, ranging from 1 to 5 mm. Capsular infiltration was found in 9 patients (33.3%).

No patient received neoadjuvant treatment, and only 16.5% of them received adjuvant treatment. Cytotoxic chemotherapy was performed in 5.1%, Interferon (INF) in 5.1%, and radiotherapy in 6.3%. None of the patients had access to treatments such as immunotherapy or BRAF inhibitors.

Table 2 Operative and postoperative outcomes.

	Sample (n = 79)
Clark, n (%)	
I	1 (1.3)
II	4 (5.1)
III	5 (6.3)
IV	46 (58.2)
V	18 (22.8)
Unknown	5 (6.3)
Ulceration, n (%)	
Yes	53 (67.1)
No	26 (32.9)
Breslow depth, mm	
Mean	4.5
Median	3.5
Surgical Margins, n (%)	
Positive	3 (3.8)
Negative	76 (96.2)
Surgical resection, n (%)	
Large resection	64 (81)
Amputation	15 (19)
Sentinel lymph node, n (%)	
Positive	27 (34.2)
Negative	52 (65.8)
Positive sentinel lymph node treatment, n (%)	
Elective lymphadenectomy	14 (51.8)
Observation	13 (48.2)
Observation Group, n (%)	
Recurrence	1 (7.7)
No-recurrence	12 (92.3)
Non-Sentinel Lymph Node, n (%)	
Positive	10 (71.4)
Negative	4 (28.6)
Adjuvant Treatment, n (%)	
Citotoxic chemotherapy	4 (5.1)
Interferon	4 (4.1)
Radiotherapy	5 (6.3)
None	
Median 5-year overall survival (%)	66 (83.5)
Median 5-year disease-free survival (%)	67.7%
Median follow-up (mo)	45.2%
Clark, n (%)	26.8

Mortality and survival

The median follow-up was 26.8-months. The mortality rate was 6.3% (5-cases), and the recurrence rate was 26.6% (21-cases). The most frequent site of recurrence was “in-transit” (8 cases – 40%), followed by distant recurrence in 35% (7-cases), being the lung the most frequent site (15%) of distant recurrence. Local recurrence occurred in 3 cases (15%), and nodal recurrence also occurred in 3 cases (15%) (Table 3).

The OS for the entire group was 67.7%, and the DFS was 45.2% (Figs. 1 and 2). In the univariate analysis, OS was better in the negative SLN group compared to the positive SLN group (70.9% vs. 53.2%) (Fig. 3), but without statistical significance ($p=0.081$), as was the case in the analysis stratified by Breslow thickness (Fig. 4) ($p=0.572$) and ulcer-

Table 3 Comparison of the sentinel lymph node status with clinical and histopathological characteristics of 79 patients with acral melanoma.

	Negative SLN* (n = 52)	Positive SLN* (n = 27)
Age, yrs		
Range (average – SD)	26–91	20–92
Median	61.33	55.02
Sex, n (%)		
Male	27 (51.9)	13 (48.1)
Female	25 (48.1)	14 (51.9)
Skin color, n (%)		
White	7 (13.5)	5 (18.5)
Nonwhite	45 (86.5)	22 (81.5)
Comorbidities, n (%)		
Yes	18 (34.6)	11 (40.7)
No	34 (65.4)	16 (59.3)
Anatomical site, n (%)		
Plantar	33 (63.4)	17 (63)
Palmar	4 (7.7)	2 (7.4)
Subungueal hand	8 (15.4)	4 (14.8)
Subungueal foot	7 (13.5)	4 (14.8)
Diagnostic modality, n (%)		
Incisional biopsy	30 (57.7)	9 (33.3)
Excisional biopsy	21 (40.4)	16 (59.3)
Punch biopsy	1 (1.9)	–
Unknown	–	2 (7.4)
Breslow depth, mm		
Mean	3.638	6.426
Median	2.350	4.5
pT Stage, n (%)		
Tis	2 (3.8)	–
T1a	1 (1.9)	–
T1b	7 (13.5)	1 (3.7)
T2a	9 (17.3)	–
T2b	5 (9.6)	2 (7.4)
T3a	4 (7.7)	1 (3.7)
T3b	7 (13.5)	7 (25.9)
T4a	3 (5.8)	2 (7.4)
T4b	14 (26.9)	14 (51.9)
Clark, n (%)		
I	1 (1.9)	–
II	4 (7.7)	–
III	4 (7.7)	1 (3.7)
IV	31 (59.6)	15 (55.6)
V	8 (15.4)	10 (37)
Unknown	4 (7.7)	1 (3.7)
Ulceration, n (%)		
Yes	30 (57.7)	23 (85.2)
No	22 (42.3)	4 (14.8)
Surgical Margins, n (%)		
Positive	51 (98.1)	25 (92.6)
Negative	1 (1.9)	2 (7.4)
Surgical Resection, n (%)		
Large resection	39 (75)	25 (92.6)
Amputation	13 (25)	2 (7.4)
Adjuvant Treatment, n (%)		
Citotoxic chemotherapy	2 (3.8)	2 (7.4)
Interferon	–	4 (14.8)
Radiotherapy	–	5 (18.5)

Table 3 (Continued)

	Negative SLN* (n = 52)	Positive SLN* (n = 27)
None	50 (96.2)	16 (59.3)
Follow-up Status		
Alive without disease	46 (88.5)	14 (51.9)
Alive with disease	5 (9.6)	9 (33.3)
Death	1 (1.9)	4 (14.8)
Recurrence Pattern, n (%)		
Non-recurrence	44 (84.6)	14 (51.9)
Local	3 (5.8)	–
Regional Lymph Node basis	1 (1.9)	2 (7.4)
In transit	3 (5.8)	5 (18.5)
Distant	1 (1.9)	6 (22.2)

ation (Fig. 5) ($p=0.106$). The OS of patients with positive SLN who were treated conservatively was 56.4%, compared to 51.5% in the group of patients with positive SLN treated with elective lymphadenectomy ($p=0.659$) (Fig. 6).

In the univariate analysis of DFS, positive SLN (Fig. 7) and Breslow thickness above 2 mm (Fig. 8) were associated with a significantly worse prognosis ($33.8\% \times 46.7\%$, $p=0.001$ and $40 \times 52,1$, $p=0.009$). The other variables, ulceration (Fig. 9) and the treatment performed in patients with positive SLN (Fig. 10) did not reach statistical significance ($p=0.222$, $p=0.147$).

In the multivariate analysis, none of the variables showed statistical significance (Breslow thickness, presence of ulceration, regression, age, race, nodal status, tumor location or Clark level) (Tables 4 and 5).

Discussion

In this study, the authors retrospectively analyzed the outcome of 79 patients with acral melanoma who underwent SLN biopsy over a 6-year period at a reference center. The present data reveals a patient profile with thicker melanomas (4.5 mm) and a higher rate of ulceration (67.1%), which is above the averages reported in studies like MSLT1, MSLT II, and DECOG.^{12–15} It also exceeds the study from SEER involving patients with acral melanoma who underwent regional SLN biopsy (median Breslow thickness of 2 mm and 34% had ulceration) and has similar results of a Brazilian study with 66.7% of ulceration and a median Breslow of 5 mm.^{16–23}

These data may explain the elevated rate of positive SLN at 34.2% in this study. Most studies on melanoma report positive SLN rates around 20%.^{24–26} Studies specifically involving acral melanoma often show divergent results, often due to a limited number of patients and their retrospective nature, with rates ranging from 11.9% to 42.2%.^{7,8,16–22} A Korean study with only 34 patients showed a positive SLN rate of 41.2%,¹⁷ while another Korean study, with a larger number of patients (107) treated over a 12-year period, reported a positive SLN rate of 20.6%.¹⁸ A retrospective study using a U.S. database with 753 patients, mostly of Caucasian descent, showed a positive SLN rate of 25.7%,¹⁶ and a Brazilian study with 201 acral melanoma patients, showed a positive SLN rate of 29.9%.²³

In all patients, SLNs were correctly identified. This is consistent with the findings of Asian studies involving acral melanoma, which can be attributed to the location of acral lesions on extremities with a more predictable drainage chain. This also explains the high rate of SLN identification using the combined technique of blue dye

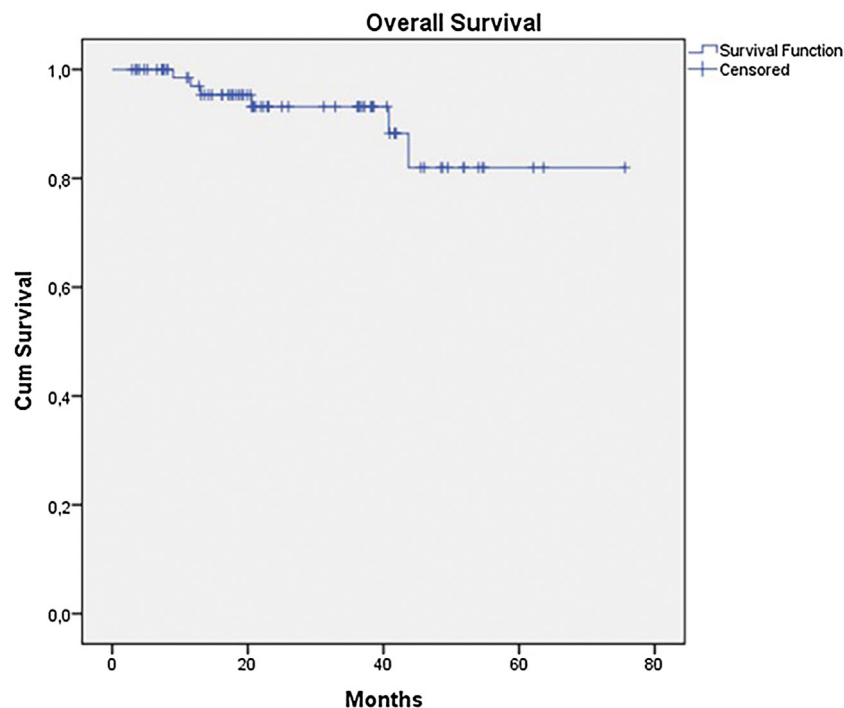


Figure 1 Kaplan-Meier overall survival curves for acral melanoma submitted a sentinel lymph node biopsy.

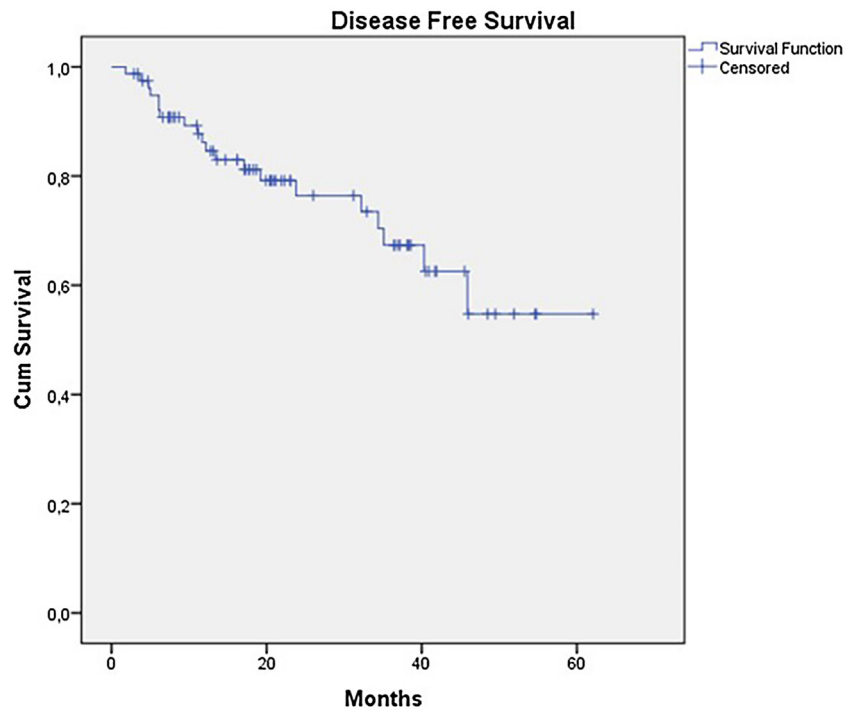


Figure 2 Kaplan-Meier disease free survival curves for acral melanoma submitted a sentinel lymph node biopsy.

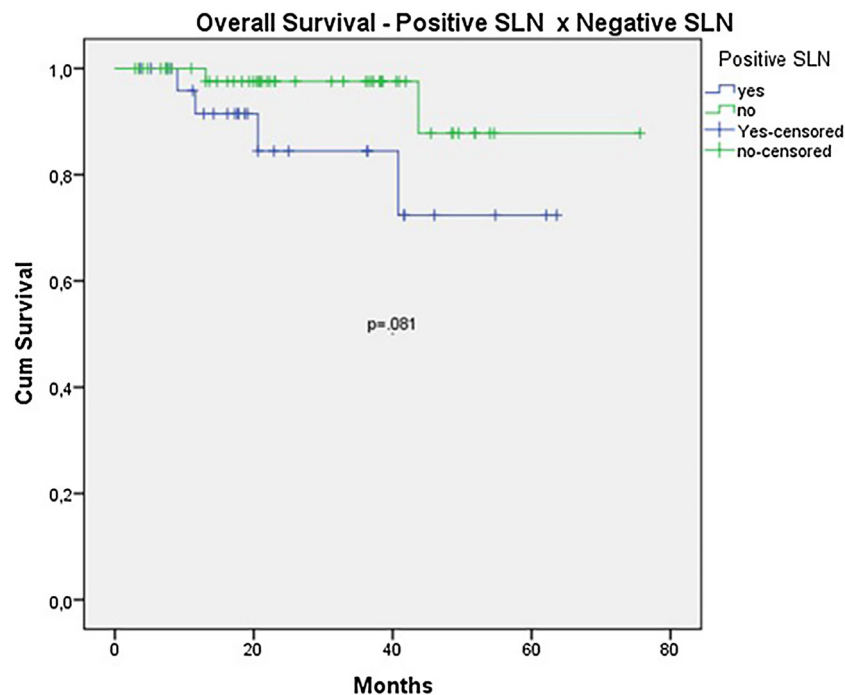


Figure 3 Kaplan-Meier overall survival curves for acral melanoma submitted a sentinel lymph node biopsy by status of sentinel lymph node.

and lymphoscintigraphy.^{7,8,17-22} Some data suggest that the false-negative rate for SLNs in acral melanoma patients could be higher. However, this data is not consistent with other studies,²⁷⁻²⁹ and it was not observed in the present study, where the recurrence rate at the drainage site after a negative SLN was only 3.8% (2 cases out of 52), which is

lower than that reported in MSLT I (5.5%) and a Korean study (11.8%).^{14,18}

The SLN biopsy has proven to be important in assessing patients' prognosis. Nevertheless, the number of patients with acral melanoma has always been limited in prospective Western studies.¹²⁻¹⁵ Specific studies on acral melanoma are

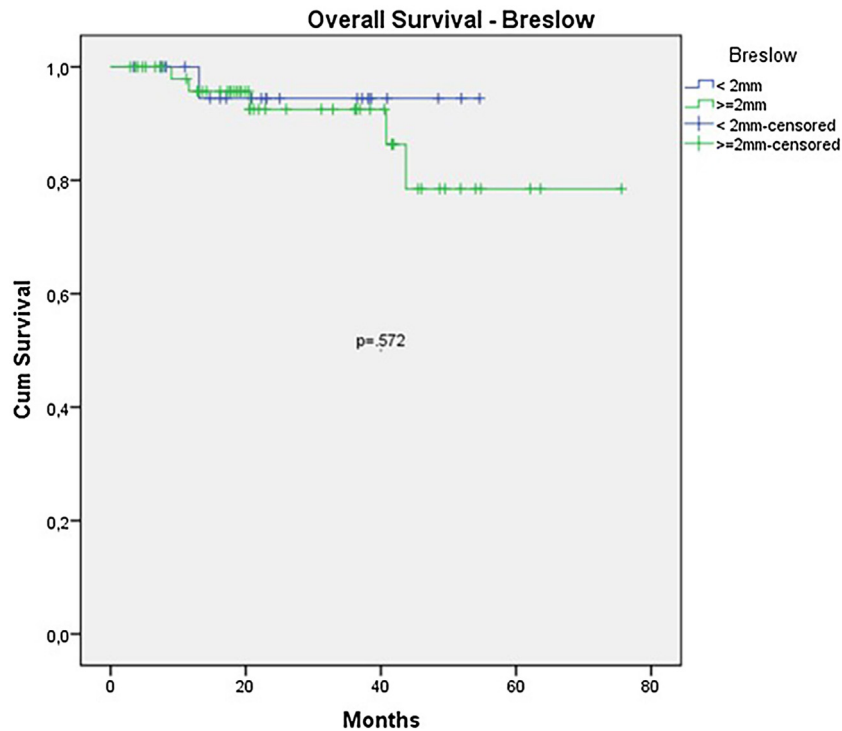


Figure 4 Kaplan-Meier overall survival curves for acral melanoma submitted a sentinel lymph node biopsy by Breslow < 2 mm versus ≥ 2 mm.

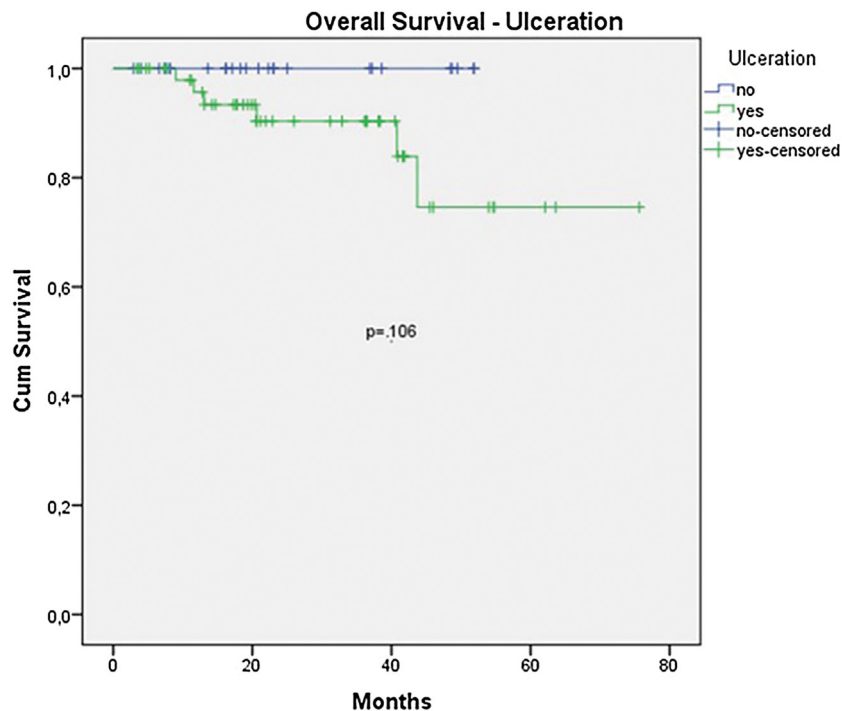


Figure 5 Kaplan-Meier overall survival curves for acral melanoma submitted a sentinel lymph node biopsy by ulceration.

retrospective and originate from Asia. Despite these limitations, seven studies have shown that the presence of SLN metastasis is a significant risk factor correlated with survival rates, especially in terms of DFS.^{8,17-21,23}

In this study, an OS of 67.7% was observed in the total group, which is lower than what is typically seen in melanoma studies, ranging around 91.7%, and lower than other retrospective studies involving acral melanoma, which

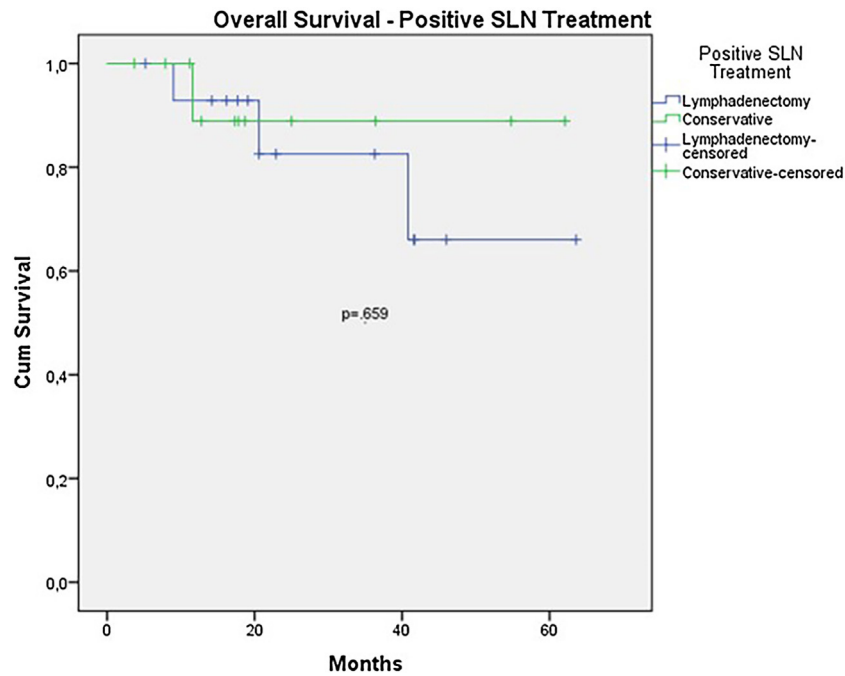


Figure 6 Kaplan-Meier overall survival curves for acral melanoma with positive sentinel lymph node by treatment employed.

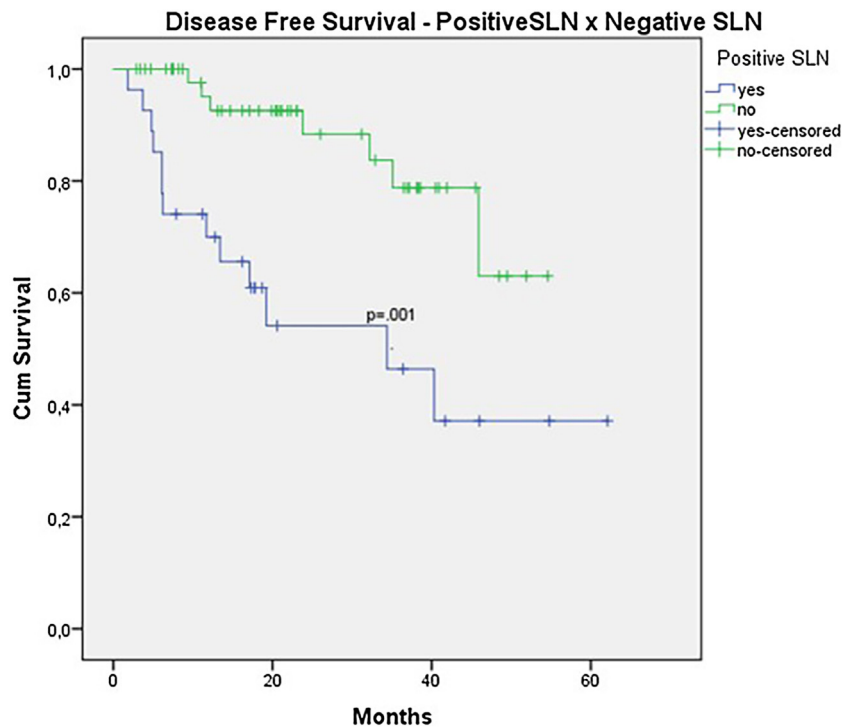


Figure 7 Kaplan-Meier disease free survival curves for acral melanoma submitted a sentinel lymph node biopsy by status of sentinel lymph node.

typically report survival rates around 80%.^{3,4} The reasons for this unfavorable prognosis can be explained by the more advanced diagnosis in the patients as the authors can observe in a Brazilian study that has similar characteristics and an even worse prognosis (OS of 44.6% and 38.6% DFS).²³

When analyzing SLN results, the authors observed a clear trend toward improved survival in patients with negative SLNs (OS 70.9% vs. 53.2% with $p=0.081$). However, statistical significance was only achieved in terms of DFS (46.7% vs. 33.9% with $p=0.001$). The authors believe that, due to the retrospective nature of the study and the limited number

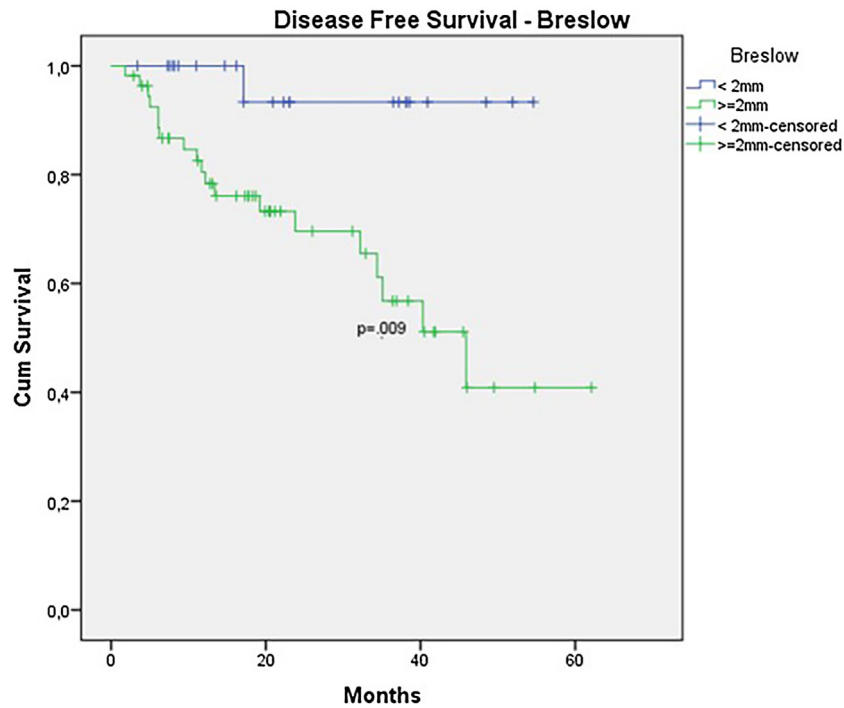


Figure 8 Kaplan-Meier disease free survival curves for acral melanoma submitted a sentinel lymph node biopsy by Breslow < 2 mm versus ≥ 2 mm.

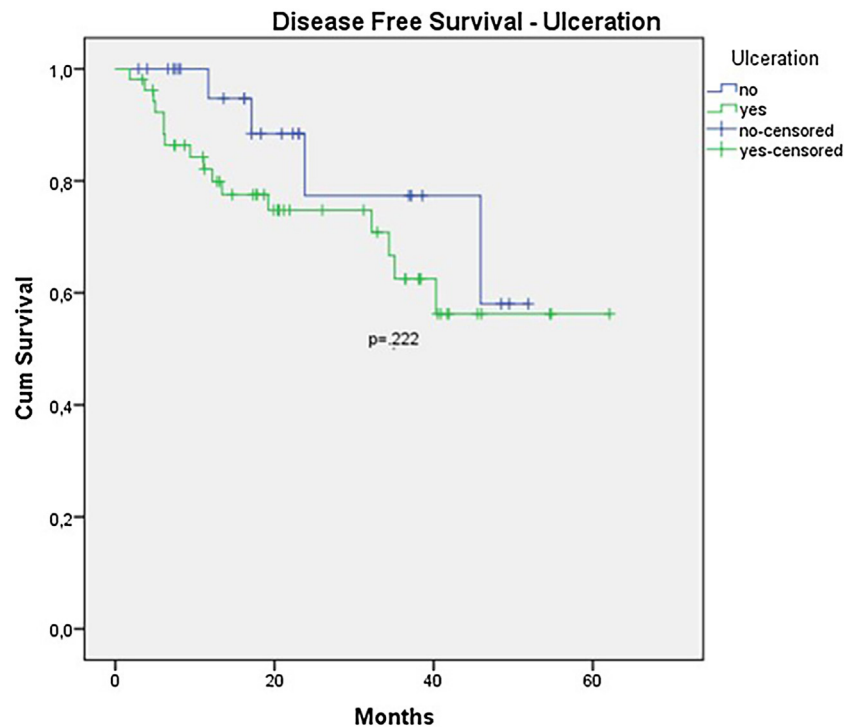


Figure 9 Kaplan-Meier disease free survival curves for acral melanoma submitted a sentinel lymph node biopsy by ulceration.

of patients, statistical significance was not reached. Other studies focusing exclusively on acral melanoma have also shown similar results. In a study involving acral melanoma patients in the United States, melanoma-specific survival was 88.5% in the negative SLN group, compared to 58.9%

in the positive SLN group.¹⁶ In six Asian studies, including three Japanese, one Chinese, and two Korean studies, positive SLN correlated with worst survival, especially in terms of DFS.^{8,17-21}

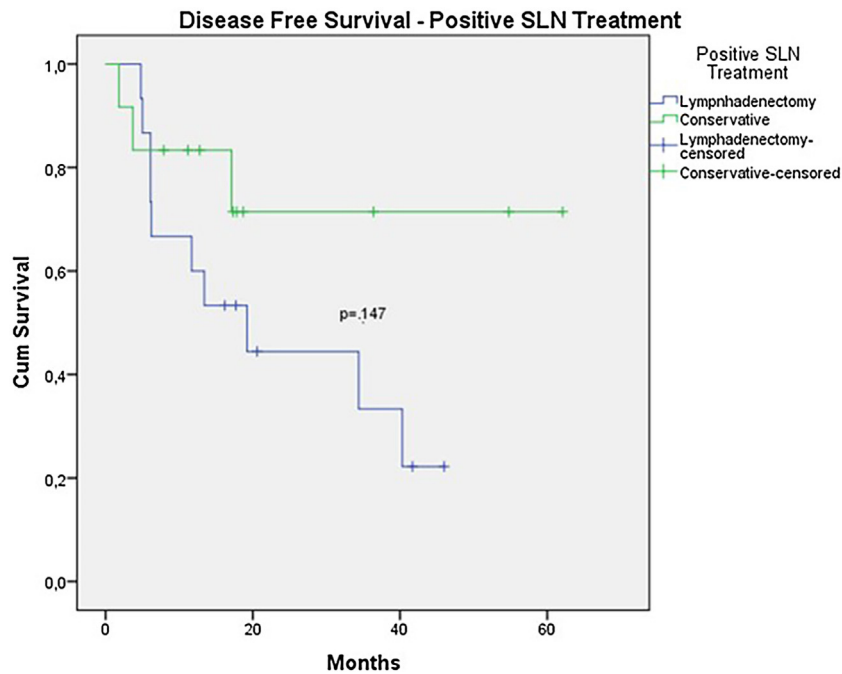


Figure 10 Kaplan-Meier disease free survival curves for acral melanoma with positive sentinel lymph node by treatment employed.

Table 4 Factors associated with 5-year overall survival.

	OR	95% CI	p-value
Age, yrs	0.967	0.925 – 1.01	0.131
Sex	1.003	0.202 – 4.974	0.997
Skin Color	1.525	0.175 – 12.279	0.702
Breslow	1.021	0.861 – 1.211	0.807
Clark	0.661	0.120 – 3.653	0.653
Ulceration	35.866	0.023 – 55313.46	0.339
Positive SLN*	0.246	0.045 – 1.351	0.107
Positive SLN* treatment	1.661	0.170 – 16.194	0.662

OR, Odds Ratio; CI, Confidence Interval; SLN*, Sentinel Lymph Node.

Table 5 Factors associated with 5-year disease free survival.

	OR	95% CI	p-value
Age, yrs	0.985	0.961 – 1.010	0.246
Sex	0.993	0.413 – 2.388	0.988
Skin Color	2.952	0.670 – 12.997	0.152
Breslow	1.117	1.047 – 1.191	0.001
Clark	0.000	0.120 – 1.141	0.952
Ulceration	1.958	0.652 – 5.882	0.231
Positive SLN*	0.240	0.095 – 0.604	0.002
Positive SLN* treatment	2.514	0.690 – 9.158	0.162

OR, Odds Ratio; CI, Confidence Interval; SLN*, Sentinel Lymph Node.

Since the publication of DECOG and MSLT II, conservative treatment after a positive SLN has been recommended.^{12,13} In the present study, only half of the patients (48%) followed this recommendation, largely because data supporting this approach emerged during the course of the study. Additionally, the authors are treating a population with more advanced lesions, with substantial tumor deposits in the

SLN, far beyond that was described in patients in the DECOG and MSLT II studies. This also justifies why Only 4 out of 14 patients who underwent elective lymphadenectomy after a positive SLN did not have any other positive lymph nodes besides the SLN.

Nevertheless, despite all these data, in the analysis of subgroups with positive SLNs, OS, and DFS were worse in

the group that underwent elective lymphadenectomy after a positive SLN. However, this difference did not reach statistical significance (OS 51.5% vs. 56.5% with $p=0.659$; DFS 23.8% vs. 46.9% with $p=0.147$). In this group, where the conservative approach was adopted, Only 1 patient underwent lymphadenectomy due to local recurrence. The mortality rate was 9.3% in the group that underwent conservative treatment and 20% in the group that underwent lymphadenectomy after a positive SLN. These data may suggest that lymphadenectomy was indicated in patients with a larger tumor volume, but it also suggests that conservative treatment after a positive SLN could be offered in acral melanoma patients.

Conclusion

In this study, the SLN biopsy in acral melanoma patients demonstrated high accuracy in identifying sentinel lymph nodes and had significant implications for determining prognosis. Patients with acral melanoma and positive sentinel lymph nodes had a worse prognosis compared to those with negative sentinel lymph nodes. Patients with positive SLN biopsy who underwent lymphadenectomy showed a prognosis like those treated expectantly, suggesting that this approach could also be recommended for this subgroup of patients. However, due to the retrospective nature of the study and the limited number of patients, each patient should be assessed individually.

Financial support

None declared.

Authors' contributions

Thiago Francischetto: Conceptualization and design of the study; original draft; critical review of the literature; final approval of the final version of the manuscript.

Ana Clara Falcão: Data collection; statistical analysis.

Adson Santos Neves: Original draft; obtaining, analyzing and data interpretation.

Ana Beatriz Lira: Data collection; statistical analysis.

Robson Freitas de Moura: Obtaining, analyzing and data interpretation.

Thiago Souza Oliveira Freitas de Moura: Original draft; obtaining, analyzing and data interpretation.

Juvandy Antonio Inacio Santos: Original draft; obtaining, analyzing and data interpretation.

André Bacellar Costa Lima: Original draft; obtaining, analyzing and data interpretation.

Marco Antonio Oliveira Lessa: Original draft; obtaining, analyzing and data interpretation.

Jussamara Britos Santos: Original draft; obtaining, analyzing and data interpretation.

Alexandre Farias de Albuquerque: Original draft; obtaining, analyzing and data interpretation.

Vaner Paulo da Silva Fonseca Pinheiro: Statistical analysis; obtaining, analyzing and data interpretation; Final approval of the final version of the manuscript.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Long-term outcome of juvenile dermatomyositis associated with lipodystrophy: experience of a University hospital[☆]



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Received 5 July 2024; accepted 3 September 2024

Available online 18 June 2025

KEYWORDS

Dermatomyositis;
Lipodystrophy;
Therapeutics

Abstract

Background: Juvenile Dermatomyositis (JDM) is a rare myopathy. Lipodystrophy is an under-reported chronic JDM complication.

Objective: Assess the long-term outcome of JDM associated with lipodystrophy.

Methods: Retrospective study of JDM patients who developed lipodystrophy, diagnosed and treated between 1st January 1990 and 31st December 2023, in a University Clinic of Dermatology. The mean follow-up was 150.8-months (range 29–291).

Results: Lipodystrophy was diagnosed in 5 children (4 girls and one boy, aged 3–14 years) of 22 JDM patients (17 girls and 5 boys). Four patients had partial, and one had focal lipodystrophy that occurred 34.2-months (mean period) after the initial JDM symptoms. All five children had antinuclear antibodies, but none had dermatomyositis-specific/associated antibodies. No malignancies or visceral involvement were found. At JDM presentation, all 5 patients had low serum vitamin D, body mass index (BMI) ranged from 14.3 to 20.7. Triglycerides and fasting glucose levels were normal in all patients, while cholesterol was elevated in one patient. Despite Standard Immunosuppressive Therapy (IST), 2/4 of patients with initially partial lipodystrophy progressed to generalized lipodystrophy and 4/5 patients developed calcinosis 46 months (mean period) after JDM diagnosis. At the last check-up, 3/5 patients had chronic JDM course, requiring IST, while 2/5 patients were in remission, without IST, with only residual lipodystrophy.

Study limitations: Retrospective study.

[☆] Study conducted at the University Clinical Center of Serbia and University of Belgrade.

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Conclusions: During the 34-year period, 5/22 (23%) JDM patients developed lipodystrophy. Metabolic complications were not found. All patients had significant delays in JDM diagnosis. Early diagnosis and IST are necessary to reduce the risk of lipodystrophy, as a severe, chronic JDM complication.

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Introduction

Dermatomyositis (DM) is a rare, chronic connective tissue disease affecting primarily skin and muscles. DM is of unknown etiology, presenting as adult and juvenile disease (onset before 18). Juvenile Dermatomyositis (JDM) is the most common pediatric myopathy with an estimated incidence of approximately 3.1 children per one million.¹ Proximal muscle weakness and characteristic cutaneous lesions are essential clinical manifestations along with signs of proximal extensor inflammatory myopathy. Before the glucocorticoid era, JDM led to death in one-third of patients, but with therapy and diagnostics advancing, mortality decreased to a currently reported 2%–3.1%.^{2–4} While many achieve remission, long-term complications and specific damage may still develop such as lipodystrophy, calcinosis, residual weakness, joint contractures, muscle atrophy, hirsutism, growth failure, and dysphagia.^{4,5}

Lipodystrophy is a less frequent but significant complication of JDM. Lipodystrophy can be localized or generalized. Lipodystrophy can be acquired or congenital and may be associated with metabolic abnormalities such as hyperlipidemia, impaired glucose tolerance, insulin-resistant diabetes mellitus, acanthosis nigricans, and hepatomegaly.^{6,7} Acquired Lipodystrophy (ALD) has been associated with autoimmune diseases.⁷ Childhood ALD has been linked to JDM,⁷ Systemic Lupus Erythematosus (SLE),⁸ panniculitis,⁹ Sjögren syndrome and juvenile rheumatoid arthritis.^{10,11} Interestingly, lipodystrophy is associated almost exclusively with JDM although there have been published case reports of lipodystrophy affecting adult-onset dermatomyositis.^{12–16} The prevalence of lipodystrophy in JDM patients varies, ranging from 7.93% to 40%.^{4,5,7,12,17–21} Lipodystrophy in JDM can be categorized as three phenotypes depending on the distribution of subcutaneous fat loss: generalized (loss in the face, trunk, abdomen, and all extremities), partial (upper and/or lower extremities, with relative sparing of abdomen and trunk), or focal (localized areas, resulting in skin surface depression or dimpling).^{6,22,23}

In this report, we present four girls and one boy with JDM who developed different phenotypes of lipodystrophy. Clinical manifestations of JDM and associated lipodystrophy, laboratory analyses, complications, and treatment options during long follow-up were described.

Materials and methods

From the database, we conducted a retrospective review and clinical data analysis of confirmed JDM patients associated with lipodystrophy at the Pediatric Dermatology Department of the University Clinical center of Serbia

between January 1st 1990 and December 31th 2023. A database search of PubMed and Medline was undertaken using the keywords “lipodystrophy” OR “lipoatrophy” AND “juvenile dermatomyositis”. A reverse search of citations and additional cases was identified.

Results

22 patients with JDM (17 girls, 5 boys – 3.4:1 female-to-male ratio) were diagnosed at and/or referred to our department. Cutaneous rash was seen in all the JDM patients (22/22) as the most frequent complaint at initial presentation, followed by arthralgia, myalgia, and weakness alone which were seen in 54.5% of patients (12/22) respectively, while 36.4% had a preceding infection (8/22). During a 34-year time frame, 477 adult DM patients (351 female, 126 male – 2.79:1.0 female-to-male ratio) were diagnosed. JDM represented roughly 4.2% of all DM cases and 26.5 times less frequent in our experience.

Lipodystrophy was found in 22.7% of JDM patients (5/22) (4 girls and one boy, aged 3–14 years). The duration between symptoms and diagnosis of JDM was 8.8-months (range 2–20). Lipodystrophy occurred 34.2-months (mean period) after the initial JDM symptoms. The mean follow-up period was 150.8-months (range 29–291). According to the European League against Rheumatism and the American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups, patients had an idiopathic inflammatory myopathies (IMM) score of 10.4, 12.1, 11.2, 12.1, and 11.3 respectively and were categorized as definite.²⁴ All patients were classified as chronic continuous. Specific internal organ involvement and malignancy were not detected during long follow-up. All five patients had normal triglycerides, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), and fasting glucose levels at the presentation of lipodystrophy. Only 1/5 patients had elevated cholesterol 6.38 (n.v. <5.20 mmol/L). No one patient had acanthosis nigricans at presentation and during follow-up. All children had Antinuclear Antibodies (ANA) (Table 1), but none had Myositis-Specific (MSA) (anti-Jo, anti PL-7, anti PL-12, anti Mi-2 and anti-SRP) and associated (anti-RNP, anti PM-Scl70, anti PM-Scl-100, anti-Ku, anti-SSA/Ro 52) antibodies. No patient had low C3 and/or C4 levels of complement. 4/5 patients developed calcinosis after JDM diagnosis (mean period 46 months, range period 18–72-months). All the patients had low serum levels of vitamin D at the presentation of JDM. At the presentation and during follow-up all patients had normal electrocardiogram, ultrasound of the abdomen and heart, chest X-Ray, and pulmonary function tests.

Table 1 Clinical presentation and long-term follow-up of five patients with JDM and lipodystrophy.

	Patient 1	Patient 2	Patient 3	^a Patient 4	Patient 5
Age at diagnosis years and sex	14, F	8, F	8, F	6, F	3, M
Duration of JDM symptoms at diagnosis (months)	6	2	20	10	6
Follow-up, months (years)	185 (15.4)	179 (14.9)	70 (5.8)	29 (2.4)	291 (24.2)
Associated diseases	Celiac disease	None	Constitutio atopica	None	None
Disease course, last check-up	Only residual lipodystrophy, no therapy	Only residual lipodystrophy, no therapy	Chronic continuous low dose IST	Chronic continuous low dose IST	Chronic continuous. Does not take IST regularly
Lipodystrophy and calcinosis					
Lipodystrophy					
Distribution, last check-up	Generalized	Focal	Generalized	Partial	Partial
Location last check-up	Zygomatic, trunk, gluteus, thighs, upper extremities	Unilateral (left) cheek	Lateral aspects of face, proximal upper extremities, lumbosacral region, gluteus	Bilateral proximal upper extremities	Shoulder girdle/hands
From JDM symptoms months	21	20	21	6	103
From JDM diagnosis months	15	18	1	0	97
Progression	+ (from partial)		+ (from partial)	-	-
Calcinosis cutis					
From JDM diagnosis, months	-	+	+	+	+
	-	37	57	18	72
JDM at diagnosis					
IIM score ^a	10.4	12.1	11.2	12.1	11.3
Muscle/joint contractures	-	-	+	+	+
Facial erythema	+	+	+	+	+
Heliotrope sign and edema	+	+	+	+	+
Gotttron's papules or sign	+	+	+	+	+
V-sign	+	-	-	-	-
Shawl sign	-	-	-	-	-
BMI, hypertrichosis					
BMI, at diagnosis	20.3	15.8	14.3	15.8	20.7
BMI, last check-up	17.0	19	17.9	15.8	27.5
Hypertrichosis, at diagnosis	-	-	-	-	-
Hypertrichosis, last check-up	-	-	-	+	+
Laboratory results and workup at the presentation					
ANA, HEp-2 cells Nucleoplasm, L/titer	Homogenous 160	Homogenous 160	Homogenous 320	Homogenous 640	Course speckled 80
C3 (0.7–1.73 g/L)	0.8	0.9	1.210	1.1	0.81
C4 (0.12–0.36 g/L)	0.18	0.24	0.18	0.2	0.24
CK (0–154 U/L)	↑ 444	↑ 783	90	90	↑ 759
LDH (F < 580, M < 760)	↑ 1691	↑ 859	↑ 1261	↑ 1261	423
Vit D3 (75–210 nmol/L)	↓ 26.4	↓ 25.8	↓ 40.5	↓ 36.3	↓ 11.2
EMNG	Mild myopathy	Mild myopathy	Normal	Normal	Mild myopathy

F, Female; M, Male; ANA, Antinuclear Antibody; JDM, Juvenile Dermatomyositis; CK, Creatine Kinase; LDH, Lactate Dehydrogenase; ECG, Electrocardiogram; EMNG, Electromyoneurography; U/S, Ultrasound. IIM, Idiopathic Inflammatory Myopathies; IST, Immunosuppressive Therapy; BMI, Body Mass Index..

^a EULAR/ACR classification criteria for adults and juvenile IIM (definite >7.5 without muscle biopsy).

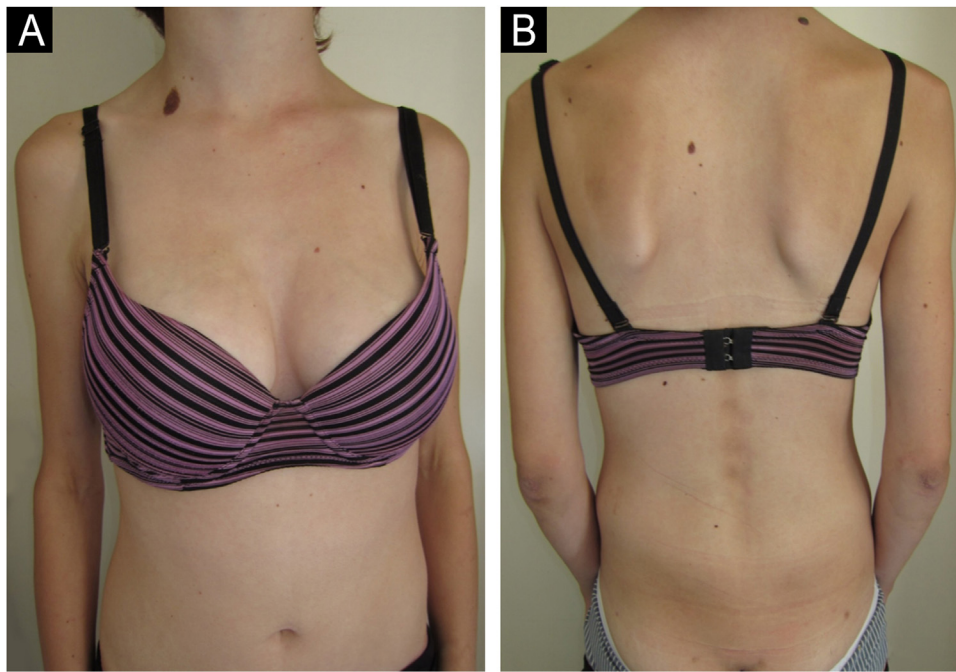


Figure 1 (A–B) Patient n° 1 with progressive generalized lipodystrophy of the gluteal regions, thighs and upper extremities, 69-months after the diagnosis of JDM.

Patient 1

A 14-year-old Caucasian female was admitted with a 6-month history of skin signs and proximal muscle weakness. Clinical features and laboratory tests are listed in [Table 1](#). Combination of prednisone 60 mg (1 mg/kg/day) with subsequent tapering, Chloroquine (CQ) 250 mg QD (later switched to Hydroxychloroquine – HCQ 200 mg BID) along with topical corticosteroids, then Topical Calcineurin Inhibitors (TCI) was initiated. After 6 months, oral Methotrexate (MTX) 15 mg weekly was instituted. Lipodystrophy first appeared in the cheeks and trunk 15 months after JDM diagnosis (21 months from initial JDM symptoms). Despite therapy, after 13 months, partial phenotype progressed to generalized lipodystrophy with the gluteal regions and thighs (28 months after the diagnosis) and upper extremities (69 months after the diagnosis) being affected respectively ([Fig. 1](#)). Five years after the diagnosis, JDM relapse occurred, 6 cycles of 3-day Pulse Intravenous Methylprednisolone (IVMP) 500 mg (≈ 10 mg/kg/day) and oral MTX led to remission without relapse for the next four years, but lipodystrophy persisted.

Patient 2

An 8-year-old Caucasian girl was referred with a 2-month history of facial and extremity erythema along with proximal muscle weakness and pain. Prednisone 30 mg daily (1 mg/kg/day, subsequently tapered), and CQ 125 mg/day, led to remission 29-months after the diagnosis. Mild subcutaneous atrophy of the left cheek occurred 18-months after the diagnosis (20-months after initial symptoms) and progressed ([Fig. 2](#)). Interestingly, 37-months after the diagnosis and 19-months after the beginning of lipodystro-

phy, mild calcinosis was noted in the atrophic region. A maintenance dose of CQ 125 mg QD was administered for 9-months in total, and then discontinued. The patient was lesion and symptom-free during the remaining follow-up period, except for lipodystrophy with calcinosis of the left cheek.

Patient 3

An 8-year-old Caucasian girl was admitted with a 20-month history of facial erythema and symmetric muscle weakness. One month after the diagnosis (21-months after initial symptoms) lipodystrophy appeared first on the proximal upper extremities. Nine cycles of 3-day pulse (IVMP) 700 mg (≈ 30 mg/kg/day), followed by prednisone 50 mg QD (2 mg/kg/day) with subsequent tapering, azathioprine 25 mg TID (3.1 mg/kg/day), and HCQ 100 mg QD (4.1 mg/kg/day) together with TCI were instituted. After 9 months, JDM remission was achieved, but partial lipodystrophy progressed to generalized as the lateral aspects of the face, the gluteal region, the lumbosacral region and the shoulders were also affected ([Figs. 3 and 4](#)). Calcinosis on the left knee was noted 57-months after diagnosis.

Patient 4

A 6-year-old girl was admitted with a 10-month history of facial erythema, arthralgia and generalized muscle weakness. Six months after the first JDM symptoms, bilateral atrophy of the subcutaneous fat tissue on her upper arms appeared and remained stable during follow-up ([Figs. 5 and 6](#)). Twelve cycles of 3-day pulse (IVMP) ranging from 320 mg (≈ 15 mg/kg/day) to 640 mg

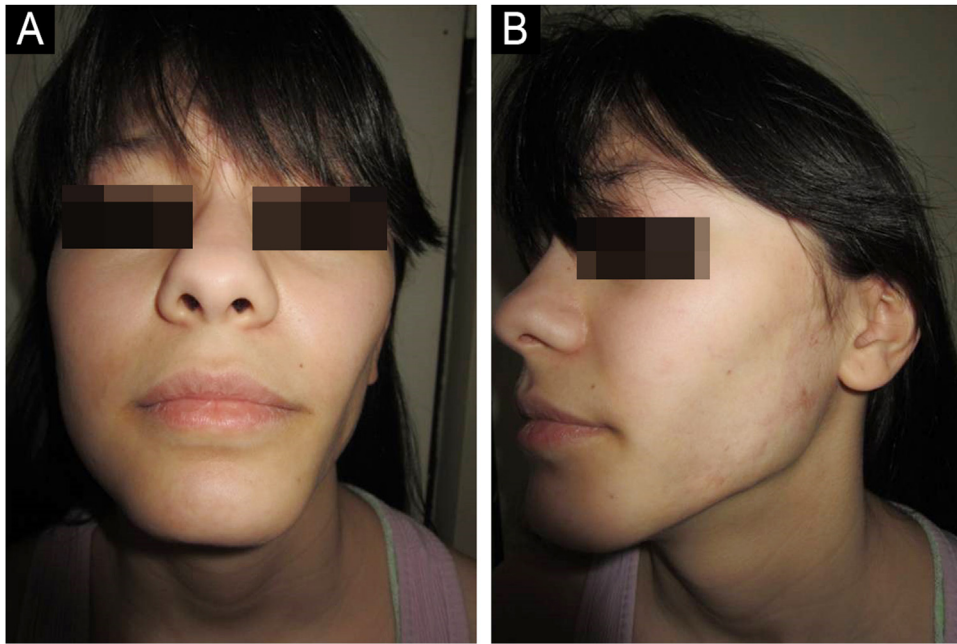


Figure 2 (A–B) Patient n° 2 with lipodystrophy with subcutaneous atrophy of the left cheek, 48-months after the diagnosis of JDM.

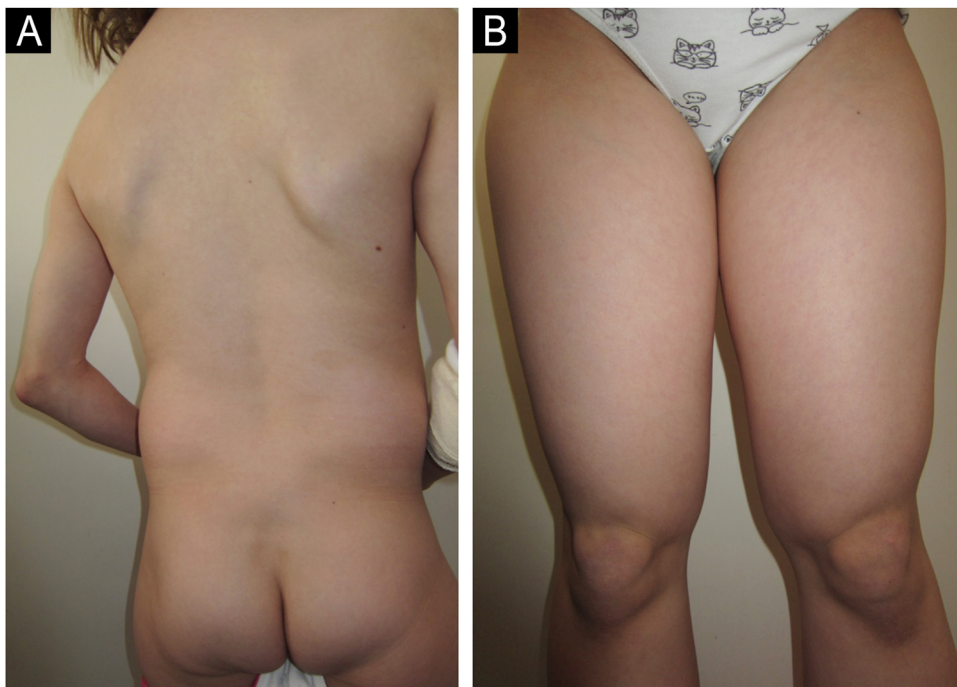


Figure 3 (A–B) Patient n° 3 with progressive generalized lipodystrophy of the proximal upper extremities, shoulders, gluteal and lumbosacral region, 13-months after the diagnosis of JDM.

(≈ 30 mg/kg/day) in the last cycle, followed by prednisone 20 mg QD (0.93 mg/kg/day) but increased to 40 mg QD (1.9 mg/kg/day) within one month due to worsening muscle weakness with subsequent tapering, MTX 15 mg s.c. weekly, and HCQ 100 mg QD (4.8 mg/kg/day) together with TCI were instituted. After 12-months, muscle strength improved but

weakness persisted especially in the lower extremities but laboratory parameters were unremarkable. Calcinosis of the knees and dorsal hands was noted 18 months after the JDM diagnosis. Lipodystrophy of the upper arms persisted during follow-up despite chronic continuous low dose Immunosuppressive Therapy (IST) (Table 1).



Figure 4 Patient n° 3 with lipodystrophy of the lateral aspects of the face and shoulders, 13 months after the diagnosis of JDM.



Figure 6 Patient n° 4 with facial erythema, heliotrope sign, and eyelid edema.

Patient 5

A 3-year-old boy presented with a 6-month history of cutaneous signs, malaise, muscle pain and weakness. A two-year course of IST (oral prednisone 1–1.5 mg/kg, two cycles

of 3-day pulse IVMP 600 mg, two cycles of Intravenous Immunoglobulins (IVIG) and MTX 12.5–20 mg/weekly) lead to improvement. Calcinosis appeared after almost six years on the forearm and progressed to the left elbow, right knee and hand (after eight years) and gluteus (after nine years).

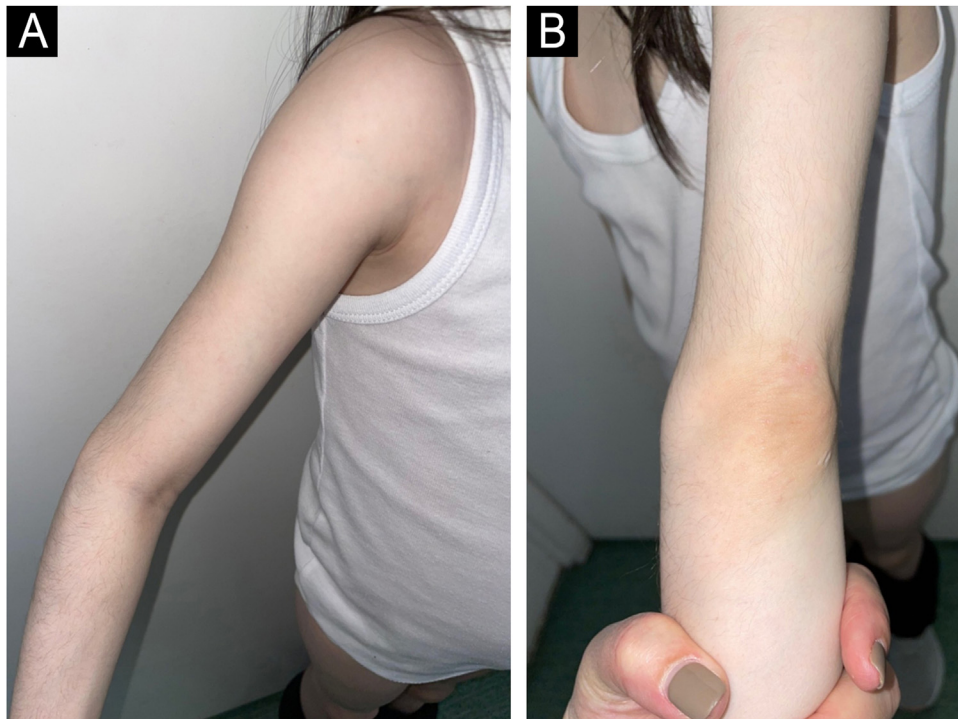


Figure 5 (A–B) Patient n° 4 with stable lipodystrophy with bilateral atrophy on her upper arms, 16-months after the diagnosis of JDM.



Figure 7 (A–B) Patient n° 5 lipodystrophy in the shoulder girdle muscles and hands, as well as calcinosis of the right hand and truncal erythema, 290-months after the diagnosis of JDM.



Figure 8 Patient n° 5 with left elbow calcinosis, 290 months after the diagnosis of JDM.

Atrophy of the subcutaneous fat tissue in the shoulder girdle muscles and hands appeared 97 months after diagnosis with no progression during the follow-up. Over the next twenty years, the patient has had multiple episodes of worsening muscle weakness and cutaneous lesions (Figs. 7 and 8). Maintenance therapy consisted of oral prednisone with varying dosages, systemic antimalarials, and TCI but the patient does not take IST regularly.

Discussion

Lipodystrophy is a rare complication of JDM and is probably under-reported. JDM onset mostly occurs between 4–10-years with a 2.7:1 female-to-male ratio in Caucasians.²⁵ Similar results were seen in the present study with onset ranging from 3–14-years and 3.4:1 female-to-male ratio. Misra et al. described 35 patients with childhood ALD, 7 of which had an associated autoimmune disease, but only one JDM.¹¹ On the other hand, in a study by Pope et al. of 30

children with childhood ALD, the most frequent underlying diagnosis was JDM with 78%, alone or associated with other autoimmune diseases such as juvenile rheumatoid arthritis in 17%.¹⁰ JDM differs from other autoimmune diseases such as SLE, which has been reported to occur 4–37-years after lipodystrophy onset,²⁶ while DM usually precedes lipodystrophy onset.^{11,12} Mean time from initial symptoms of JDM to lipodystrophy onset was 34.2-months (Table 1). Overall the time of onset is quite shorter than 3–4.6-years, as reported in the literature.^{10,12}

A study of subcutaneous fat compared 20 JDM patients (of which 40% had lipodystrophy) with controls showed that JDM patients had lower BMI (the difference between controls and patients was 7.6 ± 4.4 kg).¹⁷ Body Mass Index (BMI) was smaller compared to controls but was not statistically significant.¹⁷ In the studied patients, the BMI ranged from 14.3–20.7.

The most comprehensive review evaluating clinical and metabolic abnormalities in JDM with lipodystrophy (28 patients) and comparing them to JDM without lipodystrophy was done by Bingham et al.¹² The analysis determined muscle atrophy, joint contractures, chronic continuous dermatomyositis course, and calcinosis to be the most significant discriminating features when comparing JDM with and without lipodystrophy. Calcinosis, joint contractures, panniculitis and muscle atrophy were found to be predictors for lipodystrophy development in JDM.¹² In this report, 4/5 (80%) had calcinosis, but in the 3/5 patient's lipodystrophy preceded calcinosis, while in 1/5 patients calcinosis preceded lipodystrophy by 2 years.

The incidence of calcinosis in JDM is 12%–70%.^{4,5,17–19,27,28} In the present study, the onset of calcinosis after JDM diagnosis ranged from 37–72-months (mean 46-months).

Published reports have shown IVMP to be effective in shortening rash duration in JDM, decreasing functional impairment and preventing calcinosis development.^{27,29} It is well known that IVMP is inadequate to prevent lipodystrophy and calcinosis if the diagnosis of JDM is delayed.³⁰ Huber et al. reported 10/31 JDM patients on IVMP with calcinosis versus 12/34 with calcinosis in the non-IVMP treated group.⁵ Despite the limited number, 4/5 patients who received IVMP

had partial or full remission and stabilized muscle enzymes in all patients, but unfortunately, lipodystrophy progressed in two patients despite receiving IVMP and aggressive IST.

In terms of progression, Bingham et al. stated that out of 8 generalized lipodystrophy, only one first presented with partial lipodystrophy, while focal lipodystrophy never progressed to partial or generalized.¹²

Bingham et al. reported¹² that none of the lipodystrophy patients had MSA which is in line with these findings. All the studied patients were negative for MSA. Unfortunately, the authors did not test anti-p155 antibodies which were reported in 23%–29% of JDM patients.³¹ Anti-p155 antibody was found more frequently in JDM patients with lipodystrophy compared to JDM without lipodystrophy (6/7 [83%] vs. 27/76 [36%]; $p=0.014$), while also more frequent in generalized lipodystrophy compared to partial or focal lipodystrophy.¹² Furthermore, anti-p140 has been reported in 23% of patients with an association with calcinosis.³² In a retrospective review of 96 JDM patients, no significant difference in age, disease activity scores, or lipodystrophy was observed between anti-P155/140 positive JDM, other MSA positive JDM, and MSA negative JDM and trunk:leg fat ratios were similar among the three groups.³³ One potential mechanism of lipodystrophy is the dysregulation of the complement alternative pathway. Lipodystrophy has been associated with the presence of IgG antibody C3 nephritic factor which utilizes the capacity of the adipocytes to form C3 convertase in its surroundings and induces complement-mediated lysis of adipocytes.¹¹ Misra et al. showed that 67% of their patients with acquired partial lipodystrophy had low C3 levels and 83% had C3 nephritic factor.¹¹ On the other hand, Bingham et al., reported majority of their patients had normal C3 levels, including all partial lipodystrophy in JDM patients.¹² This is in line with the analysis, as all our patients had normal C3 levels.

Reports demonstrated that acquired generalized lipodystrophy patients have low leptin levels.^{5,34} Meanwhile in a cross-sectional study of 59 JDM patients, the JDM cohort had higher leptin levels compared to age/sex-matched controls.³⁵ Visfatin and apelin-12 were both higher in JDM-active versus JDM-inactive patients and lower adiponectin levels were found in lipodystrophy associated with JDM patients compared to JDM patients without lipodystrophy.³⁵ Metabolic dysfunction including insulin resistance, diabetes, hypertriglyceridemia, and non-alcoholic steatohepatitis can be seen. Hypertriglyceridemia has been found to be the first metabolic abnormality in JDM patients, followed by hirsutism and lipodystrophy.¹⁷ The specificity of hypertriglyceridemia in JDM patients with lipodystrophy is 71%–100% (12/18, 4/4, 17/24)^{7,12,17} while in JDM patients without lipodystrophy, it has ranged from 17% (9/53)¹⁹ – 50% (10/20).¹⁷ Low HDL, high LDL and cholesterol are also associated with JDM and lipodystrophy.^{10–12,17,35} This is a stark contrast, as in this study triglycerides were normal in all studied patients. Cholesterol was evaluated in all five patients and elevated only in patient 3. Secondly, insulin resistance and diabetes have been reported as associated complications in JDM, higher percentages in patients with lipodystrophy, especially in generalized and partial forms.^{5,7,12} Based on 20 JDM patients (8 of which had lipodystrophy) a study showed no patients had abnormal OGTT tests.¹⁷ None of these patients had elevated

fasting glucose levels despite corticosteroid therapy. There has been debate about whether the metabolic abnormalities in lipid status and hyperinsulinemia are caused by corticosteroid treatment or the JDM and/or lipodystrophy.¹¹ Ilowite et al. showed a difference in characteristic patterns of dyslipoproteinemia due to corticosteroids compared to due to disease activity in pediatric patients with lupus. Corticosteroids resulted in elevated HDL, VLDL, and triglycerides, while disease activity caused low HDL, elevated VLDL and triglycerides.³⁶ Therefore, low HDL and elevated triglycerides indicated that dyslipoproteinemia is disease-related.^{7,12}

In terms of validated biomarkers for JDM activity, neopterin, CXCL11, and galectin-9 have been considered in perspective.³⁷ Furthermore, elevated IFN type I was correlated with skin disease activity and interferon-regulated gene score was significantly higher in JDM than in controls, correlating moderately with JDM activity and strongly with skin activity in anti-TIF1 positive patients.³⁸

Metabolic complications in other forms of lipodystrophy have been shown to respond to thiazolidinediones (troglitazone 200–600 mg daily), causing decreased hemoglobin A1c levels, triglyceride levels, free fatty acid levels and a body fat increase by a mean of 2.4 percentage points.³⁹ Lebastchi et al. reported 3 cases of lipodystrophy associated with autoimmune diseases (1 child had JDM), showing 4–6 year treatment with meterleptin (0.02–0.04 mg/kg s.c.) reduced insulin resistance and hypertriglyceridemia without altering or worsening the autoimmune disease.³⁴

All the studied patients had low serum levels of vitamin D at the presentation of JDM (Table 1). The essential role of vitamin D in bone homeostasis is well known, but vitamin D has multiple immunomodulatory effects, including regulation of immune response. Previously it was shown that vitamin D deficiency is associated with disease activity in patients with JDM.⁴⁰ It is important that children and adolescents supplement vitamin D according to current recommendations. More well-designed studies are needed to determine the potential significance of low serum vitamin D levels that the authors found in all patients with lipodystrophy associated with JDM.

Conclusion

In conclusion, lipodystrophy is a rare, significant, probably under-reported complication of JDM. During the 34-year period, 5/22 (23%) JDM patients developed lipodystrophy. Metabolic complications were not found. All 5 patients had a significant delay in JDM diagnosis. Despite subsequent standard IST, 2/5 patients progressed to generalized lipodystrophy and 4/5 patients developed calcinosis. Early institution of intensive IST is necessary to reduce the risk of lipodystrophy, as a chronic complication of JDM. Further prospective studies using validated measures of outcome are needed for more accurate therapy and long-term outcomes of lipodystrophy associated with JDM.

Financial support

None declared.

Authors' contributions

Igor Kapetanović: Approval of final version; critical literature review; data collection, analysis and interpretation; participation in research orientation; preparation and writing of manuscript; statistical analysis; study conception and planning; manuscript critical review.

Mirjana Gajić-Veljić: Approval of final version; effective participation in research orientation; intellectual participation in therapeutic management; manuscript critical review; conception and planning.

Branka Bonačić-Nikolić: Approval of final version; effective participation in research orientation; intellectual participation in therapeutic management; manuscript critical review; study conception and planning; preparation and writing of manuscript.

Miloš Nikolić: Approval of final version; effective participation in research orientation; intellectual participation in therapeutic management; manuscript critical review; study conception and planning.

Conflicts of interest

None declared.

Acknowledgments

MN, BBN and MGV were supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Grant n° 100200.

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ORIGINAL ARTICLE

Predictors of PASI90 response in patients with psoriasis treated with interleukin inhibitors: observational cohort study[☆]



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Received 27 July 2024; accepted 11 September 2024

Available online 18 June 2025

KEYWORDS

Biological therapies;
Psoriasis;
Proportional hazards models;
Treatment outcome

Abstract

Background: Psoriasis is a chronic multisystem disorder, and the inhibition of different cytokine pathways has been associated with different treatment responses.

Objective: To demonstrate independent predictors of PASI90 response in patients with psoriasis under biologic therapy and compare the effectiveness of different biologic classes

Methods: This cross-sectional study was conducted in a single tertiary center between January 2023 and May 2024 and included 623 patients (M/F: 320/303). PASI90 response was the primary end-point of the study, and PASI100 was the secondary end-point. Univariate and multivariate cox-regression analyses were used to identify predictors of PASI90. The efficacy of different biologic classes for achieving PASI90 and PASI100 responses was assessed using the Kaplan–Meier method.

Results: The age of disease onset (HR=1.037, 95% CI [1.029–1.044], $p<0.001$) and being biologic-naïve (HR=1.261, 95% CI [1.046–1.521], $p=0.015$) were identified as significant predictors of PASI90 response. IL23 inhibitors showed considerably superior efficacy in achieving PASI90 response than both TNF inhibitors ($p=0.042$) and ustekinumab ($p=0.027$). Also, IL17 inhibitors exhibited near-significantly higher effectiveness than TNF inhibitors ($p=0.090$) and ustekinumab ($p=0.050$). The performance of biologic classes was not substantially different in reaching PASI100 overall.

Study limitations: The most important limitation of this study is the retrospective data collection.

[☆] Study conducted at the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Department of Dermatology, Istanbul, Turkey.

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<https://doi.org/10.1016/j.abd.2025.501132>

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Conclusion: Age of disease onset and being biologically naïve were positively associated with achieving PASI90 response, whereas ustekinumab use was negatively associated. Age of disease onset was the strongest predictor of PASI90. Also, IL23 and IL17 inhibition, especially IL23, appeared to provide a better therapeutic response.

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Introduction

Psoriasis is a chronic inflammatory disease that may affect the skin and musculoskeletal system. Skin psoriasis is characterized by the presence of erythematous plaque lesions, which tend to affect the extensor surfaces of the extremities. In addition, pustular and erythrodermic morphologies represent rarer involvement types.¹ Special areas of involvement include the face, scalp, genitalia, palms, soles, and nails, which might be challenging to treat and substantially lower health-related quality of life.² The complex interplay of cytokines resulting in rapid turnover of keratinocytes has been implicated in the pathogenesis of skin psoriasis.³ On the other hand, this inflammatory cascade can lead to systemic inflammatory signs and arthritis as well. Tumor Necrosis Factor (TNF), Interleukin (IL)17, and IL23 are major inflammatory cytokines acting as therapeutic targets for biological agents, and their inhibition provides favorable treatment responses.⁴

The PASI (Psoriasis Area and Severity Index) is a physician-assessed tool to measure the extent and severity of skin involvement in psoriasis.⁵ It is also a widely used scale to evaluate treatment response. The PASI score ranges from 0 to 72, with higher scores indicating more severe disease.⁵ In clinical practice, achieving PASI75 is often considered a meaningful treatment response.⁶ With the introduction of biologic agents in the treatment of psoriasis, the so-called biologic era, treatment expectations of physicians and patients increased, and achieving PASI90 response has become the new treatment target.⁷ PASI90 represents a 90% reduction in the PASI score from baseline and confers near-total clearance of psoriatic lesions. Furthermore, Randomized Controlled Trials (RCTs) evaluating the efficacy of biological treatments have increasingly started to assess effectiveness based on achieving a minimum PASI90 response.^{8,9}

TNF inhibitors have long been used to treat psoriasis with satisfactory PASI75 responses.¹⁰ Subsequent biologic agents targeting the different cytokine pathways expanded the therapeutic armamentarium of psoriasis, as different biologics provided better healing of distinct aspects of the disease. However, knowledge of whether there are differences in the efficacies of these agents and how the authors can predict PASI90 response is currently limited. In this study, the objective was to investigate predictive factors influencing the achievement of PASI90 response with biological treatments in psoriasis. Also, the authors compared the efficacy of different classes of biologics to reach PASI90 and PASI100 responses, so the authors aimed to see whether there are any differences regarding treatment effectiveness between pathogenesis-directed therapies.

Materials and methods

This cross-sectional study was conducted between January 2023 and June 2024 in a tertiary center in Turkey (Cerrahpasa Medical Faculty Psoriasis Diagnosis and Treatment Unit). Psoriasis patients using a biologic agent who were more than 18 years of age and consecutively seen in the psoriasis outpatient clinic were included in the study. Patients were diagnosed with psoriasis according to their clinical manifestations by an experienced dermatologist BE; then, a histopathological confirmation was made. Biologic-naïve or biologic-experienced patients were included in the study. Biologic-experienced patients consisted of patients who used at least one biologic agent prior to the latest biologic treatment and switched to another biologic agent due to insufficient response or adverse effects. Biologic agents were administered per the standard dosing scheme in Table 1.

Treatment responses with the actively used biologic agent (the last biologic therapy) were evaluated by BE, YD, and SNY, and time to reach PASI90 and PASI100 were recorded. Achieving the PASI90 response was the primary end-point of this study, and PASI100 was the secondary end-point. Clinical characteristics of patients were retrospectively collected from patients' charts. Patients administering concomitant oral immunomodulatory drugs such as methotrexate or leflunomide, having PASI scores less than five at the beginning of the last biologic agent, and receiving the latest biologic treatment for less than one month were excluded from the study. This study was approved by the Ethics Committee of Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, and was conducted following the ethical principles of the Declaration of Helsinki (ethics approval n° 840876).

Statistical analysis

All analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Normality analyses of the data were performed using the Kolmogorov-Smirnov test, Shapiro-Wilks test, and visual histograms. Categorical variables were shown as numbers and percentages. While normally distributed continuous variables were shown as mean $\pm$ Standard Deviation (SD), non-normal distributed continuous variables were given as median (min–max). The performance of different biologic classes to achieve PASI90 and PASI100 was evaluated using Kaplan-Meier analysis with Log-rank test. Cox regression analysis was used to detect independent predictors of PASI90 response. A required sample size of the total number of events for the proportional hazards regression model was calculated as 429 at 0.05 alpha and 0.05 beta error rate.¹¹

Table 1 Administration of biologic agents.

Medication	Dosing schedule
TNF inhibitors	
Adalimumab	80 mg SC at week-0, 40 mg at week-1, then 40 mg SC q2w
Infliximab	5 mg/kg IV at weeks 0, 2 and 6 and thereafter every 8-weeks
Certolizumab Pegol	Patient weight >90 kg: 400 mg SC q2w
Etanercept	50 mg SC twice weekly for first 12-weeks, then 50 mg SC weekly
IL-17 inhibitors	
Secukinumab	300 mg SC at weeks 0, 1, 2, 3, 4, then 300 mg SC q4w
Ixekizumab	160 mg SC at week-0, 80 mg at week 2, 4, 6, 8, 10, 12, then 80 mg SC q4w
IL-23 inhibitors	
Guselkumab	100 mg SC at week 0 and 4, then 100 mg q8w
Risankizumab	150 mg SC at week 0 and 4, then 150 mg q12w
IL-12/23 inhibitor	
Ustekinumab	Patient weight <100 kg: 45 mg SC at week 0 and 4, then 45 mg SC q12w Patient weight >100 kg: 90 mg SC at week 0 and 4, then 90 mg SC q12w

TNF, Tumor Necrosis Factor; IL, Interleukin; SC, Subcutaneous; IV, Intravenous.

Since anti-TNFs are the first class approved to be used in psoriasis,¹² this biologic class was accepted as a reference category for the regression model. Biologic classes and other covariates were initially evaluated with univariate analysis using the enter method. Then, covariates meeting the significance level of $p < 0.25$ were further analyzed with multivariate analysis using the forward stepwise method to constitute different prediction models; $p < 0.05$ was regarded as statistically significant.

Results

Patient characteristics are summarized in Table 2. This study included 623 patients (M/F: 320/303), and their median age was 40 (min–max: 18–72). The median age of disease onset was 23 (min–max: 8–58), and the disease duration was 15 (min–max: 0.1–68) years. Plaque psoriasis was the most common psoriasis morphology (97%). Extremities (85%) were the most commonly involved area, followed by the trunk (73%) and scalp (55%), and 30% of patients had psoriatic arthritis. Half of the patients were biologic-naïve, and there were significant difference regarding the number of biologic-naïve patients across the biologic classes (anti-TNFs [n = 55, 82%], anti-IL17 [n = 105, 62%], anti-IL23 [n = 129, 39%], and anti-IL12/23 [n = 29, 53%], $p < 0.001$). Anti-IL23 agents (53%) were most frequently used, followed by anti-IL17 class (26%). Within the anti-IL23 class, rates of risankizumab (27%) and guselkumab (26%) were almost the same. Also, anti-IL17 agents, secukinumab (13%) and ixekizumab (13%), were used at the same rates. While anti-TNFs were used in 10% of patients, anti-IL12/23 in 9%. Adalimumab (7%) was the most commonly used agent in the anti-TNF class. The median duration of using the last biologic agent was 16 (min–max: 1–72) months. The most frequent comorbidity was obesity (18%), and this was followed by hypertension (12%) and diabetes mellitus (10%). PASI90 was achieved in 519 (83%) patients and PASI100 in 278 (45%).

PASI90 responses were compared across the different biologic classes in Fig. 1 and showed significant differences ($p = 0.041$). The efficacy of anti-TNFs was sig-

nificantly inferior to anti-IL23 agents ($p = 0.042$) but similar to anti-IL12/23 agents ($p = 0.656$). Also, anti-IL23 agents showed considerably superior efficacy than ustekinumab ($p = 0.027$). The effectiveness of anti-IL17 agents was almost significantly better than anti-TNFs ($p = 0.090$). Additionally, the difference between anti-IL17 and anti-IL12/23 agents was near-significant ($p = 0.050$), with anti-IL17 agents being superior. Anti-IL17 and anti-IL23 agents had similar effectiveness overall ($p = 0.776$). There was no significant difference regarding the PASI100 response between different biologic classes ($p = 0.305$), as demonstrated in Fig. 2.

In univariate analysis, age of disease onset (HR = 1.034, 95% CI [1.027–1.041], $p < 0.001$), and palmoplantar involvement (HR = 1.034, 95% CI 1.027–1.041), $p = 0.042$) were found to be substantially associated with a higher probability of achieving PASI90. On the other hand, extremity involvement (HR = 0.765, 95% CI [0.596–0.980], $p = 0.034$) and ustekinumab use (HR = 0.611, 95% CI [0.394–0.946], $p = 0.027$) were significantly related to a lower probability of achieving PASI90 response. Multivariate analysis yielded three different models for predicting PASI90 (Table 3). Model 3 identified three independent predictors for predicting PASI90 response in patients treated with biologic agents. While the age of disease onset (HR = 1.037, 95% CI [1.029–1.044], $p < 0.001$) and being biologic-naïve (HR = 1.261, 95% CI [1.046–1.521], $p = 0.015$) were positively associated with PASI90, using ustekinumab (HR = 0.560, 95% CI [0.358–0.876], $p = 0.011$) was negatively associated. However, treatment with anti-IL17 (HR = 0.995, 95% CI [0.702–1.410], $p = 0.977$) or anti-IL23 (HR = 1.238, 95% CI [0.895–1.712], $p = 0.197$) agents did not significantly differ in terms of PASI90 response relative to anti-TNFs.

Discussion

This research revealed that older age of disease onset and being biologic-naïve were associated with the increased probability of achieving PASI90 response. In contrast, anti-IL12/23 agent use negatively affected PASI90 relative to the anti-TNFs. The age of disease onset was found to be

Table 2 Patient characteristics.

Features		Total (n = 623)
Sex (M/F)		320/303
Age, median (min–max)		40 (18–72)
BMI (kg/m ²), median (min–max)		25.5 (14.2–49.2)
Smoking, n (%)		295 (47)
Age of disease onset, median (min–max)		23 (8–58)
Disease duration, years, median (min–max)		15 (0.1–68)
Family history of psoriasis: n(%)		264 (42)
Psoriasis morphology	Plaque, n (%)	608 (97)
	Pustular, n (%)	11 (2)
	Erythrodermic, n (%)	4 (0.6)
	Genital, n (%)	151 (24)
	Scalp, n (%)	344 (55)
	Nail, n (%)	231 (37)
	Face, n (%)	232 (37)
Special areas of involvement	Palmoplantar, n (%)	91 (15)
	Trunk involvement, n (%)	456 (73)
	Extremity involvement, n (%)	530 (85)
	Psoriatic arthritis, n (%)	190 (30)
	Biologic-naïve, n (%)	318 (51)
	PASI score just before the last biologic therapy, median (min–max)	24 (5–70)
	Last biological treatments of patients	
Anti-TNFs	Adalimumab, n (%)	46 (7)
	Etanercept, n (%)	6 (1)
	Certolizumab pegol, n (%)	8 (1)
	Infliximab, n (%)	7 (1)
Anti-IL17	Secukinumab, n (%)	86 (13)
	Ixekizumab, n (%)	84 (13)
Anti-IL23	Risankizumab, n (%)	169 (27)
	Guselkumab, n (%)	163(26)
Anti-IL12/23	Ustekinumab, n (%)	54 (9)
Duration of treatment with the last biologic agent, months, median (min–max)		16 (1–72)
PASI 90 response, n (%)		519 (83)
PASI 100 response, n (%)		278 (45)
Comorbidities	Diabetes mellitus, n (%)	63 (10)
	Hypertension, n (%)	75 (12)
	Dyslipidemia, n (%)	41 (7)
	Obesity, n (%)	112 (18)
	Ischemic heart disease, n (%)	27 (4)
	Asthma/COPD, n (%)	26 (4)
	Thyroid dysfunction, n (%)	46 (7)

M, Male; F, Female; BMI, Body Mass Index; PASI, Psoriasis Area Severity Index; TNF, Tumor Necrosis Factor; IL, Interleukin; COPD, Chronic Obstructive Pulmonary Disease.

the strongest predictor of PASI90 response. Also, anti-IL23 and anti-IL17 classes, particularly anti-IL23 agents, seemed related to higher treatment efficacy.

In previous studies, the PASI score of psoriasis patients was found to be higher in early-onset psoriasis cases compared to late-onset psoriasis cases,^{13–15} and there are few studies with conflicting results evaluating the relationship between the age of disease onset and biological treatment response in psoriasis patients. In the study by Singh et al., treatment responses of early-onset psoriasis patients receiving etanercept and infliximab treatment were significantly higher than those of late-onset psoriasis patients. In contrast, no relationship was found between the age of disease onset and treatment responses in patients receiving

ustekinumab and adalimumab treatment.¹⁶ On the contrary, Griffiths et al. proposed that the PASI75 at week 12 of etanercept treatment was found to be higher in early-onset psoriasis patients than in late-onset psoriasis patients.¹⁷ The authors consider that the finding that older age is associated with a more favorable treatment response in this study may be related to cases beginning at an early age being more commonly HLA-Cw6-positive and thus showing lower treatment responses.^{18–20}

Most studies in the literature and the work suggested that the efficacy of biologic therapy is higher in biologic-naïve patients than in biologic-experienced patients.^{21–24} This might be related to cross-resistance between biologic classes, probably due to common pathways being operative

Table 3 Predictors for PASI90 response.

Covariates	Univariate analysis, HR (95% CI)	P	Multivariate analysis					
			Model 1, HR (95% CI)	p	Model 2, HR (95% CI)	p	Model 3, HR (95% CI)	p
Female gender	1.021 (0.859–1.214)	0.814	–	–	–	–	–	–
Age of disease onset	1.034 (1.027–1.041)	<0.001^c	1.035 (1.028–1.043)	<0.001^c	1.036 (1.029–1.044)	<0.001^c	1.037 (1.029–1.044)	<0.001^c
Smoking	1.032 (0.868–1.227)	0.719	–	–	–	–	–	–
BMI (kg/m ²)	0.998 (0.979–1.018)	0.869	–	–	–	–	–	–
Pustular/erythrodermic morphology	0.965 (0.603–1.545)	0.884	–	–	–	–	–	–
Family history of psoriasis	0.971 (0.819–1.151)	0.733	–	–	–	–	–	–
PASI score just before the last biologic therapy	0.999 (0.992–1.006)	0.777	–	–	–	–	–	–
Special areas of involvement								
Genital	0.842 (0.689–1.029)	0.092	–	–	–	–	–	–
Scalp	0.996 (0.837–1.185)	0.964	–	–	–	–	–	–
Nail	0.860 (0.719–1.029)	0.100	–	–	–	–	–	–
Face	0.834 (0.695–1.001)	0.051	–	–	–	–	–	–
Palmoplantar	1.293 (1.010–1.657)	0.042^a	–	–	–	–	–	–
Trunk involvement	0.970 (0.797–1.181)	0.761	–	–	–	–	–	–
Extremity involvement	0.765 (0.596–0.980)	0.034^a	–	–	–	–	–	–
Psoriatic arthritis	0.892 (0.740–1.076)	0.232	–	–	–	–	–	–
Biologic-naïve	1.118 (0.941–1.329)	0.205	–	–	–	–	1.261 (1.046–1.521)	0.015^a
Class of biologic treatment								
Anti-TNF	Reference category							
Anti-IL17	0.996 (0.721–1.376)	0.983	–	–	0.935 (0.662–1.320)	0.703	0.995 (0.702–1.410)	0.977
Anti-IL23	1.173 (0.867–1.586)	0.300	–	–	1.112 (0.813–1.521)	0.505	1.238 (0.895–1.712)	0.197
Anti-IL12/23	0.611 (0.394–0.946)	0.027^a	–	–	0.534 (0.342–0.834)	0.006^b	0.560 (0.358–0.876)	0.011^a
Comorbidities								
Diabetes mellitus	0.777 (0.578–1.044)	0.095	–	–	–	–	–	–
Hypertension	0.773 (0.584–1.022)	0.071	–	–	–	–	–	–
Dyslipidemia	0.901 (0.636–1.276)	0.556	–	–	–	–	–	–
Obesity	0.895 (0.716–1.118)	0.329	–	–	–	–	–	–
Coronary artery disease	0.803 (0.524–1.232)	0.315	–	–	–	–	–	–
Asthma/COPD	0.850 (0.554–1.303)	0.455	–	–	–	–	–	–
Thyroid dysfunction	0.798 (0.571–1.116)	0.188	–	–	–	–	–	–

PASI, Psoriasis Area Severity Index; HR, Hazard Ratio; CI, Confidence Interval; BMI, Body Mass Index; TNF, Tumor Necrosis Factor; IL, Interleukin; COPD, Chronic Obstructive Pulmonary Disease. Model 1: –2 Log likelihood=5137.3, Chi-Square=88.6, $p<0.001$. Model 2: –2 Log likelihood=5117.8, Chi-Square=106.4, $p<0.001$. Model 3: –2 Log likelihood=5111.9, Chi-Square=112.9, $p<0.001$.

^a $p<0.05$, ^b $p<0.01$, ^c $p<0.001$. Note: Univariate analysis was performed using the enter method, and multivariate analysis was performed using the forward stepwise method.

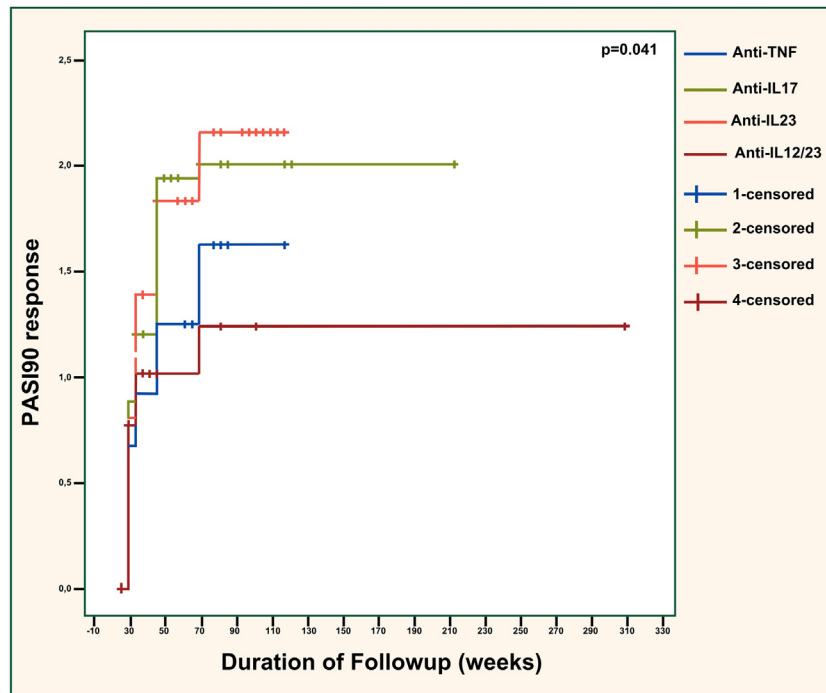


Fig. 1 PASI90 response across different biologic classes. PASI, Psoriasis Area severity Index; TNF, Tumor Necrosis Factor; IL, Interleukin. Anti-TNF vs. anti-IL17; $p=0.090$. Anti-TNF vs. anti-IL23; $p=0.042$. Anti-TNF vs. anti-IL12/23; $p=0.656$. Anti-IL17 vs. anti-IL23; $p=0.776$. Anti-IL17 vs. anti-IL12/23; $p=0.050$. Anti-IL23 vs. anti-IL12/23; $p=0.027$.

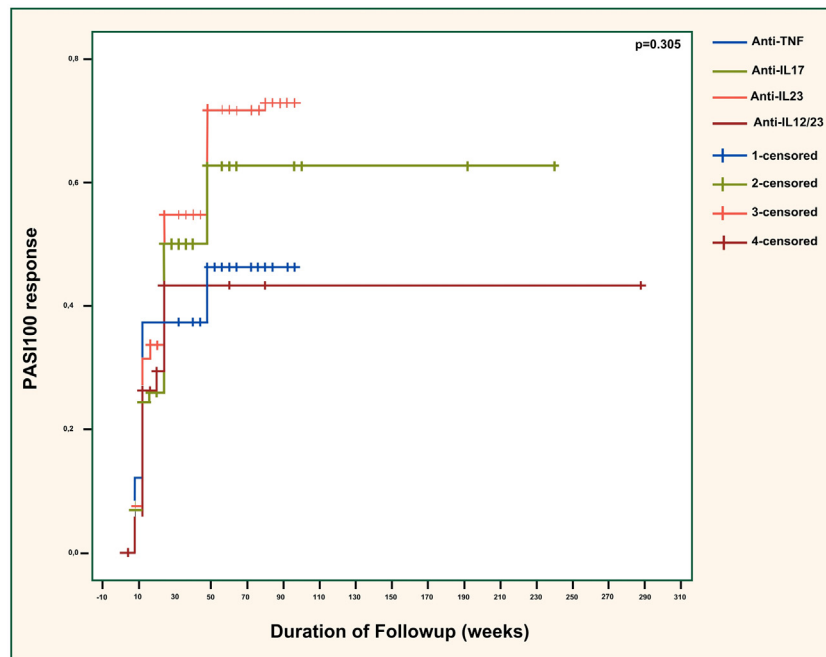


Fig. 2 PASI100 response across different biologic classes. PASI, Psoriasis Area Severity Index; TNF, Tumor Necrosis Factor; IL, Interleukin. Anti-TNF vs. anti-IL17; $p=0.416$. Anti-TNF vs. anti-IL23; $p=0.120$. Anti-TNF vs. anti-IL12/23; $p=0.832$. Anti-IL17 vs. anti-IL23; $p=0.320$. Anti-IL17 vs. anti-IL12/23; $p=0.668$. Anti-IL23 vs. anti-IL12/23; $p=0.294$.

downstream of cytokine signaling. A recent meta-analysis of 40 studies examining the clinical characteristics associated with treatment response to biologics identified that older age, higher Body Mass Index (BMI), previous or cur-

rent smoking, and prior exposure to biologic treatments negatively influenced the probability of achieving PASI90 response. Also, the authors emphasized the unclearness of how these characteristics affect treatment responses dif-

ferently for different biological therapies. In the present study, smoking status and BMI were not found to be significantly associated with PASI90 response. On the other hand, diabetes mellitus and hypertension, though statistically near-significant, were negatively related to the PASI90 response in the univariate analysis. Therefore, it can be proposed that components of metabolic syndrome impact treatment response, and distinct results of the studies are attributable to environmental factors (e.g., dietary habits) and racial genetic variances.

In the present study, the likelihood of achieving a PASI90 response was found to be significantly higher in patients with palmoplantar involvement. Yet, the authors consider this result misleading because the palmoplantar area is relatively small to evaluate the PASI response correctly. Instead, the Palmoplantar Pustulosis Severity Index (PPSI) is used to assess the severity of palmoplantar involvement and treatment response,²⁵ but the authors did not implement this scale in this study. On the other hand, extremity involvement was significantly associated with worse treatment response in univariate analysis, albeit not significant in multivariable analysis. Hence, this indicates the involvement area may have affected the assessment of treatment response.

Inhibition of cytokine pathways has been related to various adverse events, and tuberculosis merits particular attention. Tuberculosis is still an essential concern in underdeveloped or developing countries worldwide when treating psoriasis patients with biologics, and the risk is even higher with TNF inhibitors than with any other biologic class.^{26,27} Therefore, anti-TNFs opted for specific groups of psoriasis patients, such as those having concomitant inflammatory bowel disease.²⁷ Ustekinumab, an anti-IL12/23 agent, is one of the earliest biologics approved for treating psoriasis. It is mainly preferred due to its lower risk of tuberculosis reactivation compared to anti-TNF agents. However, studies demonstrated that IL12 inhibition is unnecessary for psoriasis treatment,²⁸ and IL12 inhibition may be associated with major cardiovascular events.²⁹ On the other hand, the authors and others found that ustekinumab was associated with lower rates of PASI90 response.³⁰

In the present study, the proportion of patients achieving PASI90 and PASI100 with biologic therapy was consistent with that reported in the literature.^{21-23,30} The authors also observed the maximum treatment response after the 48th week of biologic therapy. Other studies were in line with the research and they reported that the maximum therapeutic efficacy of IL23 inhibitors, as well as anti-IL17 and anti-IL12/23 agents, was reached after the 48th week of treatment.³¹⁻³⁶ Notably, the distribution of anti-IL23 (guselkumab and risankizumab) and anti-IL17 agents (secukinumab and ixekizumab) was balanced in the present study, eliminating the bias risk within these classes. However, the frequencies of anti-TNF agents were fairly distinct, potentially leading to heterogeneity in the evaluation of treatment responses to this group.

The efficacy of anti-IL23 agents was significantly higher compared to the anti-TNFs and ustekinumab in the present work. Likewise, randomized controlled trials and real-world studies showed that the PASI90 response of anti-IL23 agents was higher than that of both anti-TNF and anti-IL12/23 classes.³⁷⁻⁴² The overall efficacy of anti-IL23 and anti-IL17 agents in patients with psoriasis in this study was found to be

similar, and the literature presents varying results regarding the comparison of the efficacy and safety of these agents. In a meta-analysis, while IL17 inhibitors were found to have higher efficacy than IL23 inhibitors, IL23 inhibitors were considered safer regarding their side effect profiles.⁴³ Although some studies have found the 12–16th week PASI responses of IL23 inhibitors to be similar to those of IL17 inhibitors, the long-term efficacy of IL23 inhibitors has been reported to be higher.⁴⁴⁻⁴⁶ In a randomized, double-blind study, though the overall efficacy of IL17 inhibitors and IL23 inhibitors was found to be similar, IL17 inhibitors achieved much faster clearance of skin lesions.⁴⁷ Also, a meta-analysis showed that risankizumab, followed by ixekizumab, provides the highest rates of PASI90 and PASI100 responses compared to other biologics.³⁰ The present work was consistent with these findings, and IL17 inhibitors demonstrated a quicker PASI90 response than other classes. Furthermore, anti-IL23 agents had the highest treatment effectiveness, but no significant difference was observed in the overall efficacy of IL23 and IL17 inhibitors. However, the proportion of biologic-naïve patients was lowest in the anti-IL23 group in this study. Considering that biologic-naïveness significantly and positively affects the PASI90 response, the efficacy of the anti-IL23 agents can be expected to be higher if the number of biologic-naïve patients is evenly distributed across the biologic classes.

Several studies found that the IL-17 inhibitors provide higher rates of PASI90 compared to anti-TNF agents.⁴⁸⁻⁵⁰ Likewise, IL17 inhibitors exhibited higher performance for reaching PASI90 response than anti-TNFs in this study, but the result remained statistically near-significant. The lower proportion of biologic-naïve patients in the IL17 inhibitor group compared to the anti-TNF group might explain why statistical significance could not be achieved in the present study. Also, studies showed that the rates of PASI90 responses with IL17 inhibitors were higher than those of ustekinumab, which is compatible with this research.⁵¹⁻⁵⁵

The most important limitation of this study is the retrospective data collection. The age groups of the study participants are heterogeneous. Also, the distribution of different anti-TNF agents and biologic-naïve patients is unbalanced, which might have confounded the results. On the other hand, the inclusion of a large number of patients from a single center and the evaluation of treatment responses by a few researchers are strengths of this study.

Conclusion

In conclusion, older age of disease onset, biologic-naïve, and ustekinumab use were identified as the independent predictors of PASI90 response, and age of disease onset was the most important. Anti-IL23 and anti-IL17 agents, especially IL23 inhibitors, exhibited superior therapeutic efficacy compared to other classes. This study underlines the necessity of head-to-head comparing the effectiveness of different biological agents with well-designed prospective trials.

Financial support

None declared.

Author's contribution

Burhan Engin: Wrote the manuscript, treated and followed the patients, interpreted the results, conceived the study, and approved the final version of the manuscript.

Yusuf Demir: Performed data collection, and approved the final version of the manuscript.

Sera Nur Yucesoy: Wrote the manuscript, and approved the final version of the manuscript.

Tumay Ak: Performed the statistical analysis, interpreted the results, conceived the study, edited the manuscript, and approved the final version of the manuscript.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Prevalence of reactive allergens in contact patch testing studies using the Brazilian standard battery: a systematic review[☆]

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Received 5 June 2024; accepted 28 August 2024

Available online 23 June 2025

KEYWORDS

Brazil;
Dermatitis, contact;
Patch test

Abstract

Background: Contact dermatitis is a common dermatosis in dermatology. The patch test is the gold standard for diagnosis, using a panel of common allergens and irritants. In Brazil, a standardized battery of 30 substances is used. However, comprehensive epidemiological data on contact dermatitis are limited, and no studies have compiled and compared nationwide results. **Objectives:** This study aimed to assess the positivity rate of patch tests using the Brazilian Standard Battery in suspected contact dermatitis cases from 2000 to 2022. We also evaluated associations between reactive substances and clinical and demographic variables and examined the variation in reactivity frequency to allergenic substances over the study period.

Methods: A systematic literature review was conducted using PubMed, Scielo, and LILACS. We evaluated the prevalence of positive tests for each substance, examined associations between variables such as gender, region, and age, and assessed variations in patch test positivity over time.

Results: Initially, 55 articles were identified, and 10 were included in the review. Nickel sulfate was the most frequently positive allergen, while triclosan, P-tertiary butylphenol, and anthraquinone were the least prevalent. Test positivity increased every 5-years for kathon CG, neomycin, and nickel sulfate, while it decreased for quaternion 15 and thimerosal.

Study limitations: The results were limited by the small number of articles included in the review.

Conclusions: This pioneering study in Brazil provides valuable insights for dermatological allergy practitioners into the prevalence of patch test positivity for each substance in the Brazilian Standard Battery, aiding in informed decision-making and patient management.

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Introduction

Contact dermatitis (CD) is a prevalent inflammatory skin condition frequently encountered in dermatological practice. Its clinical presentation is characterized by erythematous, desquamative, and pruritic vesicles, papules, or plaques, often accompanied by lichenification, leading to a significant impact on patients' quality of life.¹ The CD comprises a significant proportion of occupational dermatoses and carries substantial socioeconomic implications, particularly in industrialized nations.²

CD can be classified into two main types: Irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD arises from the direct toxic and pro-inflammatory effects of certain substances, while ACD is a delayed-type hypersensitivity reaction mediated by hapten-specific T-cells.¹

While the diagnosis of CD primarily relies on clinical evaluation, patch testing (PT) serves as the gold standard complementary diagnostic tool for confirming this condition. PT aims to reproduce the elicitation phase of ACD by controlled exposure to suspected agents, thereby confirming the diagnosis and determining the etiology of ACD. The PT series typically consists of a standard battery of common allergens and irritants, including fragrances, preservatives, metals, rubber, and other chemicals to which patients are commonly exposed and may be associated with their clinical presentation.^{2,3}

In Brazil, the Brazilian Group for the Study of Contact Dermatitis (GBEDC) developed a standardized battery in 2000, approved by the Brazilian Society of Dermatology (SBD), comprising 30 substances. However, there is a scarcity of Brazilian etiological and epidemiological data on ACD across different regions that could provide population representativeness. While several studies have been published by prominent Brazilian dermatological centers, they have been conducted in isolation, and no comprehensive analyses or comparisons of results have been published at the national level.^{2,3}

It is well-established that the population profile and exposure to various substances can influence PT results, which are also known to evolve over time. Therefore, to address these gaps in knowledge, a systematic review was undertaken with the objective of collating and synthesizing information regarding PT results obtained using the Brazilian standard battery over the past 22-years.

Methods

Study design

This study presents a systematic review (SR) conducted between 2000 and 2022, with the aim of identifying relevant articles published in English, Portuguese, or Spanish. It was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).⁴

A comprehensive search was performed by two screeners who independently searched scientific databases known for housing Brazilian studies, namely PubMed, LiLACS, and SciELO. The primary objective was to gather a comprehensive body of literature to provide valuable insights into the medical field. The plan to establish data on the subject between

2000 and 2022 is related to the new research, being carried out by the Study of Contact Dermatitis and the Brazilian Society of Dermatology, which began in 2023. Articles published after 2022 will be commented on and not included in the analysis.

Data extraction and quality assessment

In the initial stage, a comprehensive assessment was conducted by two researchers to identify and remove duplicate articles obtained from the search process. Subsequently, a meticulous examination of the titles and abstracts of the retrieved records was performed, resulting in the exclusion of studies that did not meet the predetermined eligibility criteria.

In the subsequent stage, the full texts of the remaining studies were thoroughly evaluated by the authors, employing strict inclusion and exclusion criteria. This critical appraisal enabled the identification of studies that met the predefined criteria and were deemed eligible for further analysis.

Selection criteria

In order to ensure the inclusion of relevant articles, the following selection criteria were applied:

- Original articles;
- Articles with full texts available;
- Studies that performed contact tests with the Brazilian Standard Battery (Brazilian Contact Dermatitis Study Group – GBEDC);
- Studies with full results of all substances tested in patch tests;
- Studies conducted in Brazil;
- Studies that evaluated the population of patients diagnosed or suspected of having contact dermatitis;
- Studies published between 2000–2022.

Exclusion criteria

The following criteria were employed to exclude articles from consideration:

- Ongoing clinical trials without published results and case reports;
- Articles with specific subpopulations;
- Studies that performed contact tests with batteries other than the Brazilian Standard Battery (Brazilian Contact Dermatitis Study Group – GBEDC);
- Studies are not conducted in Brazil.

Quality assessment was performed using the Joanna Briggs Institute Critical Appraisal Tool.

The checklist for cross-sectional studies and the checklist for cohort studies were selected and applied, according to the study design⁵:

- Checklist for cross-sectional studies, in which studies were scored on 8 items. Each item was evaluated using the options: yes, no, unclear, not applicable. The authors considered articles to be of good quality if they received a

“yes” response for all evaluated items; of medium quality if they received a “yes” response for 5 or more items; and of low quality if they received a “yes” response for 4 or fewer items.

- Checklist for cohort studies, in which studies were scored on 11 items. Each item was evaluated using the options: yes, no, unclear, not applicable. The authors considered articles to be of good quality if they received a “yes” response for all evaluated items; of medium quality if they received a “yes” response for 6 or more items; and of low quality if they received a “yes” response for 5 or fewer items.

Search strategy

A comprehensive search was performed by two screeners who independently searched in scientific databases known for housing Brazilian studies, namely PubMed, LiLACS, and SciELO. The primary objective was to gather a comprehensive body of literature to provide valuable insights into the medical field.

The selection of search terms was guided by their relevance to the specific medical condition under investigation, encompassing both general and specific keywords. The search was conducted on October 10, 2022, and the search strategy utilized on each platform will be detailed below:

- PubMed: (“patch tests”[MeSH Terms] OR (“patch”[All Fields] AND “tests”[All Fields]) OR “patch tests”[All Fields] OR (“patch”[All Fields] AND “test”[All Fields]) OR “patch test”[All Fields]) AND (“Brazil”[MeSH Terms] OR “Brazil”[All Fields] OR “Brazil s”[All Fields] OR “Brazils” [All Fields]);
- LiLACS: (“teste de contato” or “patch test”) (Brasil or Brazil);
- SciELO: (patch test) OR (teste de contato) AND (Brazil).

To enhance the comprehensiveness of the search strategy and yield a robust dataset for analysis, reference lists of the included studies were reviewed to identify additional studies that may have been missed through the initial search process. This comprehensive approach ensured the inclusion of relevant studies within the Brazilian context.

Variables

The study examined the following variables:

- Reactivity of the 30 substances comprising the Brazilian Standard Battery;
- Gender (Sex);
- Age;
- Geographical region of Brazil.

Statistical analysis

To determine the prevalence of positive substance tests, a weighted summary meta-analysis mean was utilized, considering the sample size of each study as a weighting factor.

For the association tests, eight composite and simple linear regressions of meta-analysis were tested to select the best model. The outcome measure used was the percentage of positive contact tests, with combinations of the study’s percentage of female participants, categorized study region (with the Southeast region as the reference and the South region as the comparison), mean age of study participants (with and without a constant). To assess changes in contact test positivity rates over time, the mean value of each substance within each time interval and their corresponding coefficients were calculated using simple linear regression, considering time as a continuous variable.

Results

Through the initial search, a total of 81 articles deemed potentially relevant were identified. Following the removal of duplicates, 55 articles remained for further evaluation. Subsequently, 37 articles were excluded based on title and abstract screening. The full texts of the remaining 18 articles were thoroughly assessed for eligibility. Ultimately, 10 studies met the predefined inclusion criteria and were included in this systematic review, as depicted in Fig. 1. Table 1 provides a summary of the selected studies and their respective characteristics.

Considering the criteria of the tool used for quality assessment, the Joanna Briggs Institute Critical Appraisal Tool, the authors found 7 articles of medium quality,^{2,3,6-8,11,13} 3 considered to be of good quality,^{9,10,12} and none of the 10 articles pre-selected based on the inclusion and exclusion criteria were considered to be of low quality, with no indication for exclusion from the systematic review.

The total number of patients subjected to patch testing, considering all selected studies, was 4703. In all 10 studies, the tests were performed on patients with suspected contact dermatitis. The studies were conducted in four different states in Brazil, but only in two regions, in the South and Southeast. In the South region, there was one study in the state of Santa Catarina and two studies in the state of Rio Grande do Sul.^{2,6,7} In the Southeast region, there were five studies in the state of São Paulo⁸⁻¹² and two studies in the state of Minas Gerais.^{3,13} Regarding gender, the majority of the population included in the studies was female in all 10 studies, as shown in detail in Table 1.

As for the sites of dermatitis, the cephalic segment (face, head, and neck) was the most affected in all studies, except in Rodrigues et al.,¹³ where it ranked as the second most common after the hands. In Fernandes et al.⁹ the most common sites were eyelids (12.30%) and face (9.2%); in Silva et al.,¹² the cephalic segment including the head, face, and neck accounted for 44.79% of cases; in Duarte et al.,¹¹ the cephalic segment accounted for 45.3% of cases; in Rodrigues et al.,³ the face was affected in 24.8% of cases; in Artus et al.,⁶ the head and neck were affected in 48.9% of cases; and in Duarte et al.,⁸ the cephalic segment (head and neck) was the most frequently affected (81 cases, 29%). In Rodrigues et al.,¹³ the hands were the most affected site (44.7%), and the studies by Opperman et al.,⁷ GBEDC10, and Correa et al.² did not provide this information.

Table 1 Summary of the selected studies and their respective characteristics.

First Author/Year	Study design	City/Region	Evaluated period	Sample Size	Mean age	Sex (%)	Results: positive substances (%)
Oppermann et al. 2021	Cohort (prospective)	Porto Alegre South	2018 to 2019	77	41.3 *Unrepresented Variability *Minimum–maximum: 3–75 years	F: 77.9 M: 22.1	Nickel sulfate 38 Kathon CG 15 Perfume mix 14 Paraphenylenediamine 9 Neomycin, Thimerosal 8 Cobalt chloride 7 PPD mix, Carba mix 6 Balsam-of-Peru, Potassium dichromate, P-tertiary Butylphenol 5 Thiuram mix, Colophony 4 Etilenodiamine 3 Propylene Glycol, Benzocaine, Epoxi-resine 2 Anthraquinone, Hydroquinone, Mercapto mix, Quaternium-15, Quinine mix, Nitrofurazone, Paragon mix, Terebentine 1
Rodrigues et al. 2015	Cross-sectional	Belo Horizonte Southeast	2003 to 2010	125	14.3 ± 3.8	F: 76.8 M: 23.2	Nickel sulfate 46 Thimerosal 23 Neomycin 8 Cobalt chloride, Perfume mix 5 Formaldehyde 4 Potassium dichromate, Etilenodiamine 3 PPD mix, Balsam-of-Peru, Quinine mix Anthraquinone, Kathon CG, Hydroquinone, Mercapto mix 2 Quaternium-15, Promethazine 1 Colophony, Carba mix

Table 1 (Continued)

First Author/Year	Study design	City/Region	Evaluated period	Sample Size	Mean age	Sex (%)	Results: positive substances (%)
Duarte et al. 2013	Cohort (restro-spective)	São Paulo Southeast	2006 to 2011	618	*Unrepresented variability *Predominant age group: 30–49 years	F: 68.4 M: 31.6	Nickel sulfate 174 Thimerosal 99 Potassium dichromate 69 Cobalt chloride 65 Perfume mix 54 Neomycin, PPD mix 45 Paraphenylenediamine 43 Carba mix 41 Thiuram mix 38 Etilenodiamine 27 Promethazine 21 Balsam-of-Peru, Formaldehyde 20 Mercapto mix 19 Hydroquinone, Quaternium 15 Colophony 17 Quinine mix, Lanoline 16 Kathon CG, Benzocaine 15 Paragon mix, Nitrofurazone 14 Terebentine 11 Propylene Glycol 10 Epoxi-resine 9 Irgasan, P-tertiary Buthylphenol 5 Anthraquinone 4

Table 1 (Continued)

First Author/Year	Study design	City/Region	Evaluated period	Sample Size	Mean age	Sex (%)	Results: positive substances (%)
Rodrigues et al. 2012	Cohort (restro-spective)	Belo Horizonte Southeast	2003 to 2010	1406	42 ± 16	F: 69.7 M: 30.3	Nickel sulfate 442 Thimerosal 207 Potassium dichromate 114 Paraphenylenediamine 99 Cobalt chloride 97 Perfume mix 94 Neomycin 88 Balsam-of-Peru, Formaldehyde 72 Etilenodiamine 67 PPD mix 60 Carba mix 40 Thiuram mix 37 Colophony 30 Hydroquinone 25 Paragon mix 22 Kathon CG 20 Quaternium 15, Nitrofurazone 19 Propylene Glycol 10 Benzocaine 16 Epoxi-resine 12 Mercapto mix 14 Quinine mix 14 Terebentine, triclosan 11 Promethazine 17 Anthraquinone 7 Lanoline, P-tertiary Buthylphenol 6
Silva et al. 2020	Cohort (restro-spective)	São Paulo Southeast	2015 to 2017	267	43 ± 16	F:72.9 M:27.1	Nickel sulfate 108 Cobalt chloride 45 Neomycin 35 Potassium dichromate 34 Kathon CG 29 Thimerosal 28 Formaldehyde 25 Paraphenylenediamine 18 Perfume mix 16 Colophony 11 Balsam-of-Peru 9 Triclosan 8 Carba mix, Thiuram mix 6 Etilenodiamine, Paragon mix 5 Quaternium 15, Quinine mix, 4 Nitrofurazone, Epoxi-resine Lanoline, Mercapto mix 3 Promethazine, Hydroquinone, 2 Benzocaine, PPD mix Terebentine, P-tertiary Buthylphenol 1

Table 1 (Continued)

First Author/Year	Study design	City/Region	Evaluated period	Sample Size	Mean age	Sex (%)	Results: positive substances (%)
GBEDC et al. 2000	Cohort (prospective)	São Paulo Southeast	1995 to 1996	967	37.1 ± 15	F: 62.5 M: 37.5	Nickel sulfate 243 Thimerosal 158 Quaternium 15 109 Cobalt chloride 106 Paraphenylenediamine 84 Perfume mix 81 Potassium dichromate 78 Quinine mix 58 Thiuram mix 53 Neomycin 42 Formaldehyde 37 Carba mix, Mercapto mix, Nitrofurazone 36 Balsam-of-Peru 31 Etilenodiamine 30 Paragon mix 26 Colophony 25 Epoxi-resine, PPD mix, Promethazine 17 Kathon CG 21 Terebentine 14 Hydroquinone 13 Lanoline 11 triclosan, P-tertiary Buthylphenol 7 Anthraquinone 5

Table 1 (Continued)

First Author/Year	Study design	City/Region	Evaluated period	Sample Size	Mean age	Sex (%)	Results: positive substances (%)
Correa et al. 2018	Cross-sectional	Santa Catarina South	2004 to 2013	539	38.8 *Unrepresented variability	F: 75,9 M: 24.1	Nickel sulfate 196 Cobalt chloride 95 Thimerosal 81 Paraphenylenediamine 44 Potassium dichromate 43 Kathon CG 42 Carba mix 39 Formaldehyde 38 Perfume mix 37 PPD mix 35 Promethazine 32 Neomycin 28 Colophony 24 Terebentine 22 Etilenodiamine 18 Hydroquinone 15 Epoxi-resine 14 Nitrofurazone, Paragon mix 12 Propylene Glycol, P-tertiary Buthylphenol 11 Balsam-of-Peru, Thiuram mix 10 Irgasal 9 Anthraquinone, Quinine mix 7 Quaternium 15 6 Benzocaine 5 Mercapto mix 4 Lanoline 4
Fernandes et al. 2007	Cohort (prospective)	São Paulo Southeast	2001 to 2002	65	45.1 *Unrepresented variability	F: 90.7 M: 9.23	Nickel sulfate 24 Thimerosal 13 Neomycin 6 Formaldehyde 5 Cobalt chloride 3 Mercapto mix, Lanolin, Perfume mix, PPD mix, Paraphenylenediamin 2 Balsam-of-Peru, Thiuram mix P-tertiary Buthylphenol, Etilenodiamine, Epoxi-resine 1

Table 1 (Continued)

First Author/Year	Study design	City/Region	Evaluated period	Sample Size	Mean age	Sex (%)	Results: positive substances (%)
Duarte et al. 2007	Cohort (prospective)	São Paulo Southeast	1998 to 2003	506	*Unrepresented mean and variability	F: 64 M:36	Nickel sulfate 180 Cobalt chloride 85 Thimerosal 64 Potassium dichromate 61 Perfume mix 58 Paraphenylenediamine, Neomycin, Thiuram mix 47 Quaternium-15 45 Carba mix, Nitrofurazone 34 Etilenodiamine 27 Quinine mix 23 PPD mix 22 Balsam-of-Peru, Epoxi-resine 21 Paragon mix, Promethazine 20 Colophony 18 Lanoline 12 Hydroquinone 10 Benzocaine 9 Formaldehyde 7 Propylene Glycol 6 Anthraquinone 3 P-tertiary Buthylphenol triclosan 2
Artus et al.	Cross-sectional	Porto Alegre/South	2007 to 2010	133	42 ± 15	F: 69.2 M: 68.7	Nickel sulfate Thimerosal 45 Paraphenylenediamine 25 Neomycin 22 Cobalt chloride 19 PPD mix 17 Potassium dichromate 16 Carba mix 14 Perfume mix, Thiuram mix 12 Kathon CG, Mercapto mix, Paragon mix, 10 Promethazine, Hydroquinone 8 Balsam-of-Peru, Colophony, Epoxi-resine, Terebentine 7 Etilenodiamine, Formaldehyde, triclosan, 6 Anthraquinone, Nitrofurazone 5 Mercapto mix 4 Lanoline, Quaternium 15, Quinine mix, Propylene Glycol, Benzocaine, P-tertiary Buthylphenol 3

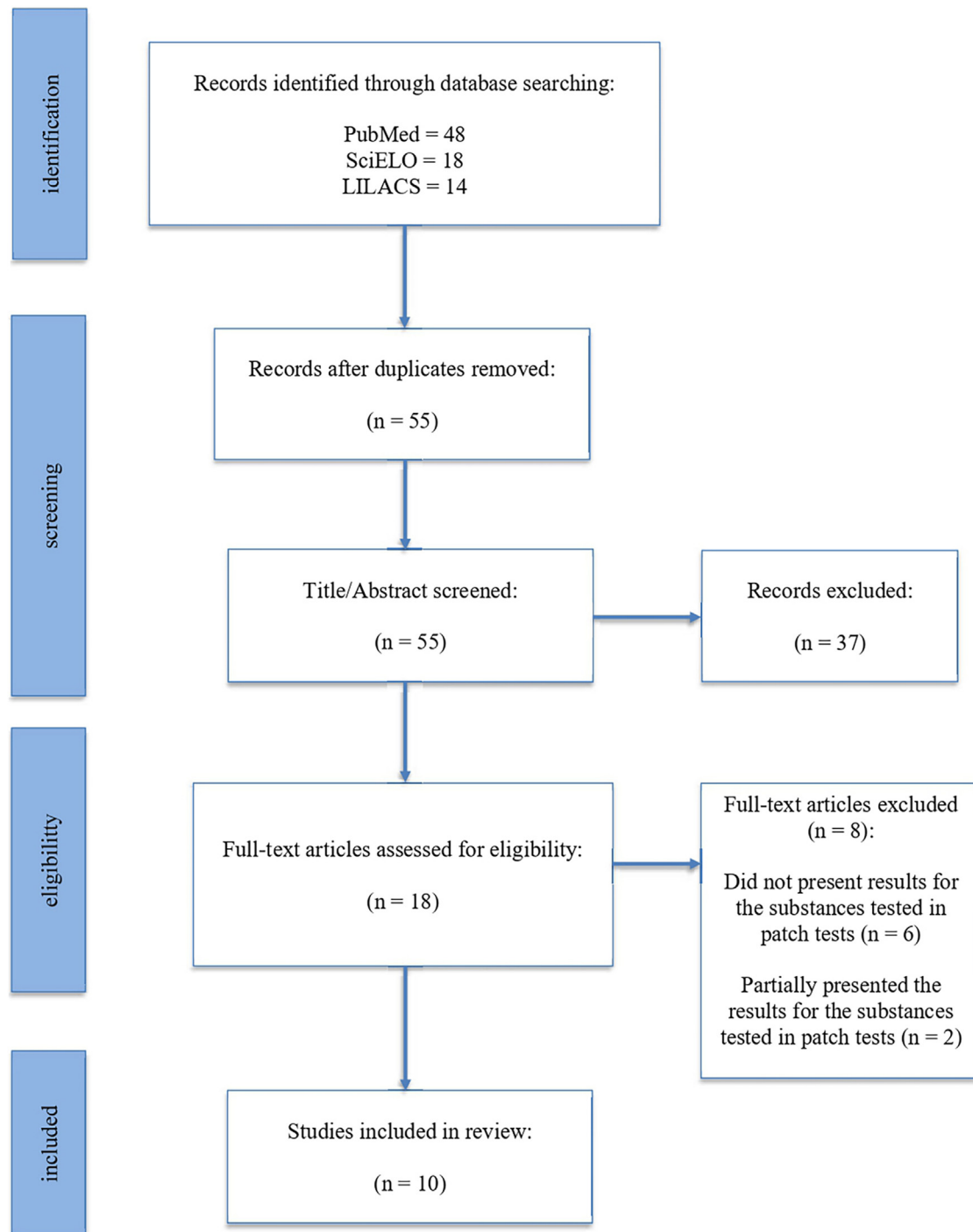


Figure 1 Search strategy results.

Technique

All studies utilized the Brazilian standard battery, composed of 30 substances recommended by the Brazilian Group of Studies in Contact Dermatitis, originally produced by FDA-Allergenic/Immunothec (RJ, Brazil).

All studies followed the criteria of the International Contact Dermatitis Research Group (ICDRG) for application and interpretation techniques. Readings were performed at 48 and 96 hours, according to the established criteria. Posi-

tive tests at 96 hours related to current and past history of contact dermatitis were considered relevant.¹⁰

Frequency of most common allergens

Among adults with suspected Allergic Contact Dermatitis (ACD), the most frequently positive allergen in patch tests was nickel sulfate, with an average prevalence of 31.8%, as shown in Table 2. Individually, it was also the test with the

Table 2 Prevalence of positive patch test reactions in Brazil, by substance, between 2000–2022 (n = 4.703).

Substance	Positive tests*	Mean (%)	Standard Deviation	Standard Error	Confidence Interval (90%)	
					Lower Limit (%)	Upper Limit (%)
Nickel sulfate	1.496	31.8	25.3	8.00	17.2	46.5
Thimerosal	727	15.5	3.2	1.02	13.6	17.3
Cobalt chloride	504	10.7	14.3	4.51	2.4	19.0
Potassium dichromate	421	9.0	5.4	1.71	5.8	12.1
Para-phenylenediamine	368	7.8	5.1	1.61	4.9	10.8
Perfume mix	362	7.7	5.4	1.71	4.6	10.8
Neomycin	335	7.1	6.1	1.92	3.6	10.6
Carba mix	219	4.7	5.0	1.58	1.8	7.6
Formaldehyde	214	4.6	4.1	1.29	2.2	6.9
Thiuram mix	206	4.4	6.1	1.92	0.9	7.9
Quaternium 15	204	4.3	17.7	5.60	0.0	14.6
PPD mix	203	4.3	5.4	1.71	1.2	7.5
Ethylenediamine	187	4.0	1.0	0.32	3.4	4.6
Balsam of Peru	178	3.8	1.5	0.47	2.9	4.6
Kathon CG	151	3.2	12.9	4.10	0.0	10.7
Colophony	137	2.9	1.1	0.34	2.3	3.5
Nitrofurazone	125	2.7	3.0	0.94	0.9	4.4
Quinoline mix	122	2.6	4.1	1.29	0.2	5.0
Promethazine	118	2.5	3.1	0.98	0.7	4.3
Paraben mix	113	2.4	1.2	0.38	1.7	3.1
Hydroquinone	94	2.0	1.0	0.31	1.4	2.6
Epoxy resin	87	1.8	1.4	0.44	1.0	2.7
Mercapto mix	85	1.8	1.8	0.58	0.8	2.9
Turpentine	67	1.4	1.7	0.55	0.4	2.4
Benzocaine	57	1.2	0.5	0.15	0.9	1.5
Lanolin	56	1.2	0.8	0.24	0.7	1.6
Propylene glycol	50	1.1	0.4	0.12	0.8	1.3
Triclosan	47	1.0	0.8	0.25	0.5	1.5
p-Tertiary butylphenol	41	0.9	0.9	0.27	0.4	1.4
Anthraquinone	33	0.7	0.4	0.12	0.5	0.9

* Unweighted N.

highest positivity in the 10 studies that examined this population, with percentages ranging from 28.1%¹¹ to 56.2%¹² of the tested patients in each study.

The second most frequently positive allergen was thimerosal and cobalt chloride, with an average prevalence of 15.5% and 10.7%, respectively. Both substances were among the top 5 most frequently positive allergens in all articles.

Considering the metal series, in addition to the high prevalence of nickel sulfate and cobalt chloride, potassium dichromate presented an average prevalence of 9%.

Among the seven most frequent substances in the included studies, the authors should also mention fragrance mix (7.7%), paraphenylenediamine (7.8%), and neomycin (7.1%). Neomycin had the highest prevalence among the included articles when compared to substances present in topical medications from the series. Promethazine was the second most positive active ingredient but showed significant variation among studies, with prevalence ranging from 0.8%³ to 5.9%,² resulting in a lower average prevalence of positive tests per substance than neomycin, at 2.5%. Nitrofurazone and quinoline also had low average prevalence percentages in the tests of the included studies (2.7% and 2.6%, respectively).

The three least prevalent substances in all studies were triclosan (1%), p-tertiary butylphenol para-tertiary (0.9%), and anthraquinone (0.7%).

Regarding the analysis by age group, the most common allergens in children and adolescents, aged 1- to 19-years, considering a single study with n = 1253, were nickel sulfate (36.8%), thimerosal (18.4%), neomycin (6.4%), cobalt chloride, and fragrance mix (4.0% each), formaldehyde (3.2%), potassium dichromate and ethylenediamine (2.4% each). Children had positive reactions only to the nickel mix and fragrance mix.³

The systematic review also included an article presenting results in the elderly subpopulation (> 65-years)⁸: The main sensitizers in this age group were thimerosal (11%), neomycin (10.5%), nickel sulfate (10%), fragrance mix (10%), nitrofurazone (7%), potassium dichromate (6%), and paraphenylenediamine (5.5%).

Associations between variables

Regarding the associations tested between the percentage of positive tests and the variables of sex, age, and region in Brazil, the results are described in Table 3. Values with p < 0.1 were considered statistically significant.

Table 3 Associations identified with sex, age, and region from the period of 2000 to 2022.

Substance	Female		Age (mean)		Region*		p-value (global)
	coefficient	p-value	coefficient	p-value	coefficient	p-value	
Anthraquinone	-0.020	0.062	-	-	1.82	0.006	0.002
Peru Balsam	-	-	-	-	2.60	<0.001	<0.001
Benzocaine	-0.006	0.628	-	-	1.25	0.075	0.005
Potassium Bichromate	-0.388	0.025	0.166	0.187	0.93	0.664	0.081
Carba mix	-0.084	0.072	0.091	0.244	5.41	0.008	0.001
Cobalt Chloride	-0.059	0.550	0.234	0.218	4.24	0.246	0.003
Colophony	-0.047	0.072	0.065	0.148	2.97	0.008	<0.001
Epoxy resin	-0.039	0.064	0.053	0.144	2.12	0.013	0.001
Ethylenediamine	0.047	<0.001	-	-	-	-	<0.001
Formaldehyde	0.088	0.041	-	-	-1.42	0.482	0.003
Hydroquinone	-0.106	0.079	-	-	2.21	0.039	0.050
Irgasan	-	-	-	-	0.94	0.016	0.016
Kathon CG	-0.073	0.293	-	-	8.09	0.047	0.012
Lanolin	0.028	0.097	-	-	-0.56	0.503	0.018
Mercapto mix	0.024	0.002	-	-	-	-	0.002
Neomycin	0.075	0.097	-	-	2.53	0.266	<0.001
Nitrofurazone	-0.138	0.007	0.042	0.184	0.91	0.134	0.021
Paraben mix	-0.161	0.016	-	-	1.65	0.097	0.029
Para-phenylenediamine	-0.150	0.016	0.262	0.019	6.45	0.007	<0.001
Perfume mix	-	-	-	-	5.80	<0.000	<0.001
PPD mix	-0.069	0.208	0.068	0.474	5.57	0.018	0.003
Promethazine	-0.021	0.447	-	-	2.95	0.071	0.012
Propylene glycol	-0.027	0.040	0.018	0.360	1.78	0.003	0.001
P-Tertiary Butylphenol	-0.027	0.443	0.007	0.913	2.57	0.069	0.046
Quaternium 15	-0.330	0.024	-	-	-1.50	0.466	0.049
Quinoline mix	-0.169	0.014	-	-	-0.34	0.712	0.034
Nickel sulfate	0.410	0.011	-0.083	0.702	6.28	0.170	<0.001
Turpentine	-0.048	0.088	0.033	0.468	2.92	0.012	0.008
Thimerosal	0.232	0.001	-	-	-1.01	0.695	<0.001
Thiuram mix	0.054	0.004	-	-	-	-	0.004

Blue: As the proportion of the variable increases, the proportion of positive tests decreases. Pink: As the proportion of the variable increases, the proportion of positive tests increases. Yellow: Statistically significant associations.

^a Southeast region considered as the reference.

Sex

A higher proportion of females in the sample was associated with a lower proportion of positive tests for the following substances: anthraquinone, potassium dichromate, carbamix, colophony, epoxy resin, hydroquinone, nitrofurazone, paraben mix, paraphenylenediamine, propylene glycol, quaternium 15, quinoline mix, and turpentine ($p < 0.1$).

For the substances ethylenediamine, formaldehyde, lanolin, mercapto mix, neomycin, nickel sulfate, thimerosal, and thiuram mix, a higher proportion of females in the sample was associated with a higher proportion of positive tests ($p < 0.1$).

Age

A higher average age in the study was associated with a lower proportion of positive tests for the substance's potassium dichromate, carbamix, cobalt chloride, colophony, nitrofurazone, paraphenylenediamine, PPD mix, propylene glycol, p-tertiary butylphenol, and turpentine ($p < 0.1$).

Conversely, only for nickel sulfate, a higher average age in the study was associated with a higher proportion of positive tests ($p < 0.1$).

Brazilian regions of the studies: The substances formaldehyde, lanolin, quaternium 15, quinoline mix, and thimerosal appeared in a lower proportion of positive tests in the

Table 4 Positivity variation of patch test results over time, using the Brazilian Standard Battery, between 2000–2022 (n = 4,703).

Substance	- 1999 ^a	2000–2005	2005–2010	2011 -	β (pp) ^b
Antraquinone	0.5	0.3	1.4	0.6	0.07
Benzocaine	0.5	0.9	1.3	1.7	0.28
Potassium Dichromate	8.1	6.0	8.0	9.6	0.73
Peru Balsam	3.2	2.8	3.4	4.9	0.54
Carba mix	3.7	3.4	5.4	5.0	0.42
Cobalt Chloride	11.0	8.6	10.4	13.0	0.91
Colophony	2.6	1.8	3.1	4.7	0.71
Epoxy Resin	1.8	2.8	2.0	2.0	-0.07
Ethylenediamine	3.1	3.4	3.9	2.9	-0.11
Formaldehyde	3.8	4.5	4.6	4.7	0.14
Hydroquinone	1.3	1.0	2.9	1.0	-0.04
Triclosan	0.7	0.1	1.6	1.5	0.31
Kathon CG	2.2	0.0	3.7	15.2	4.02
Lanolin	1.1	2.7	1.2	0.6	-0.39
Mercapto mix	3.7	1.5	1.8	1.2	-0.41
Neomycin	4.3	9.3	8.2	11.7	1.41
Nitrofurazone	3.7	3.4	1.9	1.4	-0.61
P-Tertiary Butylphenol	0.7	1.0	1.1	3.4	0.74
PPD mix	1.8	3.7	6.2	4.3	0.44
Paraben mix	2.7	2.0	2.6	1.6	-0.21
Paraphenylenediamine	8.7	6.2	7.7	9.2	0.51
Perfume mix	8.4	7.3	6.4	12.1	1.22
Promethazine	1.8	2.0	3.5	0.4	-0.43
Propylene Glycol	0.8	0.6	1.3	1.3	0.17
Quaternium 15	11.3	4.4	1.6	1.4	-1.85
Quinoline mix	6.0	2.3	1.6	1.4	-0.78
Nickel Sulfate	25.1	36.2	33.3	44.9	4.06
Turpentine	1.4	0.0	2.4	0.8	0.03
Thimerosal	16.3	18.4	16.6	10.4	-1.98
Thiuram mix	5.5	5.4	3.6	3.7	-0.49

^a Articles published between 2000–2022 were included. Data collection in two included articles was conducted between 1995–2000.

^b Linear regression coefficient (in percentage points). Positive results = average increase; Negative results = average decrease.

southern region, but without a statistically significant direct association ($p > 0.1$).

On the other hand, the substances anthraquinone, balsam of Peru, benzocaine, carbamix, colophony, epoxy resin, hydroquinone, triclosan, Kathon CG, paraben mix, perfume mix, paraphenylenediamine, PPD mix, propylene glycol, promethazine, quaternium 15, quinoline mix, p-tertiary butylphenol, and turpentine showed a higher proportion of positive tests in the studies conducted in the southeastern region ($p < 0.1$). The same suggestion is made for potassium dichromate, cobalt chloride, neomycin, nitrofurazone, and nickel sulfate, although no statistically significant significance was observed ($p > 0.1$).

No trends or associations were observed for the remaining substances.

Variation in test positivity over time

The study observed an increasing trend in test positivity every 5-years for several substances, including Kathon CG, neomycin, and nickel sulfate also exhibited increasing test positivity ($p < 0.1$). Additionally, anthraquinone, benzocaine, potassium dichromate, balsam of Peru, cobalt chloride, colophony, formaldehyde, triclosan, p-tertiary

butylphenol, PPD mix, paraphenylenediamine, perfume mix, propylene glycol, and turpentine ($p > 0.1$).

Conversely, there was a decreasing test positivity trend, every 5-years, for quaternium 15 and thimerosal ($p < 0.1$), epoxy resin, ethylenediamine, hydroquinone, lanolin, mercapto mix, nitrofurazone, paraben mix, promethazine, thiuram mix, and quinoline mix ($p > 0.1$). The results are described in Table 4.

Discussion

The primary objective of this study was to compile and compare the results of patch tests conducted on the Brazilian population, specifically focusing on patients suspected of contact dermatitis, from 2000 to 2022.

Consistent with global literature, nickel was identified as the main sensitizing agent across all studies. The positivity rates found in the Brazilian population in this study (31.8%) were higher compared to more recent reports in the European population, where nickel sensitization was found in approximately 13%–17% of adults, around 10% of adolescents, and 7%–9% of children.¹⁴

Metals emerged as significant sensitizers in most studies and are among the primary allergens causing contact

dermatitis. Apart from nickel, cobalt and chromium were notable sensitizers, likely due to the high prevalence of metal-containing products to which the Brazilian population is exposed, such as jewelry, piercings, cleaning products, eyewear, watches, buttons on clothing, and gold-plated items, along with the presence of metals in occupational dermatoses.¹⁵

According to Spiewak et al.,¹⁴ the most common sensitizers in the European population, in addition to nickel sulfate, are thimerosal and fragrances. Similarly, in the systematic review, thimerosal ranked among the top 10 most frequent sensitizers in all articles. The authors emphasize its presence in medications, vaccine preservatives, contact lens solutions, and tattoo inks, which may contribute to the high prevalence of sensitization to this substance.²

Regarding substances with a lower prevalence of positive reactions in patch tests, this study identified triclosan, p-tert-butylphenol, and anthraquinone, with average prevalence percentages of up to 1%. Considering the very low frequency of positive tests for these substances, the authors can question their real importance in the etiology of allergic contact dermatitis in the Brazilian population over the past two decades and the need to include them in the standard Brazilian patch test panel.

These results align with published data reporting infrequent contact sensitization to triclosan. The Swiss Contact Dermatitis Research Group reported a triclosan sensitization prevalence of 0.8% in a large study involving 2,295 patients.¹⁶ Schena et al.¹⁷ confirmed a low incidence of triclosan sensitization, mainly associated with the use of deodorants containing this substance in their study.

Due to reported potential risks ranging from allergies to endocrine disruption, triclosan was banned by the FDA in September 2016 in soaps (liquid, gel, foam, bar), while the European Union (EU) prohibited its use in all biocidal products for human hygiene starting in January 2017, which may explain the reduction in positive tests for triclosan.¹⁸

A study by Fransway et al.¹⁹ from the North American Contact Dermatitis Group in 2013 also reported a decreased prevalence of positive reactions to p-tert-butylphenol, a substance commonly used in adhesives, including shoe production, among other substances, when compared to rates observed in the previous ten years.

Regarding anthraquinones, they have industrial applications in the production of hydrogen peroxide, paints, and medications such as laxatives and cathartics. They are also present in plants like Senna, Cascara sagrada, Rhubarb, and Aloe.^{20,21} Anthraquinone is not included in the standard American and European patch test panels, with limited published data on its prevalence of positive reactions in patch tests.

A tendency towards a higher proportion of positive tests in women was found for a number of substances, possibly related to the greater frequency of exposure occurring in this group. Among these are ethylenediamine, primarily used in topical medications such as antifungals, antibacterial, and corticosteroids; formaldehyde, utilized in the formulation of cosmetics, personal hygiene products, and nail polishes; lanolin, a cutaneous emollient used in the cosmetics industry; mercapto mix, employed in the rubber industry and found in gloves, condoms, toys, shoes, among

other items; thimerosal, utilized as a preservative in vaccines; thiuram mix, used in the rubber industry for fungicides and pesticides, as well as repellents; neomycin, an over-the-counter antibacterial medication in Brazil; and nickel sulfate, found in jewelry, earrings, watches, bracelets, denim buttons, needles, zippers, coins, keys, buckles, eye-glass frames, orthodontic and orthopedic appliances, foods, among others.

Additionally, the authors found a higher tendency of positive test proportions for a multitude of substances in the southeastern region compared to the southern region (anthraquinone, balsam of Peru, benzocaine, carbamix, colophony, epoxy resin, hydroquinone, triclosan, Kathon CG, paraben mix, perfume mix, paraphenylenediamine, PPD mix, propylene glycol, promethazine, quaternium 15, quinoline mix, p-tertiary butylphenol, and turpentine). This finding may be justified by the greater number of studies conducted in the southeastern region (7 out of 10 studies) included in the analysis.

Moreover, a higher average age in the study population, encompassing children, adults, and the elderly, was associated with a lower proportion of positive tests for substances such as potassium dichromate, carbamix, cobalt chloride, colophony, nitrofurazone, paraphenylenediamine, PPD mix, propylene glycol, p-tertiary butylphenol, and turpentine. A possible explanation lies in the association of these substances with occupational activities such as construction work and industries like rubber, leather, and metals, which tend to be less common in older age groups.

The article by Duarte et al.¹¹ evaluated the variation in positivity rates for substances included in the standard Brazilian patch test panel recommended by the Brazilian Group of Contact Dermatitis Studies between 2006 and 2011. Three substances showed a statistically significant decrease in sensitization rates over the studied years: lanolin ($p=0.01$), neomycin ($p=0.01$), and anthraquinone ($p=0.04$). The systematic review, with more robust strength, also found a decreasing percentage, every five years on average, for lanolin; however, it observed an increasing percentage for neomycin and anthraquinone. Historically, exposure to certain allergens shows variation according to geographical areas, such as neomycin, which remains more common in North America than in Europe.²² The overall prevalence of neomycin sensitization has decreased in several countries in recent years, possibly due to its restricted availability in some locations.²³ In Brazil, neomycin is still present in over-the-counter topical medications with high consumption by the Brazilian population, which may explain the observed increase in percentage in this study.

The findings of this review regarding the frequency of common allergens in the pediatric and adolescent population are consistent with global literature.¹⁰ However, the present study was limited by the small number of articles including this age group. Nickel sulfate was the most frequently positive allergen in patch tests conducted on the pediatric population in Brazil, which aligns with a previous systematic review.²⁴ In the same review, lanolin was considered one of the top 10 most frequently positive substances, unlike the results of this study, where the authors did not observe any positive reactions to this allergen in the pediatric and adolescent population.

Despite the rigorous methodology employed in this systematic review, several limitations must be acknowledged. One significant limitation is the small number of studies included in the analysis. Eight articles had to be excluded after initial eligibility, according to exclusion criteria described in the methodology: six for not presenting patch test results²⁵⁻³⁰ and two for partially presenting patch test results.^{31,32} The limited number of eligible articles restricts the generalizability of the findings. This scarcity of studies likely reflects the early stage of research in this domain within Brazil, pointing to opportunities for further investigation and expansion.

In the most recent review of the relevant literature, the authors found, after 2022, only one article that would be possible to integrate into this systematic review, which was carried out retrospectively to investigate hand contact dermatitis. This study found in a total of 173 patients, 61.8% of irritant dermatitis and only 23.1% of allergic dermatitis and 5.2% of atopic dermatitis. The most frequent allergens were kathon cg (42%), nickel sulfate (33%) and thiuram-mix 18%.³³ The profile is compatible with the data observed in the 2000–2022 historical series current in this systematic review.

Another critical limitation pertains to the overall quality of the included studies. While the majority of the selected articles were of average methodological quality, which may increase the risk of bias, it is noteworthy that high-quality studies were also included, and no low-quality studies were admitted into the review.

Conclusion

The most frequently identified allergens in patch tests in this SR were nickel sulfate, thimerosal and cobalt. Triclosan, tertiary P-butyphenol and anthraquinone were the three least prevalent substances. A trend has been demonstrated for test positivity to increase every 5-years on average for kathon CG, neomycin, and nickel sulfate.

This systematic review offers valuable insights, despite some limitations. Although the number of included studies is small, this highlights the potential for further exploration in this research area. The compilation of these data will enable healthcare professionals working with dermatological allergies to gain a more concrete understanding of the prevalence of positive contact test reactions to each substance present in the Brazilian standard battery. These findings, in addition to their clinical relevance, may serve as a foundation for recommending useful and appropriate series of contact tests, allowing for a more comprehensive and accurate evaluation of patients suspected of allergic contact dermatitis in Brazil in the future.

Financial support

None declared.

Authors' contributions

Ana Laura Andrade Bueno: Study conception and planning; data collection, analysis and interpretation; statistical

analysis; intellectual participation in propaedeutic and/or therapeutic management of studied cases; preparation and writing of the manuscript; effective participation in research orientation; manuscript critical review; approval of the final version of the manuscript.

Nathalia Hoffmann Guarda Aguzzoli: Study conception and planning; data collection, analysis and interpretation; statistical analysis; intellectual participation in propaedeutic and/or therapeutic management of studied cases; approval of the final version of the manuscript.

Renan Rangel Bonamigo: Study conception and planning; data collection, analysis and interpretation; statistical analysis; intellectual participation in propaedeutic and/or therapeutic management of studied cases; preparation and writing of the manuscript; effective participation in research orientation; critical literature review; approval of the final version of the manuscript.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Pruritus in atopic dermatitis: a cross-sectional study of adult patients from a tertiary university hospital in São Paulo, Brazil[☆]



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Received 28 April 2024; accepted 10 September 2024

Available online 11 March 2025

KEYWORDS

Dermatitis, atopic;
Eczema;
Pruritus

Abstract

Background: Chronic pruritus is the defining symptom of atopic dermatitis (AD). Although AD is common in Latin America, there is little data regarding pruritus intensity, characteristics, and effects on quality of life in this population.

Objective: This cross-sectional study aimed to evaluate pruritus in 91 patients with AD at a tertiary university hospital in São Paulo, Brazil. Patients aged 14–65-years old were included in this study.

Methods: Patients completed the Itch Questionnaire, the ItchyQoL, and the POEM questionnaires and were asked to rate their itch severity using a 10-point peak pruritus Numerical Rating Scale (NRS). AD severity was assessed via the EASI and the vIGA-AD.

Results: The mean age was 29.68 ± 12.87 years, and 56.0% of patients were White. 97.8% of patients were currently experiencing pruritus with an average NRS of 7.32 ± 2.22 . Patients had associated bleeding (71.4%), heat sensation (63.7%), and pain (54.9%). Worsening factors included stress (93.4%), dry skin (91.2%), and sweat (75.8%). The mean total ItchyQoL score was 78.93 ± 17.20 . Female gender was significantly associated with a higher total ItchyQoL score ($p = 0.009$). Pruritus on the neck, foot, and whole body was associated with higher total ItchyQoL scores in adjusted models ($p < 0.05$). The EASI, vIGA-AD, and POEM were moderately correlated with itch intensity ($r = 0.434$, 0.406 , and 0.610) and total ItchyQoL score ($r = 0.425$, 0.436 , and 0.631).

[☆] Study conducted at the Department of Dermatology, Faculty of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil.

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Study limitations: The predominantly White population cohort may not be representative of the diverse AD phenotypes in the Brazilian patient population. Children under the age of 14 and adults over the age of 65 were excluded from the population cohort. Furthermore, patients included in the study may suffer from other non-dermatological diseases that cause itch, which may influence the outcomes observed.

Conclusions: Patients with AD in Brazil experience significant pruritus that impacts their quality of life. Gender, body location of itch, associated pain, and stress should all be taken into consideration when evaluating AD patients with pruritus.

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Introduction

Atopic Dermatitis (AD) is a chronic, relapsing inflammatory skin disease. Chronic pruritus, defined as pruritus of duration > 6-weeks, is one of the predominant and most bothersome symptoms of AD.^{1,2} Itch significantly impacts patients' Quality of Life (QoL) and mental health, and has been associated with impairments in work, sleep, and daily activities.³⁻⁵ Studies have reported a 20.1% prevalence of AD in Brazil, the highest among Latin American countries.⁶ However, there is a paucity of literature on the impact of AD-associated pruritus in Latin America, and itch intensity, characteristics, and effects on quality of life have not been well-studied in this population.

The primary objective of this cross-sectional study was to evaluate the prevalence and severity of itch in patients with atopic dermatitis at an AD clinic in a tertiary University hospital in São Paulo, Brazil. The secondary objective was to describe the characteristics of pruritus in this patient population and its effect on Quality of Life (QoL). Furthermore, the authors aimed to assess the clinical severity of AD and its association with patient-reported pruritus measures.

Methods

The authors recruited 91 patients with AD from the Atopic Dermatitis Clinic at the Department of Dermatology, University of São Paulo Medical School, São Paulo, Brazil from August 2022 to April 2023. Patients aged 14 to 65 years old diagnosed with AD according to the Hanifin and Rajka criteria were included in the study. Patients with AD who experienced pruritus were asked to complete three validated questionnaires including the Itch Questionnaire,¹ the Itch-specific Quality of Life Questionnaire (ItchyQoL),⁷ and the Patient-Oriented Eczema Measures (POEM) questionnaire. Patients were also asked to rate their itch severity using a 10-point peak pruritus Numerical Rating Scale (pp-NRS).⁸ Patients were then fully examined by a dermatologist, and AD severity was assessed via 2 measures: The Eczema Area and Severity Index (EASI), and the validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-AD). Informed consent was obtained from all participants and the study was approved by the local Ethics Committee.

Statistical analyses were performed using the Statistical Package for the Social Sciences, Version 29 (IBM Cooperation, New York). Continuous variables were presented as mean (SD), while categorical variables were presented as

Table 1 Demographic characteristics.

N = 91	n (%)	Mean (SD)
Age		29.68 (12.87)
Sex		
- Male	49 (53.8%)	
- Female	42 (46.1%)	
Race		
- Caucasian	51 (56.0%)	
- Asian	8 (8.8%)	
- Brown	26 (28.6%)	
- Black	6 (6.6%)	

Table 2 Itch characteristics.

N = 91	n (%)	Mean (SD)
Current pruritus, yes	89 (97.8%)	
Pruritus NRS in last 2-weeks		7.32 (2.22)
Associated symptoms		
- Bleeding	65 (71.4%)	
- Heat sensation	58 (63.7%)	
- Pain	50 (54.9%)	
Itchy body locations		
- Arm	76 (83.5%)	
- Thigh	71 (78.0%)	
- Forearm	66 (72.5%)	
Worsening factors		
- Stress	85 (93.4%)	
- Dry skin	83 (91.2%)	
- Sweat	69 (75.8%)	

NRS, Numerical Rating Scale.

n (%). Unadjusted and adjusted linear regression was performed on the patient's itch intensity and various scores. The Pearson correlation coefficient was used to investigate the relationship between patient's itch intensity and each of the scores, and between the various scores.

Results

Demographic characteristics are listed in Table 1. The mean age was 29.68 ± 12.87 years, and the patient cohort was predominantly White (56.0%). Only 2 patients reported having another skin disease (1 psoriasis, 1 other- not specified). Itch characteristics are listed in Table 2. The majority of patients (97.8%) were currently experiencing pruritus, with

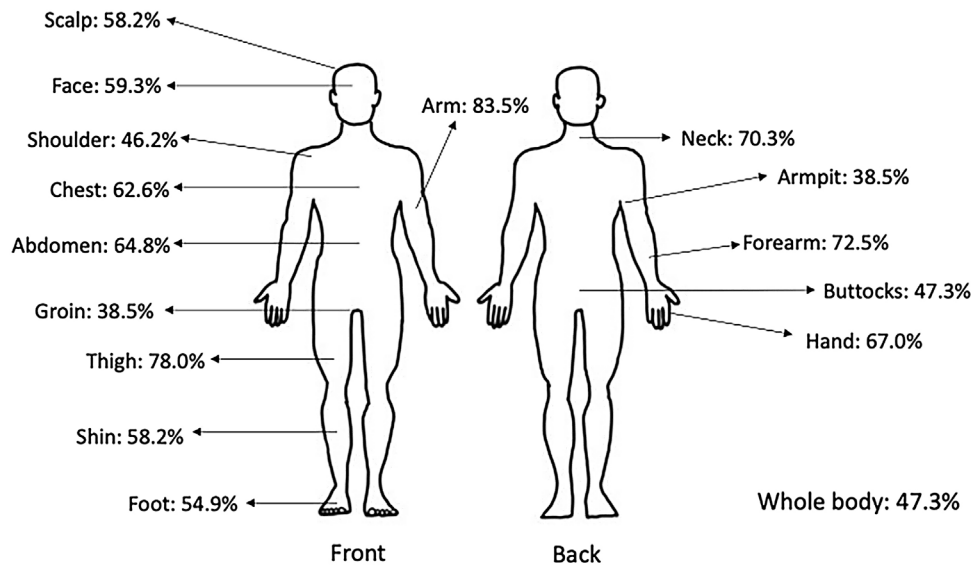


Figure 1 Pruritic body sites.

Table 3 Disease severity scores.

	Mean (SD)	Range
POEM	18.35 (6.94)	0–28
EASI	20.87 (14.76)	0–72
vIGA-AD	3.69 (0.90)	0–4
ItchyQoL	78.93 (17.20)	22–110

POEM, Patient Oriented Eczema Measures; EASI, Eczema Area and Severity Index; vIGA-AD, validated Investigator Global Assessment Scale for Atopic Dermatitis; ItchyQoL, Itch-specific Quality of Life Questionnaire.

an average peak pruritus NRS of 7.32 ± 2.22 in the last two weeks. Patients with pruritus had associated bleeding (71.4%), heat sensation (63.7%), and pain (54.9%). The most common itchy body sites included the arm, forearm, and thigh (Fig. 1). Worsening factors included stress (93.4%), dry skin (91.2%), and sweat (75.8%). The mean total ItchyQoL score was 78.93 ± 17.20 , indicating that pruritus had a significant impact on quality of life. Mean scores for measures of eczema severity revealed that patients suffered from moderate to severe disease (Table 3).

The authors found that demographic characteristics such as age and gender did not have a statistically significant effect on pruritus intensity. However, Asian race was associated with a higher pruritus intensity ($p = 0.036$). While race and age did not have an effect on the total ItchyQoL score, female gender was significantly associated with a higher total ItchyQoL score ($p = 0.009$). Furthermore, race did not affect different measures of AD severity (Supplementary Tables 1–5). The authors did not find a statistically significant association between assessed body locations and pruritus intensity in the adjusted models (Supplementary Table 1). Pruritus on the neck, foot, and whole body were statistically associated with higher total ItchyQoL scores in the adjusted linear regression model ($p < 0.05$) (Supplementary Table 2). Measures of AD severity including EASI, vIGA-AD, and POEM were moderately correlated with itch

intensity ($r = 0.434$, 0.406 , and 0.610 , respectively) and total ItchyQoL score ($r = 0.425$, 0.436 , and 0.631 , respectively).

Discussion

The present results show that pruritus affected most patients with AD from a tertiary referral University hospital in São Paulo, Brazil, with an average moderate-to-severe intensity (Fig. 2A–C). Large-scale studies in Europe and the US demonstrate that itch is the most burdensome symptom in AD patients, with a mean past week itch NRS score of 6.1.² Results from one study evaluating the burden of AD in Brazil, Mexico, and Argentina found that severe pruritus – defined as a worst pruritus NRS > 7 – was reported by 54.4% of patients.⁹ The high pruritus prevalence and intensity in Brazilian patients with AD may suggest a need for better symptomatic control. A study evaluating disease management in AD patients in Brazil revealed that common treatment options included topical corticosteroids, emollients, systemic antihistamines, and oral corticosteroids. 79% of patients had discontinued or switched AD treatment, with 33% of those being due to poor effectiveness.¹⁰ Furthermore, a Brazilian report found that 42% of severe AD patients have more than 10 disease flares per year, with a median duration of 12-days.¹¹ Dupilumab, a fully human Ig4 monoclonal antibody directed against the Interleukin-4 Receptor subunit alpha (IL-4R α) of IL-4 and IL-13 receptors, is a biologic therapy that has revolutionized the treatment of AD, with landmark trials demonstrating its efficacy in significantly reducing pruritus.^{12,13} Janus Kinase (JAK) inhibitors have also been increasingly used in patients with AD. By targeting the Janus-Kinase Signal and Activator of Transcription (JAK-STAT) pathway, these drugs downregulate inflammatory pathways and cytokines and therefore significantly reduce pruritus as well as AD severity.¹⁴ Although dupilumab and JAK inhibitors have been approved for use in many Latin American countries including Brazil and are recommended by the latest Brazilian Society of Dermatology consensus for

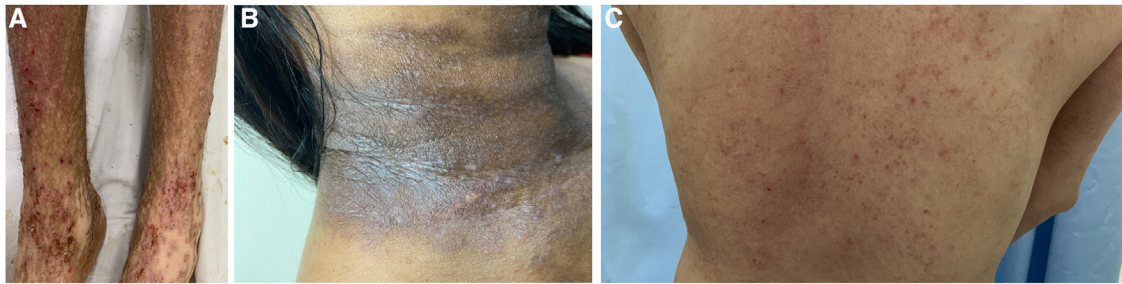


Figure 2 (A–C) Characteristic features of atopic dermatitis in Brazilian patients.

use in patients with AD, accessibility remains limited due to factors such as cost and insurance coverage.^{14,15}

Bleeding, heat sensation, and pain were the most commonly reported associated symptoms with pruritus in the population cohort. Bleeding can occur secondary to scratching and reflects the intense pruritus experienced by these patients. Heat sensation and pain have been reported in previous studies assessing itch characteristics in AD.^{1,16,17} Skin pain, in particular, is a common finding in patients with AD, with one large population study showing that 42% of patients experienced both pain and pruritus on AD lesional skin.² Patients with concomitant pain were more likely to describe their itch as tingling, burning, or stinging, characteristics that are classically associated with neuropathic pain.¹⁸ Pruritus and pain share common sensory neurons, mediators, and receptors, as well as similar mechanisms of neuronal sensitization.¹⁹ However, the relationship between these two sensations in the context of AD is not fully understood. Importantly, skin pain in AD strongly correlated with measures of AD severity and quality of life, highlighting the need to assess and treat pain in these patients.¹⁸

Most patients in this study reported that stress was an exacerbating factor for their pruritus, which is consistent with previous studies assessing itch in patients with AD.^{16,17} Psychological stress is known to exacerbate AD symptoms via its effects on the hypothalamic-pituitary-adrenal axis, immune response, neuropeptide expression, and skin barrier function.^{20–22} Stress also exacerbates scratching, thus contributing to the itch-scratch cycle that aggravates the disease.²³ Therefore, stress management should be addressed when treating patients with AD. A study from Brazil, however, found that only 11.8% of AD patients reported receiving therapy or psychological support.¹⁰

The authors found that the pruritus was most common on the arm, forearm, and thigh, and coincided with classic areas of AD lesions. After adjusting for other variables, pruritus on the neck, foot, and “whole body” was associated with a higher total ItchyQoL score, indicating a worst itch-related quality of life. Studies have shown an association between head and neck eczema and poor quality of life in AD patients.^{24,25} This may be partially due to the fact that these areas are often visible.²⁵

From the demographic factors evaluated in the present study, the female sex was significantly associated with a worse itch-related QoL. A previous study found that female sex was a predictor of poor itch-specific QoL in chronic pruritus patients.²⁶ Furthermore, a positive correlation between

Dermatology Life Quality Index (DLQI) score and disease severity in female patients with AD has been reported, although other studies did not find a meaningful gender difference in DLQI scores.^{27,28} Interestingly, race was not significantly associated with a higher total ItchyQoL score or higher AD severity scores. Studies have shown that patients with skin of color are disproportionately affected by pruritus, and that non-White patients with chronic pruritus experience a greater impact on their quality of life.^{29,30} Furthermore, AD is reported to be more common in patients with skin of color in U.S and Europe, and many genetic, immunologic, and clinical differences exist among various races and ethnicities.^{30–33} The absence of significance in the present findings may reflect the admixture of the Brazilian population and the fact that race is self-declared, leading to a lack of Black and Asian patients in the population cohort. The authors did find that patients of Asian race (Fitzpatrick III) had a significantly higher pruritus intensity when compared to other races. However, this must be interpreted carefully due to the small number of Asian participants in this study. Given the diverse, heterogeneous population of Brazil, the authors suggest that the race and ethnicity of patients with AD should be taken into consideration when making diagnostic and therapeutic decisions.

The average total ItchyQoL score indicates that pruritus causes a significant burden and impacts the quality of life of these patients. The impact of pruritus on various aspects of QoL in patients with AD is well known.^{2,3,34} Furthermore, our results demonstrate that patient-reported measures of pruritus such as pp-NRS and ItchyQoL moderately correlate with objective measures of AD severity such as the EASI and vIGA-AD. Moderate correlations between the ItchyQoL and AD severity measures such as EASI and Scoring AD (SCORAD) have been previously reported. The authors concluded that this instrument could be incorporated into the assessment of AD patients and could be used to guide decision-making.³⁵ Another study found that NRS worst itch and NRS average itch moderately correlated with EASI and objective-SCORAD, but not with vIGA-AD.³⁶ The product of vIGA and body surface area (vIGA $\times$ BSA), however, has been shown to have weak-to-good convergent validity with NRS worst itch, NRS average itch, and ItchyQoL.³⁷ The present findings indicate that itch can serve as an indicator of overall disease severity. Despite the significant QoL burden caused by pruritus, patient-reported itch outcomes in AD are not commonly evaluated using validated questionnaires in Brazil and other Latin American countries.³⁸ The authors believe the

current study highlights the importance of adding patient-reported measures of pruritus into regional consensus on AD management and incorporating them into clinical practice.

Limitations

The main limitation of this study is that the predominantly White population cohort may not be representative of the diverse Brazilian population and therefore may not accurately reflect all of the diverse AD phenotypes in the patient population. Children under the age of 14 were excluded from the population cohort, for the assessment of pruritus in children can be difficult and has limitations. This could, however, affect the overall prevalence of this study as AD is a common condition in children. Furthermore, patients over the age of 65 were excluded, as itching in the elderly can be multifactorial and can occur secondary to diagnoses other than AD. Patients included in the study may suffer from other non-dermatological diseases that cause itch, which may influence the outcomes observed in this study.

Conclusion

In conclusion, patients with AD in Brazil experience significant pruritus that impacts their quality of life. Gender, body location of itch, presence of associated pain, and stress should all be taken into consideration when evaluating AD patients with pruritus, for these factors may contribute to the burden experienced by patients and could impact therapeutic decision-making. Furthermore, the authors found that patient-reported itch measures moderately correlate with other AD severity scores, demonstrating that these could be incorporated into the clinical evaluation of patients with AD. Evaluating for certain pruritic biomarkers present in the serum and skin, and correlating them to itch intensity and other characteristics in this population could provide us with more information to better tailor and personalize treatment.

Financial support

Applebaum Foundation support to Gil Yosipovitch and Georgia Biazus Soares.

Authors' Contributions

Georgia Biazus Soares: Investigation, original draft preparation.

Raquel Leao Orfali: Conceptualization, investigation, methodology.

Beatriz Lacerda Averbach: Investigation.

Yap Qai Ven: Formal analysis.

Gil Yosipovitch: Conceptualization, methodology, review and editing.

Valeria Aoki: Conceptualization, investigation, methodology, review and editing.

Appendix A. Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.abd.2024.09.006>.

Conflicts of interest

Raquel Leao Orfali has been an investigator and/or consultant for Bayer, Sanofi, Eli Lilly, Amgen; Valeria Aoki has been an investigator and/or consultant to Abbvie, Eli Lilly, Pfizer, Sanofi and Leopharma; Gil Yosipovitch has been Advisory Board Member for Abbvie, Arcutis, BMS, Cara Therapeutics, GSK, Escient Health, Eli Lilly, Galderma, Kiniksa Pharmaceuticals, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, Inc., Sanofi, TreviTherapeutics, and Vifor; Receives grants/research funding from Eli Lilly, Kiniksa Pharmaceuticals, LEO Pharma, Novartis, Pfizer, Galderma, Escient, Sanofi Regeneron, and Celldex; Investigator for Regeneron Pharmaceuticals, Inc., Sanofi; Beatriz Lacerda Averbach is an investigator for Sanofi; Georgia Biazus Soares and Yap Qai Ven have no conflicts of interest to declare.

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ORIGINAL ARTICLE

White piedra: fungal extracellular matrix formation and its importance in pathogenesis. An ultrastructural study[☆]



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Received 4 July 2024; accepted 17 August 2024

Available online 3 July 2025

KEYWORDS

Extracellular matrix;
Scanning electron
microscopy;
White piedra

Abstract

Background: White piedra is a disease caused by some species of the genus *Trichosporon*. A case of white piedra was investigated, whose molecular examination identified *Cutaneotrichosporon* (*Trichosporon*) *debeurmannianum* as the causative agent.

Methods: Scanning electron microscopy (SEM) was used to examine the affected hairs, as well as the fungal colony of *C. debeurmannianum* obtained from the hairs. For comparative purposes, a colony of *Trichosporon mucoides* obtained from a mycotheque was also examined.

Results: Examination of the affected hairs using SEM easily demonstrates nodules on the hair shaft with a predominance of rounded yeast-like structures, adhered to each other by a cementing substance. Examination of the *C. debeurmannianum* colony demonstrates significant adhesion between the fungal cells by a reticular extracellular matrix. Examination of the *T. mucoides* colony obtained from a mycotheque demonstrates a small production of fibrillar substance between the blastoconidia.

Discussion: Examination of the colony obtained from the piedra showed significant formation of extracellular matrix, adhering to and covering the fungal structures, forming a biofilm. This matrix must correspond to the cementing substance described in the condition.

Conclusion: The synthesis of the extracellular matrix must be crucial in the formation of white piedra nodules.

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Introduction

The genus *Trichosporon* comprises yeast-like basidiomycete fungi (forming blastoconidia and hyphae),¹⁻³ with more than 50 described species, which cause dermatoses and opportunistic infections.

The genus received this name (*Trichos*-hair and *sporon*-spores) because it was first described from white piedra nodules by Beigel in 1865, and was later named *Trichosporon beigelii*.^{1,2} Currently, the main causes of disease in humans, according to the new taxonomy, are: *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. mucoides*, *T. inkin* and *T. ovoides*.¹

Fungi of this genus cause superficial mycoses such as white piedra and onychomycosis, with the latter being usually caused by *T. cutaneum*, but they also cause systemic infection, being the second cause of fungal septicemia in hematologic oncology patients, with a frequency lower only than that of the genus *Candida* spp.¹

White piedra is a condition generally caused by some species of the genus *Trichosporon*, such as *T. cutaneum*, *T. inkin*, *T. ovoides*, and *T. loubieri*. It is characterized by small nodules that form on the hair shaft and can affect various regions of the body, such as the beard, scalp, pubic hair, armpits, and eyebrows. Long hair could facilitate its occurrence and it is more common in children.³⁻⁵

This genus has undergone numerous reclassifications in recent years.^{6,7} The fungus *Cutaneotrichosporon* (*Trichosporon*) *debeurmannianum*, also called *Trichosporon debeurmannianum* by some authors, was identified in 2001,⁸ and has already been described as causing skin infection.^{9,10}

A case of white piedra and the respective fungal culture were assessed, whose molecular examination identified *C. debeurmannianum* as the cause of the condition.

Methods

Hair affected by a case of white piedra was examined using Scanning Electron Microscopy (SEM) with a Jeol microscope, JSM-6610LV at Centro de Microscopia do Sul - CEMESUL - FURG, as well as the fungal colony obtained from the hair culture on Sabouraud dextrose agar. For comparative purposes, a colony of *Trichosporon mucoides*, obtained from the mycotheque of Instituto de Medicina Tropical de São Paulo, was also examined.

The hair was examined after gold metallization. To examine the colonies, a small section of the culture obtained was removed, fixed in glutaraldehyde, dehydrated and subsequently submitted to gold metallization.

Results

The colony obtained from the affected hairs showed a typical yellowish-creamy appearance (Fig. 1A). Examination of the culture with optical microscopy revealed yeast-like structures (blastoconidia) and some filaments (Fig. 1B).

Examination of the affected hairs with SEM easily demonstrates the nodules at low magnification (Fig. 2A). At high magnification, well-formed nodules, and incipient lesions are observed (Fig. 2B). Detailed examination of the nod-

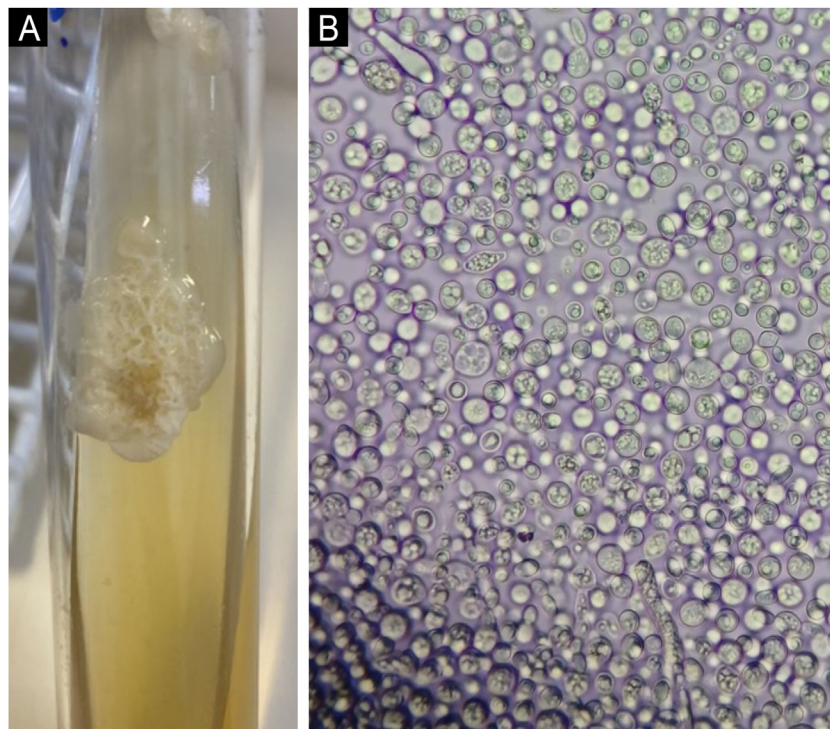


Figure 1 (A) Colony with creamy aspect. (B) Optical microscopy – predominance of blastoconidia with some hyphae.

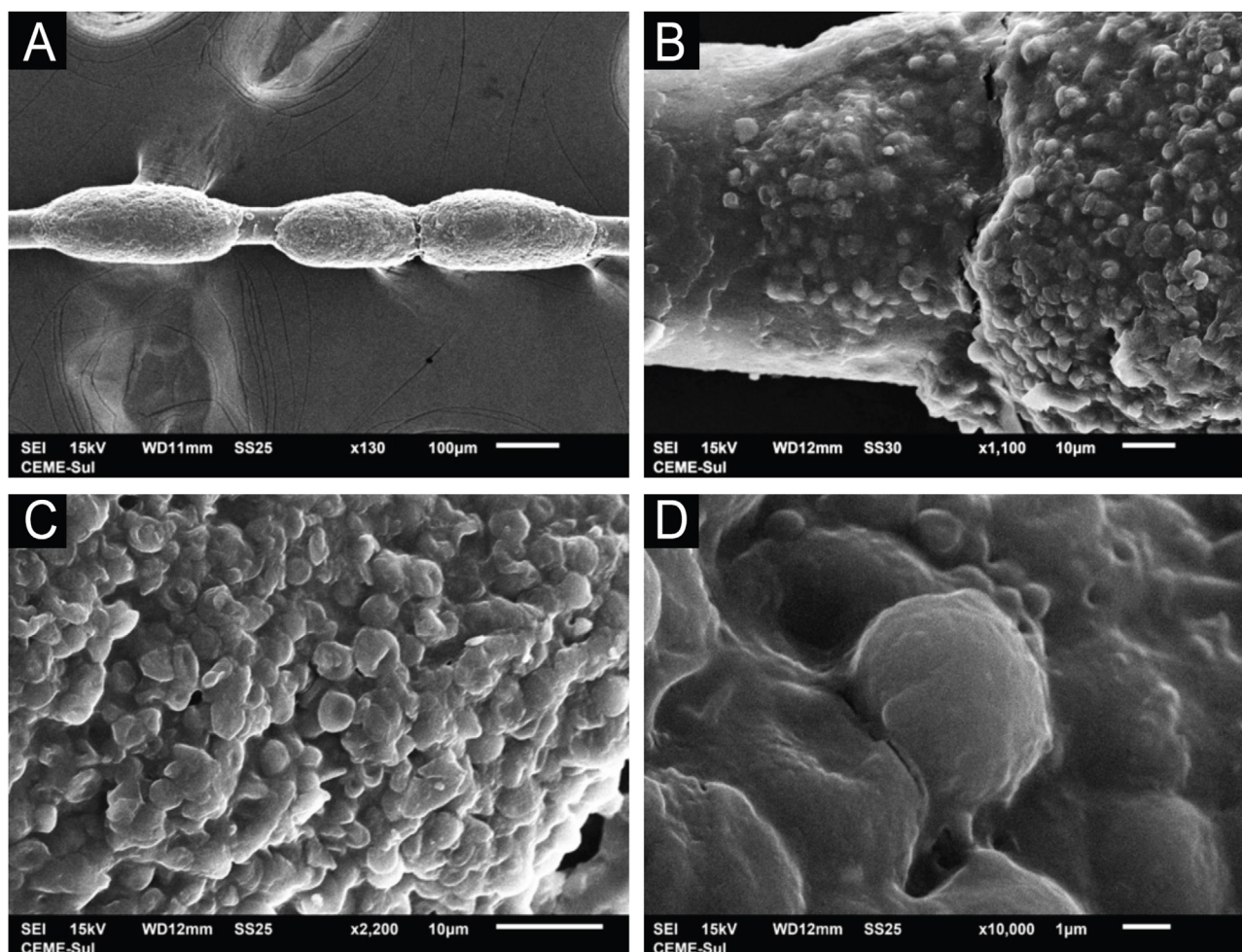


Figure 2 SEM of white piedra – (A) Low magnification identifying nodules in the hair ($\times 130$). (B) Detail of the nodule, with initial lesion on the left ($\times 1,100$). (C) High magnification demonstrating clusters of blastoconidia ($\times 2,200$). (D) High magnification with detail of blastoconidia on the surface ($\times 10,000$).

ules shows their formation with a predominance of rounded yeast-like structures, similar to the findings of optical microscopy, adhered to each other by a cementing substance (Fig. 2C–D).

Examination of the *C. debeurmannianum* colony with SEM also demonstrates a predominance of rounded structures, as seen under optical microscopy, and at low magnification, adhesion between these structures by an extracellular network is observed; the hyphae show a lower production of this network (Fig. 3). Detailed examination shows significant adhesion between the rounded cells, sometimes forming clusters that resemble “acini” (Fig. 4); the blastoconidia appear well surrounded by the extracellular matrix (Fig. 5). In some fields, this extracellular network hides the yeast-like structures, compacting them in this matrix (Fig. 6). Some hyphae were also seen with this extracellular matrix (Fig. 7).

A comparison at similar magnifications shows the similarity between the white piedra nodule and the *C. debeurmannianum* culture (Fig. 8).

The SEM examination of the *T. mucoides* colony obtained from the mycotheque shows filaments and blastoconidia, without the formation of the evident extracellular matrix adhering the fungal cells to each other (Fig. 9A), as seen in

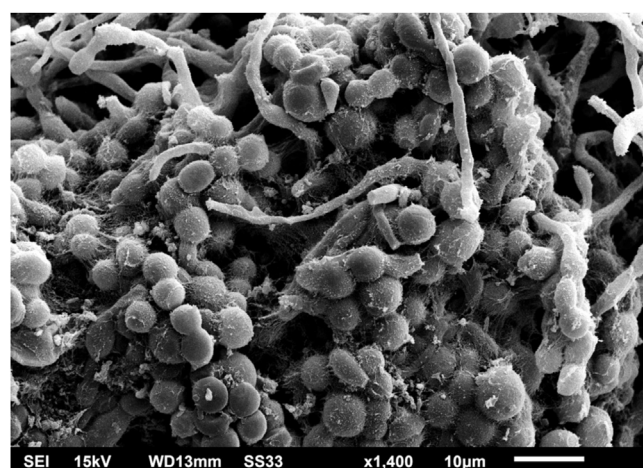


Figure 3 SEM of the *C. debeurmannianum* colony with a predominance of blastoconidia and some hyphae ($\times 1,400$).

the colony obtained in the present case of white piedra. At high magnifications, it was possible to observe a small production of a fibrillar substance between the blastoconidia (Fig. 9B).

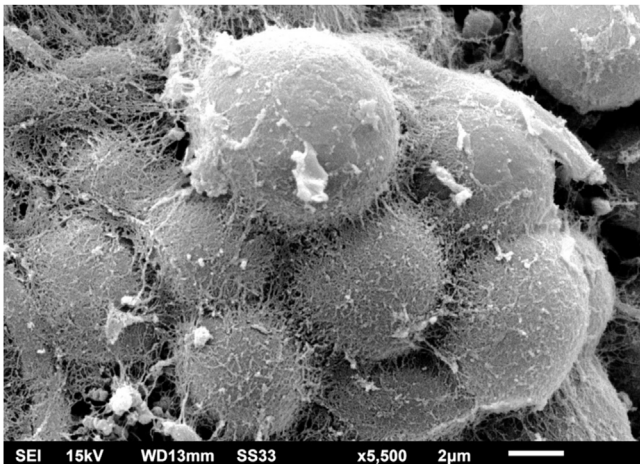


Figure 4 SEM of the *C. debeurmannianum* colony – detail of the blastoconidia adhered by reticular extracellular matrix, forming clusters resembling acini ($\times 5.500$).

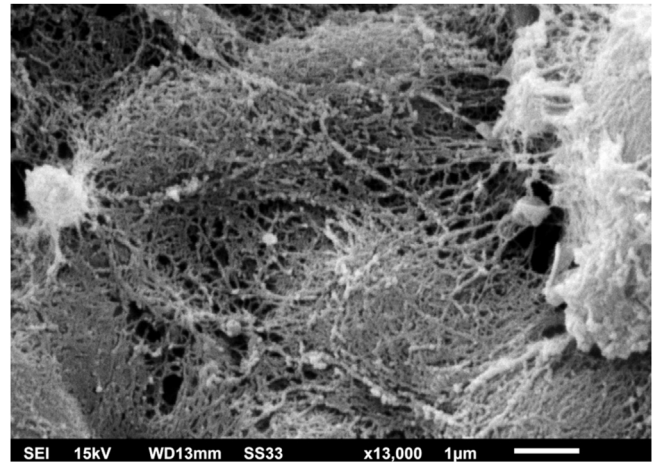


Figure 6 SEM of *C. debeurmannianum* colony – detail of dense extracellular matrix covering the blastoconidia ($\times 13.000$).

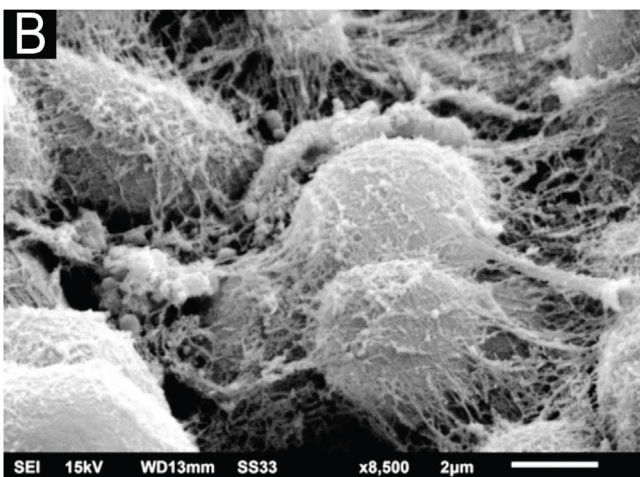
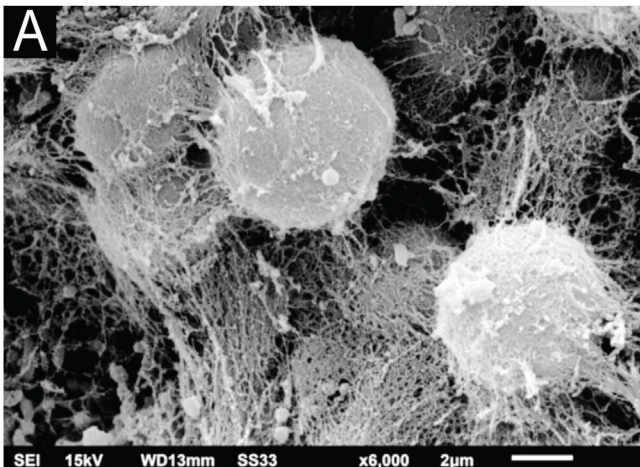


Figure 5 SEM of *C. debeurmannianum* colony – (A) High magnification of blastoconidia covered by extracellular matrix ($\times 6,000$). (B) Detail of covered blastoconidia, adhered to each other ($\times 8.500$).

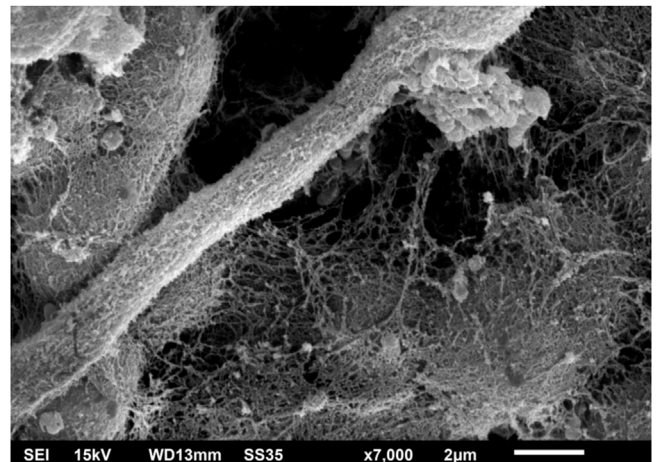


Figure 7 SEM of the *C. debeurmannianum* colony – detail of the extracellular matrix formation also by hyphae ($\times 7.000$).

Discussion

The findings from the examination of the piedra nodule in this report are similar to previously published findings regarding its ultrastructure, with hyphae (in sections with transmission electron microscopy analysis) and spores surrounded by a cementing substance on the surface, in the SEM analysis.¹¹

Regarding the examination of the colony obtained from the index case presented herein, a significant formation of extracellular matrix was observed, adhering to and covering the fungal structures, forming a biofilm. This matrix must correspond to the cementing substance described in the condition.

Biofilm formation was first demonstrated in the 1970s and is characterized by an extracellular matrix with embedded etiological agents.^{12,13} It must have the function of protecting the etiological agents against ultraviolet radiation, extreme temperatures and pH, salinity and pressure,

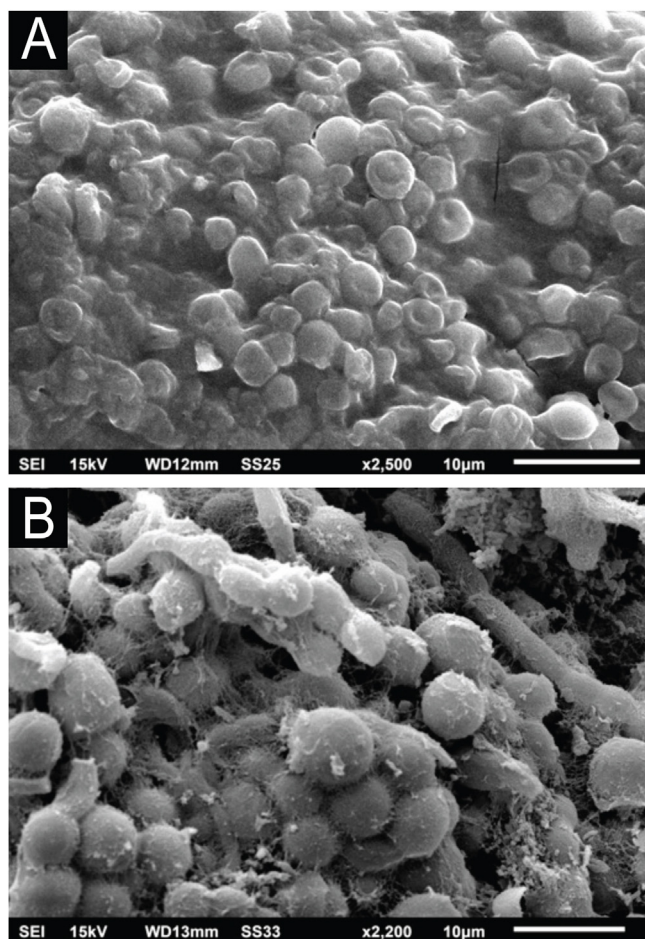


Figure 8 SEM – comparative demonstration of the similarity between the appearance of the white piedra nodule (A; $\times 2,500$) and the *C. debeurmannianum* colony (B; $\times 2,200$).

and may also be involved in resistance to antibiotics and antifungals.¹² It may be formed by polysaccharides, proteins, or fats.¹²

Several fungi of dermatological interest have been described as biofilm formers, such as *T. rubrum* and *T. mentagrophytes*, and in the genera *Aspergillus*, *Candida* and *Cryptococcus*.^{14–16}

Biofilm formation has also been reported in relation to the genus *Trichosporon*,^{17–20} and interspecies variation has been found, which can be classified as weak, medium or strong biofilm producers.¹⁷ In a publication with a series of 53 strains of *Trichosporon* obtained from urinary samples, around 10% were medium biofilm producers and the majority were weak producers.¹⁹ With *T. asahii* obtained from blood culture, it was experimentally demonstrated that the fungus adheres to culture plates and begins to produce biofilm within a few hours.²⁰

An experimental investigation has demonstrated that several species of *Trichosporon* can adhere to hair, forming piedra.²¹

Possibly, strains with low production of extracellular matrix may not form the piedra nodule, as this would be necessary to form the hair concretion. Similar to what was demonstrated here, with the intense production of extracellular matrix by the colony obtained from affected hair,

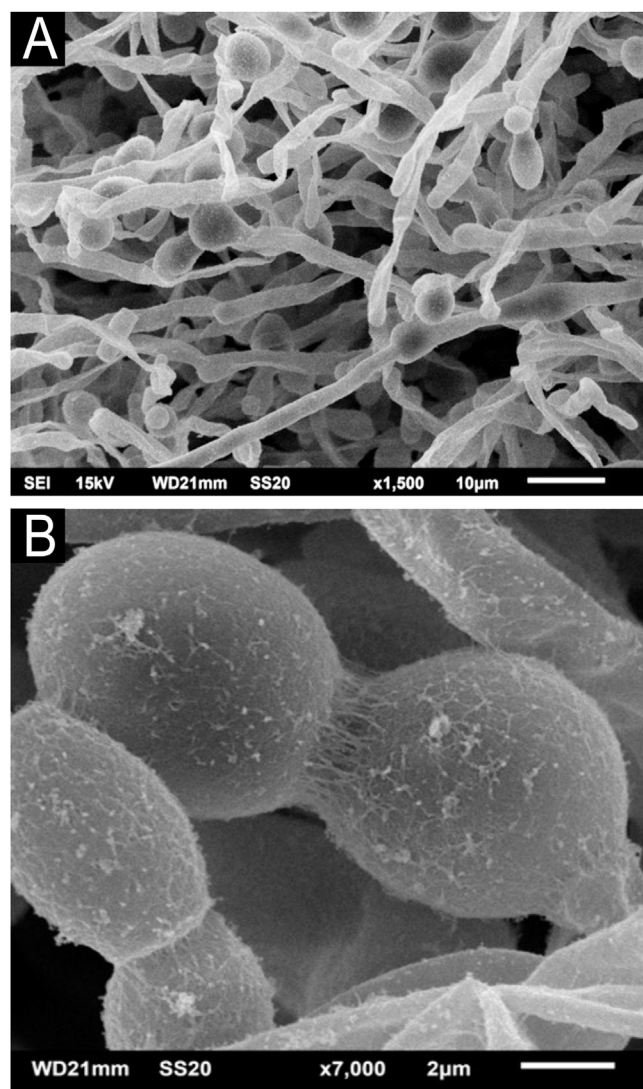


Figure 9 SEM of *T. mucooides* colony – (A) Fungal filaments and blastoconidia not adhered by extracellular matrix ($\times 1,500$). (B) Detail of blastoconidia with discrete extracellular matrix production ($\times 7,000$).

in contrast to the low production of extracellular matrix by *T. mucooides* obtained from the mycotheque, it is also possible that this strain kept frozen in the mycotheque may have modified the likelihood of producing the extracellular matrix.

The formation of the cementing substance firmly adhered to the hair and of the biofilm could be responsible for the slow response to the topical or systemic antifungal therapy in white piedra.

It is suggested that extracellular matrix synthesis plays a crucial role in the firm adhesion of fungal cells to each other, resulting in the formation of piedra nodules, as it has also been demonstrated with the etiological agent of black piedra.²² These SEM findings should be expanded to include more species of *Trichosporon*, whether piedra-forming or not.

Financial support

None declared.

Authors' contributions

Hiram Larangeira de Almeida Jr: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases, critical review of the literature; critical review of the manuscript.

Thales de Moura Assis: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Eduardo Camargo Faria: Approval of the final version of the manuscript; design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Viviane Mazo Fávero Gimenes: Approval of the final version of the manuscript; drafting and editing of the manuscript; collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; critical review of the manuscript.

Conflicts of interest

None declared.

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REVIEW

Inflammasome pathways in atopic dermatitis: insights into inflammatory mechanisms and therapeutic targets[☆]



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Received 23 October 2024; accepted 20 January 2025

Available online 23 June 2025

KEYWORDS

Cytokines;
Dermatitis, atopic;
Immunity, innate;
Inflammasomes

Abstract Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by a complex interaction between genetic, immunological, and environmental factors. The combination of immune dysregulation and skin barrier dysfunction plays a crucial role in the pathogenesis of the disease. The inflammasome, an important intracellular complex of pattern recognition receptors (PRRs), plays a crucial role in the cutaneous inflammatory response, activating caspase-1 and promoting the release of pro-inflammatory cytokines such as interleukin (IL)-1 β and IL-18. The role of inflammasome components in regulating the inflammatory response in AD highlights how the activation of these complexes exacerbates inflammation and contributes to the worsening of the disease and tissue damage. The review included observational and experimental studies investigating inflammasome activation in AD and other inflammatory skin diseases. The main mechanisms of inflammasome activation and their impact on the inflammatory environment and skin barrier integrity were discussed. Understanding the role of the inflammasome in AD is essential for the development of new therapeutic approaches aimed at both modulating the immune response and restoring the skin barrier, improving more effective clinical management and patients' quality of life.

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Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease. Skin manifestations include erythema, lichenification, xerosis, papules and desquamation. AD is characterized by intense pruritus, one of the main symptoms, which aggravates others, such as a sensation of pain,¹

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sleep disorders, fatigue^{2,3} and neuropsychiatric symptoms (attention deficit hyperactivity disorder, depression and anxiety).^{3,4} Together, all these manifestations contribute to impairing of patient's quality of life, leading to psychosocial suffering and stigma.²

The etiopathogenesis of AD is a complex multifactorial interaction between various elements: environmental factors, genetic susceptibility,⁵ changes in the function of the skin barrier, the microbiota and the immune system.⁶ Together, these factors contribute to the development, progression and chronicity of the disease. As complications, AD patients are more susceptible to infections such as those caused by the *herpes simplex virus* (HSV)⁷ and mainly by *Staphylococcus aureus* (*S. aureus*).^{8,9} Patients with AD are also susceptible to environmental impacts, indicating that climatic factors, temperature, humidity, air pollution,¹⁰ and exposure to ultraviolet rays¹¹ can interact directly with the skin barrier and significantly influence the development and exacerbation of AD symptoms.¹²

The review addresses the relevance of the interaction between alterations in skin barrier proteins, the innate and adaptive immune response, and connections with the inflammasome complex, and the consequent impact on the pheno-endotypical features of AD.

Key changes in the immune response of atopic dermatitis

Impaired skin barrier

In AD patients, changes in the skin barrier (SB) lead to increased transepidermal water loss (TEWL), defects in the metabolism of pro-filaggrin,¹³ and lower expression of filaggrin and claudin 1 (protein located in tight junctions – TJ).^{14,15} In addition, there is a decrease in ceramide levels,^{13,16} cholesterol sulfate and accumulation of sphingosylphosphorylcholine, due to increased expression of the enzyme sphingomyelin deacylase.^{17,18} Other contributors include decreased antimicrobial peptides (AMPs), increased serine protease (SP), reduced SP inhibitors and disrupted TJs.¹⁹

In addition, keratinocytes of AD patients show dysfunction in their response to environmental stimuli, undergoing apoptosis and leading to interruptions in SB function. Also, loss-of-function mutations in the filaggrin gene,²⁰ in the claudin 1 protein and single nucleotide polymorphisms in the SP SPINK5 inhibitor and SP KLK7 have been described in AD.^{21,22}

Fragility in the SB is well described as a key factor in the pathogenesis of AD, amplifying inflammatory manifestations and aggravating the symptoms associated with the disease.²³ The sum of these factors contributes to greater susceptibility to infections and inflammation, due to increased skin permeability to allergens and irritants, favoring the penetration of pathogens (Fig. 1).

Mechanisms of adaptive immunity

The Th1/Th2 paradigm in AD has been revised, with evidence of a significant role for the IL-17 and IL-22-secreting Th17 and IL-22-secreting Th22 cell subtypes.^{24–27} Thus, dur-

ing the acute phase of AD, in addition to Th2 cytokines such as IL-4, IL-13 and IL-31, there is a predominance of IL-22, as well as smaller amounts of Th17 cells.²⁸ In the chronic phase of the disease, there is an amplification of Th2 and Th22 cytokine axes, with augmented Th1 cells but no further increases in Th17 cells.²⁸ These cytokines reduce the differentiation of epidermal cells and may contribute to the reduction of filaggrin and antimicrobial peptides (AMPs).²⁹ Analysis of acute lesions, compared to non-lesioned skin or chronic lesions, showed up-regulation of the S100A7, S100A8 and S100A9 genes and concomitant activation of Th2 and Th22 cytokines.²⁷ In addition, there is an increase in IL-22 in the dermis and serum of individuals with AD, suggesting a systemic impact on the immune response (Fig. 1).³⁰

The IL-22-producing cells that infiltrate the AD skin lesion are CD4+ T-helper lymphocytes (Th22) and CD8+ T-cytotoxic lymphocytes (Tc22); clinical severity of AD correlated with the number of Tc22 cells, but not with Th22 cells.³¹ In addition, cells from AD patients were responsive to stimulation with staphylococcal enterotoxins, with a decreased response by Th22 cells and increased responsiveness by Tc22 cells, suggesting the role of both T22 cells in the immune imbalance of AD.³⁰ Stimulation with enterotoxins also promoted up-regulation of anergy-related genes (EGR2 and IL13) in AD patients, associated with impairment of the effector response of CD4+CD38+ T cells.³²

As for Th17 cells, their role in defense against bacterial pathogens is well-known and they may be crucial in the pathogenesis of chronic inflammatory skin diseases.³¹ However, there is currently no consensus on the role of these cells in the immunopathogenesis of AD. There is an increase of IL-17 in the skin and serum levels in AD patients.¹⁵ It is also known that IL-17 exerts a role as an amplifier of skin lesions and the increase in circulating Th17 cells correlates with disease severity.³³

T-cells positive for cutaneous lymphocyte antigen (CLA+; skin homing receptor) mediate pathogenic inflammation in AD. Circulating CLA+ T cells are elevated in AD, respond to allergens, infiltrate skin lesions and participate in the initiation and perpetuation of AD lesions.³⁴ In addition, bacterial toxins are also able to increase the expression of CLA.³⁵

In addition to the involvement of cellular immunity, high IgE levels in AD are strongly correlated with the prevalence of IgE autoreactivity and disease severity. More findings reveal an increase of IgG4 and IgE anti-SEB (staphylococcal enterotoxin B) antibodies.³⁶ Likewise, numerous infiltrated cells in the skin lesions of individuals with AD are positive for IgE or its high-affinity Fc IgE receptor (FcεRI).³⁷

Mechanisms of innate immunity

In addition to the physical barrier mechanisms previously discussed, epithelial cells, mainly keratinocytes, are crucial components of the skin's innate immunity. These cells behave as sentinels for danger signals or microbial pathogens, triggering immune responses and a cascade of cytokine production.^{38,39}

Keratinocytes in AD skin express high levels of thymic stromal lymphopoietin (TSLP), IL-7-like cytokine, which induces the activation and migration to the lymph nodes of dendritic cells (DCs). The DCs stimulated by TSLP induce naive T cells to produce IL-5, IL-13 and TNF-α, and initiate

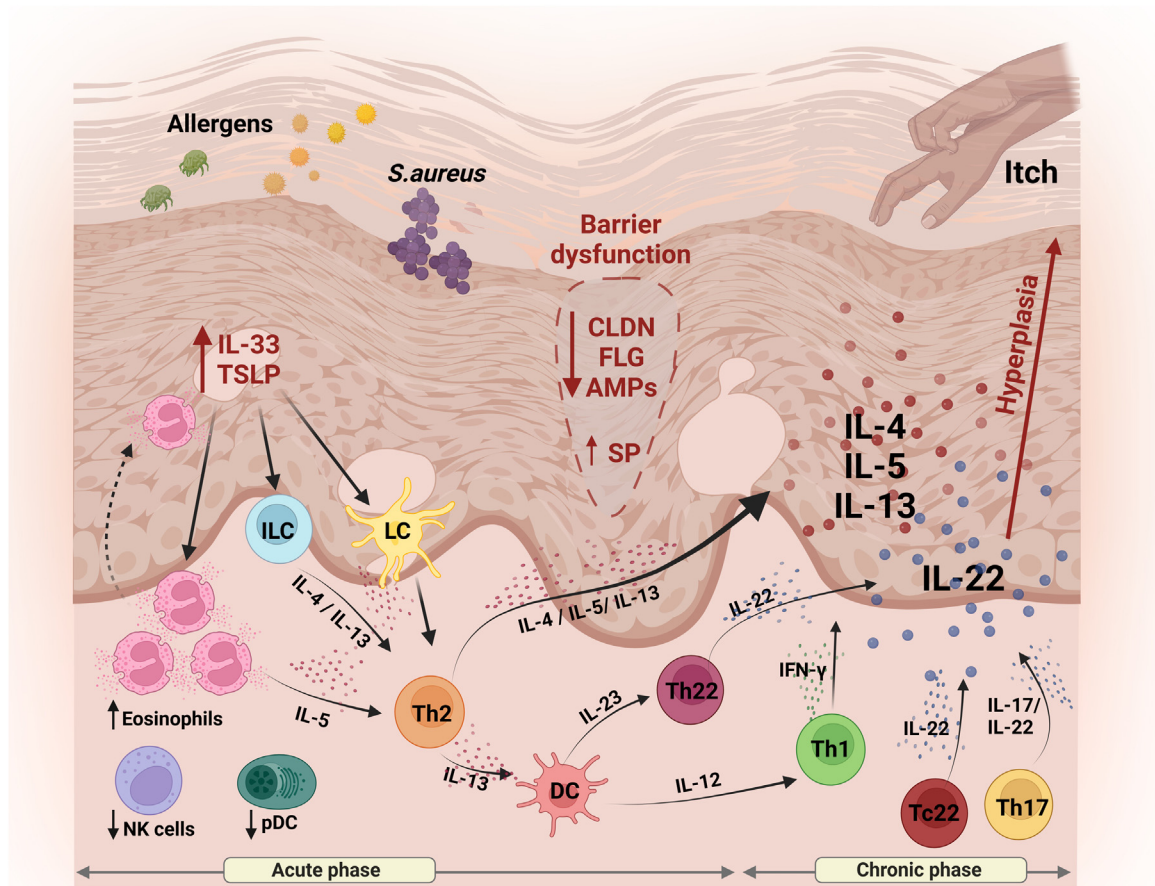


Fig. 1 Schematic representation of skin barrier (SC) alterations and the main aspects of innate and adaptive immunity involved in the pathogenesis of AD. Reduced expression of skin proteins (FLG and CLDNs) results in disruption of the BC and transepidermal water loss, facilitating the entry of external pathogens. Keratinocytes release TSLP and IL-33, amplifying the inflammatory response, attracting and activating Langerhans cells, ILCs and the recruitment of eosinophils. Together, these cells contribute to the release of Th2-type cytokines, including IL-4, IL-5 and IL-13. Dendritic cells, in turn, release IL-12 and IL-23, promoting activation of both the Th1 and Th22 profiles, resulting in the secretion of IFN- γ and IL-22, respectively. Pro-inflammatory cytokines IL-5, IL-13 and IL-31 are released by keratinocytes, which play a role in modulating pruritus, contributing to the perpetuation of the inflammatory process. In addition, IL-22 stimulates keratinocyte proliferation, promoting epidermal hyperplasia. IL, Interleukin; TSLP, thymic stromal lymphopoietin; CLDN, claudin; FLG, filaggrin; AMPs, antimicrobial peptides; SP, serine protease; ILC, innate lymphoid cells; LC, Langerhans cells; DC, dendritic cells; NK, natural killer; pDC, plasmacytoid dendritic cells; Th, T-helper. Figure generated with BioRender.

the production of chemokines by the DCs, which attract Th2 cells, an abundant subtype in AD patients (Fig. 1).^{38,39}

Epithelial cells and immune cells in the skin barrier express pattern recognition receptors (PRRs) that trigger innate immune responses. The arsenal of PRRs includes members of the Toll-like receptors (TLRs) family, C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG) cytoplasmic receptors, peptidoglycan recognition proteins (PGLYRPs) and NOD-like receptors (NLRs).^{40,41} The latter will be focused below with more details.

There are reports on the dysfunction of the TLR2, TLR9, and NOD1/2 receptors in AD patients. TLR2 recognizes peptide glycans from gram-positive bacteria and is among the most extensively studied receptors in infectious complications of AD patients. In monocytes and keratinocytes from AD patients, there was impairment of TLR2-mediated inflammatory cytokine production (IL-1 β and TNF- α).^{42,43}

In addition, the release of AMPs potentiates the strength of TJs and reinforces the defensive barrier against the invasion of microorganisms. In individuals with AD, there is a decrease in the functionality of TLRs, compromising this protective mechanism. This scenario contributes to greater susceptibility to skin infections, especially *S. aureus*.⁴⁴ *S. aureus* virulence factor itself is also an important element of the inflammation in AD patients, capable of inducing TSLP and IL-33, rather than AMPs (Fig. 1).⁴⁵

With regards to cell subtypes in AD, there is evidence of reduced function or migration to the skin of polymorphonuclear effector cells, natural killer (NK) cells and plasmacytoid dendritic cells (pDC).⁴² On the other hand, an increase in circulating eosinophils and eosinophil granule proteins has been reported in the sera and urine of patients.⁴⁶ It is worth noting that during AD crises, there is an increase in circulating IL-5 and eosinophilic chemotax-

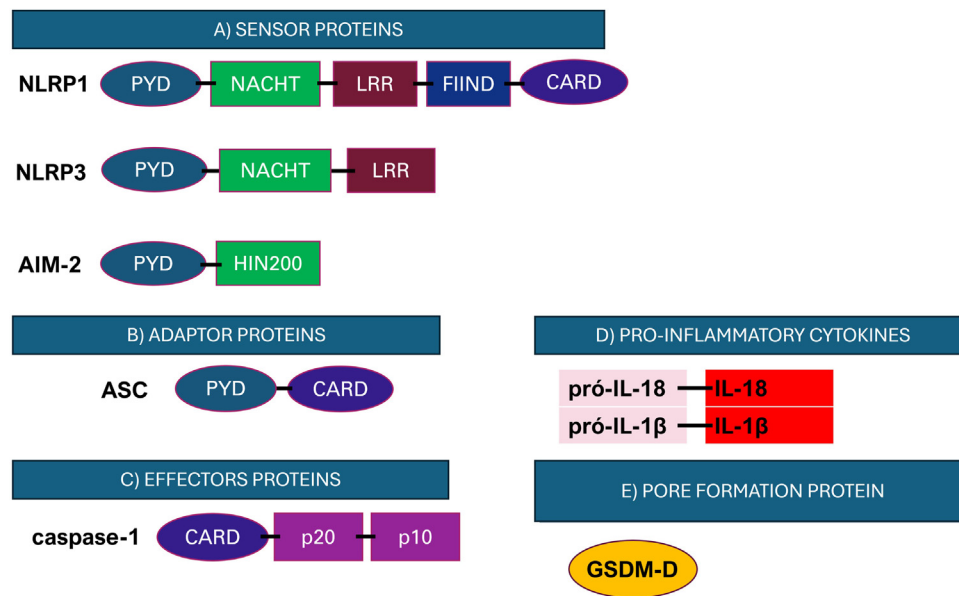


Fig. 2 Representation of the structure of the main components of the inflammasome. (A) Initiator proteins comprise cytosolic receptors; (B) ASC adaptor protein; (C) Caspase-1 effector protein; (D) Inflammatory cytokines and (E) GSDM-D pore-forming protein. NLRP, NACHT, LRR and PYD domains-containing protein; CARD, caspase recruitment domain; NACHT, Nucleotide-Binding Oligomerization Domain; LRR, Leucine-Rich Repeats; PYD, pyrin domain; HIN200, interferon-induced proteins; FIIND, function-to-find domain. Figure generated with BioRender.

ins, contributing to the extravasation of eosinophils into the skin (Fig. 1).

In AD lesional skin, there is an increased presence of activated NK cells, in contrast to their reduction in peripheral blood.⁴⁷ The authors recently found increased NK CLA+ cells in the peripheral blood of patients with severe AD and augmented expression of CD56 and granzyme in the dermis of these individuals. In addition, these cells were responsive to in vitro stimulation with microbial agonists.⁴⁸ There are reports on elevated group 2 Innate lymphoid cells (ILC2), which produce type 2 cytokines (IL-4, IL-5, IL-9 and IL-13) on the lesional skin of AD patients. More findings describe activation of ILCs by TSLP, IL-33 and IL-25, highly expressed in AD.⁴⁹

Defining inflammasomes and their role in inflammatory skin diseases

Inflammasome is an intracellular protein complex that can be activated in response to pathogens and signs of tissue damage. Its primary function is the maturation and secretion of pro-inflammatory cytokines which are fundamental for the elimination of pathogens and for tissue healing.⁵⁰ As a signaling pathway linked to the innate immune response, the inflammasome cascade is well characterized in myeloid cells, but some skin cells such as keratinocytes express its components.⁵¹ Despite its crucial role in the innate immune response, deregulated activation of the inflammasome may contribute to the development of inflammatory diseases such as rheumatoid arthritis, autoimmune diseases, inflammatory syndromes and skin diseases.⁵²

The inflammasome signaling cascade begins with the activation of initiator proteins (Fig. 2). These proteins are PRRs that recognize danger signals, such as pathogen-associated

molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).^{53,54} After activation, the initiator proteins interact with the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), which plays an essential role in the assembly of the inflammasome complex. Oligomerization of ASC via its PYD domain promotes the recruitment of pro-caspase-1, acting as a bridge between receptor interactions and pro-caspase-1.⁵⁵ This association results in the autoactivation of the pro-caspase, converting it into the effector protein caspase-1, an inflammatory caspase that cleaves its substrates pro-IL-18, pro-IL-1 β into their mature and bioactive forms IL-18 and IL-1 β (Fig. 2).^{56–58}

In addition to the processing and maturation of cytokines, the activation of caspase-1 by the inflammasome cascade may also promote the cleavage of the Gasdermin D (GSDM-D) protein.⁵⁹ GSDM-D was first described in 2015 and is expressed in immune cells and epithelial cells. After cleavage, the N-terminal portion of GSDM-D is released and inserts itself into the cell membrane, resulting in the formation of pores in the plasma membrane that lead to the release of the cytokines IL-1 β and IL-18, and a highly inflammatory cell death process called pyroptosis.^{55,57,60–62}

In addition to the canonical activation of the inflammasome mentioned above, the cytokines IL-18 and IL-1 β can also be produced through non-canonical activation of the inflammasome, when lipopolysaccharide (LPS) is directly recognized by the inflammatory caspases -4 and -5 in humans and caspase-11 in mice.^{63,64} The main activation mechanisms of the canonical and non-canonical pathways are presented in Fig. 3.

Among the inflammasome receptors, the family of NOD-type receptors is the best characterized.⁶⁵ These receptors have a tripartite structure composed of a central

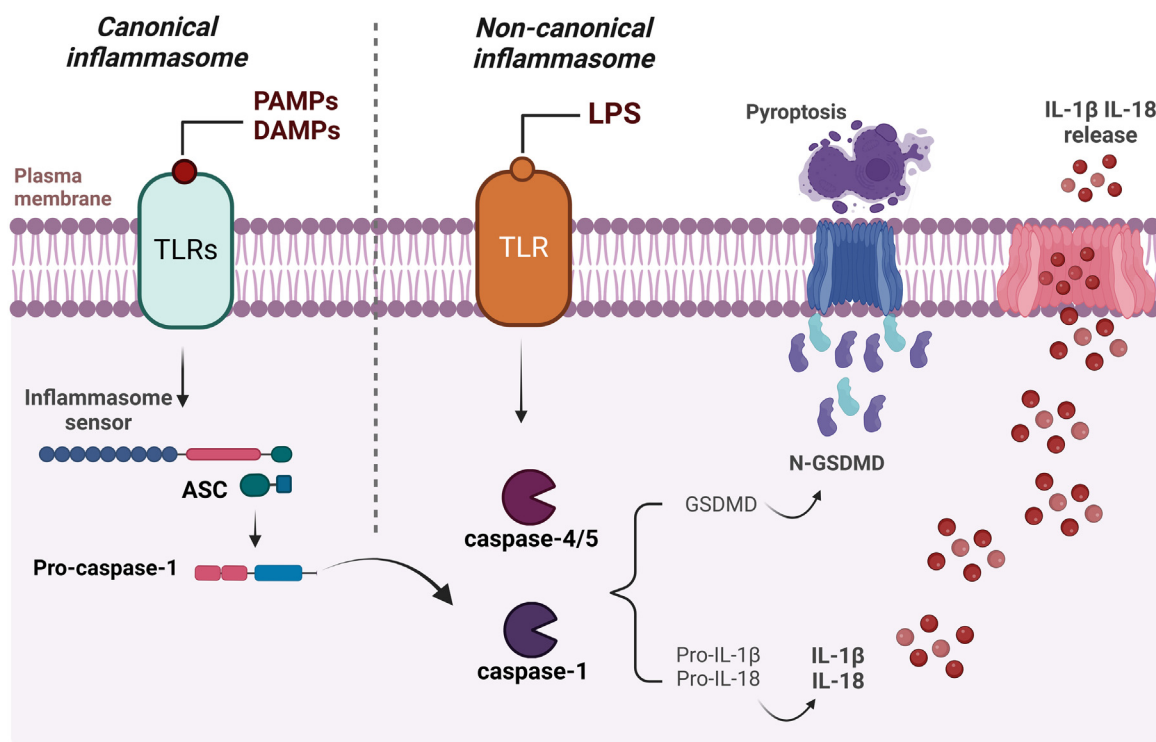


Fig. 3 Schematic representation of canonical and non-canonical inflammasome activation. The formation of the inflammasome via the canonical pathway occurs when PAMPs, DAMPs or other cytosolic disturbances are detected, resulting in the recruitment and activation of caspase-1, either directly or through the recruitment of the adaptor protein ASC. Caspase-1 initiates the process of maturation of pro-IL-1 β and pro-IL-18 into their active forms, in addition to cleaving GSDMD-D. This, in turn, interacts with the plasma membrane, creating pores and resulting in the release of intracellular content, including the inflammatory cytokines IL-1 β and IL-18. Activation of the non-canonical inflammasome begins with the detection of cytosolic LPS by caspase-4/caspase-5 (or pro-caspase-11 in mice), triggering the cleavage of GSDMD-D and subsequent pyroptosis. Figure generated with BioRender.

nucleotide-binding and oligomerization domain (NACHT), usually accompanied by leucine-rich repeats (LRRs), a C-terminal domain that recognizes and regulates ligands, and a variable N-terminal domain, which can be a caspase recruitment domain (CARD) or pyrin (PYD), responsible for the effector functions of the complex.⁶⁵ The NLR family has three distinct subfamilies: NODs (NOD1-2), NLRPs (NLRP1-14), and IPAF (ice protease-activating factor).⁶⁵

The NLRP1 inflammasome was first described in 2001 through the identification of the N-terminal PYD domain by Martinon et al.⁶⁴ The authors demonstrated the interaction of NLRP-1 with caspase-1 dependent on the presence of the ASC protein constituting the inflammasome complex.⁶⁴ NLRP1 is expressed in various immune cells, mainly in the skin by keratinocytes, and appears to play a central role as the main receptor involved in the formation of the inflammasome.⁶⁶ Indeed, UVB irradiation in primary keratinocytes causes translocation of the ASC protein to the nucleus with the formation of aggregates known as speck and this complexation is dependent on NLRP1.⁶⁷ NLRP1 also recognizes the main virulence factor of *Bacillus anthracis* and bacterial muramyl dipeptide.⁶⁸ In humans, gain-of-function mutations in the NLRP1 gene lead to syndromes mediated by inflammasome activation in keratinocytes characterized by skin inflammation and susceptibility to skin cancer.⁶⁹

The most well-known inflammasome is NLRP3, which is expressed by epithelial cells, macrophages, lymphoid cells,

chondrocytes and skin keratinocytes.⁷⁰ This receptor can be activated by a range of PAMPs and DAMPs that do not interact directly with the receptor, but induce cytoplasmic changes that lead to its activation, such as ion flows, extracellular ATP, nucleic acids, bacterial toxins, among others, and is involved in various skin diseases.⁷¹⁻⁷⁵ In keratinocytes, UVB radiation triggers NLRP3 in increased concentrations of cytoplasmic calcium (Ca²⁺), leading to the secretion of IL-1 β .^{66,76}

In patients with progressing vitiligo, NLRP3 and IL-1 β concentrations are increased in perilesional epidermal samples when compared to healthy controls.⁷⁷ In psoriasis there is higher expression of NLRP3 and of several inflammasome components such as caspase-1 and IL-1 β .^{78,79} A close relationship has been described between the pathogenesis of leprosy, colorectal cancer, rheumatoid arthritis, abdominal aortic aneurysms, inflammatory bowel disease, ulcerative colitis and AD, and the NLRP3 rs35829419 gene polymorphism.^{80,81} Bacteria (*S. aureus* and *Escherichia coli* e.g.) and environmental exposure to ultraviolet radiation led to the activation of the NLRP3 inflammasome in keratinocytes.^{71,82} NLRP3 is also necessary for the pyroptotic cell death of macrophages infected with *S. aureus*.⁷⁴

AIM-2 is a receptor first described as a tumor cell growth suppressor gene in melanoma that does not belong to the NLR family, but is capable of forming the inflammasome complex after binding directly to dsDNA (double-stranded DNA).^{83,84} Under homeostasis, DNA remains contained in

the nucleus and mitochondria, but exposure of DNA in the cytosol indicates active infection or cell damage. The AIM2 receptor responds to the cytosolic presence of the host's own DNA and amplifies sterile inflammation, as described in autoinflammatory or autoimmune diseases.⁸⁵ Furthermore, AIM2 also recognizes exogenous DNA released during bacterial infections, such as *S. aureus*,⁸⁶ or viral infections such as cytomegalovirus (CMV), and also upon detection of HPV-16 in keratinocytes, triggering an increase in the secretion of IL-1 β .^{72,87,88}

In psoriasis, cytosolic dsDNA also stimulates the activation of AIM2 expression and IL-1 β secretion. Interestingly, LL-37 inhibits the ability of DNA to induce IL-1 β production due to LL-37's strong association with DNA, which prevents it from becoming involved in the AIM-2 inflammasome and contributing to the pathophysiology of the disease.⁸⁹ In patients with lupus erythematosus, an intense expression of AIM-2 was observed in macrophages, possibly due to decreased DNA methylation in these individuals, contributing to the pathogenesis of the disease.^{90,91} Moreover, in lesions from patients with lichen planus, there is a specific increase in the AIM-2 protein in both the dermis and the epidermis, with improved dermal expression of the IL-1 β protein.⁹² Based on these findings, AIM-2 may be a therapeutic target in inflammatory and oncologic conditions, and also in autoimmune diseases.^{93,94}

Inflammasomes and atopic dermatitis

Considering the inflammatory profile of AD, the inflammasome cascade may exert a relevant role in the pathogenesis of the disease. In fact, the activation of inflammasomes by allergens or pathogens leads to increased levels of IL-1 β on the skin in autoinflammatory diseases, promoting conditions for the development of chronic inflammation.⁹⁵

Polymorphisms and mutations in the NOD1 and NOD2 genes are associated with high levels of IgE in AD patients and are relevant factors indicating susceptibility to atopy.^{96,97} Similarly, polymorphisms in the NLR4 gene, which also codes for an NLR, are associated with AD;⁹⁷ however, functional studies on the role of this receptor in the pathogenesis of the disease are still scarce.

In addition to polymorphisms, the skin of AD patients shows an increase in inflammasome components, which may favor inflammation. In fact, the highest expression of AIM-2 was found in keratinocytes from AD patients and is directly associated with acute and chronic inflammation related to SB rupture.^{98,99} These patients have intense pruritus, and the mechanical act of scratching impairs SB, causing intracellular products to be released and detected by the AIM-2 receptor. Moreover, bacterial DNA can be released after a process of bacteriolysis mediated by AMPs, and keratinocytes are able to capture exogenous DNA through receptor-mediated endocytosis.⁸⁶

The expression of NLRP1 and NLRP3 receptors is also increased in the damaged skin of AD patients and is directly associated with the severity of the disease, highlighting the importance of this signaling cascade for the inflammatory pathology of this and other skin diseases.^{70,98,100} In 2010, Grigoryev et al.,¹⁰⁰ showed that NLRP1 gene expression is inversely correlated with AD severity in skin

explants, suggesting that local inflammation could inhibit NLRP1 expression, or that reduced expression of this protein promotes skin inflammation. Furthermore, higher NLRP1 expression and caspase-1 activity were seen in mild AD patients and is associated with IL-1 β and IL-18 production.¹⁰¹ Several studies have described the relevance of variations in the NLRP1 gene in skin diseases such as vitiligo, psoriasis and leprosy, showing that NLRP1 plays a particular role in the skin.^{102–104}

Considering NLRP3, the expression of this receptor is directly associated with an increase in IL-33 in the lesions of AD patients, but this association is independent of the activation of the inflammasome cascade.⁷⁰ In addition, Cho et al.¹⁰⁵ demonstrated that IL-17 and IL-22 secreted by Th17 cells can activate NLRP3 and stimulate the secretion of IL-1 β and caspase-1 in immortalized HaCaT keratinocytes, suggesting that other pathways such as the Th17/Th22 axis play a role in the activation of the inflammasome complex. In vitro tests showed that inhibition of Drp1 (dynamin-related protein-1) – responsible for NLRP3 activation – with the compound mdivi-1 inhibited NLRP3 activation, IL-1 β and IL-18 production, as well as induction of pyroptosis.¹⁰⁶ This compound was also shown to be effective in improving the symptoms associated with AD, as well as reducing the serum IgE levels and the production of IL-4, IL-5 and IL-13 in skin lesions in a murine model of AD.¹⁰⁶ In addition, omega-3 supplementation decreases NLRP3 activation via NF- κ B, and decreases the expression of Th2 cytokines in experimental mouse models of AD, suggesting that this receptor is a target for therapeutic strategies for the disease.¹⁰⁷

Conversely, Niebuhr et al.¹⁰⁸ showed reduced expression of NLRP3 and caspase-1 in AD skin. In addition, a reduction in NLRP3 and ASC transcripts was observed in keratinocytes stimulated with Th2 cytokines (IL-4, IL-5 and IL-13).¹⁰⁸ These cytokines can also reduce caspase-1-dependent IL-1 β secretion in monocytes from AD patients stimulated with staphylococcal α -toxin, suggesting interference of the NLRP3 inflammasome in the Th2 response profile, which is relevant in the pathogenesis of AD.¹⁰⁸ The controversial findings may be the result of differences between animal and human studies, with great variability in the number of participants, indicating the need for further analysis to better understand the role of NLRP3 in the AD inflammatory response.

Recently, Ramos et al.⁹⁸ showed that there is an alteration of other components of the inflammasome beyond NLRP3 and NLRP1 receptors in AD. The authors found that ASC expression by immunohistochemistry is increased in the dermis of AD patients, as well as caspase-1.⁹⁸ Furthermore, human primary keratinocytes show enhanced ASC expression when stimulated with UV.⁶⁷

Ramos et al.⁹⁸ also identified that individuals with AD have a higher expression of GSDM-D, which may favor inflammation and local tissue damage. Interestingly, in a murine experimental model of AD induced by oxazolone, the inhibition/deletion of the GSDM-D gene decreased IL-1 β and IL-18 levels, confirming the involvement of pyroptosis in amplifying the inflammatory response in AD.¹⁰⁹ In this regard, the GSDM-D deletion promotes an improvement in AD-like lesions by decreasing the cellular infiltrate and reducing IgE and IL-4 levels.¹⁰⁹ GSDM-D is also elevated in psoriatic skin

Table 1 Association of the inflammasome with pheno-endotypical features of AD.

Inflammasome component	Main findings	References
NOD1 e NOD2	NOD1 and NOD2 gene polymorphisms associated with high IgE levels and susceptibility to atopy	96,97
NLRP1	NLRP1 expression inversely correlated with AD severity	100
NLRP3	NLRP3 gene polymorphism associated with the development of AD γ -hemolysin from <i>S. aureus</i> leads to NLRP3 activation Reduced expression of NLRP3 and caspase-1 in AD patients, relationship with Th2 response profile	80,81 112 108
NLRC4	NLRC4 gene polymorphisms associated with AD	97
AIM-2	Increased expression of AIM-2 in keratinocytes, associated with inflammation and breakdown of the skin barrier	98,99
ASC Caspase-1	Increased expression of ASC and caspase-1 in lesions of AD patients, associated with inflammation	67,98
GSDM-D	GSDM-D deletion in a murine model reduces IL-1 β , IL-18 and AD symptoms, indicating involvement in pyroptosis	109
IL-18	Elevated IL-18 levels in serum and peripheral blood mononuclear cells of AD patients	114

lesions, but serum levels of this protein are similar to the healthy control group.¹¹⁰

In counterpart, the relationship between the inflammasome cascade and colonizing bacteria in the skin microbiota of AD patients has also been studied. Recent evidence indicates that several inflammasomes are activated during an *S. aureus* infection, including NLRP3, via NF- κ B, increasing the transcription of pro-IL-1 β , activation of caspase-1, and secretion of IL-1 β , together with IL-18.¹¹¹ In macrophages, *S. aureus* γ -hemolysins can activate the NLRP3 inflammasome and caspase-1 without the participation of the P2 $\times$ 7 receptor or the Myd88/TLR adaptor. In addition, inoculation of *S. aureus* into keratinocytes led to increased secretion of IL-1 β and IL-18, and silencing of NLRP1 inhibited the production of these cytokines, suggesting that skin colonization may lead to activation of this receptor directly interfering with the inflammatory response in the disease.¹¹²

In skin diseases associated with dysregulation of the inflammasome, the effector cytokines IL-1 β and IL-18 are highly expressed, playing a significant role in the onset and exacerbation of inflammation.¹¹³ In fact, cutaneous keratinocytes are the main sources of these cytokines in the skin, and the increased expression of inflammasome components associated with exposure to *S. aureus* antigens may lead to an increase in IL-18 and IL-1 β in AD patients.^{66,114} In fact, CD68+ macrophages produce IL-1 β in the dermis of AD patients,⁹⁸ and increased epidermal expression of this cytokine is observed in AD patients with filaggrin gene mutations.¹¹⁵ Interestingly, several observations suggest that both IL-1 α and IL-1 β contribute to the development of skin inflammation with AD.¹¹⁶ Additionally, mast cells and keratinocytes from AD patients produce IL-18 in response to exposure to allergens or pathogens such as dust mites and *S. aureus*.¹¹⁷ The IL-18 produced stimulates basophils, mast cells, and CD4 T-cells to produce Th2 cytokines in acute AD lesions, while in chronic lesions, IL-18 stimulates Th1 cells to produce IFN- γ together with IL-12.¹¹⁸

The inflammatory profile triggered by inflammasome activation is also systemically reflected. Orfali et al.¹¹⁴ showed high concentrations of IL-18 in the serum of AD

patients according to the severity of the disease, regardless of the presence of staphylococcal enterotoxins. IL-18 is also increased in the culture supernatants of mononuclear cells from patients stimulated with staphylococcal enterotoxin type A (SEA).¹¹⁴ However, studies on IL-18 deficient mice show an absence of this cytokine, leading to a reduction in the worsening of skin lesions.¹¹⁹ The main changes in inflammasomes related to the pheno-endotypical features in AD are summarized in Table 1.

The above findings point out the relevance of inflammasome components in AD as potential biomarkers of the disease and possible targets for future immunomodulatory interventions (Fig. 4).

Targeted therapies and relevance of individualized therapy for key changes in AD

The use of emollients and topical corticosteroids is the first line of treatment for AD.¹²⁰ Conventional systemic therapy options for AD include cyclosporine (CsA), methotrexate, azathioprine, mycophenolate mofetil, and systemic glucocorticoids, with limited proven efficacy and potential side effects.¹²¹ With the development of new target-specific therapies aimed at inflammatory mediators, new opportunities have arisen for restoring the skin barrier, as well as for restoring the innate and adaptive immune systems in AD.¹²¹

One of the target therapies is dupilumab (DUPI), a humanized monoclonal antibody that targets IL-4R α , a subunit shared by the IL-4 and IL-13 receptors. Pivotal studies have shown significant clinical improvement and a favorable safety profile in individuals with moderate to severe AD, confirming the central role of Th2 cytokines in this disease.¹²¹ It was shown that blocking IL-4/IL-13 signaling, in addition to suppressing systemic Th2-type inflammation, increased microbial diversity, reducing the abundance of *S. aureus*, with the recovery of the altered transcriptome of epidermal proteins associated with AD. DUPI also increased the expression of FLG, LEKTI (protease inhibitor), and HBD-3

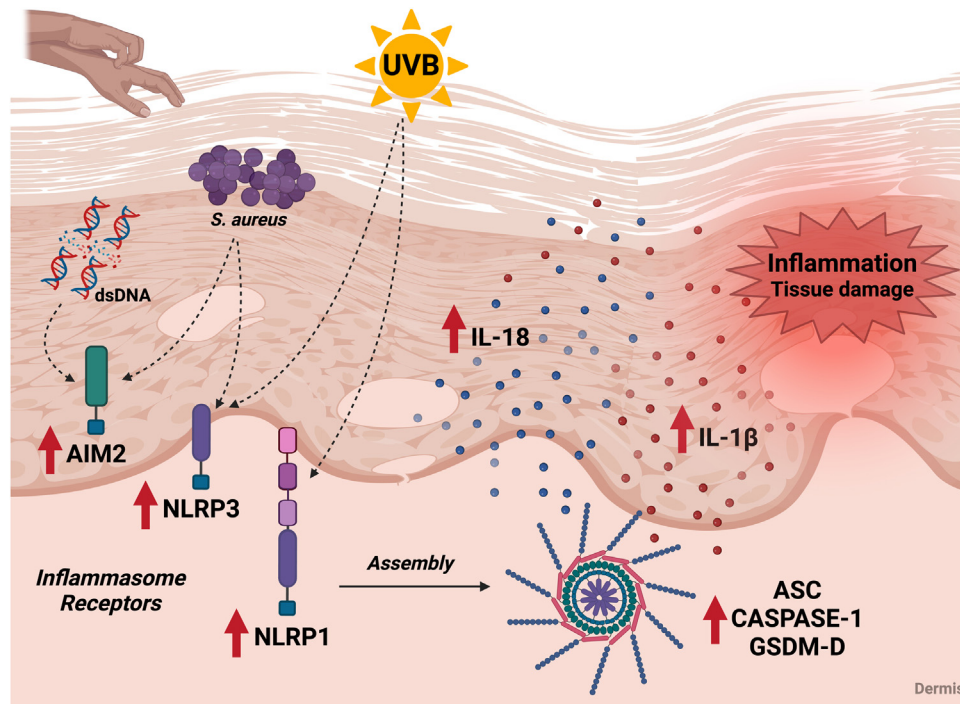


Fig. 4 Association of the inflammasome cascade with AD immunopathology. Components of the inflammasome signaling pathway are increased in the skin of AD patients. In the skin of patients, inflammasome receptors can be activated by exposure to ultraviolet radiation, by contact with *S. aureus* antigens, and by possible DNA molecules released by cell damage. These receptors promote the oligomerization of ASC and caspase-1, leading to the maturation of IL-1 β and IL-18, which are also elevated in AD patients. In addition, activation of the inflammasome leads to an increase in GSDM-D and promotion of pyroptosis. The release of pro-inflammatory and cell death cytokines contributes to tissue damage and local and systemic inflammation during the disease. UVB, ultraviolet radiation; *S. aureus*, *Staphylococcus aureus*; dsDNA, double stranded DNA. Figure generated with BioRender.

(antimicrobial peptide) after 6–8 weeks of treatment, as well as the degree of hydration of the stratum corneum, with a consequent improvement in the severity of AD after 12 weeks. Transcriptomic data from the European clinical registry (TREAT Germany) of adults with moderate to severe AD, in a comparative study of the use of DUPI vs. CsA, showed that treatment with DUPI for 12 weeks led to the normalization of BC-related genes, to a greater extent than CsA,^{122,123} and decreased expression of chemokines related to the Th2 response (e.g. CCL13, CCL17, CCL18 and CCL22). There was normalization of the expression of markers related to barrier function (e.g., CLDN8, ELOVL3, FLG, K1, K10 e LOR).^{19,124–126}

Other IL-13 antagonists (lebriquizumab and tralokinumab) have shown clinical efficacy in AD patients, demonstrating the critical role of IL-13 in the pathogenesis of AD. Since IL-4 and IL-13 reduce the expression of CB proteins such as filaggrin, loricrin, and involucrin, treatment with IL-13 antagonists is expected to positively influence the recovery of CB integrity, but more studies are needed to corroborate these findings.¹⁹

Janus Kinase (JAK) inhibitors that target JAK/STAT signaling, such as baricitinib, upadacitinib and abrocitinib, have shown promising results in some studies regarding the restoration of SB, demonstrating an increase in filaggrin expression, as well as a reduction in inflammatory signaling.¹⁹ There is a lack of publications focusing on the role of JAK inhibitors and new immunobiologicals in the recovery of SB and its components, especially targeting ele-

ments of the inflammatory response such as OX-40 Ligand (OX-40L) and OX-40 (amlitelimab and rocatinlimab),¹²⁷ as well as IL-31 (nemolizumab).¹²⁸

Regarding the therapeutic potential of inhibiting inflammasomes, NLRP3 inhibitors and their respective mechanisms in allergic diseases have been described. These include MCC950, a diarylsulfonylurea-based compound that inhibits NLRP3 activity and interferes with chloride efflux; OLT1177, an orally active b-sulfonyl cyanide molecule that binds directly to NLRP3 and inhibits ATPase activity, preventing NLRP3-ASC, NLRP3-caspase-1 interaction; CY-09, an inhibitor of cystic fibrosis transmembrane conductance regulator (CFTR) channels that inhibits NLRP3 ATPase activity; Tranilast, a tryptophan metabolite that inhibits NLRP3 oligomerization and improves NLRP3 ubiquitination; Oridonin (ent-kaurane diterpene), the main active component of *Rabdosia rubescens* that blocks the interaction between NLRP3 and NEK7; RRx-001, a pleiotropic anticancer agent that blocks the interaction between NLRP3 and NEK7. Natural products and their derivatives are also suggested as potential therapeutic strategies such as XQLD (*Xiaoqinglong Decoction*) which inhibits NLRP3 inflammasome-mediated pyroptosis; APS (*Astragalus Polysaccharide*), an inhibitor of NLRP3 activation and a blocker of NF- κ B phosphorylation, decreasing NOD2 expression; MFXD (*Mahuang Fuzi Xixin Decoction*), which inhibits the NLRP3/Caspase-1/GSDMD-N signaling pathway; *Schisandrin B*, which inhibits NLRP3 activation; *Houttuynia cordata*, which decreases the

expression of NLRP3, ASC, caspase-1, GSDMD, IL-1 β , and IL-18; and *Angelica Yinzi*, which inhibits NLRP3 activation and MAPKs/NF κ B signaling.^{129,130} Currently, there is a clinical trial for AD patients with GSK1070806, an anti-IL-18 monoclonal antibody. In phase 1b of the study NCT04975438 (<https://clinicaltrials.gov/study/NCT04975438?tab=history&a=7#study-results-card>), patients with no previous systemic treatment with biologics (non-responsive to topical therapies), and patients non-responsive or intolerant to DUPI were evaluated, with promising results. An ongoing phase 2b will evaluate the clinical effect, safety and tolerability of GSK1070806 in AD (NCT05999799 - <https://clinicaltrials.gov/study/NCT05999799?intr=GSK1070806&rank=2>).

Conclusion

AD is one of the most common chronic inflammatory skin diseases, and its persistence occurs as a consequence of the combination of genetic, environmental and immunological factors, affecting both adults and children. Skin barrier dysfunction, together with bacterial colonization and dysregulation of the innate and adaptive immune system, play a central role in maintaining inflammation and therefore the chronicity of AD. This review highlights the crucial role of inflammasomes, especially NLRP1/3 and AIM-2, in regulating the inflammatory response in skin diseases such as AD, including the release of the pro-inflammatory cytokines IL-18 and IL-1 β , which are essential in perpetuating skin inflammation. A deeper understanding of immune pathways, such as the inflammasome cascade, opens new perspectives for therapeutic interventions. Targeting treatments to modulate the immune response and restore the skin barrier may offer more effective management of the disease and improve the AD patients' quality of life.

Author's contribution

Yasmim Álefe Leuzzi Ramos: Critical review of the literature; drafting of the manuscript; preparation of figures; final approval of the final version of the manuscript.

Anna Julia Pietrobon: Critical review of the literature; drafting of the manuscript; preparation of figures; final approval of the final version of the manuscript.

Franciane Mouradian Emidio Teixeira: Critical review of the literature; drafting of the manuscript; preparation of figures; final approval of the final version of the manuscript.

Valeria Aoki: Conception and design of the study; critical review of the content; analysis and interpretation of the data; critical review of the literature; final approval of the final version of the manuscript.

Maria Notomi Sato: Conception and design of the study; critical review of the content; analysis and interpretation of the data; critical review of the literature; final approval of the final version of the manuscript.

Raquel Leão Orfali: Conception and design of the study; data collection; writing of the article and critical review of the content; obtaining, analyzing and interpreting the data; critical review of the literature; final approval of the final version of the manuscript.

Financial support

None declared.

Conflicts of interest

None declared.

Acknowledgment

The authors are thankful to FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo), grant #2018/23211-0, São Paulo, SP, Brazil.

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REVIEW

Precision medicine and Treat-to-Target approach in atopic dermatitis: enhancing personalized care and outcomes[☆]



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Received 1 October 2024; accepted 11 December 2024

Available online 18 June 2025

KEYWORDS

Dermatitis, atopic;
Epigenomics;
Multiomics;
Precision medicine;
Proteomics

Abstract

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting a significant portion of the global population. While conventional treatments effectively control and manage symptoms, there is a growing need for more personalized and precise approaches for patients. Precision medicine has emerged as a promising therapeutic strategy that tailors treatment to the individual characteristics of each patient. Complementing this, the Treat-to-Target (T2T) strategy sets specific clinical goals and involves continuous monitoring and treatment adjustments based on real-time patient responses and biomarker data.

Objectives: This review aims to explore the latest advancements in precision medicine and the T2T strategy for AD.

Methods: A comprehensive literature review was conducted to identify the most recent studies and advancements in precision medicine and the T2T strategy for AD.

Results: Recent studies highlight the effectiveness of precision medicine in achieving sustained remission and improving the quality of life for patients. The T2T strategy was shown to be effective in preventing exacerbations and adapting treatments based on real-time patient responses and biomarker data.

Study limitations: The lack of a consensus on the clinical implementation of precision medicine and T2T, limited longitudinal studies validating long-term outcomes, challenges in stratifying patients due to biomarker heterogeneity, and barriers to integrating emerging diagnostic technologies into routine practice.

[☆] Study conducted at the Department of Dermatology, Faculty of Medicine, Universidad de Chile and Department of Dermatology, Clínica Universidad de los Andes.

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Conclusions: Precision medicine and the T2T strategy represent significant advancements in the management of AD. These approaches offer the potential for more personalized, effective, and adaptive treatment protocols, leading to improved patient outcomes. Continuous research and development in these areas are essential to fully realize their potential and integrate them into routine clinical practice.

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Introduction

Atopic dermatitis (AD) is a chronic, recurrent, and multifactorial inflammatory skin disease characterized by the presence of pruritus, eczema, erythema, and xerosis. It affects people of all ages, up to 20% of children and 10% of adults in developed countries,¹ and it's associated with a significant impact on patients' quality of life. It is caused by a complex interaction of genetic, immunological, and environmental factors, leading to an alteration of the immune system that triggers inflammatory processes mainly mediated by T-cells. Among the main pathophysiological mechanisms are the disruption of the skin barrier, increased serum IgE levels, and altered synthesis of skin barrier components such as filaggrin (FLG).²

The family history of AD has been described as the most important disease risk factor,¹ and it is estimated that the heritability of AD is approximately 80%,³ highlighting the significant importance of genetic factors in this condition. Furthermore, the identification of specific disease biomarkers is crucial to understanding the pathophysiology of AD, and these biomarkers can include genetic profiles, immunological markers, and microbiome characteristics of the skin. Multiple molecules have been identified in mechanisms contributing to skin barrier damage, FLG alteration or synthesis of loricrin, changes in membrane lipid metabolism such as ceramides, loss of anchoring junction integrity, and dysregulation of the keratinocyte differentiation process.⁴ Alterations in the microbiome of AD patients have also been identified, with a reduction in commensal bacteria and an increase in the colonization of *Staphylococcus aureus* (SA) and *Streptococcus epidermidis* (SE).^{5,6} The detection and quantification of these biomarkers can provide valuable information on disease severity, treatment response, and the identification of potential therapeutic targets.

Conventional treatments for AD include topical corticosteroids and emollients, which have been the cornerstone of disease management; however, there is considerable variability in patients' responses to these therapies. Moderate to severe AD has traditionally been treated with a variety of therapeutic options, including methotrexate (MTX), phototherapy, and cyclosporine A (CsA). In recent years, the therapeutic landscape has evolved with the incorporation of new biological and targeted treatments, such as dupilumab and Janus Kinase (JAK) inhibitors.⁷ These new therapies have shown promising results in improving symptoms and patients' quality of life.⁸ However, significant challenges remain in clinical practice, particularly in determining which treatment is most appropriate for each patient and at what specific stage of their disease.⁹ Current treatment guidelines provide general recommendations

but still lack sufficient clarity and consensus regarding the personalization of treatment based on individual patient characteristics. This uncertainty highlights the need for a more precise and personalized approach to managing moderate to severe AD.

In this context, precision medicine emerges as a new perspective in the treatment of AD, allowing a more individualized approach tailored to the genetic, biomolecular, and environmental characteristics of each patient (Table 1). This review aims to explore the latest advancements in precision medicine and the T2T strategy for AD.

Material and methods

During August and October 2024, the authors conducted a narrative review of the literature by entering the terms "precision medicine," "atopic dermatitis," "treat-to-target therapy," "dermatology," "omics," "epigenomic," and "proteomic" into PubMed and Google Scholar. The search was limited to articles in English and Spanish. All three authors participated in the search and subsequently selected the articles based on their relevance.

Results

Precision medicine

The term "precision medicine" refers to the concept of tailoring the treatment and prevention of diseases by considering the different genetic, environmental, or lifestyle factors specific to groups of people.¹⁰ Currently, precision medicine uses the genetic and molecular information of a group of patients to develop specific and optimized medications or treatments; its primary goal is to ensure that each medication or treatment is the most suitable for treating an individual, focusing also on a reduction of side effects and greater efficacy.¹¹

Advances in new technologies in the areas of molecular and structural biology, also known as omics, will play a key role in understanding the pathophysiological mechanisms of this disease and could develop preventive strategies and personalized treatments.^{1,12} Precision medicine primarily focuses on human genetic information. Genetics involves the study of genes, their effects, and their relationship with inheritance. Within these areas are the "omics" sciences, which include: genomics, transcriptomics, proteomics, metabolomics, glycomics, lipidomics, epigenomics, metallomics, metagenomics, among others^{11,13} (Table 2). For the study of these omics and measurement of biomarkers, there are different techniques of transla-

Table 1 State-of-the-art of the knowledge about Precision Medicine and Treat-to-Target therapy in atopic dermatitis.

Precision Medicine	Treat-to-Target (T2T)
Is the treatment based on individual genetic, molecular and environmental characteristics.	T2T is a set of specific clinical goals for remission or disease reduction with regular monitoring and adjustments.
The goal is optimizing therapy effectiveness and personalize treatment to specific patient profile. The techniques correspond to the omics sciences, focused on the genetic insights in atopic dermatitis (FLG, SPINK5, RETN, IL-13, TSLP, among others). Tools: GWAS, NGS and PRS.	The goal is to achieve clinical goals through defined steps, constant evaluations, and treatment adjustments. Use of validated measures (e.g., EASI, Pruritus NRS, DLQI) to assess treatment effectiveness and adjust therapy.
Biomarkers focused on treatment response (IL-22, IL-16) and prognostic (CCL22 levels in the skin). It can be applied to predictive tools (e.g., Mind.Px™ patch) to determine patient response to biologics and stratification based on cytokine profiles (e.g., Th1/Th2/Th17 dominance).	Framework for systematic decisions (e.g., increasing dose, adding therapies, or switching treatment). It focusses on the integration of outcome measures and patient collaboration for better adherence and shared decision-making.
Diagnostic tools like RNA microneedle patches and gene expression profiling for non-invasive diagnosis and therapy optimization.	Adjust therapies based on treatment response criteria, transitioning from flare control to remission.
The challenges are the translating omics-based findings into clinical practice, and the higher costs and accessibility of technologies.	The challenges are the lack of universal consensus for dermatological T2T approaches, and the need for multidisciplinary agreements.
We still need the validation of biomarkers for therapy and prognosis, and more studies on response profiles for different endotypes.	The T2T still need the development of standardized criteria and tools to the correct implement of T2T broadly in atopic dermatitis.

tional immunologic approaches to measuring biomarkers in inflammatory skin conditions such as tape stripping, microneedle-based dermal biomarker patch, molecular profiling from epidermal curettage, RNA in situ hybridization staining, single-cell RNA sequencing,¹⁴ suction blistering¹⁵ and skin microdialysis¹⁶ (Table 3).

Genetics in atopic dermatitis

Precision medicine recognizes the importance of individual factors such as genetics, medical history, and the patient's environment in the development and management of AD. Personalized approaches can include selecting specific treatments based on genetic profiles, identifying and avoiding environmental triggers, and regularly monitoring treatment responses using specific biomarkers. The implementation of personalized strategies can significantly improve treatment efficacy and tolerability, as well as reduce the risk of unwanted side effects.

As previously mentioned, genetics plays a key and fundamental role in the etiopathogenesis of AD. The first genetic linkage study, which compared the inheritance of genetic markers with the presence of a clinical trait to identify AD risk genes, identified an important susceptibility locus on chromosome 3q21.¹⁷ Additionally, the *FLG* gene, which encodes filaggrin, is one of the best-known genes associated with AD susceptibility and severity.¹⁸ A similar association has been found with another mutation in the serine protease *SPINK5*.^{19,20} Studies conducted in Asian populations identified an association between the *SPINK5* gene, which encodes a serine protease inhibitor involved in maintaining the skin barrier, and AD susceptibility.²¹

In recent years, multiple genetic risk factors related to AD have been identified, including *ADAM33*, *RETN*, *TGFB1*, *CD207*, *TSLP*, *IL-13*, *IL-4*, *IL-31*, *IL6R*, *STAT3*, *KIF3A*, and *HLA-DBQ1*, among others^{13,22–27} (Table 4). Genetic risk factors for AD have been identified through genetic linkage studies, candidate gene approaches, Genome-Wide Association Studies (GWAS), and more recently, Next-Generation Sequencing (NGS) technologies, which have contributed to a better understanding of the genetic risk basis of AD.¹

GWAS is a statistical approach that compares the allelic frequency of millions of genetic variants between patients and healthy subjects to identify loci associated with clinical traits.²⁸ These studies have identified more than 40 genes associated with AD risk, including the *FLG* gene, and risk loci such as *SERPINB7*, *DSC1*, and *ITGB8*, among others.¹ In phenotype-wide association studies, a loss-of-function variant of *FLG* is associated with different clinical phenotypes of AD, such as asthma, allergic rhinitis, and food allergy.²⁹ Genetic variation in the *MMP ADAM33* genes and the *CD14* monocyte receptor has also been associated with allergic bronchitis and asthma, respectively.³⁰

Next-generation Exome Sequencing (WES) allows the identification of genetic variation in exomic regions, enabling the characterization of genetic factors underlying AD.¹ Rare variants in *FLG* and other genes such as *GTF2H5*, *EVPL*, or *NLRP1* have been identified in African populations.³¹ Another study identified a mutation in *CARD11* that generates potentially correctable cellular alterations leading to AD.³²

Among the new advances in genetic studies, Polygenic Risk Scores (PRS) have emerged. These scores are being used to identify patients at risk of developing AD and who are

Table 2 Omics sciences use in medicine.

Omics	Study	T	Detection
Genomics	The study of all the genes of a person (genome), including gene interactions with each other and their environment.	DNA	GWAS, NGS
Transcriptomics	The study of the transcriptome, the quantity, and activities of all RNAs (coding and non-coding), at a given time and place.	mRNA	NGS
Proteomics	The study of the proteins of an organism, tissue type, or cell (proteome).	Proteins	Microarrays, RNA-seq Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF-MS) and Liquid Chromatography Coupled with Tandem Mass Spectrometry (LC-MS/MS).
Metabolomics	The study of small molecules (metabolites) within tissues, biofluids, or cells; and their interactions within a biological system (metabolome). It reflects the underlying biochemical activity and state of cells or tissues.	Metabolites	Mass Spectrometry (MS)
Glycomics	The study of carbohydrates within a cell or tissue.	Carbohydrates	Mass Spectrometry (MS)
Lipidomics	The study of lipids within a cell or tissue.	Lipids	Mass Spectrometry (MS)
Epigenomics	The study of the complete set of epigenetic modifications on the genetic material of a cell (epigenome).	DNA	ChIP-Seq/Hi-C/ChIA-PET
Metallomics	The study of metalloproteins, metalloids, and metals within a cell or tissue. It is a branch of metabolomics.	Metalloproteins, metalloids, and metals.	Atomic Absorption Spectroscopy (AAS), Inductively Coupled Plasma Mass Spectrometry (ICP-MS)
Metagenomics	The study of the genomes of a microbial community.	DNA/rRNA	NGS

more likely to benefit from early therapeutic intervention. PRS is a quantitative measure that estimates an individual's genetic risk burden for developing a specific disease, calculated by aggregating the risk conferred by multiple small-effect variants distributed throughout the genome.¹

Applications of precision medicine

Recently, the development of non-invasive diagnostic tools for AD and psoriasis has helped with different conditions and guided effective therapies. Additionally, patients often experience frustration due to trial-and-error treatment approaches, which delay disease control and impact quality of life. Two companies, Mindera Health and Castle Biosciences, are pioneering non-invasive technologies to

address these challenges.³³ Mindera Health developed the Mind.Px™ dermal patch, which uses microneedles to collect RNA from skin samples. Machine learning and genetic biomarkers predict patient responses to specific psoriasis biologics, reducing trial-and-error treatments.³⁴ Clinical studies (e.g., STAMP-2, MATCH) demonstrated its economic and clinical benefits, showing high predictive accuracy in severe psoriasis cases, and reducing biological therapy costs.³³ On the other hand, Castle Biosciences uses non-invasive skin scrapings and gene expression profiling to distinguish between psoriasis, AD, and other conditions like mycosis fungoides.³³ Preliminary studies identified distinct genetic markers linked to treatment responses in patients using drugs like dupilumab and risankizumab.³⁵ Ongoing clinical trials aim to validate these findings and optimize

Table 3 Investigational approaches for precision medicine in atopic dermatitis.

	Tape Stripping	Microneedle-based dermal Biomarker Patch	Molecular profiling from epidermal curettage	RNA in situ hybridization staining	Single cell RNA sequencing	Suction Blistering	Skin microdialysis
Tecnicue	Adhesive tape strips are repeatedly applied to a patient's skin	Micron-sized needles sample RNA or protein from the skin	Curretting superficial epidermal tissue	Detects specific mRNA molecules by hybridation of complementary 18–25bp probes and using a chromogeni or fluorescent molecule	Transcriptomic analysis of individual cells in tissues	Blisters are induced with negative pressure in the dermo-epidermal junction. The blister fluid is used for proteomic analysis and cells for transcrip-tomic analysis.	A microdial-ysis probe tip is inserted at the dermoepi-dermal junction and the membrane is perfused with physio-logical solution and molecules in the dialysate are collected.
Layers of skin obtained	Superficial epidermis	Epidermis and upper Dermis	Varies depending on anatomical location	Epidermis and dermis	Epidermis and dermis	Epidermis and upper dermis	Not reported
Sequencing analysis	Yes	Yes	No	No	Yes	Yes	No
Biopsy needed	No	No	No	Yes	Yes	No	No
Limitations	Predominantly samples stratum corneum and difficulties standardiz-ing	Less invasive than biopsy and the technique could lead to irritation and discomfort	There is no data reported on the repro-ducibility of the collection method	Difficulty of analyzing large cytokine panels since each target requires a separate probe	Difficulty in integration into the clinical workflow and samples may need to be processed fresh.	Time required for blistering formation (1 hour)	The collection of molecules varied with body tem-perature, blood flow and perfusion rate. It is difficult to standardize these factors.

systemic therapy selection. These companies aim to revolutionize precision medicine in dermatology by improving diagnosis and tailoring treatment based on genetic profiles, but there still challenges to resolve, including insurance coverage, integration into clinical workflows, and patient acceptance. Successful implementation of these technologies could significantly reduce the burden of inflammatory skin diseases.

Proteomics has been useful in finding biomarkers for both treatment response and prognosis. Studies have observed

elevated levels of various inflammatory protein markers in both lesional skin and serum of patients, including proteins related to immune response activation and associated with Th1, Th2, Th17, and Th22 responses.³⁶ These methods have also been used to identify treatment response markers, measuring levels of chemokines and cytokines such as IL-22 and IL-16 before and after treatment with topical corticosteroids, showing a decrease in observed levels, and even correlating the decrease in IL-16 with clinical improvement after topical treatment.^{37,38} In 2023,

Table 4 Genes associated with atopic dermatitis.

Gene	Location	Function	Reference
Filagrin	Chromosome 1q21.3	Part of the epidermal differentiation complex. Skin barrier development and maintenance.	(Løset M, 2019) ²⁹
SPINK5	Chromosome 5q32	Protease inhibitor for epidermis homeostasis	(Bin L; 2016) ²⁸
ADAM33	Chromosome 20p13	Cell-cell and cell-matrix interactions, cell migration and cell adhesion	(Matsuse A; 2009) ²⁴
TSLP	Chromosome 5q22.1	Promotes Th2 immune response	(Bin L; 2016) ²³
IL-4	Chromosome 5q31	Part of the Th2 signaling pathway	(Bin L; 2016) ²³
IL-13	Chromosome 5q31	Part of the Th2 signaling pathway	(Bin L; 2016) ²³
IL-31	Chromosome 5q31	Part of the Th2 signaling pathway	(Bin L; 2016) ²³
IL6R	Chromosome 1q21.3	Immune response in multiple axes	(Nakajima S; 2024) ¹³
STAT3	Chromosome 17q21.2	JAK-STAT signalling in multiple immune axes	(Nakajima S; 2024) ¹³
HLA-DBQ1	Chromosome 6p21.32	Antigen presentation	(Nakajima S; 2024) ¹³
CD207	Chromosome 2p13.3	Activation of Langerhans cells	(Nakajima S; 2024) ¹³
KIF3A	Chromosome 5q31	Formation of motile and nonmotile primaria cilia. Associated to asma and atopic march.	(Stevens ML; 2020) ²⁵
RETN	Chromosome 19p13	Promotes expresión of pro-inflammatory cytokines	(Banihani SA; 2018) ²⁷
TGFB1	Chromosome 19q13.2	Modulates inflammation and tissue remodeling	(Shafi T; 2024) ²⁶

Bakker et al. conducted a review of various studies that attempted to classify AD patients based on their immunologic biomarkers.³⁹ Among the existing studies to date, Thijs et al. and Bakker et al., in different cohorts identified the following endotypes (Table 5): Dominant Th1/Th2/Th17 Profile, Dominant Th2/Th22/PARC Profile, and Dominant Th2/eosinophils Profile. The first two groups showed high levels of IL-4, IL-5, and IL-13 expression.^{40,41}

For this reason, it has been suggested that they could be good candidates for targeted therapies such as dupilumab (anti-IL-4/IL-13 monoclonal antibody), tralokinumab (anti-IL-13), and Lebrikizumab (anti-IL-13),^{42,43} while patients in the remaining group may require drugs with a broader action profile, such as JAK inhibitors (upadacitinib, abrocitinib, baricitinib).^{39,41} However, more studies are still needed to evaluate the different response profiles of each of these endotypes to the existing therapeutic options.

Thus, the authors can define 2 endotypes based on cytokine expression, referred to by Dyjack et al. as Type 2-predominant inflammatory response endotype and non-Type 2-predominant inflammatory response endotype⁴⁴ (Table 6). In turn, cytokine-based endotypes can be stratified by

patient age. It has been observed that children with early-onset AD have a Th2/Th22/Th17 predominance,^{45,46} with a lack of Th1, while adults have a Th22 predominance.⁴⁷ It has also been observed that adolescents have higher levels of IL-22.⁴⁸

Regarding prognostic biomarkers, CCL22 expression levels in the skin have been identified as a marker that predicts clinical improvement during the use of various targeted therapies such as topical crisaborole, CsA, and fezakinumab (anti-IL-22 monoclonal antibody).⁴⁹

Targeted treatment or Treat-to-Target (T2T)

In managing patients with AD, decision-making for selecting treatment and guiding evaluation in individual patients can be complex and often subjective.⁵⁰ The introduction of highly effective drugs has led to the development of treatment algorithms based on specific treatment response targets, using algorithms to guide decisions to continue, discontinue, or modify treatment.⁵¹ The “Treat-to-Target” (T2T) strategy is defined as a targeted treatment (towards remission or reduction of disease activity) and the appli-

Table 5 Bakker endotypes of atopic dermatitis.⁴¹

Endotype	Immune Pathway	Biomarkers	Clinical Characteristics	Treatment Implications
Th1/Th2/Th17 Dominant Profile	Th1, Th2, Th17	IL-4, IL-5, IL-13, IL-17.	Mixed immune activation; observed in some cohorts; associated with inflammation and barrier dysfunction.	Dupilumab (anti-IL-4/IL-13), Tralokinumab (anti-IL-13), and Lebrikizumab (anti-IL-13).
Th2/Th22/PARC Dominant Profile	Th2, Th22	IL-4, IL-5, IL-13, PARC (CCL18).	High allergic response, skin thickening (lichenification); linked to chronic AD lesions.	Dupilumab (anti-IL-4/IL-13), Tralokinumab (anti-IL-13), Lebrikizumab (anti-IL-13).
Th2/Eosinophils Dominant Profile	Th2	IL-4, IL-5, IL-13, Eosinophils.	Strong allergic sensitization with significant eosinophilia; typical of severe allergic phenotypes.	May require broader treatments like JAK inhibitors (Upadacitinib, Abrocitinib, Baricitinib) due to complex immune involvement.

Table 6 Th2 predominant and Non-Th2 predominate endotypes of atopic dermatitis.⁴⁴

Type Th2-Predominant Endotype	Non-Type Th2-Predominant Endotype
This endotype is driven primarily by Th2-mediated cytokines: IL-4, IL-13, and IL-31. It is associated with acute inflammation, itch, and barrier dysfunction due to the suppression of antimicrobial peptides and proteins like filaggrin. Treatments like Dupilumab (anti-IL-4/IL-13) and other biologics targeting Type 2 cytokines are effective in managing this subtype. This form is prevalent in most patients with AD, including children and those with early-onset disease.	This subtype involves Th1, Th17, and Th22 pathways alongside Type 2 responses, especially in specific patient populations or chronic phases. Cytokines such as IL-17, IL-22, and IFN-γ are more pronounced in this group. It is often observed in older patients or those with more complex AD presentations. Broader immunomodulators, including JAK inhibitors, may be needed for treatment due to the overlap of pathways.

cation of strict controls (scheduled visits with respective treatment adjustments) to achieve a proposed goal.⁵² Another definition of T2T could be the therapeutic strategy of defining treatment with a specific objective through defined steps with constant evaluations to determine if the proposed objectives have been achieved.⁵³

This approach provides a framework to support treatment options made using shared clinical information, and decision-making with patients, including discussion of relevant risk/benefit issues of existing or alternative treatments.⁵⁰ While T2T is well-defined in other inflammatory/immunological pathologies, there are still no clearly established consensus for dermatological diseases. However, T2T is highly relevant in AD, which represents a therapeutic challenge due to its heterogeneous clinical presentation and significant impact of symptoms on quality of life, especially pruritus.⁵⁴

A recent international consensus on T2T in AD determined that patients should be evaluated with validated measures such as the Eczema Area and Severity Index (EASI), the Maximum Pruritus Numeric Rating Scale, the Dermatology Life Quality Index (DLQI), and the Patient-Oriented Eczema Measure at 3-and 6-months, using a T2T strategy. The Committee combined clinical experience with available recommendations and guidelines, including those from Harmonizing Outcome Measures for Eczema (HOME), to develop practical T2T criteria. A unanimous agreement was reached to evaluate patients with at least 1 of 2 physician-assessed outcome measures (EASI and Physician's Global Assessment) and at least 1 of 3 patient-reported outcome measures (Pruritus Numeric Rating Scale, DLQI, and Patient-Oriented Eczema Measure). With 3 medical visits per year to achieve the ideal therapeutic transition from flare control to induction and maintenance of remission. A treatment will be considered

effective if at least one physician-assessed outcome goal and at least one patient-reported outcome goal are met. If target criteria are not met, modifications should be made to optimize the current treatment (e.g., increasing the dose or frequency of systemic therapy), adding adjunctive treatment (e.g., phototherapy or another systemic therapy), or changing the current treatment.⁵¹

In conclusion, although the T2T approach can become a useful tool to simplify therapeutic goals and management of AD, its foundation is just beginning to be built. A multidisciplinary approach, including a wide range of stakeholders, including patients, is needed to better define the essential components necessary to use T2T in AD.⁵⁵

Discussion

Precision medicine represents a new era in the treatment of AD, marking a transition from the “one drug fits all” approach, where treatments are stratified and defined based on the severity of the disease, to a more personalized view. This approach considers that it is unlikely for all patients to have the same response to treatments, so therapeutic decisions are based on the specific endotype of each patient, adapting to the biological characteristics and needs of the patient.

Moreover, precision medicine appears to be the way forward for guiding this diagnostic and therapeutic process with the T2T strategy. Unlike clinical phenotypes, which may not be useful for predicting the course of the disease,⁵⁶ considering the biological, genetic, and molecular individuality of each patient allows us to predict the response to each treatment and thereby achieve the desired goal. This is especially relevant in current times, with the introduction of new systemic treatments, including biological drugs and JAK inhibitors for the treatment of atopic dermatitis. Stratifying patients based on their predominant immunological biomarkers will enable us to use existing therapies more efficiently and targeted in patients with a specific endotype where they will achieve better results.^{39,57} This not only maximizes therapeutic outcomes in patients requiring these therapies, who often have moderate to severe cases that have not responded to other treatments previously,⁵⁰ but also allows for better use of these resources.

It is important to consider that precision medicine emerges as a response to the need for a more personalized approach to the treatment of atopic dermatitis. However, to integrate its use into daily clinical practice, it is still necessary to develop various studies. These studies should aim to validate the existing findings and evaluate the clinical response and the levels of response markers (IL-22 and IL-16), and prognostic markers (CCL22) proposed within different patient groups using the existing therapies. This way, therapeutic algorithms can be developed based on this approach, and scientific findings will translate into tangible benefits for patients.^{39,57}

Conclusion

Precision medicine represents a new era in the treatment of AD, offering more personalized approaches tailored to the individual needs of each patient. The identification of

specific biomarkers, the development of targeted therapies, and the application of personalized approaches are key aspects in the successful implementation of precision medicine in AD. T2T corresponds to a tool that should be agreed upon by local expert groups, with objectives that are modified over time, and that allow making decisions with the patient. However, further research is needed to validate these approaches and translate scientific findings into tangible clinical benefits for patients.

Authors' contributions

Dan Hartmann: Approval of the final version of the manuscript; critical literature review; manuscript critical review; preparation and writing of the manuscript

Catalina Retama: Altbir: Critical literature review; manuscript critical review; preparation and writing of the manuscript.

Fernando Valenzuela: Approval of the final version of the manuscript; critical literature review; effective participation in research orientation; manuscript critical review; preparation and writing of the manuscript.

Financial support

This research has not received specific support from public sector agencies, the commercial sector, or non-profit entities.

Conflicts of interest

None declared.

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SPECIAL ARTICLE

Latin American consensus on tapering of biological therapy in psoriasis[☆]



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Received 2 August 2024; accepted 17 October 2024

Available online 18 June 2025

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<https://doi.org/10.1016/j.abd.2025.501134>

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KEYWORDS

Biological therapy;
Consensus;
Delphi technique;
Drug tapering;
Latin America;
Psoriasis

Abstract

Background: Biologic therapy is an effective psoriasis treatment. However, its long-term use carries the risk of serious adverse effects and high costs for the healthcare system, which is particularly relevant in resource-limited Latin American countries. Therefore, there is scientific interest in exploring the feasibility of tapering therapy in low disease activity or clinical remission.

Objective: To provide expert consensus-based recommendations to guide personalized and efficient tapering of biologic agents in adult patients with cutaneous psoriasis.

Methods: Following an exhaustive systematic literature review, a consensus was developed using a modified Delphi methodology by a group of Latin American clinical dermatologists and an independent methodological team. The topics covered include treatment goals, tapering objectives and strategies, regimens, monitoring and tapering failure, and implementation considerations in patients with psoriasis treated with biological agents.

Results: The expert panel reached a consensus on five general principles and 13 recommendations for tapering biological therapy for psoriasis. These recommendations provide scientific support for dermatologists and healthcare providers regarding criteria for tapering, strategies and regimens, monitoring, failure management, and considerations for implementation.

Conclusion: Tapering of biologics appears to be effective and safe in psoriasis patients with low stable activity or clinical remission. This Latin American consensus was developed in recognition of the need for rational and optimal use of biologics, while individualizing cases to apply best clinical practices.

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Introduction

Psoriasis is a chronic inflammatory skin disease with a strong genetic predisposition and autoimmune pathogenic features.¹ It is estimated to affect between 2% and 3% of the world's population, with a higher incidence in Nordic countries and a lower incidence in equatorial countries.¹ In Latin America and the Caribbean, the incidence of psoriasis has been estimated at 120 per 100,000 patient-years among those attending a dermatology consultation,² representing a high burden on the healthcare system. Long-term therapy is often required for its management. The treatment choice is determined by disease severity, comorbidities, and access to medical care.¹

When first-line treatments, such as methotrexate or cyclosporine, fail to control the disease or are contraindicated,³ biological therapy has proven to be effective in reducing skin lesions, joint involvement, inflammatory burden, and emerging comorbidities.⁴ Despite its efficacy, the prolonged use of biological agents is associated with serious adverse events and a high cost of care. Consequently, it is of scientific interest to analyze whether a gradual dose reduction can diminish the disadvantages of prolonged use of this therapy once a stable state of low disease activity or clinical remission is achieved.⁴

The evidence remains inconsistent regarding the dose tapering of biologics once the therapeutic goal is achieved. Gradual dose tapering has been shown to offer potential benefits by reducing side effects, the burden of repeated injections, and the cost of biological therapy.⁴ However,

clinical guidelines for gradual dose tapering of biologics in patients with psoriasis are lacking, especially in low-income countries where the annual cost of this type of therapy can be double that of European countries.^{5,6}

The objective of this Latin American initiative is to provide recommendations based on expert consensus to guide the personalized and efficient management of dose reduction of biological agents in adult patients with cutaneous psoriasis, as well as to provide eligibility criteria, reduction strategies, and outcomes to be evaluated when deciding to carry out this strategy, guaranteeing the efficacy and safety of treatment.

This document is intended for dermatologists, especially those who use biological therapy in their clinical practice, and other health care and administrative professionals interested in the subject in the context of rational use of health care resources. The recommendations should be analyzed and implemented in the context of individualized care, adapted to individual clinical circumstances and the realities of Latin American countries.

Methodology**Participants**

The consensus group comprised clinical dermatologists who discussed, defined, and voted on the final recommendations. They were selected from different countries in Latin America (Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador,

Guatemala, Mexico, Paraguay, Peru) based on their specific experience with psoriasis and willingness to participate in related activities. An independent methodology team guided the entire process. All participants completed a declaration of interest, which was analyzed to identify potential conflicts. Information on the participants and their declarations of interest is described in Supplementary Appendix 1.

Scope and evidence search

The target population is people aged 18-years and older diagnosed with cutaneous psoriasis, excluding arthropathy, who are being treated with biological agents and for whom tapering has been decided. For this document, tapering refers to the reduction in dose or frequency of the amount of biological medication administered to the patient once therapeutic goals have been achieved. Topics covered include treatment goals, tapering strategies, regimens, monitoring, tapering failure, and implementation considerations.

An exhaustive systematic literature review was performed to inform the recommendations for tapering biological therapy in psoriasis patients. Searches were conducted in electronic databases, including Medline (PubMed), Embase, and Ovid, as well as databases from compiling agencies and developers of clinical practice guidelines. Search strategies were tailored to each database using the following terms: "psoriasis" AND "tapering" OR "dose-adjustment" OR "optimization" AND "biologic". Initial searches were conducted in May 2022 and updated in April 2023.

The inclusion criteria encompassed clinical trials, observational studies, and systematic literature reviews that evaluated the tapering or suspension of biological therapy. Secondary sources, such as clinical practice guidelines, evidence-based recommendation documents, and economic studies, were also considered based on information needs. Documents produced in the last seven years available as full publications, abstracts (provided they contained relevant information), in press, or gray literature were included. There were no language restrictions. Additionally, searches were conducted on the websites of relevant international scientific societies.

For the selection of identified references, two reviewers independently evaluated the documents based on the eligibility criteria. The initial screening was performed by reviewing titles and abstracts, followed by a full-text review. Disagreements regarding inclusions were resolved through discussion. For the quality assessment of the selected studies, the Cochrane risk of bias tool⁷ was used for Randomized Clinical Trials (RCTs),⁷ the Newcastle-Ottawa Scale⁸ for observational studies, and the Joanna Briggs Institute Checklist⁹ for analytical cross-sectional studies. Detailed specifications of the search, selection, and quality assessment processes are provided in Supplementary Material 1.

Delphi process

A formal consensus was reached using the modified Delphi methodology. Based on the selected evidence, a list of

statements was prepared according to a thematic matrix. The panel of experts reviewed the questionnaire to determine the need for adjustments, deletions, or additions. The final version of the questionnaire included 64 items organized into thematic blocks: criteria for tapering (goals and objectives), strategies and regimens, follow-up, definition of failure or relapse during tapering, re-treatment, and other considerations.

In the first round, all panel members completed the Delphi questionnaire asynchronously and anonymously online. The degree of agreement with the statements was recorded using a 5-point Likert scale.¹⁰ The expert judgments were tabulated and presented in a second round, maintaining the confidentiality of each member's opinions. Items lacking clear consensus and controversial aspects were addressed through exhaustive deliberations and anonymous synchronous votes to reach the final consensus. Detailed Delphi process specifications and results are provided in Supplementary Material 2 and illustrated in Fig. 1.

Presentation and interpretation of consensus statements

In the following section, the statements are organized by subject. When a statement indicates that an action "must be performed", it signifies that there is solid evidence of moderate or high quality supporting the efficacy and benefits of the recommended action. Additionally, there is a consensus among panel participants that this action should be performed in almost all cases. Conversely, when it is mentioned that an action "could be carried out" or "could be considered", it implies that the intervention is supported by limited or low-quality evidence or lacks applicability to Latin American scenarios. The general agreement among the panel is that such actions could be implemented in selected circumstances, considering the particular characteristics of the patient and the context of care.

Results and discussion

The consensus process resulted in 13 recommendations for tapering biological therapy in psoriasis patients. The use of strategies to reduce the dose or extend the interval of administration of biological agents in patients with psoriasis should be planned according to the general principles described in Table 1.

The characteristics of the selected studies are described in detail in Supplementary Appendix 3. This evidence includes eight clinical trials (10 publications) that evaluated the efficacy of dose reduction or interval prolongation of biological agents.¹¹⁻²⁰ These studies included between 111 and 2,546 patients who had been treated for ≥ 12 or 24 weeks with agents such as adalimumab, etanercept, ustekinumab, brodalumab, secukinumab, and guselkumab. Seven clinical trials (eight publications)^{13,16,19-24} evaluated the complete discontinuation of biological therapies such as etanercept, adalimumab, tildrakizumab, and risankizumab ($n = 3,298$ patients), with treatment duration ranging from 4-months to nearly 5-years before discontinuation. Furthermore, 22 observational studies investigated biologic tapering in psoriasis patients.^{11,25-45} These studies included sample sizes

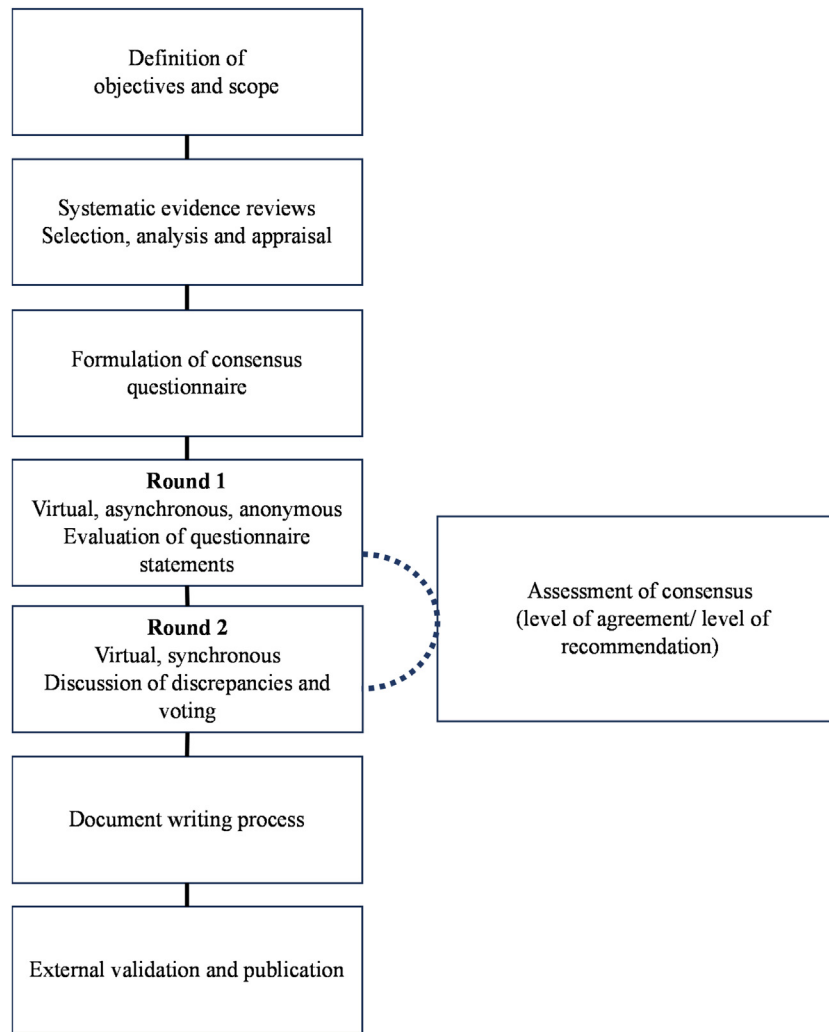


Fig. 1 Consensus development methodology.

Table 1 General principles for tapering biologic therapy in psoriasis.

General principles
The decision to taper biologic agents in psoriasis must weigh benefits and risks through an individualized assessment of each patient.
Each patient evaluation should be based on disease severity, presence of comorbidities, quality of life, and patient values and preferences.
The statements generated from this consensus serve as suggested practice recommendations without constituting a restrictive care guideline for patients with psoriasis. Particularly in the Latin American context, it is important to consider the realities of the specific clinical setting and the availability of resources when implementing the recommendations.

ranging from 2 to 223 patients with treatments such as adalimumab, etanercept, ustekinumab, infliximab, guselkumab, ixekizumab, and secukinumab, with biological treatment durations of at least six months. Information from six sec-

ondary sources was also included: consensus documents,^{46–48} practice guidelines,^{49,50} and recommendation documents.⁵¹

The evidence for each topic is described below.

Criteria for tapering

Table 2 describes the consensus statements on criteria for tapering of biological therapy in psoriasis.

Published studies have shown wide heterogeneity in scales and cutoffs to define the treatment goals and the appropriate time to taper biological therapy. Recent advances in biologics development have motivated the establishment of more stringent therapeutic targets. The evidence consistently suggests strategies for tapering in psoriasis patients with a complete or near-complete response, measured by a PGA 0–1, a PASI90, or a PASI ≤ 2.^{11,14,15,17,18,52–56}

The initiation of tapering with less demanding therapeutic goals than complete clearance has been controversial; however, there is evidence of acceptable outcomes in these settings. In the United States, tapering adalimumab in patients with a PASI score ≥ 50 resulted in the maintenance

Table 2 Consensus statements on criteria for tapering biologic therapy in psoriasis.

Statements	Agreement level
Tapering of biological therapy may be considered in patients with psoriasis who achieve and maintain the therapeutic goal of a sustained PASI100, PASI/BSA/PGA 0, for at least one year.	100%
Tapering of biological therapy may be considered in patients with psoriasis who achieve and maintain an absolute PASI < 3 for at least one year, according to individual clinical characteristics and in consultation with the patient.	67% ^a
Tapering of biological therapy may be considered in patients with psoriasis involving specific areas with complete or almost complete improvement (PGA 0–1) for at least one year.	87%
Tapering of biologic therapy may be considered in patients with mild psoriasis, good general health, a low initial PASI score, a good response to biologic treatment, and a short time to clinical remission.	88%
When considering tapering of biologic therapy, health-related quality of life should be taken into account, as it may deteriorate significantly during treatment interruption.	94%

PASI, Psoriasis Area Severity Index; PGA, Physician Global Assessment; BSA, Body Surface Area.

^a Unanimous agreement was not possible.

of response at 24-weeks.^{17,55} Observational studies in Spain and Europe^{34,35,37} have shown sustained clinical responses in the majority of patients at 6- and 12-months after tapering of biologic therapy, mainly for adalimumab and etanercept, when they achieved responses of $\geq$ PASI50, $\geq$ PASI75 or PASI < 3 maintained over time.

Evidence from the region includes a cohort study in Colombia (n = 467) that evaluated the tapering of various biologics in patients with psoriasis who achieved a sustained response, including an absolute PASI < 3, and reported that 88% of patients maintained a clinical response after eight months of follow-up.⁴³ The consensus panel extensively discussed the appropriateness of an absolute PASI < 3 as a criterion for considering tapering strategies. However, unanimous agreement was not possible due to the variability of cases, particularly in psoriasis of special localizations. The use of thresholds other than complete clearance in psoriasis patients is a decision that should be considered on an individual basis according to the clinical manifestations and in consultation with the patient.

In a survey of dermatologists worldwide (n = 57), nearly half of the physicians used a PASI $\leq$ 1 or $\leq$ 2, a BSA $\leq$ 1 or $\leq$ 2, or a PGA $\leq$ 1 as criteria for initiating tapering of biologic therapy, while a quarter indicated that they would consider dose reduction only in psoriasis-free patients (PASI/PGA0). Overall, 64.9% of patients were tapered after at least one year of treatment.⁵¹ This finding is consistent with studies showing that tapering of biologic therapy typically occurs after maintaining individualized treatment goals for at least 12-months.

Even though the DLQI is rarely used to define the start of tapering of biological therapy,¹¹ factors associated with improved quality of life, such as reduction in psoriasis-related symptoms and treatment satisfaction, are often considered. The use of the DLQI is important as a Patient-Reported Outcome (PROM) in the comprehensive assessment of psoriasis, but it requires guidance for optimal use and easy understanding by patients. According to the panel, these limitations prevent the DLQI from being established as a necessary criterion for determining the tapering of biologics in patients with psoriasis. However, the importance of the patient's perspective in tapering has been documented in dermatology clinical practice worldwide.⁵¹ Therefore, clin-

icians are urged to include a comprehensive assessment of patients and their circumstances as part of shared and informed decision-making.

Based on the results of several previous clinical studies, discontinuing biologic therapy should be considered if the patient's condition can be maintained in near remission for 40- to 52-weeks.⁵⁰ No long-term evidence beyond one year has been presented for any biological product using this strategy.^{47,50}

The studies that included biologic discontinuation as a strategy evaluated the achievement of goals using PASI scores of $\geq$ 50 or $\geq$ 75, PGA scores of $\leq$ 2, or sPGA scores 0–1, showing wide variability.^{13,16,19–24} However, the results of these studies support the continuation of biological therapy to maintain efficacy over time, given the high relapse rates and deterioration in health-related quality of life associated with discontinuation of therapy.⁵⁰

Tapering strategies and regimes

Table 3 describes the consensus statements on tapering strategies and regimens for biologic therapy in psoriasis.

The evidence supports the possibility of tapering biological therapy in psoriasis patients who achieve and maintain a therapeutic response. Strategies for tapering include extending the intervals between doses, reducing the dose while maintaining continuous treatment, and using the lowest effective dose for maintenance therapy.⁴⁷ For some molecules, studies have demonstrated the safety of reducing the initial dose by up to 50% while maintaining efficacy.³ Extending dosing intervals is the most commonly used strategy in observational studies, with 60% to 100% of patients maintaining clinical responses of $\geq$ PASI75, $\geq$ PASI90, or even PASI100 at various follow-up periods, typically up to one year.^{7,11,25,30,31,33,36,40–42,45}

The different tapering regimens for each biologic are shown in Table 4.

In general, administration intervals are prolonged within a fixed schedule, with the possibility of further adjustments to increase the time between doses if disease stability is maintained after 6-months of therapy. These strategies could be adapted to different groups of patients. For example, a study that evaluated the impact of prolonged

Table 3 Consensus statements on tapering strategies and regimens for biological therapy in psoriasis.

Statements	Agreement level
In patients with psoriasis who have achieved and maintained a therapeutic response, tapering of biological therapy aims to maintain the established goal while using the lowest possible effective dose.	92%
Tapering strategies include gradually increasing the intervals between administrations and reducing the dose for those medications that allow it.	92%
Biologic dosage regimen should allow for flexible dose modification (increasing the interval or reducing the dose).	82%
The tapering regimen should be based on the indications for each biologic, its dosing intervals and dose adjustment options (see Table 4).	100%

Table 4 Tapering regimens for biological treatment of psoriasis.

Biological	Standard Dosage	Initial Tapering Regimen	Extended Tapering Regimen ^a
Adalimumab	40 mg every 2-weeks	40 mg every 4-weeks	Then, every 6-weeks
Etanercept	50 mg every week	50 mg every 14-days	Up to 21-day interval
Infliximab	3 or 5 mg/kg every 8-weeks	Do not taper due to associated risks; prefer switching	
Ustekinumab ^b	45 mg (≤ 100 kg) every 12-weeks	45 mg every 16-weeks	Up to 24-week interval
	90 mg (> 100 kg) every 12-weeks	90 mg every 16-weeks	Up to 24-week interval
Secukinumab ^c	300 mg every 4-weeks	45 mg every 12-weeks	45 mg every 16-weeks
		300 mg every 6-weeks	Up to 8-week interval
		150 mg every 4-weeks	Up to 6-week interval
Guselkumab	100 mg every 8-weeks	100 mg every 12-weeks	Up to interval every 16 weeks
Risankizumab	150 mg every 12-weeks	150 mg every 16-weeks	Until interval every 24-weeks
Certolizumab pegol	200 mg every 2-weeks	200 mg every 4 weeks	200 mg every 6-weeks
Ixekizumab	80 mg every 4-weeks	80 mg every 6-weeks	80 mg every 8 weeks

^a If remission persists after 6-months of reduced dose therapy.

^b Efficacy was better maintained over time in the standard-dose group than in the tapering group.

^c An every 6-week regimen may result in a less pronounced PASI 90 responses in some patient groups (women, patients aged 65- to 75-years, and those with prior treatment for psoriasis).

treatment intervals and early intervention (≤ 2 -years from symptom onset) with guselkumab demonstrated the possibility of tapering in super responders (PASI0 at weeks 20 and 28) while maintaining favorable PASI and DLQI measures over time has been demonstrated.⁵²

Intermittent therapy has been considered in patients with a good response and those with a history of short exacerbations (lasting less than six months per year).⁴⁷ Evidence from randomized clinical studies with withdrawal and retreatment periods has described for guselkumab a median time to loss of PASI90 response of 15.2 weeks (23 weeks after the last dose of guselkumab)⁵⁷ and for ixekizumab, a median time to loss of response (PASI ≤ 50) of 20.4 weeks (143 days).⁵⁸

A systematic literature review⁵⁹ revealed evidence of the efficacy and safety of intermittent therapy with tumor necrosis factor inhibitors (adalimumab,¹⁶ certolizumab pegol,⁶⁰ etanercept,^{23,37,56,61,62} infliximab),^{24,63} anti-interleukin 12/23 (ustekinumab),^{64,65} anti-interleukin 23 (guselkumab)⁵⁷ and anti-interleukin 17 (brodalumab,^{54,58,66} ixekizumab⁵⁸ and secukinumab¹²). Studies have shown that 60% or more of patients on intermittent therapy achieve disease control (as defined in each study) after re-treatment, with the safety profiles of the biologics during re-treatment being as expected. The exception to these general findings

was infliximab, which had the lowest rate of achievement of the efficacy outcome (25% and 38% in the two dosing groups evaluated) and a higher incidence of adverse reactions. The consensus panel considers that infliximab tapering may impose immunological risks for patients; therefore, switching to a different biologic is preferred.

Another strategy addressed in these studies is complete treatment interruption. Clinical trials with adalimumab, etanercept, and risankizumab have reported shorter maintenance times of clinical response, with subsequent worsening of PASI scores and health-related quality of life.^{13,16,19-24}

Finally, the decision on the tapering strategy and regimen of biologics in psoriasis treatment should be based on an individualized assessment of the clinical situation, considering the duration of treatment, the achievement of the proposed goals, the specific characteristics of the biologic agent, the patient's satisfaction with the treatment, and the resources available to comply with the recommendations.

Monitoring and failure during tapering

Table 5 describes the consensus statements on monitoring and managing failures during tapering of biologic therapy in psoriasis.

Table 5 Consensus statements on follow-up and failure of tapering of biologic therapy in psoriasis.

Statements	Agreement level
Patients undergoing tapering of biological therapy should be followed up every 3-months, or sooner if there is a worsening of symptoms (skin or joint) or any other situation that warrants it.	100%
The identification of any of the following criteria at any time during follow-up is considered a failure of the tapering strategy:	
Absolute PASI >3	100%
PGA/BSA >1	93%
Unacceptable increase in disease activity as judged by the patient	100%
Change in morphology (e.g., psoriasis with pustules)	93%
Reactivation or appearance of lesions in specific areas	100%
Onset of joint symptoms	100%
In the event of a relapse with PASI ≥ 10 in a patient with psoriasis undergoing tapering of biologic therapy, the induction dose of the biologic should be restarted.	100%
In the event of a relapse with PASI < 10 in a patient with psoriasis undergoing tapering of biologic therapy, the immediately previous effective dose of biologic therapy should be reinstated.	100%

PASI, Psoriasis Area Severity Index; PGA, Physician Global Assessment; BSA, Body Surface Area.

Follow-up times in trials that reduced the dose or extended the interval between doses of the biological agent varied widely. In clinical trials, patients are usually evaluated every 4- to 12-weeks,^{14,15,17,18,52-56,67} including those who have interrupted the biologic.^{13,16,19-24} In observational studies, tapering strategies have been monitored, usually every 12- to 16-weeks or at increasingly longer intervals, depending on the time of biologic interruption.^{11,25-43} The Spanish Psoriasis Group of the Spanish Academy of Dermatology and Venereology (AEDV) recommends monitoring every 8- to 12-weeks during the maintenance phase for the majority of biological agents, the maintenance phase was defined as the period of treatment starting after the induction phase, regardless of its length, based on the patient's needs and it can last from several weeks to years, or even a lifetime, depending on the patient's needs.⁴⁷

The expert panel of this consensus considers that follow-up every three months is indicated for the Latin American context, considering the clinical circumstances and the different insurance scenarios and healthcare systems in the region.

To our knowledge, there is no consensus on the definition of biologic tapering failure. In general, a decrease in the PASI score (<50 or <75 or a decrease $\geq 50\%$ from the improvement achieved prior to discontinuation), a PGA score ≥ 3 or loss of response status, or a DLQI score > 5 has indicated tapering failure in psoriasis patients in clinical trials.^{14,15,17,18,52-56,67} In observational studies, tapering failure was defined as loss of response, individually defined and measured by PASI or DLQI, between 3- and 24-months after the start of the strategy.^{11,25-43} In trials where biological treatment was interrupted completely, failure was defined as a decrease in PASI score >50% from the initial improvement or a PGA score of ≥ 3 .^{13,16,19-24} The Spanish consensus on the evaluation and treatment of moderate-to-severe psoriasis defined relapse after discontinuation of an effective drug as a loss of $\geq 50\%$ of the improvement achieved or a PGA score of >2 if a PGA 0-1 was achieved at any time.⁴⁷

In the opinion of this expert panel, the heterogeneity in the definitions of biologic tapering failure in psoriasis

patients is a consequence of the variability in the definition of the goals of the strategy. In this context, any evidence of regression in achieving the treatment goals set for tapering indicates failure. Similarly, specific clinical circumstances, such as changes in the morphology of psoriasis (e.g., generalized erythrodermic or pustular psoriasis), reactivation or appearance of lesions in specific areas, and negative patient-reported events, such as the appearance of joint symptoms or an unacceptable increase in disease activity, must also be considered as tapering failures and require expedited evaluation to determine the appropriate course of action.

In the trials that reported relapse, less than 18% of patients who underwent tapering experienced relapse within 6-months to 40-weeks.^{13,17,19,55} Times to relapse varied and no significant differences in relapse rates were reported according to the type of biological agent.⁴³ Once loss of response has been established, therapeutic options include restarting biological therapy at the last effective dose, re-treatment with standard doses, rescue therapy or switching biological agents.^{11,25-43} According to the consensus panel, the therapeutic decision in these patients should be based on the severity of the relapse. In the studies that reported this finding, most patients achieved a target PASI within 4⁵⁶ to 12-weeks^{17,55} of treatment restart. Recovery of these responses after re-treatment has also been reported in uncontrolled follow-up cohort studies.^{31,36,45} These findings further support the efficacy and safety of tapering biologic therapy in psoriasis patients.

Considerations for implementation

Tapering strategies aim to minimize chronic immunomodulation, which is associated with opportunistic infections and other complications. In addition, tapering reduces the occurrence of side effects, and the anxiety associated with lifelong medication. Tapering is in line with the patient's preference to reduce the frequency of doses and the time spent on treatment. Strategies to reduce biological therapy in psoriasis patients also support technical-scientific rationalization within regional health-

care systems and address the general resource limitations in Latin America. Dermatology groups have reported cost savings as one of the main outcomes of reducing the dose of biologic agents.⁵¹ Cost studies have shown that dose reduction or prolongation of the administration interval, as well as intermittent therapy regimens, are viable alternatives to optimize biologic treatment and reduce therapy costs.^{28,46}

This document is based on the best available evidence at the time of its production. However, it is recognized that the results of ongoing studies or future research may require modifying some of the recommendations described here or generating new recommendations. The biologics addressed in the consensus are currently available or may soon be available in Latin American countries. Some molecules for which there is evidence to support tapering, such as brodalumab,^{54,58,66} were not included in specific recommendations because they are not available in Latin American countries. There are currently very few reports on tapering molecules such as risankizumab, so specific guidelines for these should be developed in future updates of this consensus.

The guidance provided in this consensus is intended to support the development of efficient and safe tapering strategies for biologics, but it is not a rigid guideline. As previously emphasized, flexibility in biologic tapering regimens must be maintained through detailed and individualized clinical assessments, considering patients' values, preferences and circumstances in the context of shared decision-making. In this context, it is expected that physician-prescribed strategies for tapering or reinitiation of biologic therapy for psoriasis will be administratively facilitated to promote adherence, ensure timely follow-up, and improve the chances of maintaining stable disease with reduced pharmacological requirements.

Conclusions

Tapering of biological therapies appears to be effective and safe in psoriasis patients with low stable activity or clinical remission. This Latin American consensus was developed in recognition of the need for rational and optimal use of such therapies, including both their administration and discontinuation, to maintain the best health outcomes for patients. This consensus aims to facilitate decision-making by incorporating the best and most recent available evidence, especially in heterogeneous populations with limited healthcare resources. Encouraging local research is essential to advance knowledge on issues related to biologic suspension and to inform future tapering updates.

External review and consensus update

A preliminary version of this manuscript, previously approved by the authors, was submitted for external peer review. The need to update this consensus should be evaluated in three years or sooner if necessary.

Financial support

This consensus is endorsed by the Latin American Psoriasis Society (SOLAPSO) and the Colombian Group of Psoriasis and Immunodermatology (COLPSOR), affiliated with the Colombian Society of Dermatology (ASOCOLDERMA). It was developed thoroughly and independently, with transparency and impartiality. The funders did not participate in the development of the consensus, the decisions of the panel, or the final manuscript.

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Appendix A. Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.abd.2025.501134>.

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LETTER - RESEARCH

Botryomycosis: series of cases diagnosed between 2000 and 2023 in the Dermatology division of a tertiary hospital[☆]



Dear Editor,

Botryomycosis is a rare chronic granulomatous disease that can present as a cutaneous or visceral disease.¹ It is important to differentiate it from other diseases that produce grains as a parasitic form of the etiological agent, including eumycetoma and actinomycosis, aiming targeted and assertive treatment, preventing disease progression and ensuring better quality of life for the affected individuals.

Therefore, the objective of this case series is to present seven cases of botryomycosis treated at a university dermatology service, from January 2000 to 2023, analyzing the patient's individual characteristics, locations of the lesions,

therapeutic approaches, and responses to the proposed treatments.

Table 1 summarizes the main information of the cases. Seven patients were followed, five males and two females. The ages at onset of the condition ranged from 17 to 79 years. Five of the cases had lesions on the feet, one on the leg, and one on the dorsum of the hands and fingers. Only three cases reported previous trauma. One patient had a history of Cushing's syndrome secondary to a pituitary microadenoma, which was excised through transsphenoidal surgery. Another patient had a history of immunosuppression with 38 radiotherapy sessions due to prostate cancer; however, after the onset of the skin condition. Two cases had other comorbidities such as systemic arterial hypertension, congestive heart failure, hypothyroidism, and dyslipidemia. Three cases had no comorbidities.

The majority presented clinically with nodules and tumors with fistulous tracts and three cases had grain discharge. None of the patients had systemic symptoms, except

Table 1 Summary of botryomycosis cases.

Age	Sex	Location	Agent	Treatment	Evolution
17	Male	Hands	<i>Staphylococcus aureus</i>	Sulfamethoxazole and Trimethoprim	Improvement
33	Male	Foot	<i>Staphylococcus aureus</i>	Sulfamethoxazole and Trimethoprim	Improvement
17	Male	Foot	<i>Staphylococcus aureus</i>	Multiple antibiotic regimens	Progressive worsening, requiring amputation
17	Male	Foot	<i>Staphylococcus aureus</i>	Sulfamethoxazole and Trimethoprim	Improvement
79	Male	Pre-tibial	<i>Staphylococcus aureus</i>	Sulfamethoxazole and Trimethoprim	Loss to follow-up
44	Female	Foot	<i>Staphylococcus warneri</i>	Sulfamethoxazole and Trimethoprim	Improvement and recurrence
34	Female	Foot	Not reported	Surgical resection and Sulfamethoxazole and Trimethoprim	Loss of follow up

[☆] Study conducted at the Department of Dermatology, Faculty of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil.



Fig. 1 Clinical. (A) Tumor showing fistulae in different stages of evolution located on the dorsum of the right foot. (B) Nodules and fistulae on the fingers.



Fig. 2 Computed tomography of the right foot showing voluminous expansive and infiltrative solid tissue with extensive bone and soft tissue involvement.

for one who developed anemia and thrombocytopenia due to continued bleeding from the lesion.

The isolated microorganism was *Staphylococcus aureus* in six cases, whereas *Staphylococcus warneri* was repeatedly cultured in one case.

In all cases, treatment was carried out with the use of sulfamethoxazole associated with trimethoprim (800 + 160 mg) for approximately six months to two years. Three patients responded well and two lost follow-up. In one case, surgical resection was proposed in combination with amikacin, but the patient did not agree to the procedure and did not return for follow-up appointments. One patient did not respond

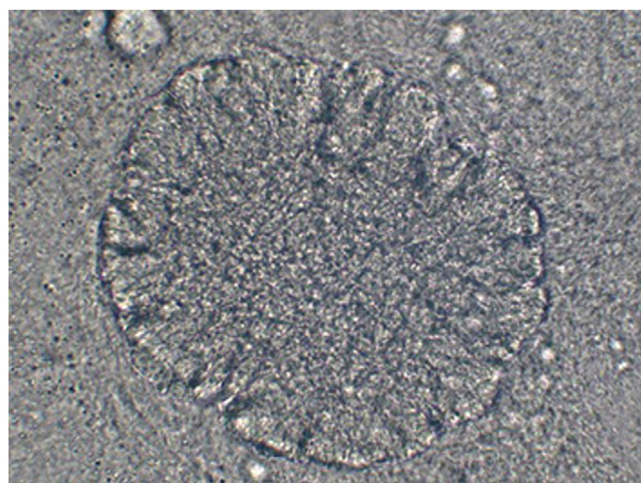


Fig. 3 Botryomycosis grain analyzed through direct microscopic examination, showing aggregates of cocci.

to all antibiotic and antifungal treatments, and after two years, transtibial amputation was necessary due to mobility difficulties and blood loss from the lesion.

Botryomycosis is a rare chronic granulomatous disease caused by non-filamentous bacteria, the main one being *Staphylococcus aureus*. Other bacteria occasionally involved are *Pseudomonas* spp., *Escherichia coli*, *Proteus* spp. and *Streptococcus* spp. The term botryomycosis derives from the Greek "botrys" = grains; "mycosis" = fungus, as it was believed that the condition was of fungal origin.^{1,2}

The disease pathogenesis is not well established; it is believed that an antigen-antibody complex, immunoglobulin G and C3 are precipitated around the microorganisms, preventing phagocytosis and intracellular bacterial destruction.¹

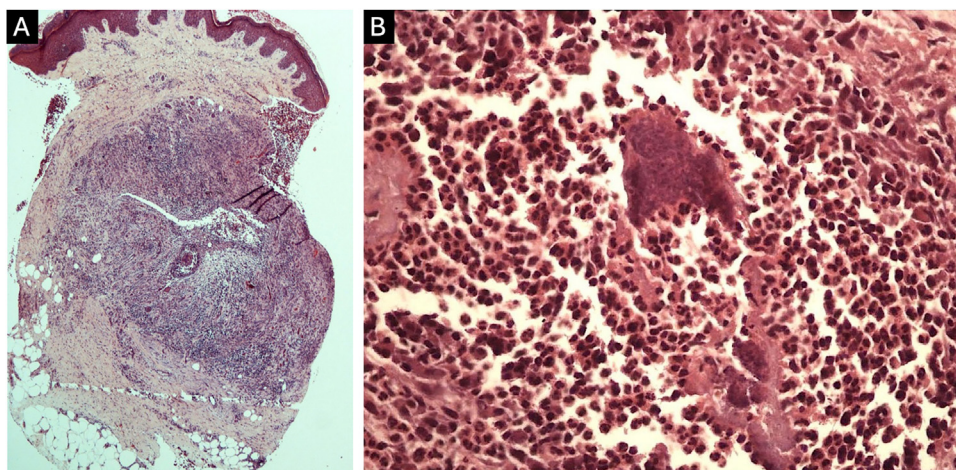


Fig. 4 Histopathology. (A) Histological section showing chronic suppurative granulomatous dermatitis containing grain in the deep dermis (Hematoxylin & eosin, $\times 40$). (B) Rounded structures forming a grain, are involved by the Splendore-Hoeppli phenomenon (Hematoxylin & eosin, $\times 400$).

The condition generally affects areas prone to trauma and may present as cutaneous or visceral disease.³ The cutaneous form manifests clinically as tumors or plaques that show fistulous tract openings on their surface that drain white grains, which may invade deep tissues, leading to extensive local destruction.⁴⁻⁶

Diagnosis includes clinical suspicion, histopathological and microbiological studies. It is important to differentiate it from other diseases that produce grains as a parasitic form of the etiologic agent, including eumycetoma and actinomycosis (Figs. 1–4).^{2,5}

The histopathological examination allows the identification of the microorganism type, since the grains consist of true fungi in eumycetoma, whereas in actinomycetoma it is possible to visualize filamentous bacteria and the botryomycosis grains consist of non-filamentous bacteria. Histochemical stains such as Grocott and Gram are useful for the characterization of fungi and bacteria.²

Treatment involves targeted antibiotic therapy, surgical approach with local debridement, and, in selected cases, when there is antibiotic response failure and when the limb becomes dysfunctional, amputation of the affected limb may be necessary, as occurred in one of the presented cases.²

Most publications on the subject are case reports and, due to its rarity, there are few published series. Early diagnosis of botryomycosis should favor prognosis and response to treatment since extensive cases with large volume and fibrosis show poor response to therapeutic agents.

Authors' contributions

Nicole de Souza Aranha: Design and planning of the study; collection of data; drafting and editing of the manuscript; interpretation of data; critical review of the literature; approval of the final version of the manuscript.

João Avancini: Analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic con-

duct of the studied cases; approval of the final version of the manuscript.

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Financial support

None declared.

Conflicts of interest

None declared.

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Received 9 November 2024; accepted 16 December 2024
Available online 7 July 2025



LETTER - RESEARCH

Translation, cultural adaptation and validation of the Brazilian version of the Alopecia Areata Quality of Life Index (AA-QLI-BRA)[☆]

Dear Editor,

Alopecia areata (AA) is a chronic autoimmune disease that affects up to 1% of the population during their lifetime, regardless of age, gender, or ethnicity. Severe forms are challenging, requiring treatments that include corticosteroids, immunomodulators, and, more recently, Janus Kinase (JAK) inhibitors, which represent a new hope for refractory cases.^{1,2}

The impact on the Quality of Life (QoL) of patients with AA goes beyond hair loss. Because it is a socially noticeable condition, it affects self-esteem and self-image and can lead to feelings of shame, isolation, and stigmatization. Therefore, many patients develop symptoms of anxiety and depression, especially in more severe cases. The psychological impact is more pronounced in children and adolescents due to their greater emotional vulnerability. Moreover, its unpredictable and recurrent nature contributes to a state of uncertainty, affecting daily activities, relationships, and work productivity.³⁻⁵

Fabroccini et al. developed a specific unidimensional instrument to investigate the impact on QoL in adults with AA, the Alopecia Areata Quality of Life Index (AA-QLI).⁶ This self-administered instrument consists of 21 items related to Symptoms (S), Relationship (R) and Objective (O) signs.

A methodological study was carried out to adapt and validate the Brazilian version of the AA-QLI. After authorization for the translation of the material (#2023-5634220334356), four dermatologists, fluent in English, translated it into Brazilian Portuguese, generating a consensual version (AA-QLI-BRA), which was back-translated into English by a non-specialist and compared to the original version. To obtain the cultural adaptation, ten patients with AA eval-



uated the instrument and were asked about the clarity of the questions, the language used, and its applicability. The version adapted to Brazilian Portuguese is available at <https://doi.org/10.17632/jw2fxprgd3.1>.

For content validation, seven dermatologists with experience in trichology evaluated and scored (from 0 to 10) each item for relevance, with 0 being – Not at all relevant and 10 being – Extremely relevant.

For the other validations, 80 adults with AA (diagnosed by a dermatologist) were investigated using an online questionnaire containing demographic data of AA-QLI-BRA and the DLQI-BRA (Dermatology Quality of Life Index), for concurrent validation. The study was conducted at the Trichosis outpatient clinic of FMB-UNESP, the Trichology outpatient clinic of Hospital Regional da Asa Norte (HRAN), the Trichology outpatient clinic of UERJ, Hair Studies Center of the Santa Casa da Misericórdia do Rio de Janeiro and the Alopecia outpatient clinic of Santa Casa de São Paulo.

A subgroup of nine participants completed the questionnaire again within a 14-day period to investigate its temporal stability. The instrument's internal consistency was assessed using the McDonald's coefficient. The "floor" and "ceiling" effects were defined when extreme responses ("not at all" or "too much") accounted for more than 50% of the responses to an item.⁷

The participants' demographic and QoL findings are shown in Table 1. There was a predominance of women over 30 years of age, with higher levels of schooling and extensive forms of AA. During the in-person application, the instrument was completed in less than ten minutes.

The scores for each item of the AA-QLI-BRA are shown in Fig. 1. Item S4 (worry that the problem will last for the rest of one's life) showed a ceiling effect. The floor effect occurred in items R15 (people are afraid of contagion) and R17 (difficulty establishing relationships).

Content validity was confirmed by the mean score of experts >8 for all the instrument items, except S1 (uncomfortable with a wig), S8 (expenses for hair care) and O21 (pruritus in the scalp).

The internal consistency of the AA-QLI-BRA was 0.95 (95% CI 0.94–0.97) and of the DLQI was 0.93 (95% CI 0.91–0.95). The correlation (Spearman's rho) between the AA-QLI-BRA and DLQI scores was 0.88 ($p < 0.01$). The correlation of

[☆] Study conducted at the Faculty of Medicine, Universidade Estadual Paulista, Botucatu, SP, Brazil.

Table 1 Demographic, clinical and quality of life data of 80 patients with AA.

Variables		Values
Age (years)	Mean (SD)	36 (15)
Sex ^a	Female	60 (75%)
	Male	20 (25%)
Level of schooling ^a	Elementary School	7 (9%)
	High School	13 (16%)
	Higher Education	60 (75%)
Marital status ^a	Married	25 (31%)
	Divorced	8 (10%)
	Single	47 (59%)
Self-declared skin color ^a	White	49 (61%)
	Non-white	31 (39%)
Age at onset (years)	Mean (SD)	24 (15)
Extent of alopecia	Small areas	36 (45%)
	Total	19 (24%)
	Universal	25 (31%)
DLQI-BRA	Median (Q1–Q3)	7 (1–15)
AA-QLI-BRA	Mean (SD)	53 (17)

^a n (%). SD, Standard Deviation; Q1–Q3, First and third quartiles.

the scores of the AA-QLI-BRA items among themselves and between them and the total (Fig. 2) indicated lower coefficients related to item O21.

The exploratory factor analysis, using the principal axis factoring method, indicated that 49.0% of the construct variance was explained by the unidimensional factor. The KMO coefficient for the matrix was 0.91 and the sphericity test (Bartlett) was $p < 0.001$, indicating sample adequacy for analysis. All items showed a factor loading > 0.45 , except for O21, which was 0.33.^{7–9}

The network analysis using the EBICglasso method (Fig. 3) showed greater influence for the AA-QLI-BRA items: R11

(people notice my problem) and S5 (I can't forget that I have the problem). Items S4, S6 (fear of the disease spreading), R15 and O21, on the other hand, showed less influence in the network.

The exclusion of items S4, S6, R15 and O21 did not change the instrument's internal consistency, and the variance of the explained latent variable increased to 54.7%.

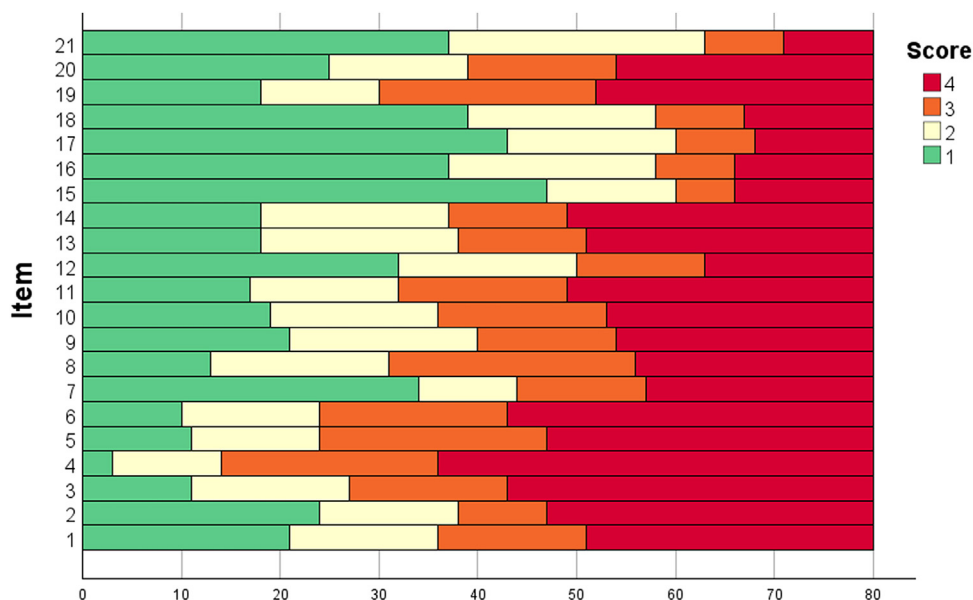
In the temporal stability assessment, the mean (standard deviation) of the test scores was 58 (11), and in the retests, 57 (14), resulting in an intraclass correlation coefficient (agreement) of 0.89.

The psychometric analysis of the AA-QLI-BRA showed the instrument's adequate internal consistency, content validity and temporal stability, indicating its use in Brazil, allowing more precise quantification of the patients' demands perception, improving their care.

In this study, the mean DLQI scores indicated a moderate impact on QoL, although there is still no categorization of the AA-QLI scores regarding the dimension of impact on QoL. In general, generic questionnaires do not detect all the aspects affected in the patients' lives, confirming the preference for specific instruments.¹⁰ The greater internal consistency and the centralized positioning of the AA-QLI-BRA items in the network confirm the superior psychometric performance of the DLQI in AA.¹¹

Some items of the AA-QLI-BRA showed a psychometric behavior less aligned with the others and should be carefully evaluated during the instrument use. Item O21 is not directly linked to the clinical course of the disease. Item S6 may not be relevant in those who already have total/universal AA, item S4 may not be realistic in patients who are responding to treatment and item R15 may not reflect the main stigma of extensive AA: the impression of being submitted to chemotherapy.

Further research should explore the correlation between AA-QLI scores with clinical and cultural variables and affective disorder scores since AA can inflict a chronic

**Fig. 1** Distribution of item scores of patients with AA-QLI-BRA (n = 80).

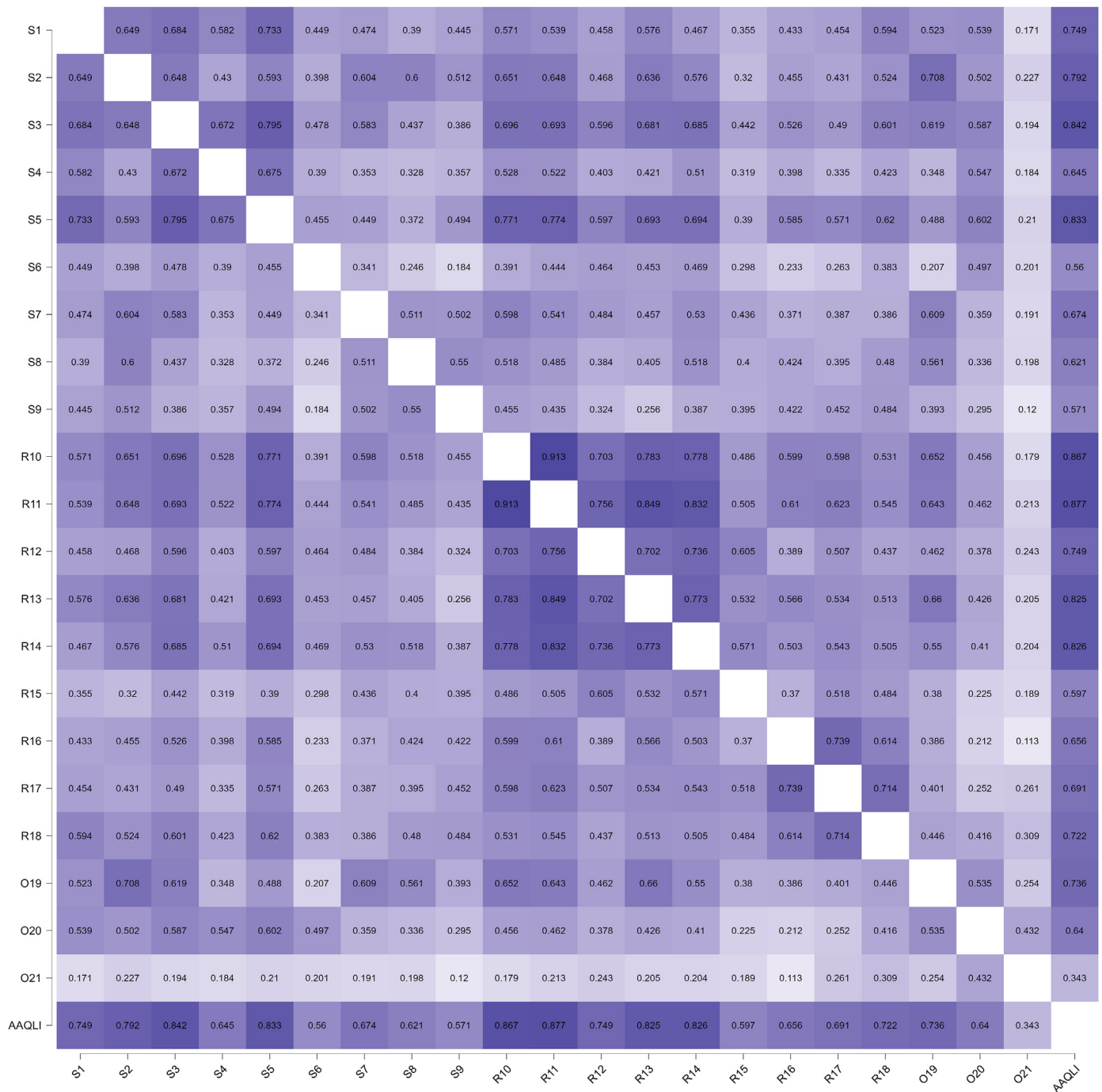


Fig. 2 Heat map of correlations (Spearman's rho) between AA-QLI-BRA items and the total score (n=80).

contingency that favors the development of psychiatric illness.^{12,13}

This study has limitations related to the sampling of more severe patients with a higher level of schooling than the average of the Brazilian population.

In conclusion, the Brazilian version of the AA-QLI was adapted and proved to be valid and consistent, establishing itself as a useful instrument in clinical practice, as well as in clinical studies in AA.

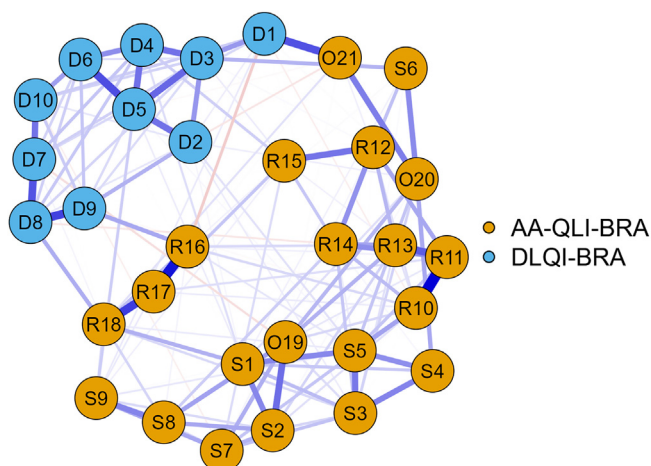


Fig. 3 Network diagram between DLQI-BRA and AA-QLI-BRA items (n=80).

Financial support

None declared.

Authors' contributions

Paula Rosa Coutinho Goulart Borges Mariotoni: Design and planning of the study; collection of data; drafting and editing of the manuscript; critical review of the literature; critical review of the manuscript; approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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Received 28 November 2024; accepted 23 January 2025

Available online 28 June 2025

LETTER - RESEARCH

Use of imiquimod in 21 patients with molluscum contagiosum: better results in specific areas[☆]



Dear Editor,

There are several therapeutic options for Molluscum contagiosum (MC), including physical treatments (electrocautery, curettage, cryotherapy), chemical treatments (potassium hydroxide, imiquimod) and even waiting for spontaneous resolution.¹⁻⁴ Imiquimod (IMQ) is a topical immunomodulator that acts by stimulating the innate and adaptive immune pathways. Initially approved for the treatment of anogenital warts, actinic keratosis, and superficial basal cell carcinoma, there are other off-label indications in both benign and malignant dermatological diseases due to its potential antiviral, antitumor, and immunoregulatory effects.^{5,6}

A retrospective study was conducted analyzing medical records of patients with MC treated at a dermatology clinic in a public tertiary hospital in São Paulo, Brazil, from March 2016 to March 2024, evaluating: (i) The number of patients treated with IMQ, (ii) Therapeutic response, and (iii) Side effects presented by patients. Of the 1,256 patients treated in eight years, IMQ was indicated in only 21 (Table 1); the gender ratio was similar (11 women, 10 men), and only three (14.28%) were over 18 years old. All treated lesions were located on the face (8, 38.09%) or in the anogenital region (13, 61.91%). All patients used a similar dose to that used for the treatment of anogenital warts (three times a week) for a period of four to 33 weeks. Regarding the therapeutic response, 15 patients showed complete resolution (Figs. 1, 2 and 3), three showed partial response and three others showed no response. Patients without response used the product for four weeks, whereas those with partial response used it for four to eight weeks and all patients with complete response used the product for eight weeks or more.

Given the number of patients treated during the analyzed period, it is clear that IMQ is not the first-choice treatment at the institution where the study was conducted. One of the

reasons is that the study was conducted in a public hospital that does not provide IMQ free of charge to patients, and few of them can afford the high cost of the medication; another reason is that the drug was prescribed only to immunocompetent patients without comorbidities, a rare characteristic of those treated in a tertiary public hospital. This low IMQ prescription for MC is consistent with data published in the United States of America, where the IMQ prescription rate among 6.4 million consultations for MC was only 7.0%.⁷

However, it is important to remember that the removal of Molluscum contagiosum (MC) on the face or anogenital region, based on physical methods such as curettage, is also challenging. These procedures can cause physical and emotional impact, especially in patients younger than 18 years. Therefore, a topical home therapeutic option, such as the use of IMQ, becomes valuable for both patients and physicians.

The use of Imiquimod (IMQ) for the treatment of Molluscum contagiosum (MC) is widely discussed in the scientific literature, but there is still no consensus on its indication. Previous studies have shown divergences: while some authors report favorable results with IMQ use, demonstrating efficacy in selected cases,^{2,3,7} others question the actual drug effectiveness, stating that there are not enough randomized clinical trials to support it as an effective treatment for MC, especially when compared to conventional methods, such as curettage.⁸⁻¹¹ These divergent studies state that, in trials involving 470 children aged two to 12 years, the application of IMQ three times a week, for up to 16 weeks, did not result in a significant difference compared to control groups, with complete resolution rates of 24% (52/217) and 26% (28/106), respectively. Similar observations were made in another study, where the resolution rate was 24% (60/253) in the treated group, versus 28% (35/126) in the control group.^{4,8-11} However, it is worth noting that these studies did not evaluate IMQ efficacy in specific anatomical regions, such as the face and anogenital area, which may influence the overall conclusions. In the present study, when focusing on lesions located in areas with thin skin, a complete cure rate of 71.42% (15/21) of patients was observed, with 73.33% (11/15) of these cases achieving cure within 16 weeks.

However, the limited sample size should be taken into account, since the small number of treated patients influences the success rates. Furthermore, in four cases with a

[☆] Study conducted at the Dermatology Clinic, Hospital da Santa Casa de São Paulo, São Paulo, SP, Brazil.

Table 1 Characteristics of 21 patients with molluscum contagiosum treated with imiquimod.

Patient	Sex	Age (years)	Location	Treatment duration (weeks) ^a	Response to treatment	Adverse effects
1	Female	4	Genital	8	Partial	-
2	Female	11	Genital	4	Total	-
3	Male	5	Face	4	Total	-
4	Male	5	Face	28	Total	-
5	Female	5	Face	20	Total	-
6	Male	8	Face	8	Total	Erythema
7	Female	12	Face	4	Absent	-
8	Male	55	Genital	8	Total	-
9	Female	21	Anal	4	Absent	Bacterial infection
10	Female	48	Genital	4	Partial	-
11	Male	8	Face	8	Total	-
12	Male	5	Face	4	Total	-
13	Male	6	Face	4	Partial	-
14	Male	8	Genital	4	Total	Erythema
15	Male	6	Genital	4	Absent	-
16	Female	3	Anal	16	Total	-
17	Male	4	Genital	12	Total	-
18	Female	7	Anal	33	Total	-
19	Female	5	Anal	8	Total	Bacterial infection
20	Female	3	Anal	28	Total	-
21	Female	7	Anal	4	Total	Erythema

^a All patients used imiquimod three times a week; (-) Absent.

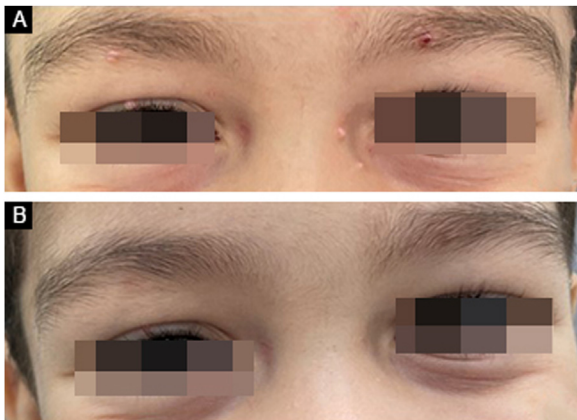


Figure 1 Patient with molluscum contagiosum around the eyes treated with imiquimod. (A) Before treatment; (B) Clinical outcome after four weeks.

positive response after 16 weeks of treatment, it is important to consider the possibility of spontaneous involution of the lesions, a phenomenon observed in MC. Finally, one of the patients required 28 weeks (seven months) of treatment, reinforcing the importance of duration of use for therapeutic success.

The careful selection of patients and lesions to be treated with Imiquimod (IMQ) was essential for the positive results observed in the present study. Only lesions located in small areas of the face and anogenital region were treated, regions where the skin is thinner, which may have favored product absorption and local immune system activation, contributing to treatment effectiveness. In addition, the profile of the selected patients – immunocompetent and without comorbidities – also seems to have been decisive for

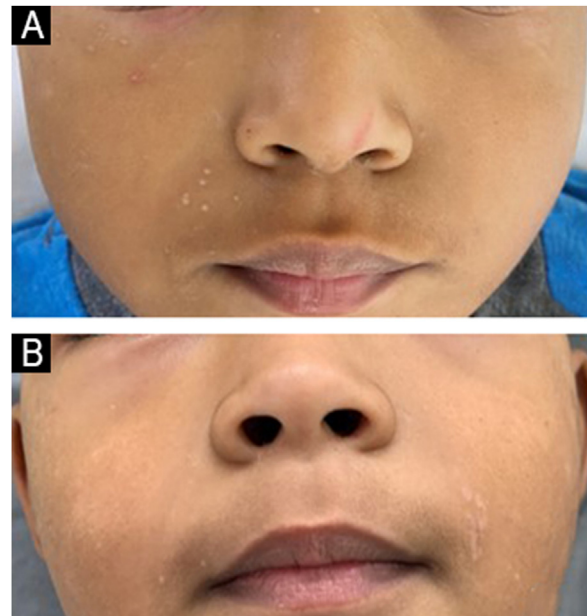


Figure 2 Patient with molluscum contagiosum on the right side of the face treated with imiquimod. (A) Before treatment; (B) Clinical outcome after 28 weeks.

therapeutic success, since these patients respond better to the immune stimulation provided by IMQ. These factors may explain the complete cure rate observed in 71.42% (15/21) of the cases, a more effective result than that reported in previous studies. Farhangian et al.⁷ also highlight that, although some studies show limited efficacy, the use of IMQ may be beneficial in localized diseases, especially in areas of thin skin, reinforcing the results observed in the

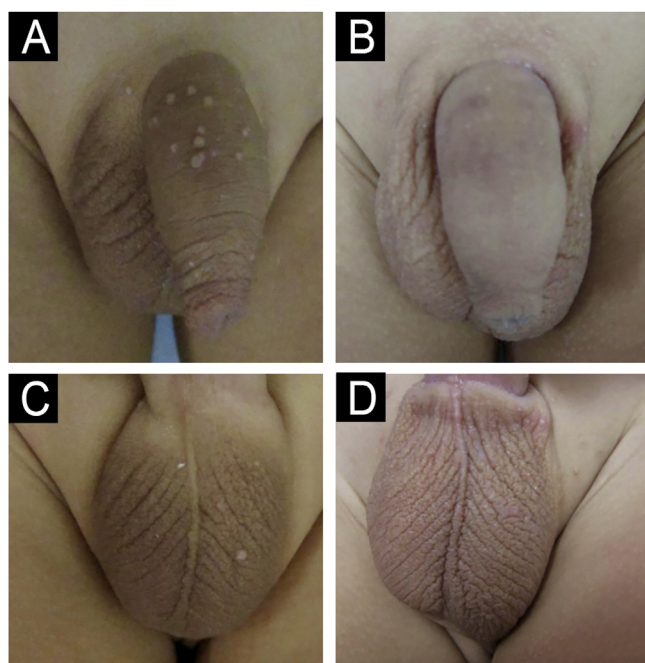


Figure 3 Patient with molluscum contagiosum in the genital region treated with imiquimod. (A–B) Before treatment; (C–D) Clinical outcome after 12 weeks.

present study. Therefore, the choice of the patient and the appropriate lesion, combined with the application in areas with characteristics that favor drug absorption, seem to be essential for the success of IMQ treatment in molluscum contagiosum.

Regarding imiquimod safety, five patients (23.8%) showed mild side effects, such as erythema (three cases) and impetigo (two cases). All adverse effects were quickly resolved with temporary drug discontinuation and, in cases of impetiginization, a brief course of topical antibiotic therapy was sufficient for control. These events are consistent with the literature findings, which generally indicate a favorable safety profile when used in limited areas and at adequate doses. Although rare, more severe adverse events, such as leukopenia or Stevens-Johnson syndrome, have been described in other studies but were not observed in this group of patients, reinforcing the relative safety of the treatment in selected and well-monitored populations.^{3,4,12}

MC treatment is challenging; despite being a benign lesion, it is an infectious disease that is easily transmitted, which causes a psychological impact on patients and their families who seek a rapid, effective resolution with few side effects. Although IMQ is not the first-choice treatment in clinical practice, it is possible that its use in immunocompetent patients with MC located in regions where the epithelium is thinner may result in better cure rates. It is important to note that, as with all other treatments, the use of IMQ may lead to side effects, most of which are mild and reversible.

Financial support

None declared.

Authors' contributions

Bruna Cavaleiro de Macedo Souza: Design and planning of the study; collection of data, or analysis and interpretation of data; statistical analysis; drafting and editing of the manuscript or critical review of important intellectual content; collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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Received 1 July 2024; accepted 24 November 2024

Available online 7 July 2025



LETTER - RESEARCH

Using ChatGPT 4.0 for diagnosis in Dermatology: performance analysis in clinical cases from Anais Brasileiros de Dermatologia[☆]

Dear Editor,

Artificial intelligence (AI) has become a topic of growing interest in medical research and is increasingly being applied in dermatology. One of the main branches of AI is Deep Learning, a predominant technology in the processing of complex and high-dimensional data.¹ Deep Learning uses artificial neural networks that automatically learn the relationships between input data, such as images, and outputs, such as diagnoses, without the need for detailed programming by humans. Inspired by the functioning of the brain, neural networks adjust the intensity of their connections as they learn essential patterns, such as visual characteristics, facilitating the prediction of results.²

In this context, ChatGPT is an example of an advanced language model that uses Deep Learning techniques. Belonging to the series of generative pre-training transformer (GPT) models developed by OpenAI, ChatGPT stands out as one of the currently available largest language models, with free public access since 2023.³

ChatGPT has already been tested in certificate examinations for different medical specialties, such as ophthalmology (Canada), dermatology (United Kingdom), and in the Title of Specialist in Dermatology (TED) exam in Brazil.^{4,5} In the study that evaluated ChatGPT in TED, the accuracy was 75.34%. Another study in the United Kingdom, with questions from the Specialty Certificate Examination in Dermatology, obtained an accuracy of 63.1% using ChatGPT 3.5, and 90.5% with ChatGPT 4.0.⁶

This study aims to explore the diagnostic performance of ChatGPT in dermatological clinical scenarios published in the "What is your diagnosis?" section of *Anais Brasileiros de Dermatologia* (ABD). A retrospective observational study was conducted to evaluate the performance of ChatGPT



4.0 in dermatological clinical cases published between 2019 and 2023. Cases with complete clinical information, images, laboratory, anatomopathological, and immunohistochemical tests, followed by multiple-choice questions, were included. Cases without multiple-choice questions were excluded.

The interaction with ChatGPT 4.0 followed this sequence: a) Type "I would like you to answer the correct diagnosis of the following clinical case" and press Enter; b) Paste the complete clinical case, including uploaded images and captions; c) Paste the question "What is your diagnosis" and the four alternatives, press Enter; d) Wait for the AI's response and compare it with that of the authors of each case.

The ChatGPT 4.0 responses were compared with the correct option predefined in the ABD, categorizing them as "correct" or "incorrect". The cases were then classified according to the diagnostic method (clinical, anatomopathological, microbiological). The AI's performance was assessed by the proportion of correct diagnoses in relation to the total number of analyzed cases.

Twenty-five cases were selected, and the AI correctly diagnosed 21, resulting in an accuracy of 84%. [Fig. 1](#) shows the performance of ChatGPT categorized by diagnostic methods, with better performance in cases resolved clinically or by anatomopathological diagnosis and lower accuracy in those that required a microbiological method.

The study assessed the performance of ChatGPT 4.0 in dermatological diagnoses with multiple choice, with four pre-determined options for each clinical case. Unlike a traditional diagnostic accuracy test, in which the AI would provide an open diagnosis, here it selected the correct option among limited alternatives. This does not allow one to state that the diagnostic accuracy of the AI was tested, but rather its performance in a specific context.

Several barriers to the application of AI in dermatology are discussed, including technical issues such as lack of generalizability, standardization of images, and integration of complex clinical data, as well as ethical and regulatory issues such as acceptance of the technology and legal liability in cases of error.⁷

The AI errors in the study were associated with diagnoses involving the integration of clinical, anatomopathological, and microbiological data, suggesting AI limitations in integrating different sources of information in atypical cases.

[☆] Study conducted at the University Hospital, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil.

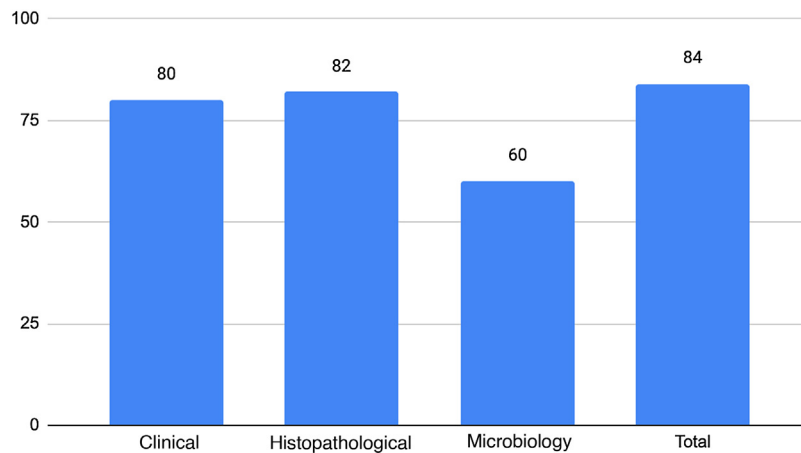


Figure 1 ChatGPT and *Anais Brasileiros de Dermatologia*: ChatGPT performance in different diagnostic methods.

Therefore, medical practice, especially in a complex specialty such as dermatology, involves a continuous process of learning and improvement, both for human professionals and for artificial intelligence models.

Financial support

None declared.

Authors' contributions

Matheus Alves Pacheco: Design and planning of the study; drafting and editing of the manuscript or critical review of important intellectual content.

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Conflicts of interest

None declared.

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Received 12 October 2024; accepted 5 December 2024

Available online 3 July 2025

LETTER - CLINICAL

Adult T-cell lymphoma/leukemia following infective dermatitis in an adult with HTLV-1 infection: a case report[☆]



Dear Editor,

Human T-lymphotropic Virus Type-1 (HTLV-1) was the first retrovirus directly linked to cancer development in humans. It exhibits CD4⁺ T-cell tropism, resulting in cell cycle acceleration, formation of immortal CD4⁺ and CD8⁺ clones, and exaggerated immune response.¹ It is estimated that 10 million people worldwide are infected with HTLV-1, Brazil being the endemic country with the largest absolute number of infected individuals (almost one million).² Diseases associated with HTLV-1 include Adult T-cell Lymphoma/Leukemia (ATLL), HTLV-1-Associated Myelopathy (HAM), Sjogren's syndrome, uveitis, thyroiditis, pneumonitis, arthritis, polymyositis, infective dermatitis (ID), other skin manifestations, urinary symptoms, erectile dysfunction, and periodontal disease.³⁻⁵ Infective dermatitis may be associated with HAM in up to 50% of cases.⁶

ATLL has five clinical forms: acute, lymphomatous, chronic, smoldering, and primary cutaneous tumoral.⁷ Infective dermatitis is a chronic relapsing disorder that affects children, with few reports of late-onset disease, and rare cases progressing to ATLL.⁷ We describe a case of adult-onset ID and ATLL.

A 71-year-old woman infected with HTLV-1 for 22 years presented xerosis and generalized pruritus on the whole body for 12 months. She was diagnosed with atopic dermatitis and was treated unsuccessfully with topical and systemic steroids for eight months before she was evaluated in our department. She presented erythematous-exudative plaques associated with xerosis on the limbs (Fig. 1A).

She reported weight loss and night sweats, but no neurological symptoms. Skin biopsy of an exudative plaque revealed hyperparakeratosis, spongiosis, exocytosis of lymphocytes, and superficial perivascular infiltrate, and a diagnosis of ID was made. She also presented multiple infiltrated papules and purpuric lesions on the trunk (Fig. 1B-C), and histopathology revealed infiltration by atypical CD4⁺CD7⁻ T-cells, compatible with ATLL (Fig. 2). She had no lymph node or visceral involvement. HTLV-1 proviral load was 189copies/10⁴ Peripheral Blood Mononuclear Cells (PBMCs) and T-cell proliferation assay revealed 1243 counts/minute, ten times higher than HTLV-1-negative control. Immunophenotyping showed reduced CD3 intensity and 79% of abnormal CD4⁺CD26⁻ cells (Fig. 3). Polymerase chain reaction of rearranged γ T-cell receptor gene revealed monoclonal expansion of T-cells in the blood (Fig. 4). Diagnosis of unfavorable chronic ATLL was made. She received intramuscular betamethasone and oral antihistamines with partial response. After the recurrence of symptoms, zidovudine (400mg/day) and pulse therapy with methylprednisolone three times every 45 days were started, resulting in marked improvement of ID and ATLL skin lesions and blood alterations. During follow-up, she developed bone marrow involvement and died after four years of diagnosis of ID and ATLL.

Infective dermatitis is the primary pediatric manifestation in vertically infected HTLV-1 patients and is rare in adults.^{5,8} Average age of onset is two years, and its prevalence decreases with age, probably due to maturation of the immune system.⁹ Clinical features comprise chronic erythematous-exudative eruptions affecting the scalp, retro auricular area, eyelids, the skin of paranasal sinus, axillae, neck, and groin.⁸ Lesions are aggravated by bacterial superinfections, particularly *Staphylococcus Aureus* (SA) and *Beta-Hemolytic Streptococcus* (BHS).⁸ Non-bacterial infections can also complicate the disease, such as cutaneous dermatophyte or *Candida* infections, and scabies.⁸

Development of ID has been associated with increased viral load, presence of HTLV-1 antibodies, and genetic predisposition.⁸ The possible pathogenesis would be the tax protein encoded by HTLV-1, which transactivates genes related to inflammatory cytokines (interferon- γ , tumor necrosis factor-alpha, interleukin-1, and interleukin-6).⁹ It has also been suggested that damage to the skin barrier due to HTLV-1-related dysregulation of epidermal proteinase and

[☆] Study conducted at the Department of Dermatology, University of São Paulo Medical School, São Paulo, Brazil; Laboratory of Investigation in Dermatology and Immunodeficiencies, Department of Dermatology, Faculty of Medicine, Universidade de São Paulo, São Paulo, Brazil; Institute of Infectious Diseases "Emílio Ribas", São Paulo, SP, Brazil.

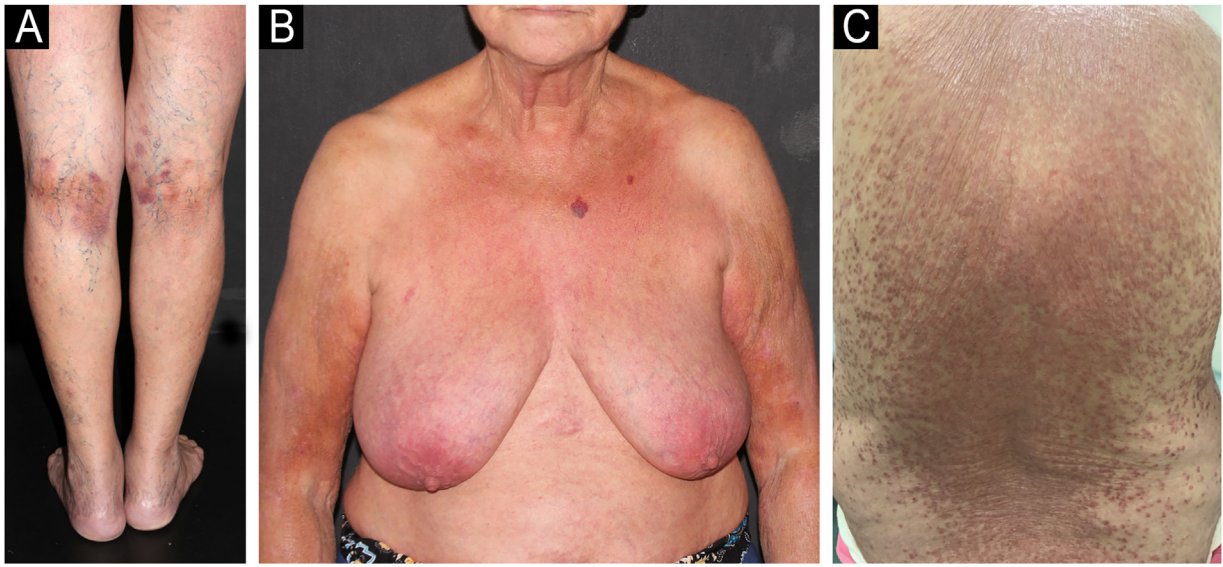


Figure 1 Erythematous and purpuric plaques on the popliteal fossae (A). Diffuse erythematous rash on the trunk and upper limbs (B). Multiple infiltrated papules on the back (C).

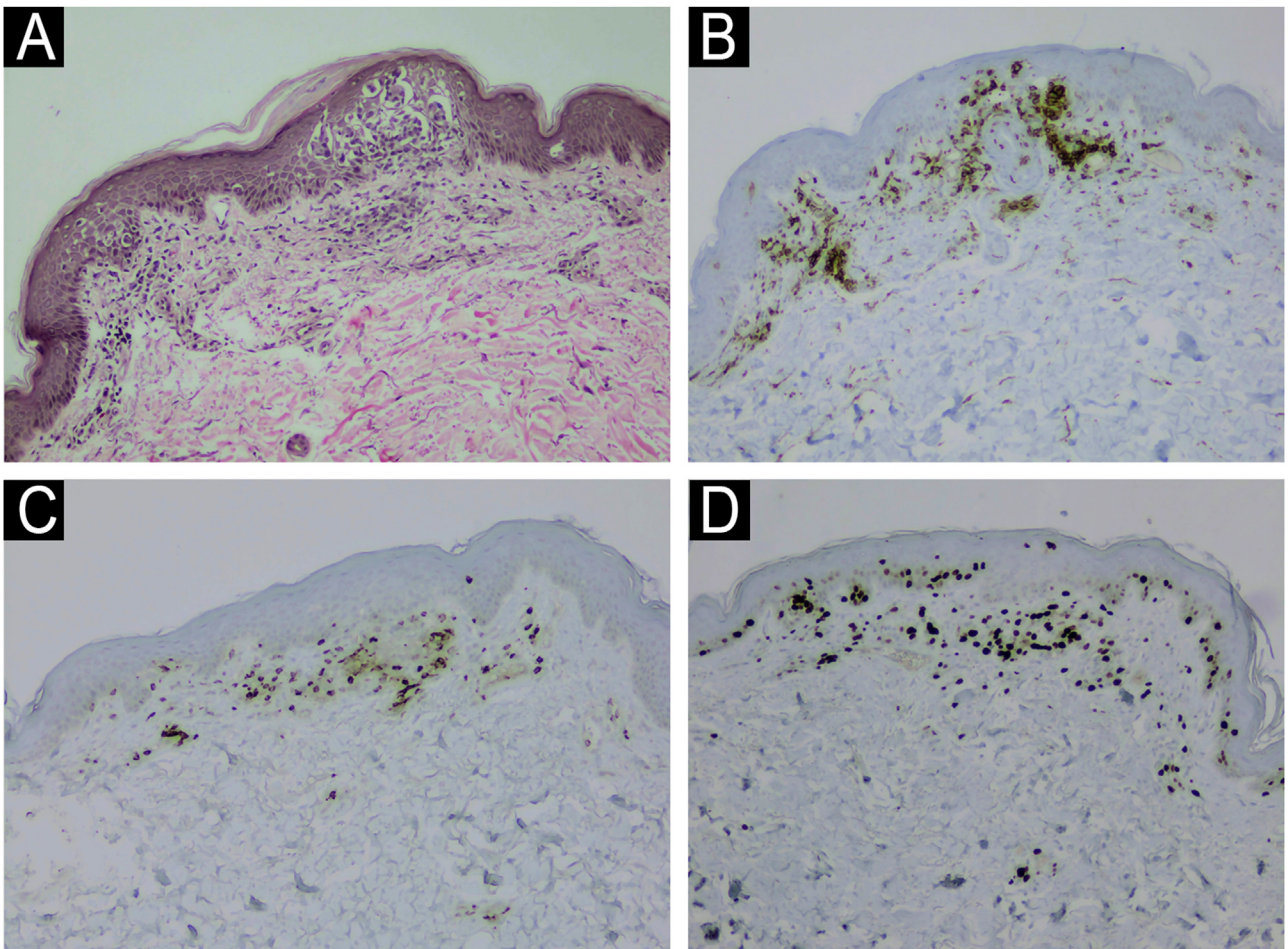


Figure 2 Histology of ATLL lesion showing exocytosis of lymphocytes with aggregates of atypical cells on the epidermis, and perivascular atypical lymphocytes on the superficial dermis (A, Hematoxylin & eosin, $\times 100$); CD4 positivity (B, $\times 100$); partial loss of CD7 (C, $\times 100$); Ki-67 of 60% (D, $\times 100$).

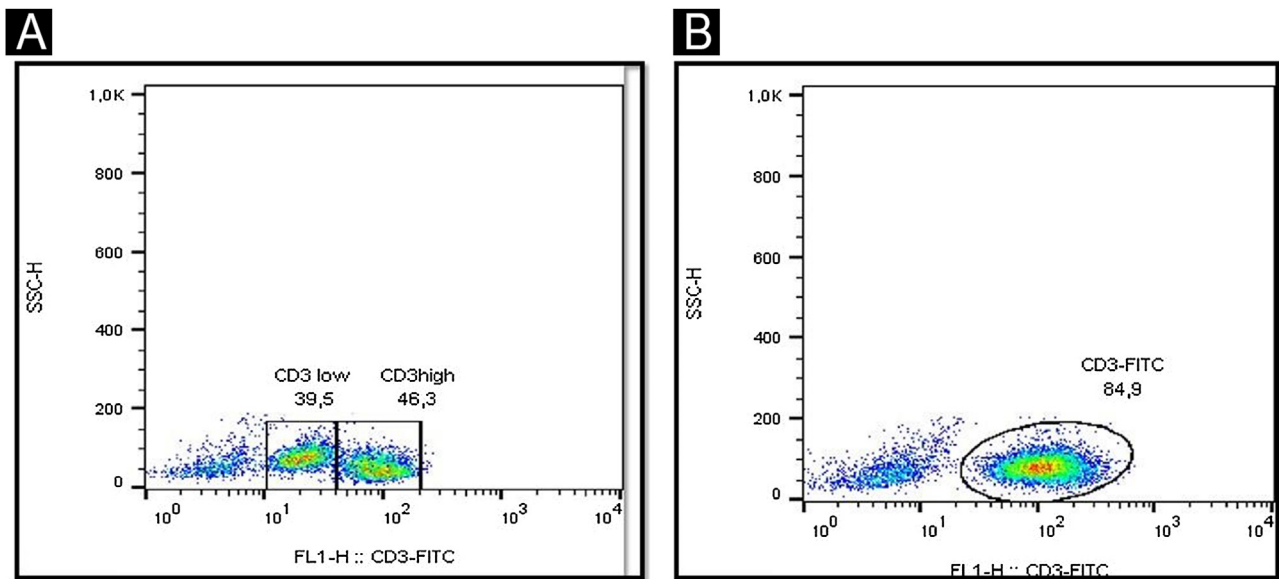


Figure 3 Immunophenotyping of lymphocytes in peripheral blood by flow cytometry showing lower CD3 intensity in abnormal T-cells (A) compared to a normal control (B).

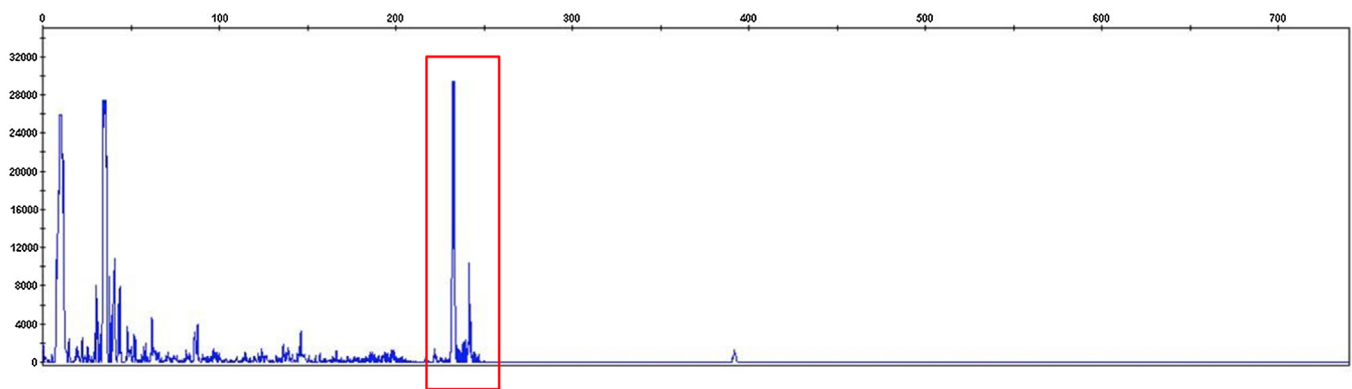


Figure 4 T-cell receptor gene rearrangement analysis show monoclonality with two differently sized gene rearrangements (red box).

infection of Langerhans cells by HTLV-1 may lead to precarious modulation of immune responses in the skin and increased rate of SA and BHS infection.¹⁰ This chronic inflammation could induce malignant transformation of infected cells.^{7,8} However, if ID in childhood predicts a higher risk for ATLL development in adulthood must be further investigated.

Prolonged antibiotic therapy is the best strategy for ID control. In this case, the patient received zidovudine, a nucleoside reverse transcriptase inhibitor, an effective therapy for ATLL as it exerts cytostatic effects by terminating DNA replication.⁴ We hypothesize that zidovudine may lower HTLV-1 replication in the skin and reduce inflammatory effects and immunological impairment of ID. In addition, steroid pulse therapy reduced cutaneous inflammation, resulting in significant improvement of ID and ATLL.

Financial support

None declared.

Authors' contributions

Denis Miyashiro: The study concept and design; data collection, or analysis and interpretation of data; writing of the manuscript or critical review of important intellectual content; effective participation in the research guidance; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied case; critical review of the literature; final approval of the final version of the manuscript.

Tatiane Assone: The study concept and design; data collection, analysis, and interpretation of data; writing of

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José Antonio Sanches: Writing of the manuscript or critical review of important intellectual content; effective participation in the research guidance; final approval of the final version of the manuscript.

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Conflicts of interest

None declared.

Acknowledgment

This work is in memory of HSM, our patient who was treated in our clinic.

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Received 23 October 2024; accepted 13 December 2024

Available online 1 July 2025

LETTER - CLINICAL

Exuberant terra firma-forme dermatosis in an elderly patient[☆]

Dear Editor,

Terra firma-forme dermatosis (TFFD), also known as Duncan's dirty dermatosis, is a benign acquired condition characterized by keratotic papules and plaques, sometimes appearing verrucous, and varying in color from gray, brown to black, without associated symptoms.¹⁻⁴ The lesions typically form a reticulated pattern interspersed with areas of normal skin, most commonly affecting the neck, trunk, and ankles. The term "terra firma" and "forme" originates from Latin, meaning "dry land", describing the resemblance of the lesions to clods of sand.⁵⁻⁸



The etiology of TFFD remains unclear, with a hypothesized incomplete maturation of keratinocytes in association with melanin and sebum in the epidermis.^{1,3,7} It predominantly affects children and young adults, and diagnosis is typically clinical.^{2,3,8} Dermoscopy can aid diagnosis by revealing brown, polygonal scales arranged in a mosaic pattern.^{6,8} A diagnostic and therapeutic friction test using gauze soaked in 70% isopropyl alcohol is effective, whereas daily baths with soap and skin exfoliation are ineffective.^{2,4,7,8} Although not mandatory, histopathological examination may show lamellar hyperkeratosis with focal areas of spiral and compact orthokeratosis, along with acanthosis and papillomatosis.^{1,5,6}

The clinical resemblance to dirt makes dermatosis neglect a primary differential diagnosis. Other differentials include acanthosis nigricans, reticulated and confluent



Fig. 1 Clinical presentation of terra firma-forme dermatosis (TFFD).

[☆] Study conducted at the Department of Dermatology, Centro Universitário Lusiada, São Paulo, SP, Brazil.

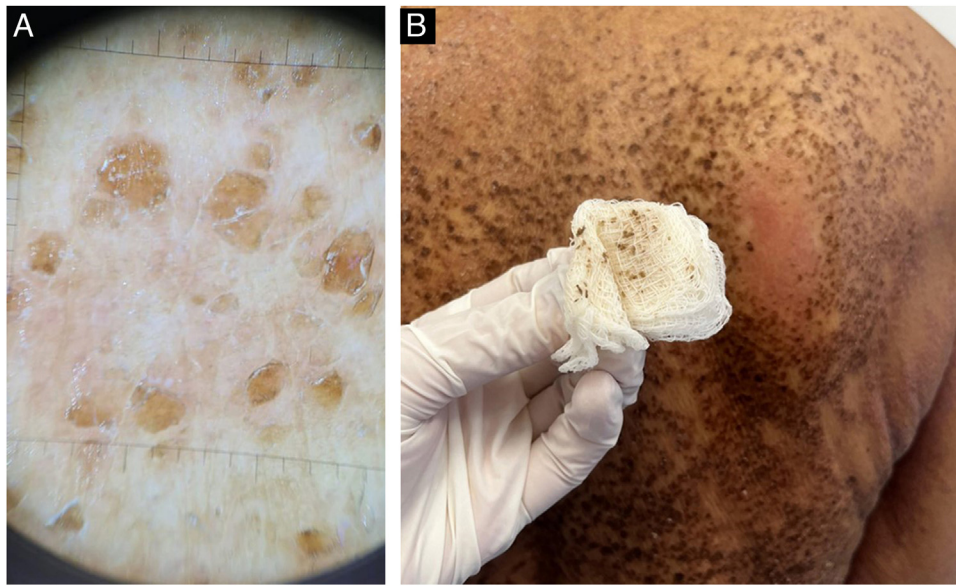


Fig. 2 Terra firma-forme dermatosis (TFFD) – (A) Dermoscopic examination and (B) Friction test using 70% isopropyl alcohol.

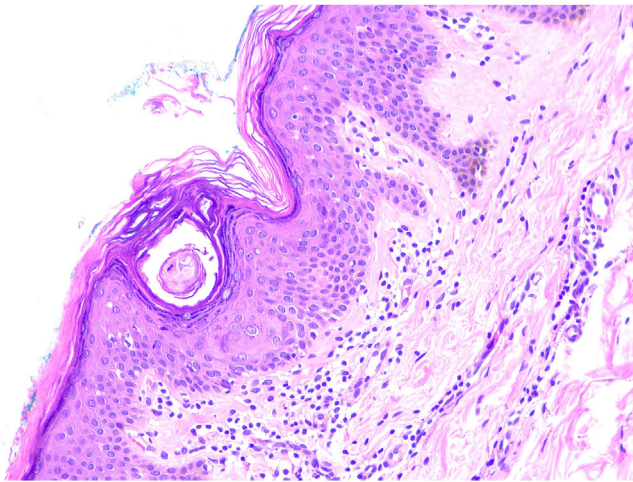


Fig. 3 Hematoxylin & eosin, $\times 40$. Areas of orthokeratotic hyperkeratosis with intracorneal spiral formations, hypogranulosis, mild acanthosis, and focal mild papillomatosis.

Gougerot-Carteaud papillomatosis, epidermal nevus, and seborrheic keratosis.^{1,3}

A 68-year-old woman with brown skin, who has hypertension and diabetes, sought dermatological care due to hyperchromic lesions covering most of her skin, accompanied by mild itching that had progressively worsened over four years, causing aesthetic discomfort. The patient reported daily baths and sporadic use of sponges. On dermatological examination, the patient presented with multiple flat papules with adherent scales measuring 1–4 mm in diameter, and brownish-black plaques grouped diffusely on the trunk, flexor region of the arms, inner thighs, and popliteal fossa (Fig. 1). Dermoscopic examination revealed grouped polygonal scales (Fig. 2). A friction test using gauze soaked in 70% isopropyl alcohol resulted in scale detachment and lightening of the lesion (Supplementary Material_Video) (Fig. 2).

Histopathology showed areas of orthokeratotic hyperkeratosis with intracorneal spiral formations, hypogranulosis, mild acanthosis, and focal mild papillomatosis; a discrete lymphohistiocytic infiltrate was found around superficial capillaries in the dermis (Fig. 3).

Despite TFFD predominantly affecting children and young adults, its consideration in elderly patients is crucial.^{2,3,7,8} Patients with extensive lesions should be cautioned about the risk of alcohol intoxication from the application of 70% isopropyl alcohol on the skin, which can lead to symptoms ranging from drowsiness and lethargy to mucous membrane irritation and respiratory depression.⁶ Moisturizer use is recommended to prevent cutaneous xerosis.^{1,3,6} Salicylic acid and other keratolytic can aid in scale removal, whereas topical corticosteroids are generally ineffective.^{2,6,8} Clinically recognizing TFFD can prevent unnecessary costs from additional tests and unsuccessful attempts at skin cleansing.^{3,6,7}

Financial support

None declared.

Author's contribution

Marinna Sampaio Campos: The study concept and design; writing of the manuscript and critical review of important intellectual content; critical review of the literature.

Loanda Oliveira Fukuma: Writing of the manuscript; analysis and interpretation; critical review of the literature.

Juliana Carvalho Delgado: Analysis and interpretation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature.

Paulo Ricardo Criado: Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; final approval of the final version of the manuscript.

Karla Calaça Kabbach Prigenzi: Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; final approval of the final version of the manuscript.

Sandra Lopes Mattos Dinato: Critical review of the literature; final approval of the final version of the manuscript.

Conflicts of interest

None declared.

Appendix A. Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.abd.2025.501131>.

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Received 18 July 2024; accepted 28 August 2024

Available online 18 June 2025

LETTER - CLINICAL

FGF22 heterozygous and FGFR2 mosaic mutations in Munro acne nevus: a case study[☆]



Dear Editor,

Munro acne nevus, also known as nevus comedonicus (MIM 617025), is a rare developmental anomaly of the pilosebaceous unit, classified as a subtype of epidermal nevus. Recent studies have implicated several genes in its pathogenesis, including *FGFR2*, *FGFR3* and *NEK9*. Herein, we report a case of Munro acne nevus associated with a germline heterozygous *FGF22* mutation (c.104A>G) and a somatic mosaic *FGFR2* mutation (c.755G>C).

A 22-year-old female presented with a congenital, asymptomatic plaque on her back that had progressively enlarged (Fig. 1A). Physical examination revealed an irregularly shaped, erythematous patch with well-demarcated borders in the right lumbosacral region. In the affected area dark red to black follicular papules with acuminate tips were observed (Fig. 1B). Comedones and hypopigmented terminal hairs were evident within the affected area. A comprehensive clinical evaluation revealed no systemic abnormalities.

Histopathology (Fig. 2A) demonstrated mild acanthosis and hyperkeratosis of the epidermis (Fig. 2B), focal basal layer hyperpigmentation, and dermal collagen hyperplasia. A hair follicle with prominent sebaceous hyperplasia was noted (Fig. 2C), accompanied by mild perifollicular fibrosis and lymphocytic infiltrate. The superficial dermis exhibited sparse perivascular lymphocytic infiltration.

Genetic analysis identified a germline heterozygous mutation in *FGF22* (rs574406266, c.104A>G, p.His35Arg) in both lesional skin and peripheral blood, based on Whole Exome Sequencing (WES) of DNA extracted with TIANamp Genomic DNA Kit (DP304, TIANGEN, China). Additionally, a somatic mosaic mutation in *FGFR2* (rs79184941, c.755G>C, p.Ser252Trp) was detected exclusively in the affected skin, with a variant allele frequency of 17%, confirmed by Sanger sequencing (Fig. 3).

Immunofluorescence analysis (Fig. 4A–B) revealed an uneven distribution of Ki-67-positive cells in the epidermis

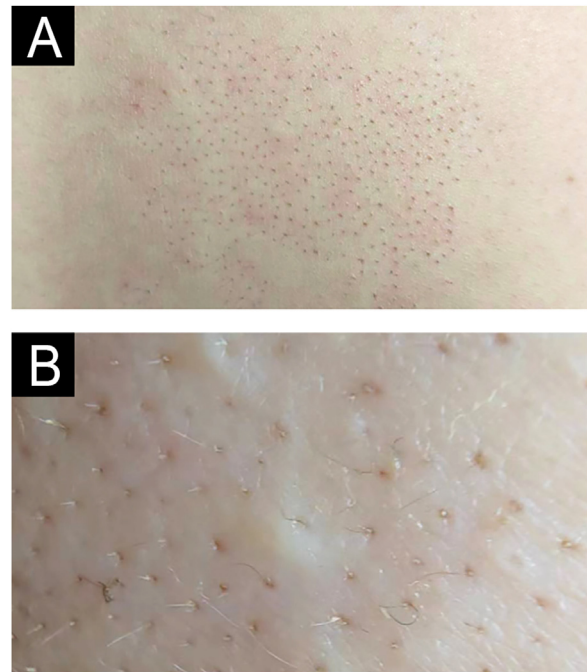


Figure 1 Clinical aspect (A) and close-up view (B).

and sebaceous glands, with a higher abundance compared to normal control skin. Aberrant upregulation of CK6 and downregulation of CK5 were observed in the epidermis and peripheral basal cells surrounding the sebaceous glands. Notably, both basal and suprabasal keratinocytes demonstrated increased and colocalized expression of *FGF22* and *FGFR2*, as evidenced by intense yellow fluorescence signals. In contrast, the sebaceous glands displayed expression of *FGFR2*, with minimal expression of *FGF22*.

Cutaneous mosaic-activating *FGFR2* mutations have been identified in several cases of nevus comedonicus, including c.755G>C (p.Ser252Trp),^{1,2} c.758C>G (p.Pro253Arg),³ and c.1144T>C (p.Cys382Arg).⁴ Apert syndrome also involves mutations at these sites of *FGFR2*, but is typically associated with extensive acne, along with craniosynostosis and severe syndactyly of the hands and feet.⁵ The p.Ser252Trp and p.Pro253Arg mutations of *FGFR2* are located in the extracellular topological domain, specifically in the linker

[☆] Study conducted at the Department of Dermatology, Peking University Third Hospital, Beijing, China.

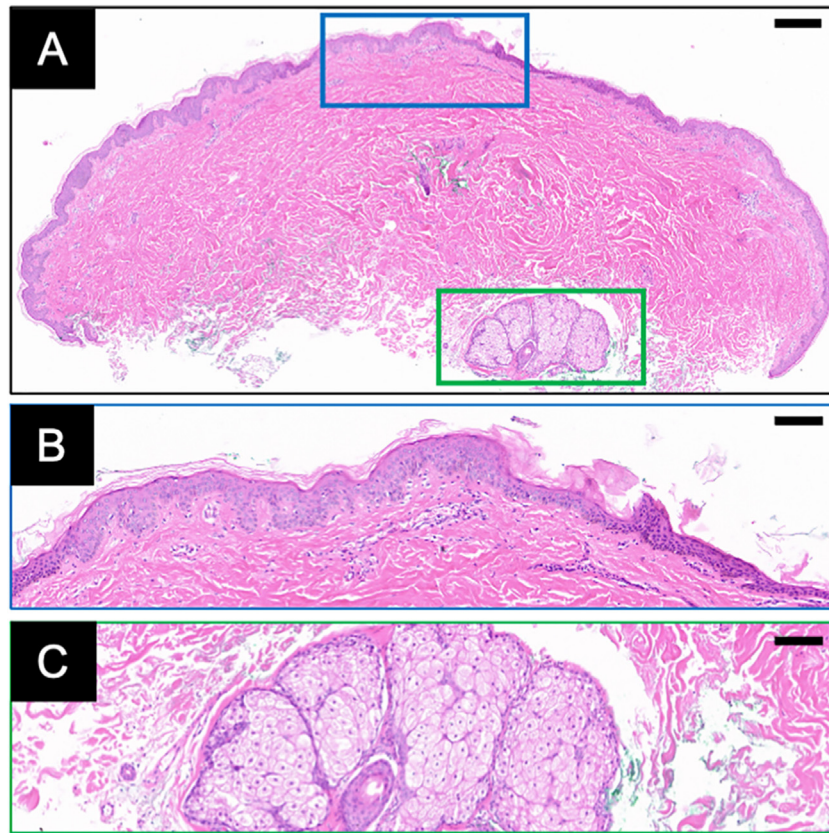


Figure 2 Overview of the lesional biopsy with Hematoxylin & eosin staining (A). The blue and green boxes represent the magnified views of the epidermis (B) and sebaceous glands (C), respectively. Scale bar: 300 μ m for (A), 100 μ m for (B and C).

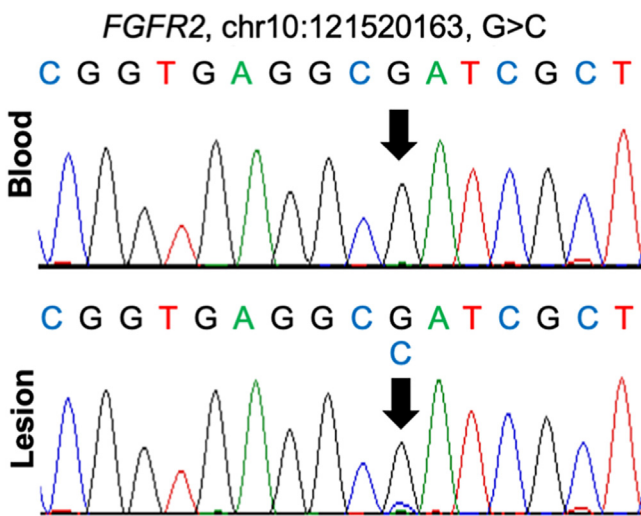


Figure 3 Sanger sequencing validation of the *FGFR2* mutation identified by WES in the patient's peripheral blood and lesional tissue.

region between immunoglobulin-like domains II and III. These gain-of-function mutations create additional non-specific FGF-FGFR contacts, enabling pathological binding of FGFs to FGFR2. Our case firstly reports a Chinese

Munro acne nevus patient harboring the *FGFR2* c.755G>C (p.Ser252Trp) mutation. Interestingly, this specific mutation has been associated with diverse phenotypes: M. Larsabal et al.¹ described naevoid acanthosis nigricans with localized skin thickening and hyperpigmentation, while B.C. Melnik et al.² reported inflammatory papules and pustules with hypopigmentation. In comparison, our case exhibited relatively milder skin lesions compared to these two cases.

FGF22 is a potent activator of FGFR2 in the skin, binding to FGFR2 IgIIIc. *FGF22* p.His35Arg (c.104A>G) mutation is novel in epidermal nevus and remains largely uncharacterized (SIFT score = 0.001, Polyphen2 HVAR score = 0.998). His35 is proximal to the N-terminal signal peptide region, suggesting that p.His35Arg mutation may affect FGF22 secretion and extracellular localization. In our case, FGFR2 and FGF22 were clearly colocalized in the epidermis, suggesting a potential ligand-receptor interaction *in situ*. Along with increased CK6 and Ki-67 expression in this area, this indicates that disrupted epidermal stratification and abnormal keratinocyte proliferation may be associated with FGF22/FGFR2 signaling. We propose a model wherein mutant FGF22 acts as a hyperactive ligand for constitutively activating FGFR2, resulting in sustained activation of downstream pathways.

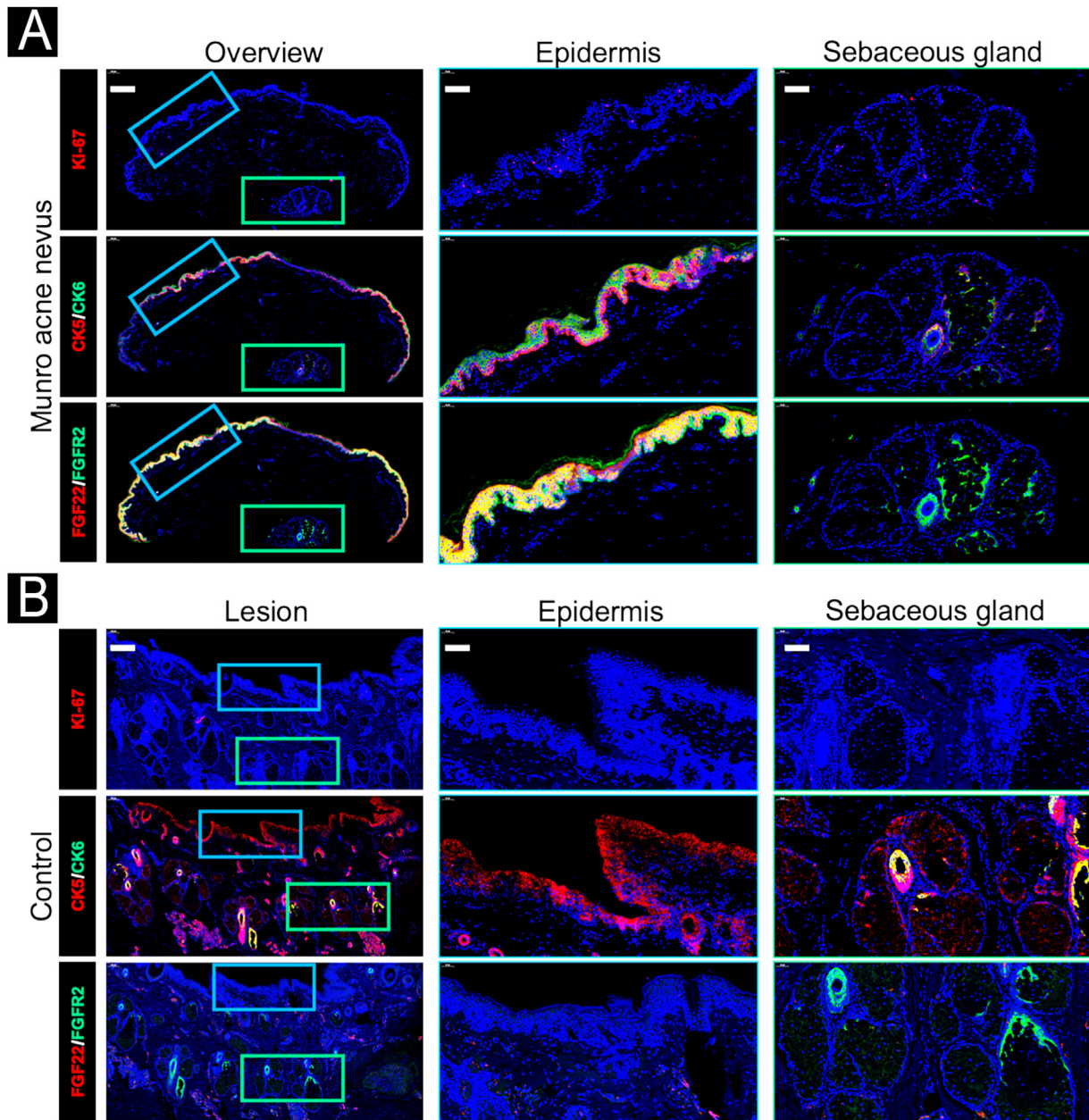


Figure 4 Immunofluorescence staining of the lesional biopsy (A) and healthy control (B). In the lesional skin (A), an uneven distribution of Ki-67-positive cells was observed in the epidermis and sebaceous glands, with higher abundance compared to normal control skin. CK6 was upregulated and CK5 downregulated in the epidermis and peripheral basal cells of the sebaceous glands. Basal and suprabasal keratinocytes showed increased and colocalized expression of FGF22 and FGFR2. In contrast, the sebaceous glands exhibited FGFR2 expression but minimal FGF22. In the healthy control skin (B), there was minimal presence of Ki-67-positive cells or CK6 in the epidermis and sebaceous glands. CK5 was expressed in the epidermis and peripheral basal cells of the sebaceous glands. Basal and suprabasal keratinocytes exhibited no expression of FGF22 or FGFR2. In the peripheral basal cells of the sebaceous glands, FGFR2 expression was observed, with FGF22 absent. Scale bar: 200 μm for overview; 50 μm for the epidermis and sebaceous glands.

Financial support

None declared.

Author's contribution

Jiachen Sun: Performed the experiments and data analysis, and wrote the manuscript, critically reviewed the manuscript.

Yimeng Wang: Performed the experiments and data analysis, and wrote the manuscript, critically reviewed the manuscript.

Lihua Zhang: Performed the experiments and data analysis, and wrote the manuscript, provided the pathological analysis, critically reviewed the manuscript.

Chunlei Zhang: Conceptualized the study and designed experiments; critically reviewed the manuscript.

Chuan Ma: Conceptualized the study and designed experiments; critically reviewed the manuscript.

Conflicts of interest

None declared.

Acknowledgments

We express our sincere gratitude to the patient for her participation and consent in this study.

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Received 30 August 2024; accepted 6 November 2024

LETTER - CLINICAL

Intravenous immunoglobulin in the treatment of scleromyxedema associated with monoclonal gammopathy[☆]



Dear Editor,

Scleromyxedema is a chronic disease of the spectrum of primary cutaneous mucinosis that affects young adults of both sexes.¹ According to Rongioletti et al.,^{2,3} the diagnostic criteria are: generalized papular and sclerodermiform rash, mucin deposition in the upper dermis, fibroblast proliferation and collagen fiber thickening, monoclonal gammopathy (90% monoclonal gammopathy of undetermined significance [MGUS]) and normal thyroid function.

Extracutaneous involvement may occur, with neurological, rheumatological, cardiovascular, gastrointestinal, respiratory, renal and ocular alterations. "Dermatoneuro syndrome" is a severe complication characterized by fever, epileptic seizures and coma. The mortality rate of scleromyxedema reaches over 20%.¹

The pathogenesis and action mechanism of human intravenous immunoglobulin (IVIG) in this disorder is still a matter of debate. It has been observed that serum from affected patients induces fibroblast proliferation *in vitro* and that, after IVIG infusion, there is a reduction in IL-17 levels and TGF- β gene expression.^{4,5}

The present report describes a 34-year-old female patient who developed a disseminated rash with waxy, pruritic papules, some assuming a linear arrangement, on thickened, difficult-to-fold skin (Fig. 1). She showed infiltra-



Fig. 1 Linear arrangement of papules.

[☆] Study conducted at the Complexo Hospitalar Padre Bento de Guarulhos, Guarulhos, SP, Brazil.

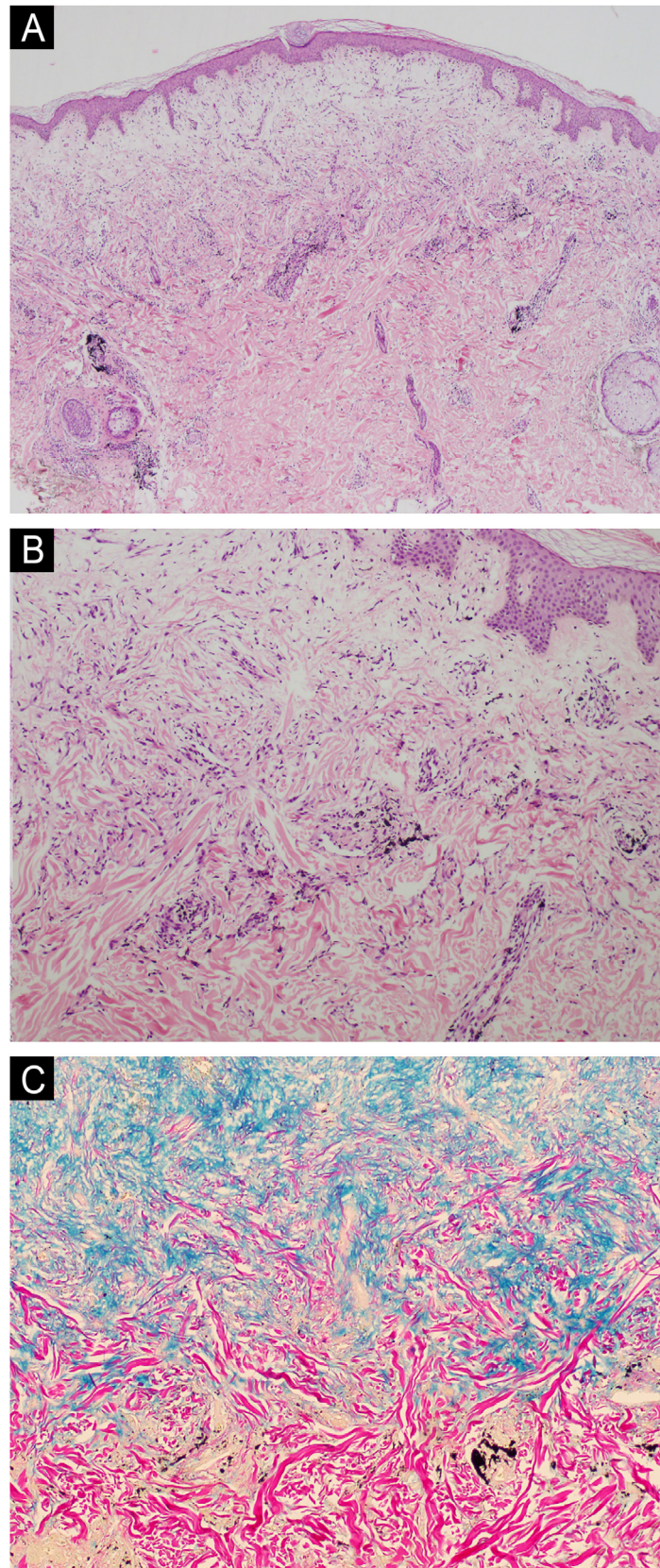


Fig. 2 (A) Pallor of the superficial dermis (Hematoxylin & eosin, $\times 40$); (B) Increased number of fibroblasts and collagen fiber thickening in the middle dermis (Hematoxylin & eosin, $\times 100$); (C) Mucin deposition (Colloidal iron, $\times 100$).



Fig. 3 Infiltration improvement and papule reduction on the upper back (A) before treatment and (B) after treatment.



Fig. 4 Infiltration improvement of the face in profile (A) before treatment and (B) after treatment.

tion of the face and ears, longitudinal furrows in the glabella and madarosis. Histopathology showed fibroblast proliferation, collagen fiber thickening, and mucin deposits in the dermis with colloidal iron staining (Fig. 2).

Based on the physical and pathological examination, the investigation was started for monoclonal gammopathies with electrophoresis and immunofixation of serum and urinary proteins, which revealed a monoclonal peak in gamma globulin (IgG) and IgG kappa monoclonality; myelogram, which showed 8% of plasma cells; bone marrow (BM) immunophenotyping, showing 0.8% of plasma cells with kappa light-chain monoclonality; in addition

to BM karyotype, the ratio between serum free light chains, measurement of serum immunoglobulins, thyroid function, renal function, calcium metabolism, blood count and bone inventory by tomography, all without alterations. These complementary exams led to the diagnosis of MGUS, an asymptomatic premalignant condition that eventually transforms into Multiple Myeloma (MM).

Six infusions of IVIG 2 g/kg were performed, each lasting three days and with an interval of four to six weeks, with significant improvement in the condition (Figs. 3 and 4). This result was similar to the report by Guarneri et al. with eight

patients and an 81.6% improvement in the modified Rodnan score.⁶

The patient will continue to receive IVIG indefinitely since most patients experience recurrence if treatment is interrupted. There is only one case report in which there was spontaneous remission.^{1,7,8}

Since this is a rare disease, randomized controlled clinical trials are not feasible. Based on systematic reviews and two prospective uncontrolled clinical trials, the best scientific evidence available regarding treatment advocates in favor of high-dose IVIG every four to six weeks. Thalidomide with corticosteroids can be used as a second-line treatment. Bortezomib and, more drastically, autologous bone marrow transplantation (BMT) are third-line treatments. Melphalan, despite being mentioned, has a high risk of hematological malignancy development with increased mortality due to the treatment itself.^{1,6,9}

Despite the association with monoclonal gammopathies, a review with 17 patients demonstrated sustained remission of scleromyxedema in only 2% of patients after BMT, even though the hematological disorder had been cured.⁸

Bortezomib is a reversible inhibitor of the 26S proteasome pathway that prevents the activation of the NF- κ B transcription factor and induces apoptosis in neoplastic cells. Its main indication is for the treatment of MM. Like IVIG, the action mechanism in scleromyxedema is unknown. Despite having been the therapy with the longest remission period described in the literature to date, emerging as a new treatment perspective, for now, it is limited as a third-line recommendation due to the few published studies.^{1,9,10}

Although rare, scleromyxedema has its importance due to its chronicity and high morbidity and mortality. Its low prevalence limits the establishment of research protocols for the development of new therapies with better cost-benefit. Although the strengthening of genetic and immunological knowledge facilitates this endeavor, case reports, such as this one, demonstrating the success of the employed therapy, provide data to the literature for future systematic reviews.

Authors' contributions

Amanda Cochlar Medeiros Perrella: Design and planning of the study; collection of data, or analysis and interpretation of data; drafting and editing of the manuscript; or critical review of important intellectual content; collection, analysis, and interpretation of data; Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; critical review of the literature; approval of the final version of the manuscript.

Alexandre Michalany: Collection of data, or analysis and interpretation of data; effective participation in research orientation; approval of the final version of the manuscript.

Mário Cezar Pires: Design and planning of the study; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; approval of the final version of the manuscript.

Cassio Oliveira Lima: Design and planning of the study; collection of data, or analysis and interpretation of data; drafting and editing of the manuscript; or critical review

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Financial support

None declared.

Conflicts of interest

None declared.

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Received 20 August 2024; accepted 29 November 2024

Available online 8 July 2025

LETTER - CLINICAL

Lymphangiectasia and genital lymphedema secondary to metastatic Crohn's[☆]



Dear Editor,

A 34-year-old male with Crohn's disease (CD) diagnosed in 2006 and treated with adalimumab since 2022, presented with persistent genital lymphedema (GL) starting in 2013. Extensive serological testing for sexually transmitted infections (STIs), autoimmune markers, and imaging studies were performed, leading to a diagnosis of idiopathic GL in 2018. The patient underwent circumcision in 2019, but the procedure did not improve his symptoms. In 2023, he was referred to dermatology due to genital warts of one year's duration.

On physical examination, genital swelling, predominantly involving the penis, was observed, causing distal deformity often described as "saxophone penis" (Fig. 1A). Multiple skin-colored popular lesions, 3–5 mm in size, were identi-

fied on the penile shaft and scrotum, some of which were umbilicated, while others were pedunculated (Fig. 1B). Histological examination of one papule revealed dilated vascular channels in the papillary dermis. Immunohistochemical staining demonstrated positive expression of D2-40 (podoplanin) and CD31 by the endothelial cells, confirming the lymphatic origin of the lesions (Fig. 2). Based on these findings, the lesions were diagnosed as lymphangiectasia secondary to GL. Further serological tests for STIs, autoimmunity, and blood parasites returned negative results. Imaging with ultrasound and abdominopelvic CT revealed edema of the penile subcutaneous tissue (SCT). A biopsy of the penile base demonstrated lymphoplasmacytic perivascular infiltrates in the deep dermis and SCT, with no evidence of microorganisms (Fig. 3). Considering the history of CD, the subsequent development of GL with lymphangiectasia, and the histological findings, the condition was classified as GL secondary to CD or anogenital CD, a form of metastatic Crohn's disease (MCD).



Figure 1 (A) Genital edema predominantly involving the penis. Distal deformity often referred to as "saxophone penis". (B) Skin-colored popular lesions located on the penile shaft and scrotum.

[☆] Study conducted at the Hospital Universitario Rey Juan Carlos, Móstoles, Madrid, Spain.

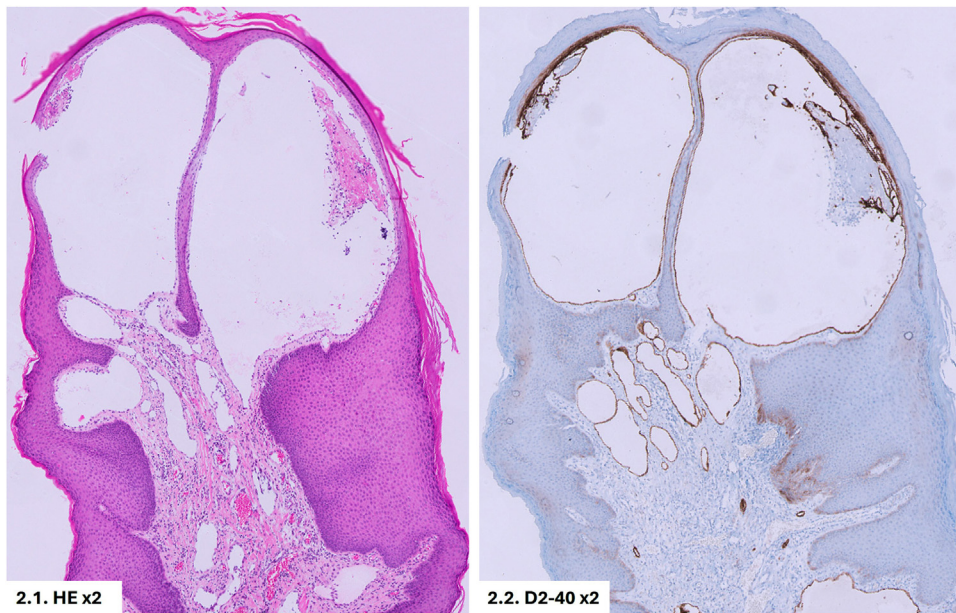


Figure 2 (1) Hematoxylin-eosin staining of a papular lesion, showing dilated vascular channels in the papillary dermis (Hematoxylin & eosin, $\times 2$). (2) Immunohistochemical staining with D2-40 positive in endothelial cells, confirming the lymphatic origin of the vascular structures (D2-40 $\times 2$).

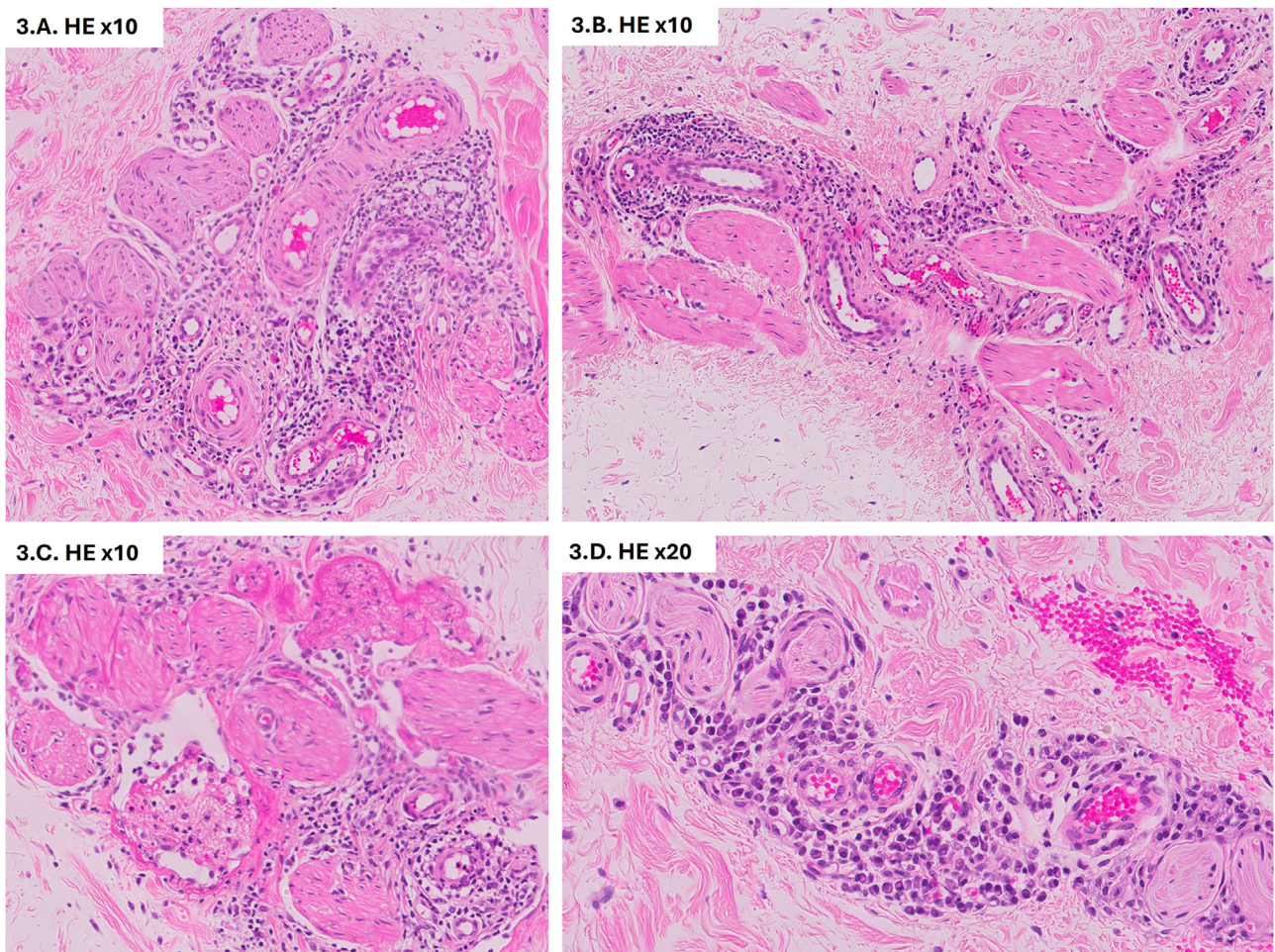


Figure 3 (A–C) Lymphoplasmacytic perivascular infiltrates observed in the deep dermis and subcutaneous tissue of the penile base (Hematoxylin & eosin, $\times 10$). (D) Detailed view of lymphoplasmacytic perivascular infiltrates (Hematoxylin & eosin, $\times 20$).

Lymphangiectasias are dilated lymphatic vessels in the superficial dermis, typically occurring in areas of pre-existing lymphedema. These vessels are confirmed by positive immunohistochemical staining for podoplanin (D2-40), a specific marker for lymphatic endothelial cells. In the literature, the terms lymphangiectasia and lymphangioma are often confused and used interchangeably, which can lead to diagnostic confusion.^{1,2} Penile lymphedema is a rare, chronic condition that may be idiopathic or secondary to causes such as neoplasms, surgeries, radiation, infections (e.g., STIs, filariasis, tuberculosis), sarcoidosis, hidradenitis suppurativa or CD.³ Diagnostic tools include ultrasound, CT or MRI of the abdomen and pelvis, lymphoscintigraphy, and screening for STIs, filariasis, and angiotensin-converting enzyme levels. Biopsy is recommended when specific etiologies are suspected.³⁻⁵

Anogenital Crohn's disease (AGCD), also referred to as metastatic Crohn's disease or anogenital granulomatosis (AG), is a rare condition that is challenging to diagnose, particularly in the absence of gastrointestinal symptoms.⁶⁻⁸ MCD involves granulomatous inflammation in skin areas non-contiguous to the gastrointestinal tract and often presents as nodules, plaques, or ulcerative lesions, primarily affecting the extremities, genitalia, or perianal region.^{7,9} In our case, this rare presentation highlights the diagnostic challenges associated with AGCD. A systematic review of AGCD found that genital edema was the most common clinical manifestation in both males and females.⁶ Histological findings may include granulomas (seen in up to 70% of cases), lymphocytic and plasma cell inflammatory infiltrates, and occasionally lymphangiectasia.⁶ In this case, the absence of granulomas does not rule out the diagnosis of MCD if other characteristic features are present, and the use of anti-TNF therapy (adalimumab) could have suppressed granuloma formation.

A study by Shim et al. described 41 cases of GL, including 10 patients with a prior diagnosis of CD, and four diagnosed with CD during the evaluation of their lymphedema. Most of these patients had no gastrointestinal symptoms, and GL was considered a manifestation of MCD. GL typically appears years after CD diagnosis in adults but may be the first manifestation in pediatric patients.^{6,10}

Treatment of AGCD is challenging due to the absence of standardized guidelines. Management options include oral antibiotics, biologics (anti-TNF, ustekinumab), and JAK inhibitors.^{6,10} Surgical interventions, such as lymphatic drainage or lesion excision, can improve symptoms but do not address the underlying cause.⁶

In conclusion, AGCD is a rare condition with frequent diagnostic delays. Genital edema is its most frequent presentation and, in some cases, the first manifestation of CD. Early recognition of GL and lymphangiectasia in patients with CD is crucial to avoid unnecessary surgical interventions. Multidisciplinary management involving imaging, histopathology, and clinical expertise is essential for optimal outcomes.

Financial support

None declared.

Authors' contributions

Nelly Marlene Román Mendoza: Writing of the manuscript or critical review of important intellectual content; critical review of the literature.

María Dolores Caro Gutiérrez: Writing of the manuscript or critical review of important intellectual content; critical review of the literature; final approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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Received 11 October 2024; accepted 16 December 2024

Available online 3 July 2025

LETTER - CLINICAL

Lymphocytic thrombophilic arteritis, an infrequent cause of livedo reticularis – Case report[☆]



Dear Editor,

Lymphocytic thrombophilic arteritis (LTA), also known as macular lymphocytic arteritis (MTA), is a small-to-medium vessel arteritis. LTA shares many similarities with cutaneous polyarteritis nodosa (cPAN) i.e livedo reticularis but does not exhibit systemic features like c-PAN.¹ The objective of this report is to present the first documented case of LTA in a Chilean patient.

A 27-year-old female consulted in dermatology service asking for a second opinion in the context of a prior history and diagnosis of cutaneous leukocytoclastic vasculitis (CLV) of two years of duration, which had been treated with corticosteroids without success.

She reported an increase in lesions, accompanied by fatigue and arthralgias in the lower extremities. She denies having arthritis, oral ulcers, photosensitivity, symptoms of sicca syndrome, or neuropathy. Physical examination revealed non-palpable confluent hyperpigmented macules with a livedoid distribution located on the legs, arms, and

trunk, with mild infiltration (Fig. 1). Only two scars were observed in the internal malleolar area (attributed by the patient to footwear), with no ulcers or cutaneous pain. There were no abnormalities detected in the lymph nodes, thyroid, breasts, chest, abdomen, or joints.

Laboratory tests showed a slight elevation of the erythrocyte sedimentation rate (ESR) and a myositis panel strongly positive for threonyl-tRNA synthetase (PL-7). Antinuclear antibody (ANA) was positive at 1:80 with a fine granular pattern (AC-4), while other blood tests were negative (extractable nuclear antigen [ENA], rheumatoid factor [RF], anti-cyclic citrullinated peptide [anti-CCP], anti-double stranded DNA [anti-DNA], perinuclear anti-neutrophil cytoplasmic antibodies [ANCA-p], and cytoplasmic ANCA [ANCA-c]) or within normal levels (complement C3, C4, renal, and liver function tests). There was no evidence of anemia, leukocytosis, or thrombocytopenia. A chest Computed Tomography (CT) scan revealed no pathological findings.

A biopsy performed two years ago described: "Small vessels with abundant fibrin in the walls and scant inflammatory cells, primarily neutrophils, with minimal leukocytoclasia. Deep vessels showed no significant morphological alterations" which was consistent with CLV.



Fig. 1 Non-palpable confluent hyperpigmented macules with a livedoid distribution are observed on the legs and feet.

[☆] Study conducted at the Clínica Dávila Recoleta, Santiago, Chile.

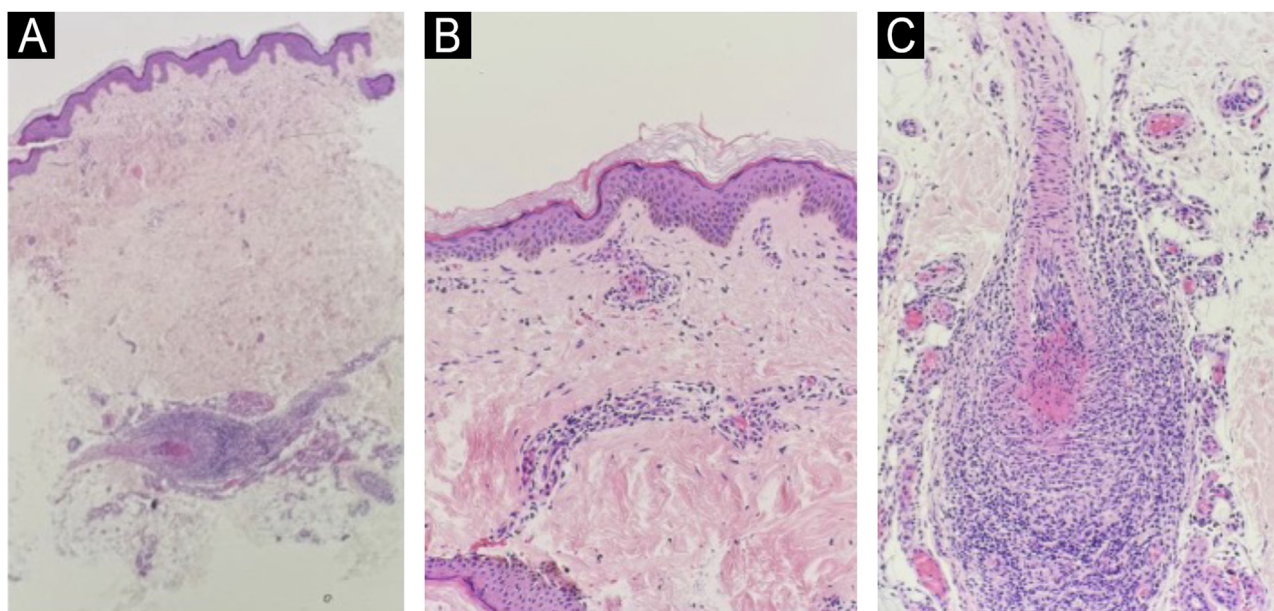


Fig. 2 (A) Low magnification view ($\times 10$) showing orthokeratosis and a preserved epidermis. There is erythrocyte extravasation with scant lymphocytic infiltrate around the walls of superficial and deep dermal postcapillary venules. A medium-caliber vessel exhibits fibrin deposition within the intima and subtotal to total luminal occlusion. (B) Medium magnification view ($\times 40$) highlighting a closer look at the epidermis and the underlying dermis. Erythrocyte extravasation is evident, and a mild lymphocytic infiltrate is seen in the superficial dermis, with preserved tissue architecture and no signs of granulomas, leukocytoclasia, or interstitial dermal mucinosis. (C) High magnification view ($\times 100$) focusing on a dense mixed infiltrate predominantly composed of mononuclear cells, including lymphocytes, plasma cells, and histiocytes, along with a few polymorphonuclear cells. There is no perivascular tissue involvement, nor any granulomas, leukocytoclasia, or thickened basement membrane, consistent with deep dermal small and medium vessel vasculitis without leukocytoclasia.

Given the diagnosis of macular cutaneous vasculitis without systemic features and the strong positivity for PL-7, further tests (ANA, myositis panel, Creatine Kinase [CK], Hepatitis B Virus [HBV], Hepatitis C Virus [HCV], Human Immunodeficiency Virus [HIV]) were conducted, confirming elevated PL-7 again with all other results negative. A new punch biopsy was requested, and initial treatment with hydroxychloroquine (Plaquinol) was initiated.

The patient returned with the new biopsy results (Fig. 2). The pathology service suggested considering lymphocytic macular arteritis, vasculitis associated with connective tissue disease (including lupus, rheumatoid arthritis, morphea/scleroderma, and Sjögren's syndrome), Behçet's disease, and viral infections based on histopathological patterns. Clinical suspicion leaned towards lymphocytic thrombophilic arteritis.

The patient developed frank Raynaud's phenomenon (previously non-existent), hand arthralgia, and alopecia, without sicca symptoms, reflux, or dysphagia. Treatment was initiated with acetylsalicylic acid, oral nifedipine, and topical nifedipine and arnica with good response.

In conclusion, LTA is an infrequent arteritis and is probably underreported. To the best of our knowledge, this is the second case report in Latin America.

The clinical presentation of LTA is characterized by the appearance of hyperpigmented macules primarily on the lower limbs, and less commonly on the upper limbs, particularly in women over 40 years old. Additionally, livedo racemosa/reticularis or nodules may be observed, under-

scoring the clinical resemblance to c-PAN.² Both conditions often manifest in a similar distribution and morphology, making the differentiation challenging based solely on clinical features.³

Histologically, LTA is distinguished by lymphocytic infiltration and thrombophilic features in the dermal and subcutaneous vessels. Key characteristics include luminal fibrin deposition and a hyalinized fibrin ring within the vessel lumen, both of which are markers of a thrombophilic state. The intense lymphocytic infiltration surrounding the affected vessels in LTA also resembles cPAN in its chronic stages. However, while LTA primarily shows lymphocytic involvement, cPAN may transition from a neutrophilic to a lymphocytic infiltrate as the disease progresses through acute to reparative stages. The shared features of luminal fibrin deposition and lymphocytic infiltration create histopathologic overlaps with cPAN, yet LTA generally lacks the systemic manifestations commonly associated with cPAN.^{3,4}

Treatment of LTA remains challenging as there are few reported cases, leading to a lack of consensus or studies supporting a definitive treatment approach. Further research is needed to establish the most effective treatment strategies for this condition.

In summary, LTA and cPAN share clinical and histopathologic similarities, such as the presence of livedo-like lesions and lymphocytic vascular infiltration. However, LTA is typically confined to the skin with a more indolent course, while cPAN carries the potential for systemic involvement,

painful nodules, and other inflammatory features not usually present in LTA.³

Financial support

None declared.

Authors' contributions

Dominga Peirano: Study concept and design; Data collection, or analysis and interpretation of data; Writing of the manuscript or critical review of important intellectual content; Final approval of the final version of the manuscript.

Maria Hubner-Garretón: Study concept and design; data collection, or analysis and interpretation of data; Writing of the manuscript or critical review of important intellectual content; Final approval of the final version of the manuscript.

Martha Fernandez: Study concept and design; Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; Critical review of the literature; Final approval of the final version of the manuscript.

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Conflicts of interest

None declared.

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Received 2 October 2024; accepted 9 November 2024

Available online 14 July 2025

LETTER - CLINICAL

Mycoplasma-Induced Rash and Mucositis (MIRM) mimicking herpetic stomatitis[☆]



Dear Editor,

A 20-year-old male presented with a 3-day history of painful oral lesions, impeding oral intake, and scrotal lesions. He recalled an episode of sore throat and cough 10 days prior, which had completely resolved after self-treatment with ibuprofen and two doses of amoxicillin-clavulanic acid. The patient had a history of herpes labialis but had not experienced an outbreak in recent months. He was otherwise well, afebrile, and without systemic symptoms.

On examination, confluent whitish aphthous lesions in a herpetiform pattern on the oral mucosa and mild gingivitis were noted (Fig. 1A–D); along with three annular plaques with crusted center on the scrotal skin (Fig. 1E). There was no ocular or genital mucosal involvement. Cardiopulmonary auscultation and blood test, including complete blood count and general biochemistry panel, were normal. Microbiological samples and a scrotal lesion biopsy were collected.

The initial differential diagnosis included Mycoplasma-Induced Rash and Mucositis (MIRM) or Reactive Infectious Mucocutaneous Eruption (RIME); toxicodermia within the Erythema Multiforme (EM) – Stevens-Johnson Syndrome (SJS) – Toxic Epidermal Necrolysis (TEN) spectrum; and herpetic stomatitis with minor EM. The patient was initiated on dexamethasone 4mg daily for three days, valacyclovir, and topical triamcinolone acetonide. Upon follow-up 72 hours later, the lesions had disappeared.

Serology was positive for Mycoplasma Pneumoniae (MP) (both IgM and IgG antibodies), Herpes Simplex Virus (HSV) (IgG antibodies only), and negative for HIV, hepatitis viruses, and syphilis. Polymerase Chain Reaction (PCR) from oral lesions was negative for HSV types 1 and 2.

The histopathology revealed a dense inflammatory infiltrate in the superficial and mid-dermis, predominantly

composed of lymphocytes and polymorphonuclear cells. Interface damage was evident, with subepidermal splitting and apoptotic keratinocytes (Fig. 2).

Acute mucositis with minimal or absent skin involvement has been described under terms like “atypical SJS”, “SJS without skin lesions”, and “Fuchs syndrome”.¹ In 2015, Canavan et al. introduced the term MIRM to distinguish the unique mucocutaneous eruptions linked to MP from drug-induced SJS, TEN, and herpes-related EM.^{1–4} In recent years, other pathogens such as Chlamydia Pneumoniae (CP), influenza B, parainfluenzavirus, adenovirus, metapneumovirus, rhinovirus, enterovirus, group A Streptococcus, and SARS-CoV-2 have been reported to trigger similar mucocutaneous reactions.^{1,2} This has led to the concept of RIME, which reflects the spectrum of infectious agents capable of inducing these eruptions.^{1,2}

MIRM is an uncommon condition, predominantly affecting children and young adults, marked by prominent mucositis with limited skin involvement, typically preceded by non-specific flu-like symptoms that manifest 7–10 days before mucocutaneous onset.¹ The vesiculobullous and atypical targetoid skin lesions bear a resemblance to those in EM, SJS, and TEN. However, MIRM presents with distinctive clinical, pathophysiological, and prognostic outcomes that set it apart from these conditions.^{2–4} The differential diagnosis should also encompass viral infections (e.g., HSV, Epstein-Barr, cytomegalovirus, Coxsackie A6, and HIV), oral candidiasis, exposure to caustic substances, and autoimmune diseases like pemphigus vulgaris.^{4–6}

The pathophysiology underlying MIRM remains unclear; however, it is hypothesized to involve polyclonal B-cell proliferation and antibody production following MP infection, leading to immune complex deposition and complement activation. Additionally, molecular mimicry between mycoplasma P1 adhesion molecules and a keratinocyte antigen, as well as genetic susceptibility, have been proposed.⁴

Histologically, MIRM/RIME lesions share features with EM, SJS, and TEN, including apoptotic keratinocytes, full-thickness epidermal necrosis with subepidermal splitting, and superficial dermal infiltrate with sparse perivascular lymphocytes.^{1,5,6}

PCR has emerged as the “gold standard” for establishing the microbiologic etiology of community-acquired pneumonia, offering higher sensitivity to detect MP or CP,

[☆] Study conducted at the Dermatology Department, Complexo Assistencial Universitario de Salamanca, Salamanca, Espanha.

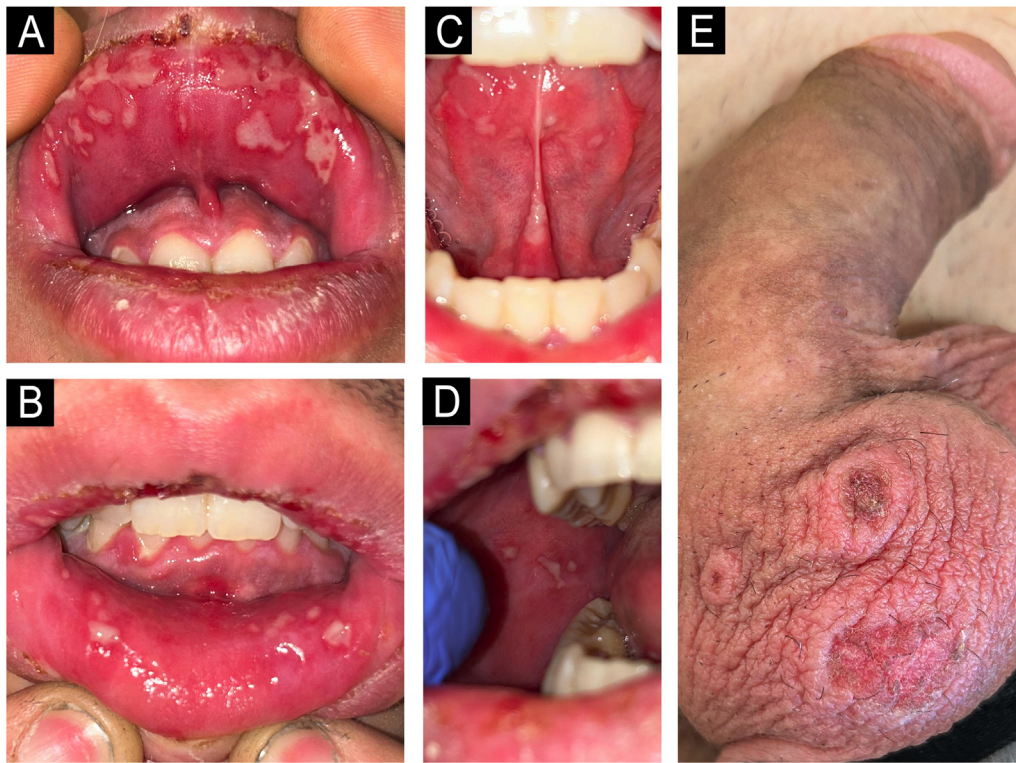


Figure 1 Clinical images. Confluent whitish aphthous lesions in a herpetiform pattern on the oral mucosa and mild gingivitis (A–D). Three annular plaques with crusted center on the scrotal skin (E).

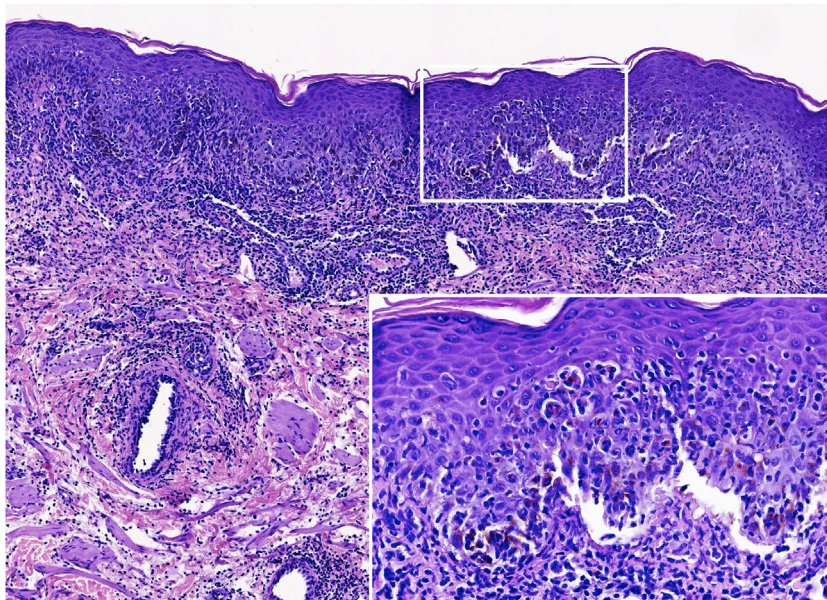


Figure 2 Histological images. Scrotal lesion showing a dense inflammatory infiltrate in the superficial and mid-dermis, predominantly composed of lymphocytes and polymorphonuclear cells. Interface damage is evident, with subepidermal splitting and apoptotic keratinocytes (Hematoxylin & eosin; $\times 160$ and $\times 800$ – inset).

particularly in the earlier stages of infection.^{5,7} Specific serological detection can be valuable for retrospective diagnosis, particularly when samples are taken at least two weeks apart to assess seroconversion or a fourfold increase in antibody titers.^{4,5,7} MP-IgM antibodies appear within one

week of clinical onset, peaking around the third week, and serving as a marker of recent infection.^{5,7} MP-IgG antibodies appear about two weeks post-infection, peak at five weeks, and persist long-term.^{5,7}

The prognosis is generally good, with low rates of sequelae and a good therapeutic response to antibiotics and/or systemic steroids.⁴

This case highlights the importance of considering MIRM/RIME in the differential diagnosis of mucositis. The history of recent respiratory symptoms without drug exposure may suggest MP or CP infection, helping to distinguish these conditions from SJS and TEN. Early recognition and targeted treatment are essential for optimal management.

Authors' contributions

Sara Becerril Andrés: Had access to the data and played a role in writing this manuscript.

Adolfo Alejandro Cabanillas Cabral: Had access to the data and played a role in writing this manuscript.

Gloria Baeza-Hernández: Had access to the data and played a role in writing this manuscript.

Financial support

None declared.

Conflicts of interest

None declared.

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Received 26 November 2024; accepted 30 December 2024
Available online 28 June 2025

LETTER - CLINICAL

Optical super-high magnification dermoscopy *versus* standard dermoscopy in basal cell carcinoma[☆]



Dear Editor,

The recent emergence of super high dermoscopy (SHD) allows magnifications of up to 400 times, which brings new perspectives to the interpretation of dermoscopic images. This technology is available with non-polarized light and the images are obtained using the Fotofinder Medicam 1000 device (Fotofinder System, Bad Birnbach, Germany) replacing the conventional terminal lens with the super high dermoscopy (SHD) lens.

To demonstrate the potential of using SHD, this report describes the case of a 78-year-old female patient with Fitzpatrick skin phototype III, with a brownish papule in the left preauricular region with progressive growth. The patient was photographed using conventional dermoscopy and super high dermoscopy with ultrasound gel immersion (Figs. 1–3).



Figure 1 Digital dermoscopy with x20 magnification. Fotofinder System, Bad Birnbach, Germany.

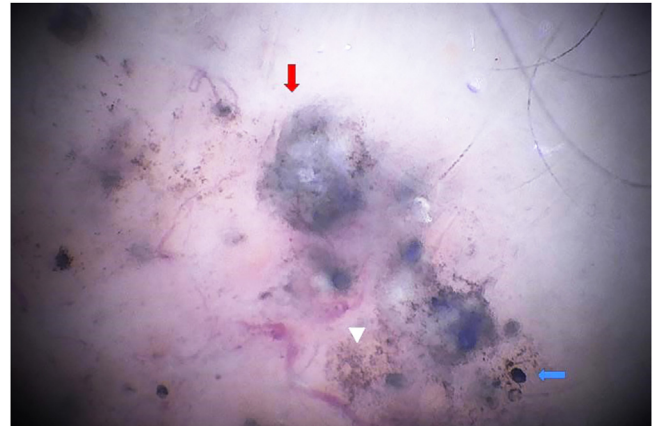


Figure 2 SHD with x180 magnification. The image shows blue ovoid nests at higher magnification (red arrow), rounded blue globules (blue arrow) and irregular pigmented structures (triangle).

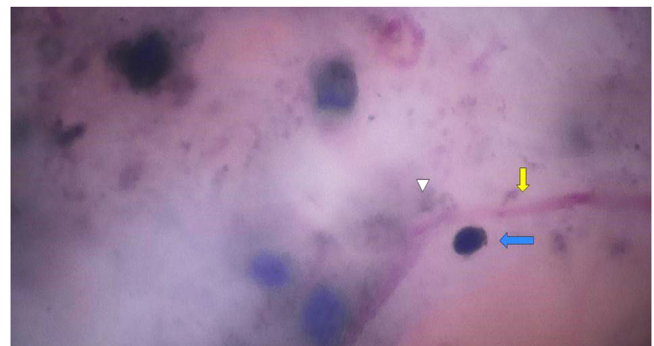


Figure 3 SHD of the same region with x400 magnification. Telangiectasias can be seen at higher magnification, with focus (yellow arrow), surrounded by irregular pigmented structures (triangle) and rounded blue globules (blue arrow).

The patient was subsequently referred for tumor excision and the material was sent for histopathological examination, with a report compatible with pigmented solid basal cell carcinoma with an adenoid component.

SHD allows the visualization of structures that are not perceptible through conventional dermoscopy.¹ In the literature, there are reports on the use of SHD in the identification

[☆] Study conducted at the Department of Dermatology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil.

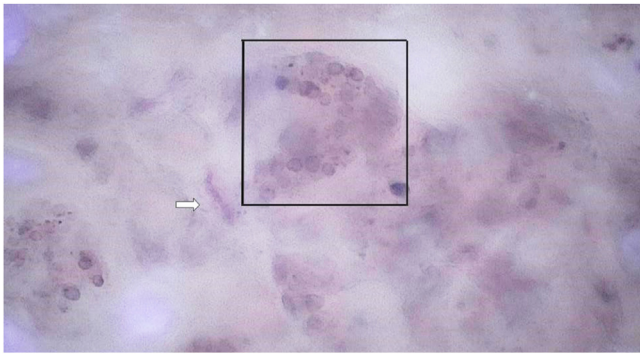


Figure 4 SHD at x400 magnification demonstrates a globule of an intradermal melanocytic nevus. Telangiectasias without focus (white arrow) can be observed.

and differentiation between melanomas and atypical nevi in melanocytic lesions,² as well as in the differential diagnosis between benign facial lesions and lentigo maligna.³ Regarding basal cell carcinomas, irregularly pigmented structures, corresponding to melanocyte deposits containing melanin,⁴ linear vessels with peripheral dots and globules,⁵ vessels with a pattern similar to oak leaves,⁶ and hairpin vessels,⁴ have already been described exclusively through SHD.

The case described herein illustrates the easier identification of dermoscopic structures observed by SHD when compared to conventional dermoscopy. In Fig. 1, conventional dermoscopic examination ($\times 20$ magnification) allows the visualization of structures that less experienced examiners may mistake for globules of melanocytic lesions. Figs. 2 and 3 show the same structures observed at SHD (x180 and x400 magnification). It is clear that these are bluish-gray globules, structures that are characteristic of basal cell carcinomas. The morphological characteristic of telangiectasias is also more easily observed at SHD, with focus and showing the characteristic peripheral dots previously described for SHD.⁵ Fig. 4, for comparison purposes, shows structures in an intradermal nevus with a tendency to an annular arrangement (globule), corresponding to nests formed by the union of nevus cells.

The nomenclature and description of the different structures observed at SHD are not yet standardized and the use of this technique is still in the experimental phase. It is not a substitute for conventional dermoscopy, but rather a new tool capable of aiding in diagnoses through additional information.

Financial support

None declared.

Authors' contributions

Izadora Moreira do Amaral: Collection, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; drafting and editing of the manuscript or critical review of impor-

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Conflicts of interest

None declared.

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Received 5 November 2024; accepted 12 December 2024

Available online 3 July 2025

LETTER - CLINICAL

Primary extramedullary plasmacytoma: a rare case presentation[☆]



Dear Editor,

Plasma cell dyscrasias are a group of clonal disorders characterized by the proliferation of neoplastic plasma cells. Plasma cell neoplasms include three categories: plasmacytoma (single lesions); plasma cell myeloma (multiple myeloma); and plasma cell neoplasms with associated paraneoplastic syndrome.¹ Plasmacytomas develop primarily in osseous tissue (solitary plasmacytoma of bone) and less frequently in soft tissues (Solitary extramedullary plasmacytoma – SEP). The latter represent approximately 3% of neoplasms of this cell type, manifesting predominantly in the airway and gastrointestinal tract, although other organs and tissues may be involved.² Cutaneous involvement is extremely rare, accounting for approximately 6% of all SEPs.³

We herein present a case report of an adult male who developed a primary extramedullary solitary plasmacytoma of sudden onset on his right leg.

A 66-year-old male sought consultation after the sudden onset of a lesion on his right leg. The patient denied pain or pruritus associated with the lesion. He exhibited an 8 × 8 mm painless, firm, slightly mobile erythematous-violaceous tumor, located in the right pretibial region (Fig. 1). There were no other significant cutaneous lesions or palpable lymph nodes at physical examination. The patient denied other past medical histories, did not receive any chronic medication, and did not present systemic symptoms.

A partial punch biopsy of the lesion revealed a dermal infiltration of diffuse mononuclear cells with a basophilic cytoplasm and small central nucleolus, some of which had a plasmacytoid appearance. Immunohistochemistry showed an atypical lymphoplasmacytic proliferation, which was CD79a positive, CD138 positive, CD20 negative, and exhibited clonality of lambda light chains (Fig. 2).



Figure 1 Right pretibial region; a painless, firm, slightly mobile erythematous-violaceous tumor.

An extensive workup performed in conjunction with the hematology department ruled out plasma cell myeloma. The results evidenced normal hemogram, serum electrophoretic proteinogram, and renal function; a bone marrow biopsy reported slight reactive changes but less than 5% of plasma cells, and flow cytometry showed no abnormalities. A total-body PET-scan did not reveal any hypermetabolic foci in the right leg or in other locations. These findings led us to confirm the diagnosis of solitary cutaneous extramedullary plasmacytoma.

The patient received three-dimensional conformal radiation therapy with a dose of 40 Gy over 4 weeks exhibiting a complete response. At his last follow-up a year after completion of radiotherapy, there was no evidence of cutaneous recurrence, plasma cell myeloma, or light chain disease.

Primary cutaneous plasmacytoma is a plasma cell dyscrasia (neoplasm) that is difficult to classify and diagnose due to its extreme rarity. There are fewer than 100 cases reported in the literature.⁴ The mean age of presentation

[☆] Study conducted at the Hospital Universitario Austral, Pilar, Buenos Aires, Argentina.

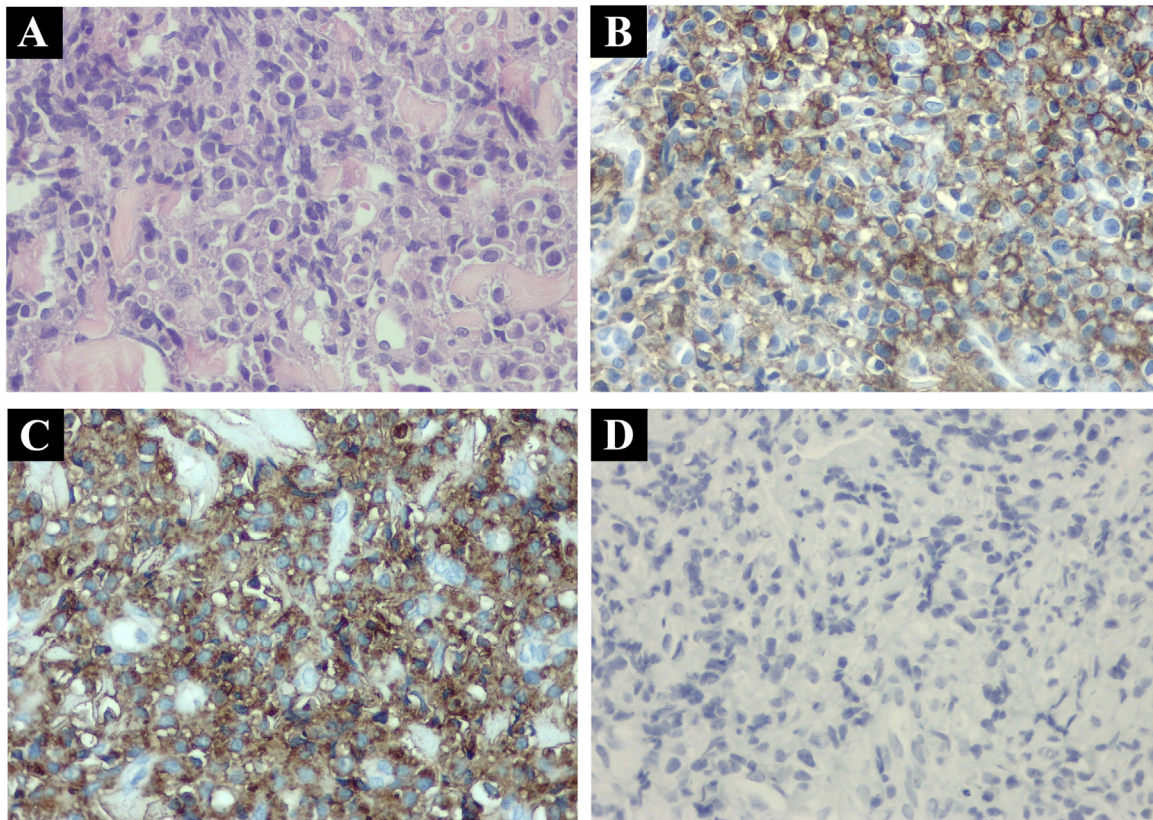


Figure 2 (A) Hematoxylin & eosin staining. Multiple ovoid cells with basophilic cytoplasm and eccentric nucleus demonstrating plasmacytoid differentiation. (B) CD 138 positive membranous staining. (C) Lambda chain positive staining. (D) CD 20 negative staining.

is around 60, with a male predominance (approximately 3:1). The presenting single or multiple lesions are often reported as erythematous or violaceous nodules, plaques, or papules which are very rarely ulcerated and do not show any predilection site.⁵

The diagnosis of solitary extramedullary plasmacytoma requires the exclusion of associated multiple myeloma.⁶ Laboratory testing is performed to screen for evidence of end-organ damage such as anemia, hypercalcemia, or kidney impairment, and serum-free light chain ratio. Imaging such as 18F-FDG PET/CT must show no evidence of other extramedullary or lytic lesions, and a bone marrow biopsy should demonstrate no clonal plasma cells.

Therapeutic approaches for SEP include radiation, surgical excision, or a combination of both. Localized Radiation Therapy (RT) is generally the treatment of choice, most published series report using a dose of 30 to 60 Gy.^{7,8} Similar studies suggest that a surgical approach with complete resection is also a viable alternative, especially in small lesions.⁸

Cutaneous SEP tends to follow an indolent clinical course, but local recurrence may occur. Does et al. showed a 5-year overall survival of 90% for SEP presenting in skin or lymph nodes.³ Prognostic factors of recurrence appear to be multiple lesions and an age of onset ≥ 65 .^{5,8} Overall, less than 7% of patients with SEP develop local recurrences after RT, and only 10% to 15% will ultimately develop multiple myeloma.⁹ Periodic follow-up is advised every 3- to 6-months.

This case is presented due to its extreme rarity, complex clinical and histopathological diagnosis, and the necessity for strict patient follow-up, as a small percentage of patients may show local or systemic progression and develop multiple myeloma in the future.

Authors' contributions

Pedro Barbosa: Design and planning of the study; drafting and editing of the manuscript; collection, analysis and interpretation of data; critical review of the literature; critical review of the manuscript; approval of the final version of the manuscript.

Clara De Diego: Drafting and editing of the manuscript; collection, analysis and interpretation of data; critical review of the literature; critical review of the manuscript.

Javier Anaya: design and planning of the study, critical review of the literature; critical review of the manuscript.

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Financial support

None declared.

Conflicts of interest

None declared.

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Received 20 November 2024; accepted 27 January 2025

Available online 18 June 2025

LETTER - CLINICAL

Rare case of lymphomatoid papulosis type E[☆]



Dear Editor,

Lymphomatoid papulosis (LyP) is a chronic, self-limited, usually relapsing papulonodular skin condition. Despite belonging to CD30-positive cutaneous lymphoproliferative disorders and malignancies, most cases follow a benign course, however, patients possess an increased risk of developing other hematological malignancies. According to the 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas histologically, six different subtypes are differentiated: LyP type A–E and a rare variant including the presence of DUSP22-IRF4 rearrangement.¹ LyP type E with papules and plaques developing into eschar-like necrotic lesions is responsible for less than 5% of LyP cases, histologically characterized by angiodestructive, angioinvasive pleomorphic CD30+ T-cells.^{2,3}

A 71-year-old male patient with an extensive history of non-melanoma skin cancers was referred to our clinic, showing erythematous papulonodular lesions, progressing into ulcerated, necrotic lesions symmetrically on the lower extremities (Fig. 1). As the first symptoms appeared, levofloxacin therapy was administered with little to no result. The location and appearance of skin lesions made differential diagnosis challenging; necrotizing vasculitis, ecthyma gangrenosum and hematological malignancies were the most probable conditions. An investigation of the patient's history ruled out new medications and infections previous to symptoms. Laboratory test results were normal, cryoglobulin level was not detectable. The immunological panel showed no abnormalities, viral serology was positive for CMV and EBV IgG. An X-ray of the chest and ultrasound of the abdomen did not find pathological anomalies. The excision specimen depicted epidermal ulceration and dermal-based angiodestructive medium-sized, to large-sized atypical lymphocytic infiltrate without extension into the subcutaneous fat. Mitotic figures were not infrequent. In addition to fibrin deposition, thrombosis was detected in some of the

affected vessels. Tumor cells were extensively immunoreactive for CD3 and CD30 but did not stain positively for CD20. The neoplastic cells also expressed CD8, CD4, CD56, TIA-1 and Mum-1 (Fig. 2). Monoclonal TCR-g gene rearrangement was detected by PCR. The main histological differential diagnosis of an angiocentric/angiodestructive cutaneous lymphoid infiltrate includes lymphomatoid papulosis type E, extranodal NK/T cell lymphoma nasal type, hydroa vacciniforme-like lymphoma, lymphomatoid granulomatosis and cutaneous gamma/delta T-cell lymphoma. To effectively rule out systemic hematological malignancies, flow cytometry and peripheral blood smear were performed. Leukocytes and red blood cells showed no abnormalities, lymphocytes' CD4/CD8 ratio was decreased (0.8). Physical examinations showed rapid progression; papulonodular lesions extensively became ulcerated leaving behind slowly healing necrotic lesions (Fig. 3). Upper body regions were not affected, nor were enlarged lymph nodes found. The patient did not report B symptoms. Due to rapid progression, 25 mg acitretin was administered, local disinfectant and a potent topical corticosteroid were used. Following three months of continuously developing new nodules and persisting necrotic ulcers, the patient reported fewer and fewer new lesions in which the ulcers were gradually healing. Regular follow-ups showed regression of all skin lesions by six months, adverse events were not reported with acitretin and frequent lab tests showed normal results. At the time of publishing, the patient has been followed up regularly for four years and showed no sign of relapse.

Most LyP cases are self-healing, however, therapeutic intervention is recommended only in progressive and severe cases. Distinctively, the "wait and see" strategy is preferred among asymptomatic patients. Several treatment modalities are available, including local and systemic immunomodulators with or without the use of UVB. In the case of severe symptoms, methotrexate 2.5–20 mg/week is the standardized, opted therapeutic choice preventing the formation of new lesions.⁴ Due to the significantly increased risk of non-melanoma and melanoma skin cancer in methotrexate-treated patients⁵ and our patient's decades-long skin cancer history, a different treatment strategy was chosen. Acitretin, known for its anti-tumor proliferation effect, especially in UV-induced carcinogenesis and successful use in cutaneous CD30-positive anaplastic large cell lymphoma,⁶ was our first therapeutic choice

[☆] Study conducted at the Department of Dermatology, Venereology and Oncodermatology, University of Pécs, Pécs, Hungary.

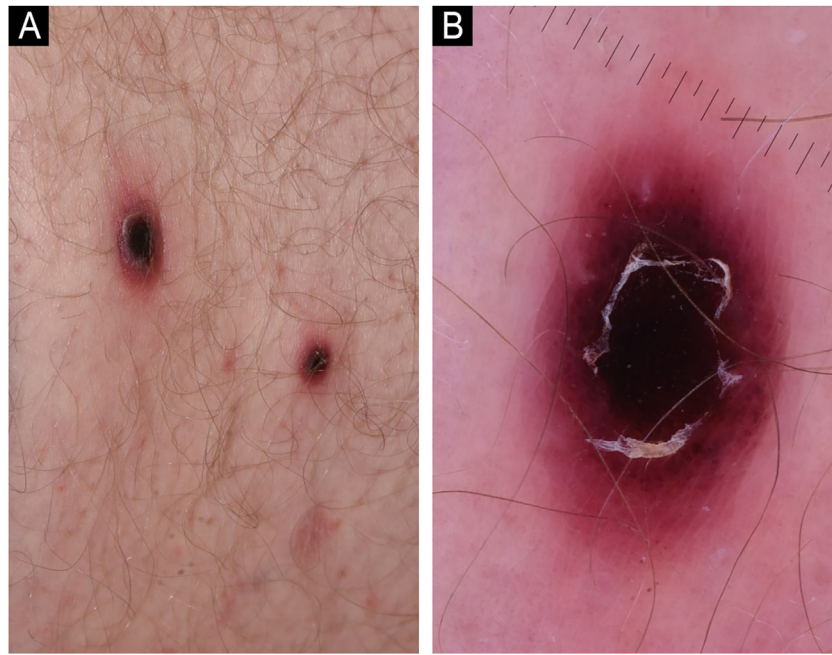


Figure 1 Erythematous papulonodular lesions (A) progressing into necrotic ulcers (B).

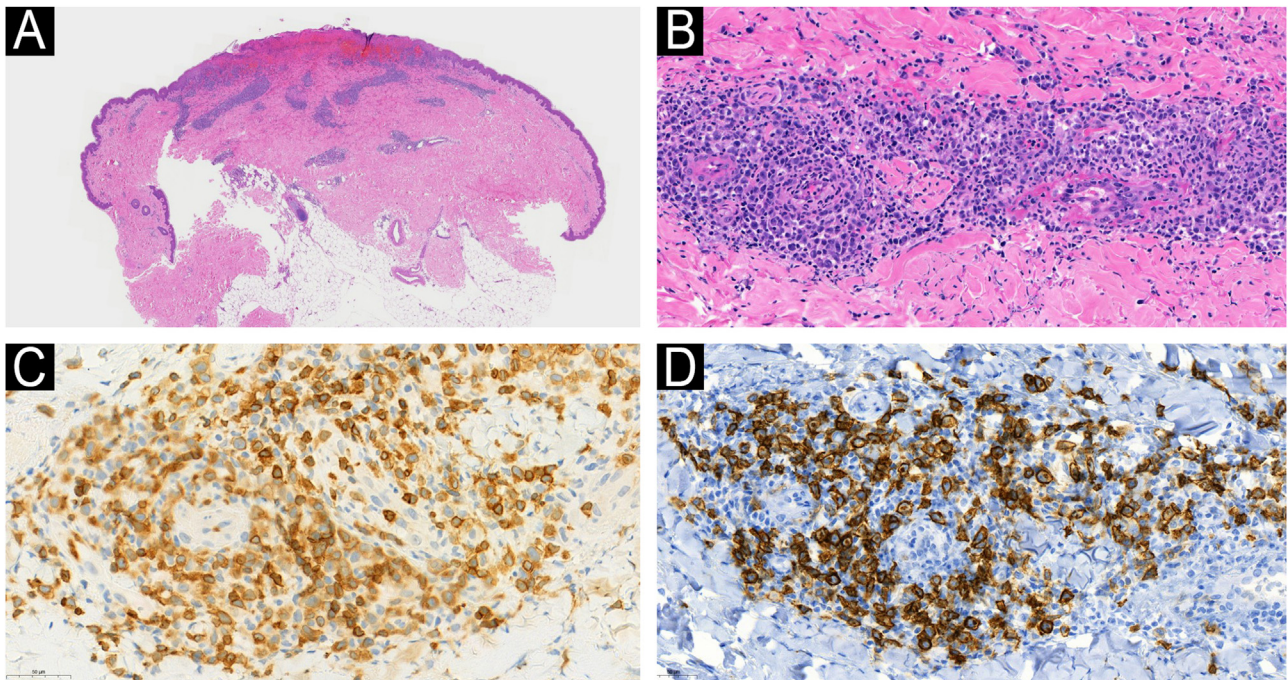


Figure 2 Low-power view showing epidermal ulceration and a dermal-based angiocentric lymphocytic infiltrate (Hematoxylin & eosin, original magnification 15 $\times$) (A). High-power image showing an angiodestructive medium-sized, to large-sized atypical lymphocytic infiltrate (Hematoxylin & eosin, original magnification 400 $\times$) (B). The tumor cells were extensively immunoreactive for CD3 (C) and CD30 (D) (CD3 and CD30 immunostain, original magnification 384 $\times$ and 279 $\times$).

deemed suitable in the treatment of our patient. Despite LyP being benign in nature, a majority of cases typically experience relapsing within months to years, while 10%–40% of patients developing other hematological malignancies or transformation into CD30-positive Anaplastic Large Cell Lymphoma (ALCL), a regular follow-up is recommended even

following total remission. Methotrexate, being the most effective systemic treatment regarding LyP, bears potential side effects in which patients' intolerance can limit its use. In our case, we successfully administered acitretin with complete remission. After ceasing treatment, the patient reported no relapses over the four-year follow-up period.



Figure 3 Extensive ulceration and necrosis of the lesions (A-B).

Financial support

None declared.

Authors' contributions

Máté Attila Bognár: Drafting and editing of the manuscript; collection, analysis, and interpretation of data; preparing the manuscript; critical review of the literature.

Csaba Gyömörei: Analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied case; critical, approval of the final version of the manuscript.

Zsuzsanna Lengyel: Design and planning of the study, analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied case; critical review of the literature; critical review of the manuscript; approval of the final version of the manuscript.

Conflicts of interest

None declared.

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Received 28 August 2024; accepted 20 October 2024

Available online 18 June 2025

LETTER - TROPICAL/INFECTIOUS AND PARASITIC DERMATOLOGY

Epidemiological profile of anogenital lesions in 4,029 consultations at a Sexually Transmitted Infections Clinic in São Paulo, Brazil[☆]



Dear Editor,

Sexually transmitted infections (STI) are a public health problem due to their high prevalence in developing countries, such as Brazil, and their potential to cause morbidity.^{1,2}

A wide range of diseases of inflammatory and neoplastic etiology can affect the skin of the anogenital region, representing important differential diagnoses of STI.^{3,4}

Knowledge of diseases that affect the anogenital region is of utmost importance, since a delayed diagnosis exposes the patient to inadequate treatments, worsening their clinical condition and perpetuating the transmission of STI.^{3,4} Data from the scientific literature on the epidemiology of these diagnoses are scarce, demonstrating the need for new population surveys.⁵

Therefore, the present study was conducted to identify the most frequent anogenital diagnoses in patients treated at the STI outpatient clinic of a tertiary hospital in the city of São Paulo, Brazil. This is a retrospective study analyzing the care provided between October 2012 and August 2024. Data on gender, age, and primary diagnosis were obtained from the institution's electronic medical record system.

During the evaluated period, 4,029 medical consultations were carried out due to anogenital complaints, 1,182 of which were female and 2,847 were male patients. The average number of consultations per year was 309.84 ± 192.08 . Of the total number of patients, 2,992 were aged between 20 and 55 years. The average age of the patients was 42.77 ± 15.86 years, with a minimum age of 10 months (diagnosis of condyloma acuminatum) and a maximum of 92 years (condyloma acuminatum).

The main clinical diagnoses related to the consultations (Table 1) were condyloma acuminatum (CA) in 2847 consul-

Table 1 Distribution of the 4029 consultations by diagnosis and year.

Diagnosis	Number of consultations	%
Condyloma acuminatum	2841	70,5%
Syphilis	303	7,5%
Herpes simplex	177	4,4%
Squamous cell carcinoma	171	4,2%
Lichen sclerosus et atrophicus	89	2,2%
Molluscum contagiosum	79	2,0%
Eczema	50	1,2%
Lichen planus	40	1,0%
Others ^a	279	6,9%
Total	4029	100,0%
Year	Number of consultations	%
2012	18	0.4%
2013	266	6.6%
2014	702	17.4%
2015	524	13.0%
2016	451	11.2%
2017	498	12.4%
2018	365	9.1%
2019	430	10.7%
2020	192	4.8%
2021	219	5.4%
2022	197	4.9%
2023	149	3.7%
2024	104	2.6%
Total	4029	100.0%

^a Candidiasis, Buschke-Lowenstein tumor, lymphogranuloma venereum, chancroid, lupia, vitiligo, pilonidal cyst, scar lesion, comedones, neuroma, plicoma, seborrheic keratosis, foreign body, varicocele, lymphangioma, Kaposi's sarcoma, hand-foot-and-mouth syndrome, melanocytic nevus, psoriasis, hidradenitis suppurativa, scabies, folliculitis, pharmacodermia, epidermodysplasia verruciformis, hemorrhoids, Behçet's disease, Paget's disease and Crohn's disease.

[☆] Study conducted at the Dermatology Clinic, Hospital da Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil.

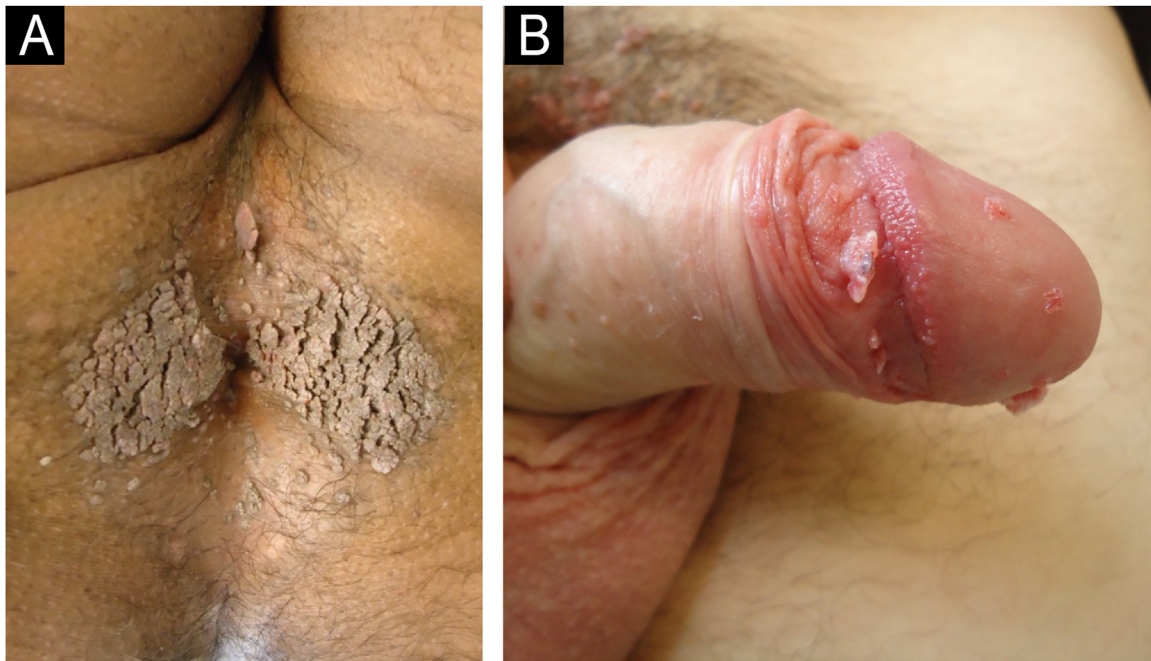


Fig. 1 (A) Anal condyloma. (B) Penile condyloma.

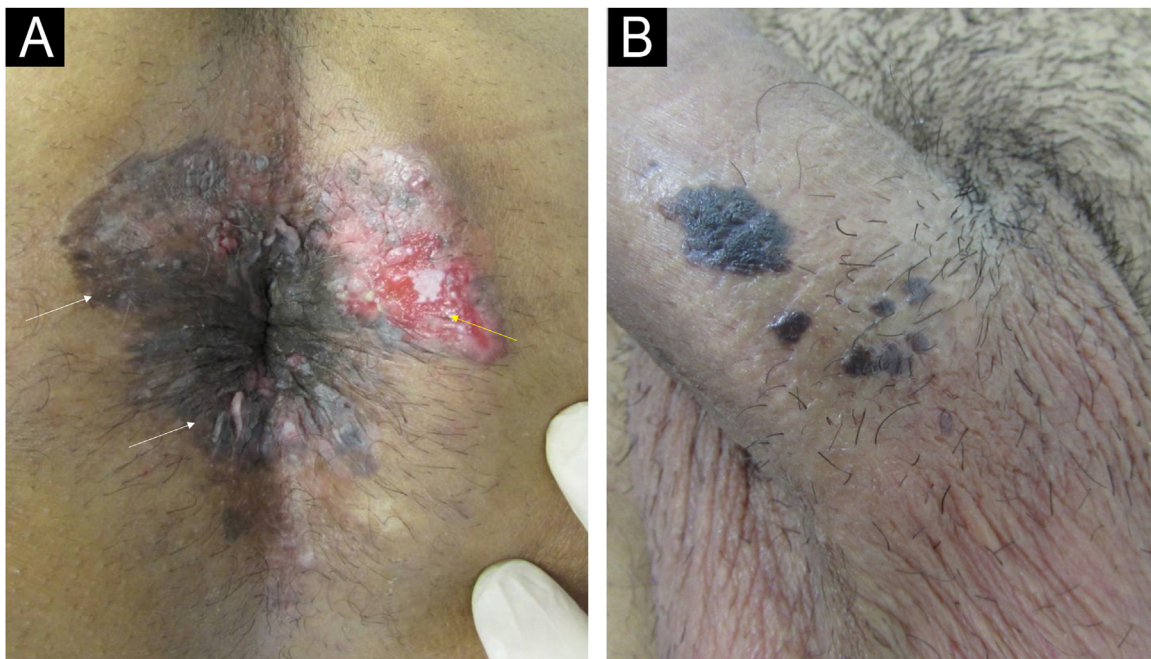


Fig. 2 (A) Patient living with HIV using antiretroviral therapy with undetectable VL and CD4 327 cells/mm³ showing concomitant lesions caused by HPV: squamous cell carcinoma (SCC) *in situ*/Bowen's disease (white arrows) and invasive SCC (yellow arrow) in the perianal region. (B) Patient with follicular lymphoma undergoing chemotherapy with SCC *in situ*/Bowen's disease in the penis shaft.

tations (70.8%) – shown in [Fig. 1](#), followed by syphilis in 303 (5.7%), herpes simplex in 193 (4.4%), squamous cell carcinoma in 172 (4.3%) – shown in [Fig. 2](#), lichen sclerosus et atrophicus in 98 (2.4%) – shown in [Fig. 3](#), molluscum contagiosum in 80 (2%), eczema in 50 (1.2%) and lichen planus in 46 (1%). All cases of syphilis were primary syphilis (hard chancre, Follman's syphilitic balanitis, and "cord-like" lesion).

Other diagnoses with less than 1% were grouped together, totaling 8.2% of the consultations.

The significant number of consultations recorded in this study represents a relatively reliable scenario of the distribution of diagnoses of patients with anogenital complaints seeking public care in the city of São Paulo.

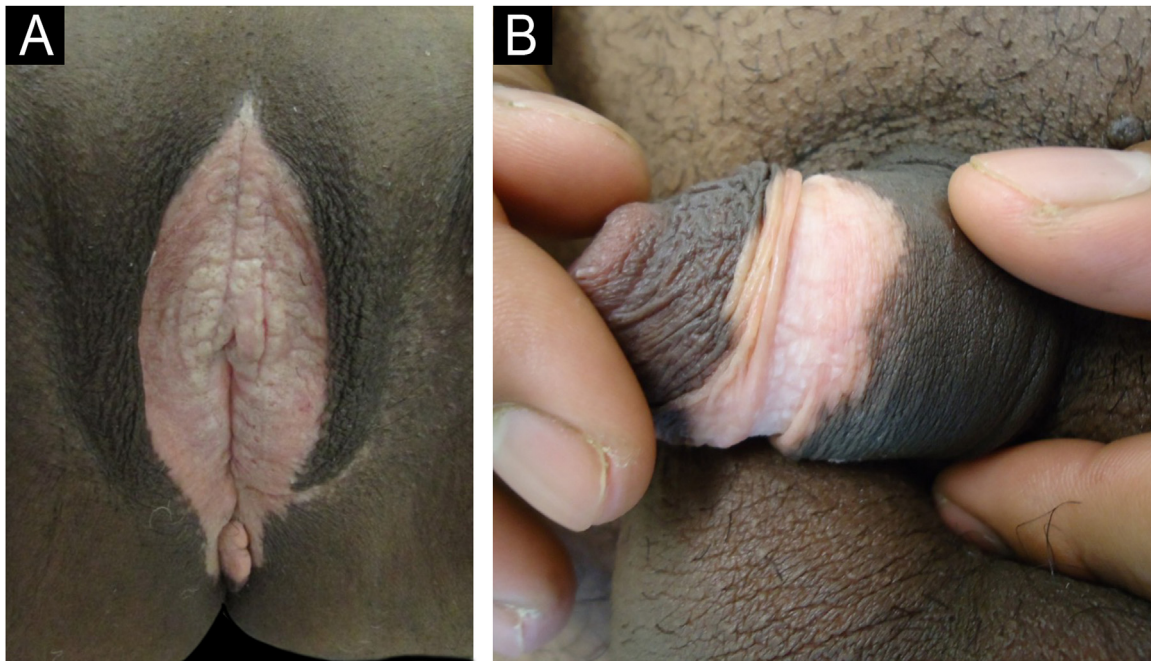


Fig. 3 (A) Lichen sclerosus et atrophicus of the vulva (differential diagnosis of vitiligo). (B) Lichen sclerosus et atrophicus of the penis showing a ring of circumferential constriction in the center of the achromic lesion characteristic of the disease.

When analyzing the year-by-year distribution of consultations during the study period, a progressive reduction can be observed from 2013 onwards, with a marked decrease from 2020 to 2024, probably as a consequence of the COVID-19 pandemic.

The fact that the vast majority of consultations were related to the diagnosis of CA is consistent with data in the literature, as is the sequence of the other most prevalent diagnoses, syphilis, and herpes simplex. It is believed this epidemiological trend observed in a tertiary hospital may be related to the chronicity of CA, syphilis, and herpes simplex. More acute conditions, such as chancroid and anogenital discharge, were rarely reasons for consultation, probably because they were resolved by seeking medical care from primary care physicians or emergency rooms. The negative impact on the quality of life of patients with condyloma may also be another reason that makes them keep trying to seek medical care.^{2,6,7}

It is important to note the significant number of diagnoses not related to STI, such as inflammatory and neoplastic diseases. Studies conducted in other countries show that inflammatory lesions are the most frequently diagnosed in clinics treating genital lesions.^{3,4}

It is also important to highlight that the number of patients treated for squamous cell carcinoma in the anogenital region took fourth place. This diagnosis is intrinsically related to the neoplastic potential of the HPV virus, which is also responsible for CA and is more aggressive in immunocompromised patients. In a study conducted in 2019 covering the entire national territory, it was observed that among the 6,388 healthy young adults assessed, the prevalence of general HPV was 53.6%. Of these, the majority (35.2%) had at least one high-risk HPV.⁸ These data show that not only is a large part of the population carrying this potentially oncogenic virus, but it is also following its pathogenic course,

possibly in a significant fraction of this population. This fact reinforces the extreme importance of public measures focused on vaccination against HPV.

Although the data collection period included Mpox outbreaks that occurred worldwide – and therefore in Brazil^{1,2} – there were no records of patients with Mpox lesions being treated due to structural impediments to the flow of care at the studied hospital.^{9,10}

The numbers presented herein represent, within their limitations, the reality of the different aspects involving anogenital dermatoses in the city of São Paulo and may serve as indicators for the development of public health policies, especially those regarding STI.

Authors' contributions

Julia Aires Thomaz Maya: Collection of data, or analysis and interpretation of data; drafting and editing of the manuscript or critical review of important intellectual content; collection, analysis and interpretation of data; critical review of the literature; approval of the final version of the manuscript.

Kaique Arriel: Collection of data, or analysis and interpretation of data; drafting and editing of the manuscript or critical review of important intellectual content; collection, analysis and interpretation of data; critical review of the literature; approval of the final version of the manuscript.

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John Verrinder Veasey: Design and planning of the study; collection of data, or analysis and interpretation of data; statistical analysis; drafting and editing of the manuscript or critical review of important intellectual content; collection, analysis and interpretation of data; effective participation in research orientation; intellectual participation in the propaedeutic and/or therapeutic conduct of studied cases; critical review of the literature; approval of the final version of the manuscript.

Financial support

None declared.

Conflicts of interest

None declared.

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- Received 17 November 2024; accepted 22 January 2025
 Available online 10 July 2025

LETTER - THERAPY

Acneiform rash secondary to trametinib in two patients with neurofibromatosis[☆]



Dear Editor,

Trametinib is a reversible, selective inhibitor of Mitogen-activated protein Kinase (MEK) blocking enzyme phosphorylation and activation, affecting both the proliferation and survival of tumor cells.¹

The most commonly reported side effects of trametinib are dermatologic; acneiform eruptions are the most prevalent. In these cases, the dose of the MEK inhibitor can be reduced; nevertheless, this may be associated with decreased treatment efficacy.

We report two cases of acneiform rash secondary to trametinib.

A 14-year-old male diagnosed with NF1 at age 4, presented an optic chiasm glioma, associated with two extensive, plexiform neurofibromas (PNF). One neurofibroma was located on the right foot, causing an inoperable deformity. The other, emerged from the second branch of the right trigeminal nerve (V2), producing facial disfigurement. It was also inoperable. Medical treatment with trametinib was started. After a year of treatment, the facial mass had decreased by 30% in size. Upon reaching the maximum dose of trametinib, the patient developed an acneiform eruption (Fig. 1), affecting the nasal region, forehead, upper eyelid, cheeks, and chin. He received topical treatment with clindamycin and benzoyl peroxide, in addition to reducing the dose of trametinib. As papules and pustules persisted, oral treatment with doxycycline was initiated. After evidencing clinical improvement, the trametinib dose was increased without presenting further complications. To date, oncological treatment is ongoing, and a mild dermatitis persists, evidencing no other adverse events.

The second patient is a 21-year-old female diagnosed with NF1 during her first year of life, presenting a left orbital neurofibroma. The tumor was resected on five occasions;

unfortunately, it recurred. Onco-specific treatment with trametinib was then initiated. A month later, she presented an acneiform rash, involving her face and back (Fig. 2). She started treatment with lymecycline, as well as a reduction of trametinib. This treatment was successful, although when tetracyclines were discontinued the papulopustular eruption reappeared. Lymecycline was reintroduced alongside a progressive increase in the dose of trametinib. This treatment was well tolerated and resulted in both aesthetic and clinical improvement.

Two years later, trametinib was discontinued as the lesion remained stable and Lymecycline was also suspended without relapse.

Trametinib is a selective, reversible inhibitor of MEK1/2 activation and kinase activity.² Several studies have shown the efficacy of MEK inhibitors in patients with NF-1 associated with non-surgical low-grade gliomas and PNF.

NF1 is caused by the loss of neurofibromin, the protein product of the *NF1* gene. Neurofibromin is a ras-GAP protein, a negative regulator of RAS signaling. Loss of functional neurofibromin results in activation of the classic RAS-MAPK signaling cascade, cell proliferation, and subsequent tumor formation.

MEK inhibitors have been found to stabilize or even reduce the volume of these tumors. During the course of therapy, many patients display side effects.³ Acneiform eruptions are the most common dermatologic side effect, occurring in 77% of the population studied by Anforth et al.¹ It is a dose-dependent follicular, papulopustular eruption compromising the face, scalp, chest, and upper back.⁴

The precise mechanism which triggers this side effect is not clear. What is known is that insulin-like growth factor-1 induces sebaceous gland lipogenesis via sterol response element-binding protein-1, which is activated by the Phosphatidylinositol 3-Kinase (PI3K)/protein Kinase B (AKT) signaling pathway, and is related to the pathogenesis of acne. Unknown interactions between BRAF-MEK-ERK and PI3K-AKT pathways might also be responsible for this effect.¹

The lesions usually develop in the initial 2 weeks of treatment, worsening during the first month. Mild cases are treated with twice-daily dosing of topical antibiotics. For moderate cases, systemic tetracyclines are recommended.

[☆] Study conducted at the Hospital Aleman de Buenos Aires, Ciudad Autónoma de Buenos Aires, CABA, Argentina.



Figure 1 In the left picture it can be seen Patient 1 presenting generalized comedones, papules and pustules all over his face. In the right picture, the acneiform rash also compromises the right parietotemporal scalp.



Figure 2 In the left picture, on a frontal view, it can be seen Patient 2 presenting an acneiform rash on her face. In the right picture, a close-up, it can be seen in detail multiple papules and pustules just like Patient 1.

Topical steroids can be added if a severe inflammatory reaction is present. Refractory patients could be treated orally with antibiotics and steroids.

Based on the response to the established treatment, the reduction of the oncology drug dose should also be considered. Severe refractory cases might even require suspending oncologic treatment.^{5,6} Effective treatment may be continued for the duration of the trametinib therapy.¹ It is

important to highlight that these reactions are associated with good antitumor activity.

To conclude, MEK inhibitors have shown good results in the treatment of neurologic-associated tumors. Effective treatment should aim to ideally not decrease the dose of trametinib, but should be considered in refractory cases, requiring a mandatory multidisciplinary approach between oncology and dermatology specialists.

Financial support

None declared.

Authors' contributions

Macarena Nougues: Manuscript writing and editing; data analysis.

Luciana Laura Tirelli: Manuscript writing and editing; supervision of the project.

Paula Carolina Luna: Data collection; revision of the manuscript.

Darío Macas Ordoñez: Manuscript editing; data visualization and graphical layout.

Margarita Larralde: Critical review and revision of the manuscript.

All authors reviewed and approved the final version of the manuscript.

Conflicts of interest

None declared.

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Received 23 October 2024; accepted 18 November 2024

Available online 3 July 2025

LETTER - THERAPY

Oxcarbazepine induced systemic lupus erythematosus: a clinical challenge[☆]



Dear Editor,

Systemic lupus erythematosus triggered by medications is a serious adverse effect that is often incorrectly identified within the range of erythema multiforme diseases, posing significant diagnostic challenges.

A 46-year-old man was referred because of an erythematous, targetoid, and coalescent rash of acute onset over the last 48 hours. Patient history included elevated blood pressure and borderline psychiatric disorder under treatment with hydrochlorothiazide and oxcarbazepine for over two years. Recently, paracetamol and metamizol were added because of EBV infection a month prior. On physical examination, confluent erythematous violaceous and targetoid lesions affected the face with a "butterfly wing" distribution, as well as the oral mucosa, neck, and upper trunk. Denudation was intermittently observed (Fig. 1 and 2). Joint tenderness and stiffness were also present.

Histopathology revealed vacuolar degeneration of the basal layer, necrotic keratinocytes, and a superficial and perivascular lymphocytic and polymorphonuclear inflammatory infiltrate (Fig. 3). Concurrently, Direct Immunofluorescence (DIF) demonstrated granular deposits of IgM and C3 at the dermo-epidermal junction. Other DIF markers (IgG, IgA and fibrinogen) resulted negative.

Blood tests showed thrombocytopenia ($110 \times 10^9/L$), lymphopenia ($0.5 \times 10^9/L$), positive nuclear antibodies at 1/40 tittle with a homogeneous pattern, and low C3 levels (70). Proteinuria was absent.

Oxcarbazepine and metamizole were withdrawn, and treatment with intravenous methylprednisolone 60 mg daily in descending regime was initiated, with complete resolution of skin lesions and hematological and immunological parameters. Subsequently, a Lymphocyte Transformation Test (LTT) with oxcarbazepine ($0.2 - 2 - 20 \mu g/mL$) and metamizol was conducted (Fig. 4). The test shows prolifer-



Figure 1 Erythematous targetoid coalescent rash with cephalocaudal distribution and central erosion involving the face, neck and upper trunk.

eration of mainly CD3 and CD4, with some proliferation of CD19 and CD56 cells, with oxcarbazepine. No proliferative response was observed with metamizol.

Oxcarbazepine-induced systemic Lupus Erythematosus was therefore diagnosed.

The rare coexistence of EM-SSJ-NET and LES lesions presents a diagnostic challenge when discussing a patient with both an infectious disease (EBV) and a pharmacological treatment (oxcarbazepine) history.

Initially, the morphology of both EM and LES lesions could be reminiscent of Rowell Syndrome (RS), but Torchia et al., who updated the RS criteria in 2012, argued for a stricter definition, restricting its use if infectious or pharmacological triggers were present.¹

[☆] Study conducted at the Hospital Regional Universitario de Málaga, Málaga, Spain.



Figure 2 Erythematous coalescent rash with central erosion in upper back.

Although anti-histone antibody titration could not be performed, the normalization of complement, leukocytes, and ANA titers after drug suspension support the diagnosis of drug-induced lupus.² The distinction between classic SSJ-NET and lupus with SSJ-NET-like lesions relies on clinical history (latency of exposure to the suspected drug), seroimmunological criteria (ANA+), and lesion distribution (photodistribution in SLE, trunk predominance in SSJ-NET).^{2,3} Anatomopathological criteria can provide addi-

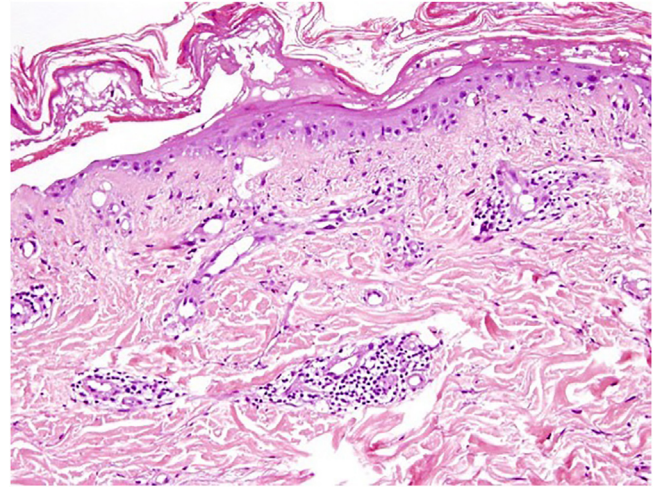


Figure 3 Histological findings showing focal epidermal necrosis and vacuolar degeneration of the basal layer, with lymphomonocytic and neutrophilic perivascular and upper-dermal infiltrates (Hematoxylin & eosin, $\times 100$).

tional insights, although findings in these entities often overlap.^{1,3}

Therefore, our patient's clinical course suggests an oxcarbazepine-induced LES with SSJ-NET-like lesions, probably precipitated by prior EBV infection.

Whereas EBV infection has already resolved, it is a known immunity disruptor, which can lead to the development of certain neoplasms, autoimmune diseases, and toxicodermas.⁴

Oxcarbazepine itself has been linked to several conditions, including SLE, erythema multiforme, SSJ, and NET. In this patient, the in vitro reactivity of Cytotoxic T Lymphocytes (CTL) to oxcarbazepine suggests it as the causal factor.^{2,5}

A wide variety of drugs have been associated with Drug-Induced LES (DIL). Procainamide, hydralazine, and quinidine

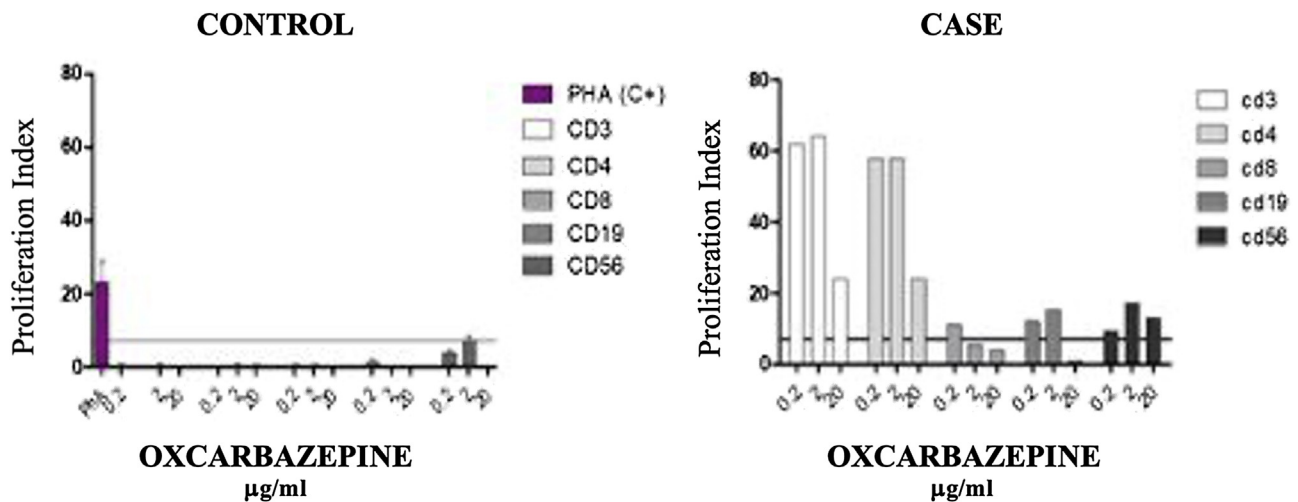


Figure 4 Controlled lymphocyte Transformation Test (LTT) with oxcarbazepine (0.2 – 2 – 20 $\mu\text{g/ml}$). The test shows proliferation of mainly CD3 and CD4 drug specific T-cells, with some proliferation of CD19 and CD56 cells, with oxcarbazepine. The proliferation of CD56 cells suggests a cytotoxic reaction.

typically produce classical DIL, which is more strongly associated with the production of anti-histone antibodies.⁶

Nevertheless, other pharmacological groups have been found linked to DIL, with lower anti-histone positiveness rates such as anticonvulsants, minocycline, propylthiouracil, and statins.^{3,6,7}

In conclusion, while classifying patients with SSJ-NET and SLE symptoms can be challenging, its management is similar and involves the withdrawal of the triggering drug, providing supportive care, and using corticosteroids or immunosuppressants in refractory cases.

Financial support

None declared.

Authors' contributions

Eduardo López Vera: Contributed to the conceptualization of the case report and review; Collected and analyzed the clinical data; Conducted the literature review; and drafted the manuscript. Played a central role in coordinating the article's development and ensuring its completion.

Elisabeth Gómez Moyano: Supervised all aspects of the study, including the conceptualization and study design. Provided critical revisions to the manuscript, ensuring its scientific accuracy and alignment with clinical guidelines. Offered guidance during the interpretation of clinical findings and literature synthesis. Approved the final version of the manuscript for submission.

María Ayala Blanca: Contributed to the review of the literature by identifying relevant references and incorporating key findings into the discussion section. Provided revisions and feedback on the clinical aspects of the manuscript, particularly related to the discussion of anatomopathological findings.

María Salas Cassinello: Contributed to the review of the literature by identifying relevant references and incorporating key findings into the discussion section. Provided revisions and feedback specifically on the laboratory findings within the clinical case.

Conflicts of interest

None declared.

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Received 14 November 2024; accepted 29 November 2024

Available online 28 June 2025



LETTER - THERAPY

Paradoxical psoriasiform alopecia secondary to secukinumab: a case report[☆]



Dear Editor,

Psoriasis is a chronic immune-mediated disease that can often be associated with other immune-regulated pathologies. One of these is hidradenitis suppurativa, which has been observed to increase the risk of psoriasis by 3.24 times compared to the general population (95% IC 2.27–4.62).¹

The development of biological therapies has enabled the treatment of both conditions. Currently, adalimumab, a monoclonal antibody against Tumor Necrosis Factor- α (TNF- α), and secukinumab, an antibody targeting Interleukin (IL) 17A, is approved for the treatment of both diseases. Both are generally safe and well-tolerated, but they may cause adverse effects, such as paradoxical reactions.

We present the case of a 42-year-old woman diagnosed with Hurley II stage hidradenitis suppurativa and long-standing plaque psoriasis affecting the scalp, armpits, inframammary folds, and genital area. She had received multiple systemic treatments for hidradenitis control with insufficient results, including antibiotics (doxycycline and rifampicin-clindamycin combination) and retinoids (isotretinoin and acitretin). Psoriasis lesions were primarily managed with topical treatments, achieving partial control.

To address both conditions, biological therapy with adalimumab was initiated, achieving a good initial response. However, after a year, the treatment lost effectiveness in controlling hidradenitis suppurativa, prompting a switch to secukinumab in December 2022.

Three months after starting secukinumab, the patient experienced a significant worsening of psoriasis, with widespread lesions and two large erythematous and keratotic plaques on the scalp (occipital and parietal regions) with follicular pustules and areas suggesting fluctuation. Differential diagnosis included folliculitis decalvans, dissecting

cellulitis, and other causes of cicatricial alopecia (Fig. 1). Biopsies were performed on both plaques, and samples were taken for bacterial and fungal cultures.

Given this clinical deterioration, secukinumab was discontinued, and therapy was switched to guselkumab, an IL-23 inhibitor. Additionally, treatment with fluocinolone acetonide and framycetin cream, as well as oral doxycycline for three months, was prescribed.

Histopathological analysis of the biopsies, processed in vertical and horizontal sections, revealed a significant increase in the telogen and vellus indices. Loss and atrophy of sebaceous glands, infundibular dilation with thinning of the follicular epithelium, and a dense perifollicular lymphocytic inflammatory infiltrate were observed without interface involvement. The epidermis exhibited psoriasiform acanthosis and parakeratosis. These histological findings were consistent with psoriatic alopecia (Fig. 2). Cultures were negative.

After the treatment, the patient showed significant improvement in both conditions, including complete regrowth of alopecic plaques on the scalp, with no signs of psoriasis except for minimal residual scaling (Fig. 3).

Paradoxical reactions involve the onset or worsening of immune-mediated diseases due to the use of monoclonal antibodies. The main paradoxical psoriasiform reactions to biological treatment include palmoplantar psoriasis (42.9%), plaque psoriasis (14.7%) and scalp psoriasis (7%).²

Paradoxical psoriasiform alopecia is an emerging and poorly understood type of paradoxical reaction described in recent years. It has been reported more frequently with anti-TNF- α drugs, with few cases documented with IL-17 and IL-12/23 inhibitors.^{3–7} Psoriasiform alopecia can be histologically distinguished from other types of alopecia by sebaceous gland atrophy.⁸ This is a controversial issue, as some authors accept it might be possible to distinguish this condition from primary psoriatic alopecia by the presence of eosinophils and plasma cells in the inflammatory infiltrate. Meanwhile, other authors stand up for the same spectrum of diseases, with similar histopathological findings on skin biopsies.⁹ Cases of permanent alopecia have been described in patients with paradoxical scalp psoriasis.^{5,8}

It is recommended to consider discontinuing the causative drug to prevent progression to cicatricial alopecia, especially in severe cases unresponsive to conservative measures.¹⁰ However, the decision to suspend treatment

[☆] Study conducted at the Hospital Universitario Infanta Cristina, Parla, Madrid, España and Hospital Universitario Fundación Alcorcón, Alcorcón, Madrid, España.



Figure 1 Large plaques on the scalp, in the occipital and parietal regions, initially more erythematous (A), which developed significant hyperkeratosis (B and C).

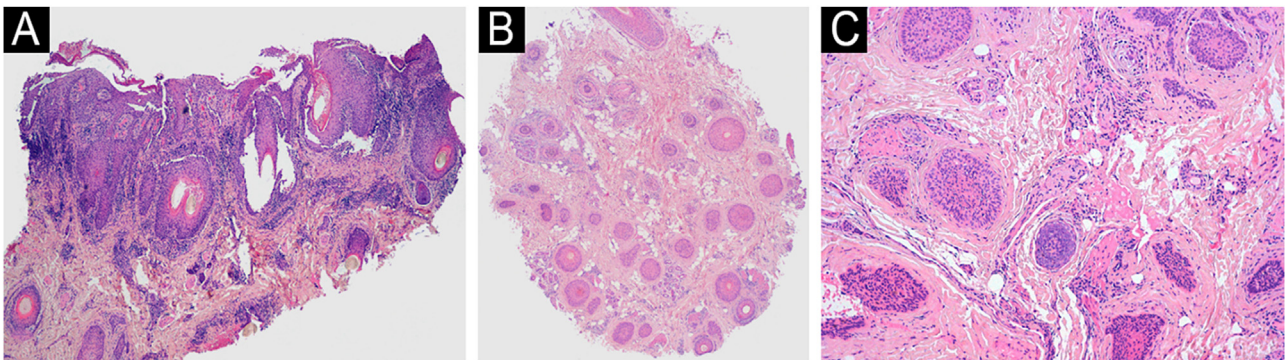


Figure 2 Hematoxylin & eosin histopathology: (A) Vertical section showing psoriasiform hyperplasia, parakeratosis, and a dense lymphoplasmacytic inflammatory infiltrate ($\times 40$); (B) Horizontal section showing preservation of follicular units and an increase in the telogen index ($\times 40$); (C) Atrophy of sebaceous glands ($\times 100$).



Figure 3 Partial regrowth of psoriatic alopecia plaques after 2 months of guselkumab treatment (A and B). Complete regrowth after 5 months of treatment (C).

should be individualized based on the risk-benefit ratio and the severity of the alopecia.

In this case, the temporal sequence, clinical findings, and histopathological features led us to a paradoxical psoriasiform alopecia diagnosis induced by IL-17 inhibitors (secukinumab). This is one of the few cases reported in the literature, demonstrating a very good response after discontinuing secukinumab and initiating guselkumab therapy.

Financial support

None declared.

Authors' contributions

Inés Segovia Rodríguez: Original draft preparation, review, editing, read and agreed to the published version of the manuscript.

María Castillo Gutiérrez: Original draft preparation, review and editing, read and agreed to the published version of the manuscript.

Fernando Pinedo Moraleda: Original draft preparation, supervision, review and editing, read and agreed to the published version of the manuscript.

Beatriz Aranegui Arteaga: Conceptualization, methodology, supervision, review, editing, read and agreed to the published version of the manuscript.

Conflicts of interest

None declared.

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Received 26 November 2024; accepted 1 January 2025

Available online 1 July 2025

LETTER - THERAPY

Stabilization of a recalcitrant and aggressive necrobiotic xanthogranuloma with tofacitinib[☆]



Dear Editor,

Necrobiotic Xanthogranuloma (NXG) is a form of non-Langerhans histiocytosis characterized by the development of yellow-orange infiltrated papules and plaques, with the most common location being the periorbital area. Occasionally, there is extracutaneous involvement, including ocular, respiratory, cardiac, or cerebral. Up to 80% of cases are associated with monoclonal gammopathy and other neoplasms.¹ The treatment of NXG is complex and data on therapeutic options are limited, making the best approach to treatment unclear. We describe the case of a patient with refractory NXG who experienced an adequate response to tofacitinib, a non-selective inhibitor of Janus Kinases (JAK), which preferentially blocks JAK1 and JAK3.

A 54-year-old woman presented to the Department of Dermatology with refractory NXG. Specifically, the lesions had appeared at 18–20 years of age (>30 years of evolution), and throughout her life, she had been treated with topical, intralesional, and systemic corticosteroids, methotrexate, multiple surgeries, CO₂ laser, hydroxychloroquine, extracorporeal photochemotherapy, rituximab, Intravenous Immunoglobulins (IVIG), and cyclophosphamide. Despite the latter treatment (cyclophosphamide), combined with systemic corticosteroids, the clinical condition was progressive. There was no other cutaneous or systemic involvement, and laboratory tests, including protein electrophoresis, were normal. On examination (Fig. 1), yellowish plaques of bilateral palpebral and periocular involvement were observed, predominantly on the left side. The lesions had a shiny surface and a slightly erythematous surrounding edge. They were hard, deeply adherent, and caused some

visual restriction in the left eye. The latest histopathology (Fig. 2) and all previous ones were compatible with NXG with deep involvement (muscular invasion), also confirmed by ultrasound and Magnetic Resonance Imaging (MRI). Given the refractory clinical condition, active lesions, and multiple previous treatments, it was decided by a multidisciplinary team to initiate tofacitinib therapy, initially at a dose of 5 mg/12 hours, and due to good tolerance, the dose was increased to 10 mg/12 hours after 3 months. After one year of treatment (Fig. 3), the lesions had stabilized, and even the size of some of them had reduced, especially the left upper eyelid, where the visual restriction had improved. They were also less evident on palpation, and the surrounding rim was less erythematous. The lesions remained the same at the 18-month review. Tolerability during the 1.5 years of treatment was adequate, except for an upper respiratory condition that required discontinuation of treatment for a few days at 10 months of treatment, during which time he reported worsening of the lesions. There were no other adverse effects, and follow-up laboratory tests were normal. On follow-up brain MRI at 1.5 years, the lesions remained stable. Given the adequate therapeutic response, it was decided to continue treatment.

The etiology of NXG, which is thought to be related to altered macrophage lipid homeostasis, has not yet been elucidated. Recently, ABCG5/G8 variants have been identified that encode heterodimers containing transporter and transmembrane domains essential for reverse cholesterol transport and sterol clearance.¹ The accumulation of lipid particles can lead to the upregulation of pro-inflammatory cytokines such as Interleukin (IL) 6 and tumor necrosis factor-alpha. Animal studies have shown that JAK inhibitors can prevent IL-6 trans-signaling, which may explain the efficacy of tofacitinib on NXG in our patients.² Similarly, the JAK pathway has been reported to play a role in the maintenance of granulomas. Thus, JAK inhibition may promote granuloma resolution, as has been described in other granulomatous diseases such as granuloma annulare³ and sarcoidosis.^{3,4} On the other hand, treatment of NXG is challenging and the best approach to treatment is uncertain. Randomized clinical trials are lacking, so most recommendations are based on studies with limited evidence.

[☆] Study conducted at the Hospital Universitario y Politécnico La Fe, Valencia, Spain.

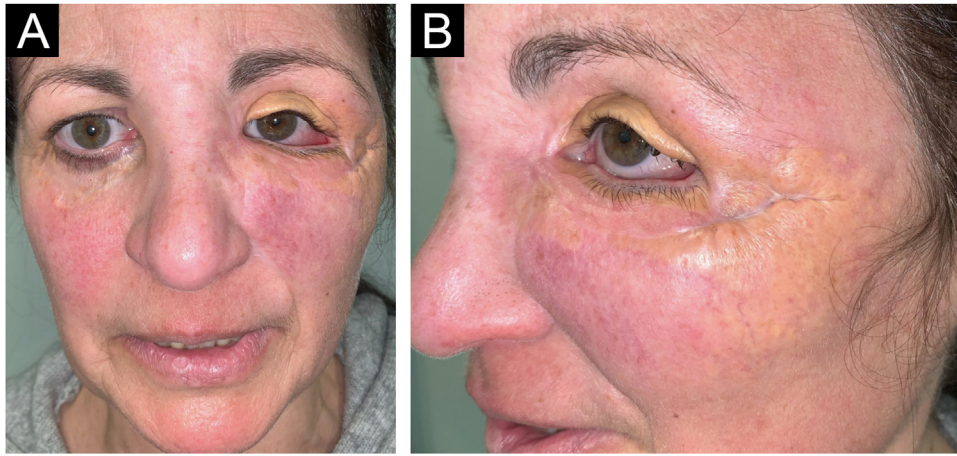


Fig. 1 Clinical presentation of the lesions before starting tofacitinib. Yellowish, shiny, and infiltrated plaques located around the eyelids and periorcular region bilaterally, with more pronounced involvement in the left eye, where they caused visual restriction. Surrounding erythema around the plaques.

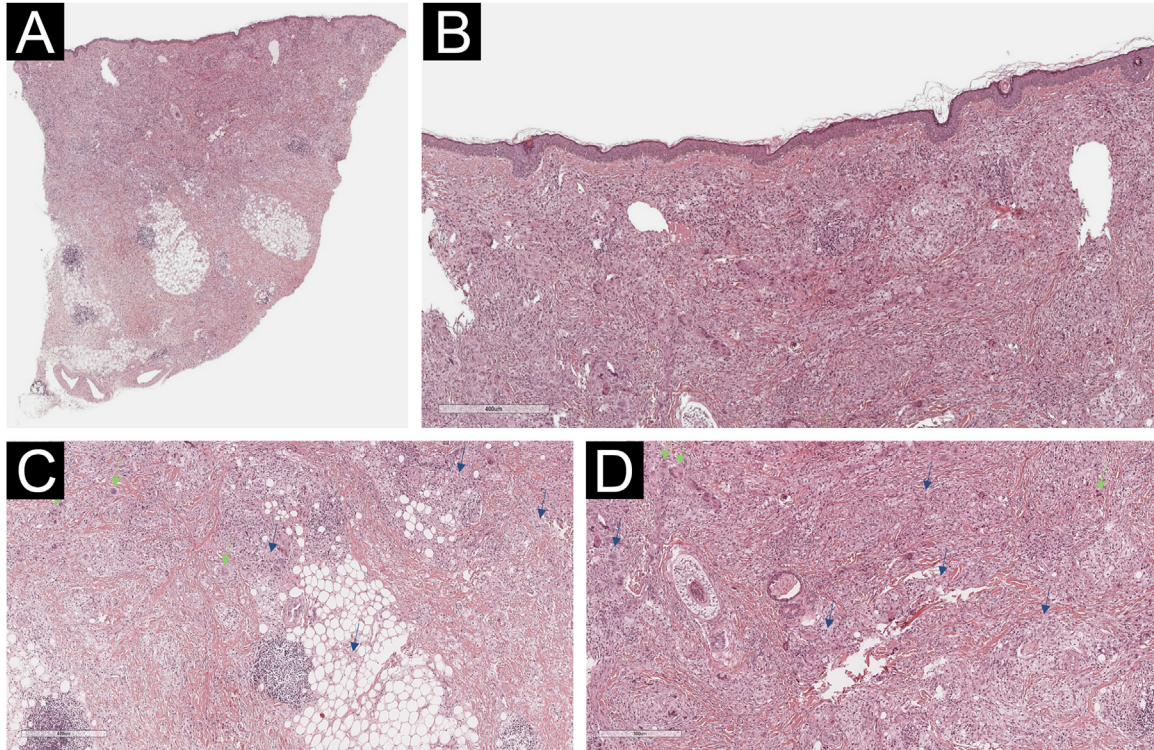


Fig. 2 Histological examination of the left lower eyelid lesion (Hematoxylin & eosin; panel A 20 $\times$, panel B 80 $\times$, panel C 140 $\times$, panel D 160 $\times$). Histology showed collagenous fibrous tissue in the dermis, interspersed with increased lymphohistiocytic cellularity with abundant foamy histiocytes (blue arrows in panels C and D) and multinucleated giant cells (green arrows in panels C and D).

Before starting treatment, it is essential to rule out monoclonal gammopathy and associated malignancy.^{5,6} Generally, the first-line therapy consists of alkylating agents such as chlorambucil, cyclophosphamide, or melphalan, administered with or without systemic glucocorticoids. Other treatments used include IVIG, thalidomide, lenalidomide, interferon α -2a, plasmapheresis, dapsone, antimalarials,

phototherapy, azathioprine, methotrexate, or rituximab. For localized lesions, local treatments such as surgery or CO₂ laser therapy can be employed.⁵⁻⁷ Our patient had undergone most of these treatments and still had refractory lesions with progressive growth. For this reason, and based on the reported efficacy of tofacitinib in isolated cases in granulomatous diseases, including histiocy-

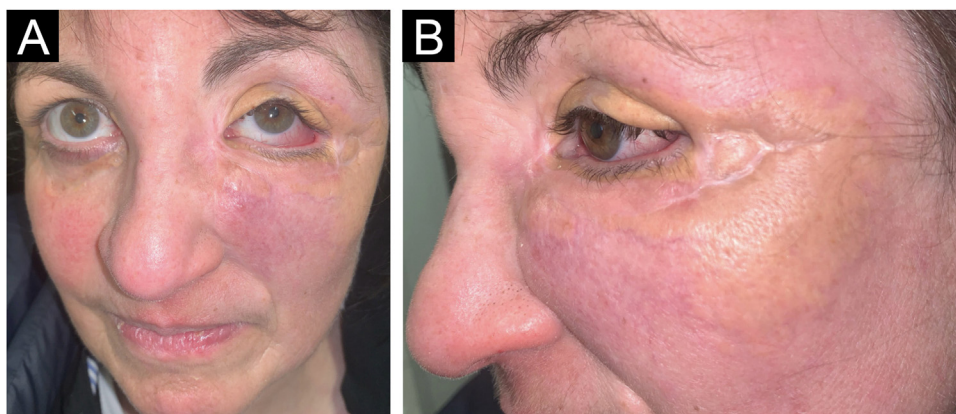


Fig. 3 Clinical presentation of the lesions one year after starting tofacitinib. Improvement of the lesions, with a slightly smaller diameter, less active border, and improvement in left visual restriction. Similarly, upon palpation, the lesions felt less infiltrated.

tosis such as necrobiotic xanthogranuloma² and multicentric reticulohistiocytosis,⁸ and non-histiocytosis such as granuloma annulare³ or sarcoidosis,^{3,4} it was decided to initiate treatment with tofacitinib. Although caution must be exercised when drawing conclusions from the treatment of isolated cases, the efficacy of tofacitinib observed in our patient, a refractory case, suggests it is a therapeutic option for such NXG cases. However, it should be noted that JAK inhibitors have been associated with numerous side effects, including infections (especially herpes zoster, respiratory infections), cardiovascular events (thrombosis, infarction), hematological changes, and a possible increased risk of neoplasia.^{9,10} Therefore, their use should always be justified, and safer therapeutic alternatives should be offered to the patient if available.

Financial support

None declared.

Authors' contributions

Miguel Mansilla-Polo: Managed clinical treatment and procedures; contributed to the development of this paper, had access to the data, and played a role in writing this manuscript.

Carlos Abril-Pérez: Managed clinical treatment and procedures; contributed to the development of this paper, had access to the data, and played a role in writing this manuscript.

Daniel Martín-Torregrosa: Managed clinical treatment and procedures; contributed to the development of this paper, had access to the data, and played a role in writing this manuscript.

Rafael Botella-Estrada: Supervised the work, had access to the data, and played a role in writing this manuscript.

Conflicts of interest

None declared.

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Received 27 October 2024; accepted 22 November 2024

Available online 28 June 2025

LETTER - THERAPY

Successful intravenous immunoglobulin therapy in paraneoplastic pemphigus associated with hepatocellular carcinoma[☆]

Dear Editor,

Paraneoplastic pemphigus (PNP), or paraneoplastic multiorgan autoimmune syndrome (PAMS), is an autoimmune blistering disease characterized by severe, often intractable, mucous membrane involvement and polymorphous skin lesions, that is classically associated with hematological neoplasms and, more rarely, with solid tumors.¹ Given the rarity of this disorder and the heterogeneity of clinical presentation, clinicians should maintain a high index of suspicion for PNP/PAMS to avoid delayed diagnosis. In 2021, the diagnostic criteria for PNP/PAMS were revised to better encompass the heterogeneous nature of this syndrome: the diagnosis is established when the three major criteria are met (mucositis with or without skin



involvement, concomitant internal malignancy, and evidence of anti-plakin autoantibodies), or when two major and two minor criteria are present (acantholysis and/or interface lichenoid dermatitis observed in histopathology with or without keratinocyte necrosis; and direct IF showing intercellular and/or basement membrane staining).² The treatment of PNP remains a clinical challenge.³ Systemic corticosteroids remain the first line of treatment for patients with PNP. Additional options for disease control include conventional steroid-sparing agents, rituximab, and intravenous immunoglobulin (IVIG).

Herein, we report a rare case of paraneoplastic pemphigus associated with hepatocellular carcinoma, successfully controlled with IVIG therapy in combination with systemic corticosteroids.

An 81-year-old Caucasian male, recently diagnosed with inoperable hepatocellular carcinoma was referred to our department for painful oral mucositis with six months' duration, associated with dysphonia, dysphagia, and significant weight loss (34%). He had already completed several therapies for oral mucositis, including antiviral, antifungal, and systemic corticosteroid therapy, without improvement. Also



Fig. 1 (A and B) Disseminated erythematous brownish hyperkeratotic papules and plaques on the trunk. (C) Erosions on the tongue and labial mucosa covered by hemorrhagic crusts.

[☆] Study conducted at the ULS Almada-Seixal, Almada, Portugal.

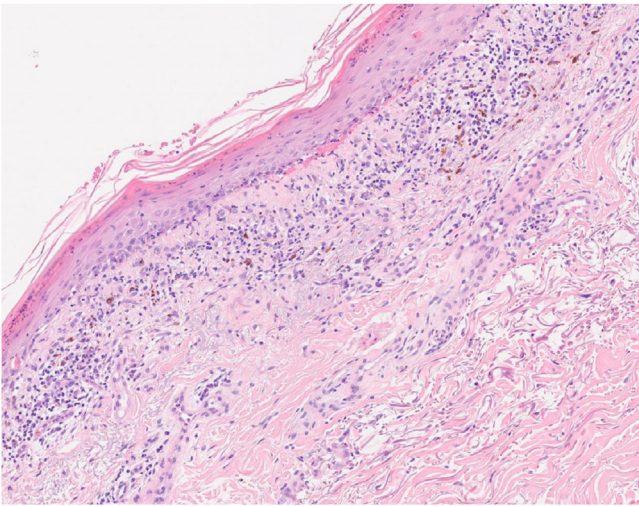


Fig. 2 In the dermis, a moderate lymphohistiocytic interstitial inflammatory infiltrate is observed, with moderate pigment incontinence, associated with interface changes (Hematoxylin & eosin; 150×).

noteworthy, in the context of the dysphagia investigation, he had undergone an upper gastrointestinal endoscopy that revealed low-grade erosive esophagitis.

In addition to oral mucositis, in the past three months, the patient developed a disseminated skin eruption characterized by erythematous-brownish hyperkeratotic papules and plaques on the trunk (Fig. 1A and B). Clinical examination of the oral mucosa showed erosions on the tongue, buccal, and labial mucosa, covered by hemorrhagic crusts (Fig. 1C).

The histological examination of the skin biopsy revealed a lichenoid interface dermatitis (Fig. 2). Serum IgG anti-desmoglein 3 and IgG anti-envoplakin antibodies were detected by enzyme-linked immunosorbent assay (ELISA). Direct immunofluorescence study of perilesional skin was negative.

Therefore, the diagnosis of paraneoplastic pemphigus was established considering the clinical picture of chronic

erosive mucositis associated with a malignant neoplasm, along with the detection of anti-envoplakin antibodies.²

In addition to sorafenib for the treatment of hepatocellular carcinoma, the patient was treated with prednisolone 1 mg/kg/day (60 mg) with progressive dose reduction. Approximately six weeks later, there was a significant improvement in the skin lesions (Fig. 3A and B).

Despite treatment with prednisolone and targeted therapy for hepatocellular carcinoma, the symptoms of oral dysphagia and dysphonia worsened due to persistent painful oral erosions, compromising the patient's nutrition. At this point, IGIV (2 g/kg/cycle divided into 5 days) was administered in combination with oral prednisolone 60 mg/day with progressive dose reduction, which resulted in significant clinical improvement. One month after the intravenous cycle, there were only a few lesions on the oral mucosa (Fig. 3C). The patient remained clinically controlled, completing monthly cycles of IVIG and prednisolone 30 mg/day. One year after the diagnosis he died at home following a head injury.

This case of PNP was associated with a solid tumor. In this context, the evidence supporting the use of rituximab is less clear. Furthermore, the administration of rituximab or other conventional immunosuppressants may promote tumor progression due to significant immunosuppression. Therefore, the combination of systemic corticosteroids with IGIV was considered the safest choice. Additionally, IVIg has been successfully used in other autoimmune blistering diseases such as pemphigus vulgaris and pemphigus foliaceus, being particularly useful in refractory cases to first-line therapy or when the use of conventional immunosuppressants is not safe.^{4,5}

In conclusion, our case illustrates a rare association between PNP and hepatocellular carcinoma. Importantly, we highlight the efficacy and safety of IGIV therapy in association with systemic corticosteroids in this condition. To the best of our knowledge, there are only two other cases of PNP related to hepatocellular carcinoma reported in the literature, which were both treated with systemic corticosteroids and azathioprine, with a clinical improvement of the oral lesions in only one.^{6,7}



Fig. 3 (A and B) Clinical picture six weeks after treatment with systemic corticosteroids with an improvement of skin lesions. (C) Clinical picture four weeks after initial IVIG cycle in association with systemic corticosteroids with significant improvement of oral mucositis.

Authors' contributions

José Ramos: Writing of the manuscript or critical review of important intellectual content; Critical review of the literature; Final approval of the final version of the manuscript.

Cláudia Afonso: Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; Final approval of the final version of the manuscript.

Ângela Roda: Writing of the manuscript or critical review of important intellectual content; Critical review of the literature; Final approval of the final version of the manuscript.

Cristina Fonseca: Intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases; Final approval of the final version of the manuscript.

Financial support

None declared.

Conflicts of interest

None declared.

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Received 9 November 2024; accepted 12 December 2024

Available online 1 July 2025

LETTER - THERAPY

Successful repigmentation with ritlecitinib and combined home-based phototherapy in an intractable case of generalized vitiligo[☆]



Dear Editor,

Generalized vitiligo usually requires systemic treatment due to its large lesion areas. Systemic glucocorticoid and traditional immunosuppressants have a limited role due to their side effects. Recently, novel agents targeting Janus kinase (JAK), a family of tyrosine kinases that regulates cytokine signaling, have emerged. JAK inhibitors are a promising option for the treatment of vitiligo orally or by topical application.¹ Ritlecitinib is an oral JAK inhibitor approved by the FDA for the treatment of severe alopecia areata. In a Phase 2b trial, ritlecitinib demonstrated significant improvement in the Facial Vitiligo Area Scoring Index in patients with active nonsegmental vitiligo.²

Here, we report a case with generalized vitiligo refractory to systemic and topical corticosteroids, which responded well to oral ritlecitinib combined with phototherapy by a 308 nm excimer lamp for home-based use.

The case is a 26-year-old man who has been suffering from vitiligo for 5 years. A small white patch initiated on the abdomen, which then increased gradually. The patient began to take traditional herbs and apply tacrolimus 0.1% ointment on the affected areas, but the lesions were still progressing, and finally spread to the trunk, thighs, palms, and soles. In 2021, he visited our clinic. The patient was diagnosed with progressive vitiligo and started receiving betamethasone injections to control the disease combined with whole-body Narrow-Band Ultraviolet B (NB-UVB) phototherapy. Diprosan® (suspension of 7 mg compound betamethasone) was injected intramuscularly four times at an interval of 3–4 weeks. The radiation source of the phototherapy was the Waldmann UV therapy system, which used Phillips TL-01 fluorescent lamps with a radiation spectrum of 310–315 nm and a peak of 311 nm. The patient

was exposed to NB-UVB therapy two times per week, on non-consecutive days for 45 sessions. However, these treatments showed no obvious effectiveness. Most areas of the trunk, thighs, palms and soles were involved by vitiligo. The treatment was changed to ritlecitinib 50 mg once a day, combined phototherapy with a handheld 308 nm excimer lamp every other day. Excimer light starting doses ranged from 180 mJ/cm² to 360 mJ/cm², depending on the body site, and post-treatment erythema-guided adjustments of subsequent doses. Approximately 2 months after that, the vitiligo of this patient was well controlled, with 80% repigmentation of the lesions at the trunk (Fig. 1) and thighs, while palms and soles remained with no obvious repigmentation. The patient received ritlecitinib orally for half a year and currently undergoing maintenance therapy at a dose of 50 mg every other day. No adverse effect including abnormality of biochemistry metabolism was found, showing ritlecitinib safety.

Ritlecitinib, a JAK3/TEC inhibitor, shows therapeutic effects on alopecia areata by inhibiting IL-5 and IFN- γ (ritlecitinib may decrease the production of IFN- γ via an indirect mechanism, related to TEC kinase inhibition), which are also pathogenic cytokines in vitiligo and can therefore be used to treat this condition. A recent study revealed that ritlecitinib-treated vitiligo patients showed downregulation of immune biomarkers and upregulation of melanocyte-related markers.³

Given the encouraging results of the phase 2 clinical trial of ritlecitinib for the treatment of vitiligo, the patient accepted the off-label use this medicine after experiencing failures in previous treatments. The oral ritlecitinib therapy achieved great improvement within 2 months. Although the repigmentation was partly attributed to phototherapy, ritlecitinib played a key role in the success of this case, since the patient has already used phototherapy multiple times in the past with poor efficacy, and ideal therapeutic effects appeared only after oral administration of ritlecitinib. In a report, oral tofacitinib also could stop the progression of active vitiligo, when combined with phototherapy.⁴

Furthermore, ritlecitinib is highly selective for JAK3. The most common adverse events of ritlecitinib were nasopharyngitis, upper respiratory tract infection, and headache as observed in clinical trials for vitiligo² and long-term treatment of alopecia areata.⁵ No adverse reactions

[☆] Study conducted at the Department of Dermatology, Hangzhou Third People's Hospital, Hangzhou, Zhejiang Province, China.

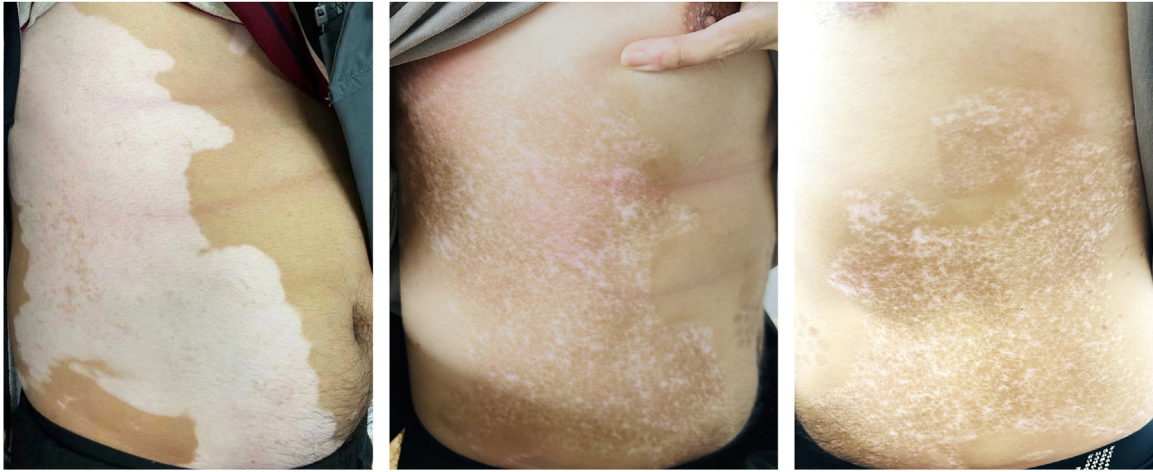


Figure 1 Right truncal lesions of vitiligo at baseline; repigmentation of bilateral truncal lesions after 2 months of ritlecitinib combined with 308 nm excimer light phototherapy.

were found in our patient, but it is still necessary to closely monitor the occurrence of side effects.

Finally, home phototherapy should be considered for its economic value, good tolerability, adherence, and efficacy.⁶ In this case, both oral medication and 308 nm excimer light phototherapy are performed at home, providing a convenient treatment option for the patient.

Financial support

None declared.

Authors' contributions

Xiu-Kun Sun: Contributed to the conception, design, and data analysis of this study.

Ai-E Xu: Contributed to the conception, design, and data analysis of this study.

Conflicts of interest

None declared.

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Received 1 October 2024; accepted 15 December 2024
Available online 14 July 2025

LETTER - THERAPY

Use of ustekinumab in the treatment of severe psoriasis in a liver transplant recipient[☆]



Dear Editor,

Biologics represent an important advancement in the treatment of psoriasis, especially in moderate to severe cases that do not respond to conventional therapies. These agents act precisely on specific molecular targets, providing effective disease control and substantially improving patients' quality of life.¹

In solid organ transplant recipients (OTR), the use of biologics gains even greater clinical importance. These patients, who require continuous immunosuppression to prevent graft rejection, often experience psoriasis exacerbation induced by medications like corticosteroids. Additionally, the toxicity of drugs like cyclosporine on transplanted organs and the increased risk of infections and malignancies make the management of these cases even more complex.²

Recent literature highlights the efficacy and safety of biologics in treating psoriasis in OTRs but emphasizes the need for a cautious approach when selecting these therapies. Documented clinical cases demonstrate that, while biologics offer significant improvement, careful patient monitoring is essential due to potential interactions with immunosuppressive drugs and the risk of serious complications.^{3,4}

In 2023, a study reviewed the literature on patients with psoriasis who had undergone solid organ transplantation and received biologic therapy. The analysis identified 13 cases, including 8 liver transplants, 4 kidney transplants, and 1 pancreas-kidney transplant, in which patients, primarily treated with etanercept and ustekinumab, showed positive responses without complications over periods ranging from 5 months to 6 years.⁴

The study also highlighted three specific cases: the first, a man who underwent a kidney transplant and showed significant improvement after a severe psoriasis relapse, treated with ustekinumab; the second, a liver transplant

patient with severe psoriasis who responded positively to treatment with etanercept; and finally, a female kidney transplant recipient with psoriasis since childhood who achieved an excellent response after 30 weeks of treatment with risankizumab.⁴

We report the case of a 35-year-old man with a history of hypertension and mild plaque psoriasis, treated with methotrexate (15 mg weekly) for seven months, who developed acute liver failure due to cryptogenic cirrhosis, necessitating a liver transplant. Initially, after the transplant, the patient was maintained on immunosuppressive therapy with tacrolimus and mycophenolate mofetil, showing a good response in his skin condition (PASI score < 5). However, one year later, there was a progression of the disease to extensive plaques across the body and scalp, negatively impacting his quality of life.

Treatment with acitretin (50 mg/day or 0.5 mg/kg/day) provided partial improvement for three years, but there was secondary failure. Narrowband UVB phototherapy was initiated, resulting in clinical worsening with transformation to pustular psoriasis (Fig. 1), which gradually resolved with the reintroduction of acitretin. After the transplant, the patient developed obesity, chronic kidney disease, and hepatic steatosis. The elevation of serum lipids with the use of acitretin and the contraindication to methotrexate and cyclosporine due to additional complications limited therapeutic options.

After a multidisciplinary evaluation, the patient was treated with ustekinumab, a monoclonal antibody targeting the p40 subunit common to interleukins 12 and 23. With an induction dose of 90 mg (weight 100 kg), he achieved PASI 100 after the first maintenance dose (12 weeks later). Control of psoriasis was maintained with dosing every 12 weeks for three years, although there was a recurrence of plaques on the limbs and abdomen, reaching PASI < 75. PASI 90 was again achieved by reducing the interval to 8 weeks, as dose optimization or interval reduction is recommended in the product information, without compromising treatment safety. The patient has remained well-controlled for five years, with no evidence of lesions and stable liver function (Fig. 2).

The risk of hepatotoxicity and the complex interactions between immunosuppressants and therapies for psoriasis are among the conditions that make treatment in organ transplant recipients challenging. Ustekinumab (UST) offers

[☆] Study conducted at Dermatology Division, School of Medical Sciences, Universidade Estadual de Campinas, Campinas, SP, Brazil.

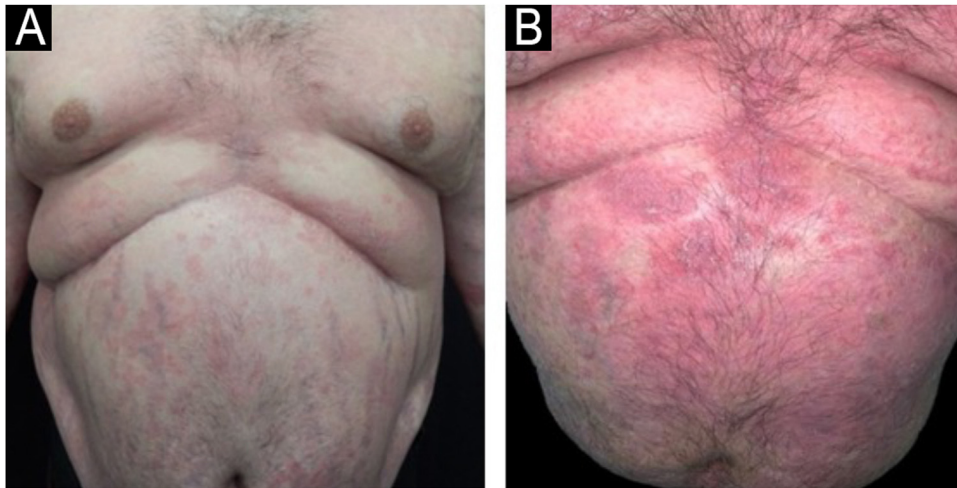


Figure 1 (A) Plaque psoriasis and striae on the trunk before acitretin. (B) Pustular eruption after phototherapy.

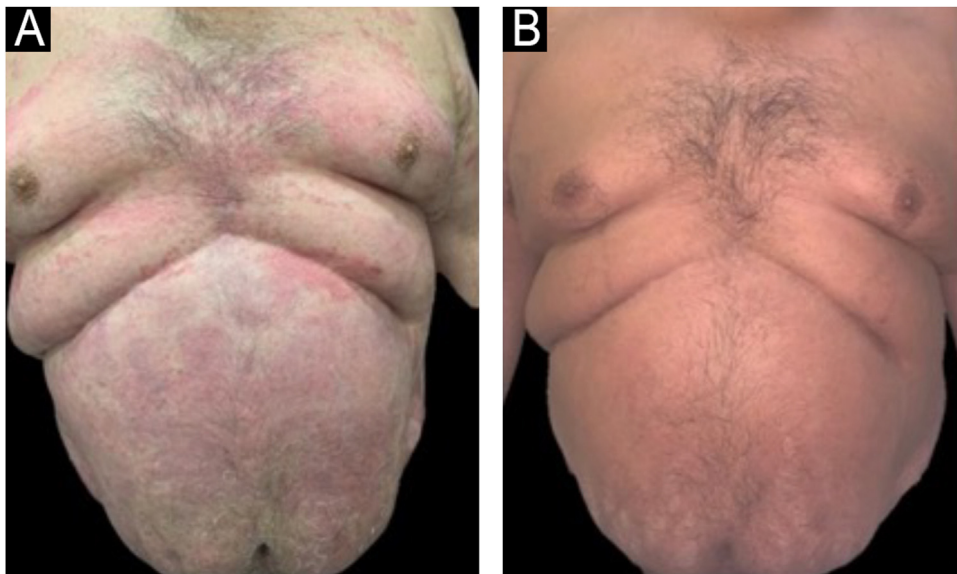


Figure 2 (A) Infiltrative erythematous-scaly plaques on the trunk before Ustekinumab. (B) Ten months after starting ustekinumab, no lesions present.

an alternative with proven safety, as it is the longest-standing anti-interleukin available in the Brazilian market and has several reports in this patient profile. However, the absence of specific guidelines and the need for individualized approaches underscore the complexity of managing this condition, highlighting the importance of further research to enhance treatment.⁵

This case reinforces that ustekinumab can be an effective and safe option for controlling psoriasis in liver transplant recipients without compromising liver function over a long period, highlighting the importance of personalized therapeutic strategies and the need for rigorous monitoring and further research.

Financial support

None declared.

Authors' contributions

Tiago Almeida Santos Costa: Study conception and design; data collection; manuscript drafting; critical literature review.

Juliana Schinzari Palo: Manuscript drafting; critical literature review.

Renata Ferreira Magalhães: Critical revision of important intellectual content; effective participation in research supervision; final approval of the manuscript version.

Conflicts of interest

None declared.

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Received 18 September 2024; accepted 6 November 2024
Available online 3 July 2025