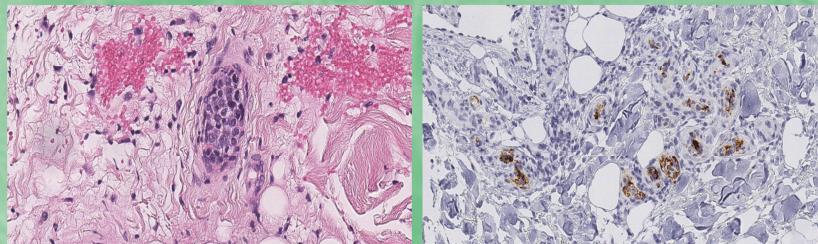


Anais Brasileiros de Dermatologia

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Intravascular large B-cell lymphoma: presentation with generalized dendritic-type telangiectasias. A diagnostic challenge

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EDITORIAL

Anais Brasileiros de Dermatologia: management experiences and perspectives of a Latin American scientific journal –2021-2025 period[☆]



Dear Colleagues,

After five years of working with authors, reviewers, and readers, we, the current Editors, have reached the end of our tenure at the helm of the Anais Brasileiros de Dermatologia (ABD). It is time to report and highlight the implemented changes and the challenges ahead. We understand that the dynamics of the succession process in scientific journals, and in the ABD in particular, are similar to the passing of the baton in a relay race. The principle is to do our best to hand over management in the best possible position to the new leaders, who, in turn, will do their best to hand over the baton in an even better position than when they received it. This philosophy has been clearly demonstrated and practiced over the last 25 years of the ABD's history.¹ This change in Editors is welcome because it brings new experiences and different perspectives.

As explained in previous Editorials, particularly those in volume 99 (1)² and volume 100 (4),³ the metrics used to analyze scientific journals may incorporate biases depending on the methodologies employed and certainly require different interpretations when comparing different medical specialties. However, despite these facts, the Editors of a scientific journal must reflect on future paths, different proposals, and initiatives to achieve a better ranking when comparing their metrics with those of similar journals. Therefore, based on the Impact Factor, CiteScore, and Scimago Journal Rank (SJR) reports, and aware that each has its own methodology and different databases, this ABD management took several initiatives, notably eliminat-

ing low-impact sections, transforming others into letters, expanding the clinical cases section, including therapy letters, and expanding space for research and review articles. This was evidently done gradually, as the existence of articles approved for a given section implied its maintenance until the articles allocated to it were exhausted. Another imperative initiative for change was the need to reduce the waiting time for publication. We did this by reducing the number of accepted articles, increasing the number of articles per issue, and accelerating the publishing of online articles, which proved effective. Furthermore, inherent to the importance of a scientific journal is its visibility and its consistency in publishing what is of greatest interest to readers. However, without neglecting the graphic quality and the quality of clinical, histological, dermoscopic, and general images. As a result of the changes implemented over the period and the collective effort of Scientific and Technical Editors, Authors, and Reviewers, the ABD expanded its scope, gained greater visibility, and improved all its metrics. For example, the impact factor grew from 2.1 in 2021 to 3.6 in 2024 and rose from the 3rd quartile to the 1st quartile among 96 audited journals.³ These were also determining factors for the growth of the ABD, maintaining and expanding its plural tradition: articles on infectious dermatology coexist with articles on micrographic surgery, the ones on tropical dermatology with those on cosmiatry, those on basic research with those on clinical or epidemiological research.⁴⁻⁶ Moreover, it houses articles on stomatology originating from or in association with Schools of Dentistry, on chronic ulcers with the participation of or originating from Departments and Schools of Nursing.⁷⁻¹⁰

It is also consolidating itself as a scientific journal with international reach, featuring articles from several countries and, as expected, with an emphasis on those from

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

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Ibero-Latin America. Of course, there are challenges to overcome, including one that could have a growing impact on scientific journals: the correct and potentially incorrect use of Artificial Intelligence (AI). The ABD will have a page in their rules that will indicate how and when to declare the use of AI, for which and what insertions in the submitted text. However, it is already clear that the use of AI to improve text quality in terms of fluency, grammatical correctness, and English editing is permitted and even welcome. However, whether or not reviewers will allow the use of AI, among other issues inherent to scientific texts, will be a topic of internal and external debate.

Other issues of collective impact, such as whether the ABD is online-only, whether or not to charge for article publication, and if so, from everyone, including members? These issues will be debated and voted on by the Board of the Brazilian Society of Dermatology (SBD, *Sociedade Brasileira de Dermatologia*). Furthermore, how to address the apparent cultural reasons that prevent some authors publishing abroad from citing the ABD, even when pertinent articles exist and are authored by the authors themselves. Decisions have already been made and are yet to be implemented, such as having the ABD published in print and online exclusively in English, which will be challenging at first. And, certainly, new proposals and initiatives will be debated and implemented. But, as mentioned above, this involves rotating leadership, with different names or roles, but with the same foundations, objectives, and certainly new visions, methodologies, and requirements.... *E pur si muove*

Our thanks to the Authors and Reviewers who have walked with us, to the SBD Board of Directors for their unwavering support, to Elsevier Publishing for their presence and contribution to the discussions and improvements implemented, and to the Technical Editors for their excellence. And welcome and best wishes for success to the new Editors, for the 2026–2031 term.

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CONTINUING MEDICAL EDUCATION

Pressure Injuries: prevention, treatment, and complications – Part II[☆]



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Dressings;
Pressure ulcer;
Wound Healing

Abstract Pressure injuries must be identified and managed early to prevent them from becoming difficult to heal. In this review, the main complications inherent to pressure injuries will be highlighted, as well as the expected prognosis for patients with this health condition. Furthermore, the most current preventive measures are emphasized and supported by robust references from systematic reviews and guidelines. In the treatment section, an updated and comprehensive conceptual model is presented to guide dermatologists and healthcare professionals in assessing injuries in general, as well as pressure injuries. The focus on the debridement and management of infections and biofilm is emphasized. The importance of preparing the wound bed and the peri-wound area will also be addressed, unifying concepts with the best scientific evidence.

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Introduction

Pressure injuries (PIs), also known as “pressure ulcer”, are considered chronic and should be identified and managed early to prevent them from becoming difficult to heal.¹ Their high incidence and global prevalence,² make prevention a current concern and necessity on the agendas of healthcare organizations.³ PIs have a significant economic

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impact related to both direct and indirect costs involved in their management, such as costs for wound care materials, nursing time, surgery, debridement, additional hospitalization time, medications, laboratory and imaging tests, and secondary prevention measures (to prevent further deterioration, occurrence, or recurrence of PIs), treatment of complications, and medical consultations.⁴ In addition, there are unquantifiable expenses related to the negative impact of PIs on patients and their families.⁵

Dermatologists may contribute significantly to the care of patients with PIs because their training makes them valuable members of the wound care team through the appropriate diagnosis of PIs, indicating diagnostic tests necessary for evaluation, recommending correct care for the surrounding skin, and indicating proper treatments and specialized dressings. They may also guide strategies for the prevention and treatment of complications. Thereby saving resources for the healthcare system and improving the quality of life of the patients.⁶

In Part I, PIs general concepts, clinical aspects, and laboratory findings were updated. Part II focuses on its prevention, treatment, and complications.

Prevention of pressure injuries

Risk assessment for pressure injuries

The risk assessment for developing PIs should be structured, including a valid and reliable risk prediction scale, a thorough skin assessment, and a critical interpretation of the results.⁷ The latter has been emphasized as a key element in identifying potential risk factors that the scales may not cover.⁸

Risk assessment for PIs assists in the selection of effective preventive interventions, including the frequency of skin assessment and repositioning. Some interventions are directly related to specific risk factors (e.g., managing moisture when present), while others are assigned based on the overall estimated risk score.⁹ Thus, risk prediction scales highlight vulnerable areas, reinforce the importance of continuous assessment, and support preventive mechanisms.¹⁰ In addition, the scales can contribute to epidemiological studies by identifying groups of individuals at risk. Ideally, risk prediction scales for PIs should be used specifically for the population for which they were developed.⁷ For adult patients in general, the gold standard is currently the Braden Scale,¹¹ which was translated into Brazilian Portuguese in 1999,¹² it covers six risk domains: mobility (ability to change and control body position); activity (degree of physical activity); sensory perception (ability to respond appropriately to discomfort related to pressure); moisture (degree of skin exposure to moisture); friction and shear (horizontal forces acting in conjunction with the vertical pressure); and nutrition (usual dietary intake pattern). These domains are scored from one to four (except the last one, which is scored from one to three). The score ranges from six to 23, classifying individuals based on the total score obtained as follows: no risk (score 19–23), low risk (score 15–18), moderate risk (score 13–14), high risk (score 10–12), and very high risk (score ≤ 9).¹²

The Braden-Q Scale was modified for children, specifically developed for neonates up to 18-years-old.^{13,14} More recently, for neonates, the Braden QD Scale has been introduced,¹⁵ and it has already been adapted for Brazil.¹⁶ The Glamorgan Scale,¹⁷ developed for hospitalized children and adapted to Portuguese, has demonstrated higher accuracy than the Braden-Q.¹⁸ More recently, it has been applied to pediatric Intensive Care Units (ICUs).¹⁹

Patients are at high risk for the development of PIs during surgical procedures. The first scale developed to assess this risk was the Munro Scale.^{20,21} However, in addition to the intrinsic characteristics of the patient, surgical positioning during the perioperative period becomes the most important challenge in preventing PIs. The ELPO Scale²² developed by a Brazilian nurse for this purpose, is widely used and validated, and utilized in other countries.^{23,24} Recently, a new scale called PRASI (Proactive Risk Assessment for Skin Integrity) has been introduced, primarily assessing skin integrity.²⁵

For critically ill patients in ICUs, the most studied scales currently, which have already been adapted to Portuguese, are: EVARUCI,^{26,27} CALCULATE^{28,29} and Cubbin & Jackson.^{30,31} Studies have shown that these scales have superior risk prediction compared to the Braden Scale.^{32,33} In agreement, a systematic review from 2024,³⁴ highlighted that the use of the Braden Scale in ICUs is not recommended due to the inconsistency of its psychometric properties, as it does not fully address the risk factors for this patient profile.³⁴

Preventive measures

In addition to scales and clinical judgment, prevention bundles have become more widespread. These are a set of evidence-based interventions that, when implemented together, aim to impact patient outcomes,^{35,36} including risk assessment, moisture control, patient mobility, nutrition, support surfaces,⁷ and team training.³⁷ However, in a systematic review, studies on bundles showed bias, particularly in the post-intervention assessment of the application of these measures, indicating that further research is needed to evaluate their effectiveness.³⁸

Clinical awareness and appropriate resource allocation are necessary to prevent PIs.³⁹ Minimizing compressive (pressure) and shear forces at the interface between the body and the support surface or between the body and a medical device are valid clinical interventions to reduce the risk of developing PIs.⁷

Table 1 lists the main preventive measures recommended for patients at risk of developing PIs, including evidence related to skin assessment and care,⁷ and preventive dressings (Fig. 1), repositioning,^{7,37,44,45} bed head,^{7,40,46} surfaces (bed and mattresses),^{7,40,47,52} and nutrition.^{7,40,48–51,53}

Treatment of pressure injuries

The first step in the care pathway for PIs is to relieve pressure in affected areas and prevent the development of injuries in new areas. The treatment of a PI should occur at the earliest stage to prevent the development of hard-to-heal or chronic wounds, which do not reduce by 40%–50% in size within four weeks⁵⁴ when treated with a good stan-

Table 1 Main preventive measures for patients at risk of developing pressure injuries (PIs) and their respective recommendations.^{7,36,37,40–53}

Preventive Measures	Recommendations
Skin Assessment and Care	• Daily skin assessment in areas of bony prominences and medical devices, paying attention to areas of erythema, oedema, or changes in skin temperature or texture. • Keep the skin clean and hydrated, avoiding the use of alkaline soaps. • Avoid rubbing and vigorously massaging skin at risk of pressure injuries, especially over bony prominences.⁷ • Use a barrier cream or barrier spray, especially in areas with persistent moisture exposure, such as the diaper area in incontinent patients.
Preventive Dressings ^a	• Recommended for all patients at risk of PIs, especially those in intensive care units, in areas of bony prominences. • Use silicone and multilayer foam dressings, especially on the sacral area and heels.
Repositioning	• The exact interval for repositioning is not known and is done empirically. • When repositioning, consider individual factors such as skin tolerance, overall medical condition, treatment goals, comfort, and pain. • Repositioning every two hours has been reported in some studies to contribute to a reduction of up to 25% in the incidence of PIs^{37,44} having a specific team (turning team) to perform repositioning has been shown to reduce this risk by 51%.⁴⁴ • On the heels, a foam pillow or cushion should be used to distribute the weight of the leg along the calf without applying pressure to the Achilles tendon and the popliteal vein. • Manual techniques and equipment, such as rotation mattresses and sliding sheets, assist in proper repositioning, reducing friction during movement, and helping with comfort. • When repositioning, consider individual factors such as skin tolerance, overall medical condition, treatment goals, comfort, and pain.
Head of bed ^b	• Ideally, the head of the bed should be kept at the lowest elevation possible, consistent with clinical conditions and other constraints. • When elevation of the head of the bed is necessary, precautions should be taken to avoid patient sliding or migration.
Surfaces (bed and mattress)	• When choosing the best surface, individual patient characteristics should be considered, including the risk of PIs.⁴⁰ • Choose mattresses that allow a minimum thickness of 2.5 cm between the patient's body and the rigid surface of the bed. • Evaluate mattress density to ensure the patient does not "sink" into the mattress. • Recommended mattresses: pneumatic mattresses (air-alternating mattresses) offer better cost-effectiveness compared to foam mattresses (pyramid-shaped or "egg crate" type).⁵²
Nutrition	• Nutritional status is a significant factor in preventing PIs, as both malnourished lean and obese patients face a heightened risk of developing them due to compromised tissue integrity and reduced healing capacity.⁵³ • Screen all patients for nutritional risk using a validated tool, such as the Malnutrition Universal Screening Tool (MUST).⁴⁹ • Nutritionist assessment to develop an appropriate plan for at-risk patients. • For neonates and children with or at risk of PIs who have inadequate oral intake, consider enriched foods, age-appropriate nutritional supplements, or enteral or parenteral nutritional support. • Supplements, in general, still have low evidence in prevention and require studies on special diets (e.g., high-protein, vegetarian).⁵¹

^a According to a systematic review,³⁷ foam dressings have been shown to reduce the incidence of pressure injuries by 30%.

^b Elevating the head of the bed creates higher interface pressures between the skin and the bed surface at the sacrococcygeal area. Mechanically ventilated patients, when at a 45 ° elevation, have almost a 50% higher risk of pressure injuries compared to a 30 ° elevation.⁴⁶



Fig. 1 Prophylactic polyurethane foam and silicone dressing on the sacral region in a patient at high risk for developing pressure injuries.

dard of care.⁵⁵ Moreover, the treatment of PIs should focus on the underlying cause, which has been explained earlier and is directly related to the factors that led to the injury, the most important of which is usually pressure. All pressure on the injury should ideally be removed. In many cases, this may be impossible, and therefore, optimization of the patient's environment is necessary. An essential intervention is pressure relief and load redistribution through frequent repositioning.⁷ Thus, physical measures are necessary to remove mechanical loads and redistribute pressure in order to prevent additional risks and tissue damage, and to promote healing.⁵⁶ Some patients, due to severe conditions, may have compromised repositioning. Therefore, the dressing of a PI, in addition to promoting healing, should also interfere with the loading state in the soft tissues at and around the wound. An adequate dressing with a protective biomechanical effect should absorb compressive and shear deformation energy from the surrounding tissues and the wound itself, alleviating the transferred loads.⁵⁶ Examples of biomechanical performance dressings are multi-layered anisotropic ones, which aim for different resistances to compression or tension depending on the direction in which the force is applied. This type of dressing has proven effective in the prophylaxis of sacral PI^{57–59} and has also demonstrated efficiency with a focus on treatment, that is, when a PI already exists and is subjected to bodyweight forces.⁵⁶

The improvement of patient mobility taught by physical therapists helps reduce incontinence and immobility, thereby decreasing the risk of PI development.⁶⁰ An example is the treatment of PIs with electrical stimulation, where clinical trials have provided ample evidence of its effectiveness,⁶¹ as already recommended by international guidelines.⁷

Optimizing nutrition has not been shown to be definitive, but research has shown that specialized nutritional supplementation, in addition to standard wound care, can

effectively improve the healing of PIs.^{62,63} Therapeutic nutrition can support wound healing by increasing collagen production and helping to replenish the critical nutrients needed for healing.⁶⁴ Patients with PIs are generally malnourished and protein-deficient, even those who are overweight or obese, as evidenced by low levels of nutritional biomarkers. Successful healing depends on collagen synthesis/deposition and epithelial resurfacing, both of which are highly reliant on adequate nutrient stores and support.⁴⁰

Once the causes that originated or perpetuated the PIs have been addressed and corrected or improved, the next step is wound bed preparation or a local approach to the PIs.^{65,66}

When choosing the most appropriate local approach and dressing (primary and secondary), it is essential to consider the treatment objectives, which may include: protecting the wound bed during healing, promoting granulation tissue formation, supporting autolysis to aid in the debridement of devitalized tissue, managing local and systemic infection, controlling excess exudate and unpleasant odor, managing hypergranulation, and assessing the peri-wound.⁶⁷ In line with this, it is essential to consider the size and depth of the wound, its classification and duration, and patient-related aspects such as emotional and social factors, access to healthcare, environment, and adherence to the treatment plan.¹ Also, it is essential to consider the overall health and goals of the family and patients. Palliative care for PIs refers to the relief of symptoms and suffering related to wounds in the context of a serious illness. Moreover, it is essential to consider the overall health and goals of the family and patients.⁴⁰ Injuries that occur at the end of life should focus on interventions for symptom management, patient comfort, and well-being, rather than on healing the wound.⁶⁸ Topical pain treatments include viscous lidocaine gel and dressings that deliver ibuprofen and local opioids. Wound odor may be reduced with charcoal dressing, antiseptics, ionized silver dressings, or metronidazole gel. Alginates, gelling fibers, and absorbent foam dressings can manage excess drainage and protect surrounding skin from moisture-related damage.⁶⁹

All these previously mentioned aspects have been incorporated into the acronym TIMERS (Fig. 2), essential for facilitating efficient wound care, focusing on rigorous assessment, and implementing interventions to optimize the healing process.^{7,55}

T (Tissue): Assessment of Tissue viability in the injury bed

Assessment of tissue viability in the injury bed involves identifying devitalized or non-viable tissue, which hinders the healing process and facilitates infections.¹ Removal of devitalized tissue (debridement) is essential, including slough, necrotic tissue, debris, toxins, microorganisms, and biofilm, both in the ulcer bed and in the peri-wound area, as well as hyperkeratosis.⁷⁰

Cleaning or hygiene is the first step in the process. Its primary goal is to minimize microbial load and remove surface contaminants, debris, and microorganisms from the wound, aiming to establish a clean environment that reduces

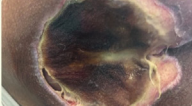
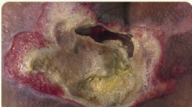
Acronym TIMERS	Specification	Characteristics	Treatment Options
T (Tissue) Tissue Viability	Viable Tissue	Vascularized granulation tissue 	- Maintain a moist environment; - Use non-adherent dressings; - Protect the tissue to prevent infection.
		Epithelialization tissue 	- Protect the tissue with hydration - barrier film/cream; - Protect with silicone foam dressing.
	Non-viable Tissue	Dry necrosis 	AUTONOMOUS METHODS OF DEBRIDEMENT - Surgical Debridement - Scalpel, scissors, curettes; - Mechanical - Hydrosurgery - pressurized water jet; - Ultrasound/Ultrasonic, low or high frequency; - Negative pressure therapy with instillation. - Enzymatic - Proteolytic enzymes: papain, collagenase;
		Wet necrosis 	
		Slough 	
I (Infection/ Inflammation)	Infection and/or inflammation (biofilm)	Local infection 	- Surgical debridement and cleansing; - Topical antimicrobial dressing according to the level of exudate; - Surfactants and concentrated surfactants, such as polyhexamethylene biguanide.
		Dissemination and systemic infection 	- Consider systemic antimicrobials (guided by culture); - Continuous monitoring of tests; - Integrate techniques to treat local infections with topical treatments; - Topical antimicrobial dressing according to the level of exudate.
M (Mouster) Moisture balance	Excess/ Absence of exudate	Wound 	Absent or Very Dry - Hydrogel; - Hydrogel-impregnated dressing. Moist (in the right amount) - Hydrocolloid; - Foam dressing; - Acrylic dressing; - Collagen-based dressings. Very Moist - Gelling fiber dressing (hydrofiber); - Alginate dressing; - Collagen dressing; - Foams. Saturated - Highly absorbent dressings; - Superabsorbent dressings containing polyacrylate polymers; - Negative Pressure Wound Therapy (NPWT).
		Periwound 	Healthy or Abnormal Appearance (maceration, erythema, irritation, or excoriation): - Barrier products (liquid barrier film/cream, including cyanoacrylate); - Moisturizers.
E (edge) Edge of the wound	Poor wound edge advancement: epibole / hyperkeratosis / calluses	Attached or adhered to the wound bed 	- Cleaning of edges and margins (hyperkeratosis or necrosis); - Skin protectors in cream or spray; - Photobiomodulation.
		Unattached with or without a space or cavity between the wound edge and the underlying tissue 	- If there is epibole (rolled edge) or hardening (fibrosis) - debridement may be necessary; - If tunneled, it is necessary to fill the spaces/cavities with dressings (e.g., collagen, foams), gelling fiber dressing; - If macerated, it is necessary to choose the correct size of the dressing and use barrier products with cyanoacrylate for the wound edge.
R (Repair/ Regeneration)	Slow or stagnant healing with failure in conservative therapy	Topical interventions	- Local flaps for pressure injuries stages 3 and 4; - Tissue engineering: Amnion/chorion membrane, cell scaffold, etc; - Platelet-rich plasma (PRP).
S (Social) Social and Patient- Related Factors	Social Situation	Analyze family and patient dynamics	Patient support network, including family, caregivers and friends.
		Psychosocial factors	- Living with a chronic wound; - Environment and hygiene; - Level of education and literacy.
		Financial factors	- The financial impact of living with a chronic wound; - Access to medical care.
PW (Peri-wound)	Area around the lesion, also known as the margin; It comprises 2-4 cm; More advanced stage pressure injuries and other more complex wounds (Assessment of larger dimensions).	It may be hyperkeratotic, very dry, macerated, erythematous, or infected	- Evaluate, clean, treat, and protect the wound; - Promote healthy and intact tissue to improve wound healing; - Protect the periwound tissue with a barrier product for drainage or maceration; - Hydrate the periwound tissue if it is dry; - Use a barrier product (liquid barrier film or spray, including cyanoacrylates); - Apply an antifungal component if necessary.

Fig. 2 TIMERS adapted by adding the Peri-Wound approach (PW).^{1,55,67,70}

the risk of infection and promotes the formation of healthy granulation tissue.^{65,70} Cleaning also ensures better visualization of the wound bed and access to non-viable tissue.^{7,70} Proper hygiene should be performed on the wound bed and the peri-wound skin.^{1,55} It is primarily recommended to use 0.9% sodium chloride solution or clean (drinking) water for irrigation.⁷¹

Therefore, in cases of hard-to-heal PIs, it is necessary to clean both the wound and the peri-wound area with antiseptic products suitable for skin (Ph 4–6), such as Poly-hexamethylene Biguanide (PHMB).⁷¹

Debridement, on the other hand, is a critical step in wound bed preparation, aiming to remove barriers that impede the healing process.⁶⁵ Its goal is to remove necrotic and sloughy tissue, reduce bacterial load, and eliminate biofilm.¹ It contributes to removing fibroblasts and keratinocytes that undergo phenotypic changes (senescence), leading to chronic inflammation, fibrosis, and delayed healing.⁷² Thus, debridement converts chronic wounds stagnated in the inflammatory phase into an environment more similar to acute wounds, promoting healing.^{1,73} The following non-viable tissues require management with debridement (Fig. 2):

- Necrotic tissue: Resulting from localized tissue death due to infection or ischemia. It may appear black, brown, or Gray, and can be dry (generally non-infected) or moist (often infected), and is usually adhered to the wound bed.
- Slough: A complex mixture of exudate proteins, degraded extracellular matrix proteins, white blood cells, and various microorganisms in planktonic and biofilm phenotypes.⁷⁰

The different types of debridement are described in Fig. 2. Integrated debridement involves combining debridement methods according to the individual needs of the patient, preferences, and environment, as well as available resources and the skills of healthcare professionals.⁷⁰ In addition, professionals need to be aware of the contraindications for each procedure. Surgical debridement, for example, should be carefully evaluated in patients on anticoagulants, those with a high surgical risk, or those who have ischemia, especially if the wounds are extensive.¹ Other debridement methods, such as autolytic or mechanical debridement, are less invasive and require less training, making them more widely used.⁷⁰ However, autolytic debridement (e.g., with hydrogels and hydrocolloids) is not the method of choice in cases of active infection with large amounts of devitalized tissue (e.g., gangrenous tissue). In these cases, surgical debridement should be considered.”

I (Infection/Inflammation)

Infection and inflammation prevent healing and are crucial factors to be monitored.⁷⁴

Local infection is characterized by the presence and proliferation of microorganisms within the wound, triggering a host response that often causes delayed healing.⁷⁵ Local infection is confined to the wound and the immediate peri-wound area (less than 2 cm) and often presents with subtle signs and symptoms that may not be immediately recog-

nized, such as hypertrophic granulation tissue, bleeding, friable granulation, epithelial bridges, formation of pockets in the granulation tissue, and increased exudation.⁷⁵

Almost all chronic wounds contain biofilms, complex community structures surrounded by an extracellular polymeric substance secreted by various pathogenic bacteria to evade host defenses and increase resistance to antimicrobial drugs.^{76,77} Combined with laboratory and clinical studies, biofilm in the wound can manifest as a thin layer of yellowish, gelatinous, and translucent material visible to the naked eye.⁷⁸ Additionally, it can be present both on the surface and in deep tissues, stimulating chronic inflammation and delaying the healing process.⁷⁷ Surgical debridement is the gold standard for removing biofilm, making the wound clean and conducive to repair by temporarily disrupting the mature biofilm.⁷⁷ In addition, there is treatment with nanotechnology where dressings containing silver or zinc ions compete with the extracellular polymeric matrix of biofilms for binding sites, reducing the intercellular adhesion of pathogenic bacteria.⁷⁷

In general, topical antibiotics alone are no longer recommended for wounds, as they may promote the development of bacterial resistance.¹ Antiseptics rarely induce antimicrobial resistance.¹ A wide range of antiseptics is available, like povidone iodine, cadexomer iodine, chlorhexidine, PHMB, silver (nanocrystalline or ionic), octenidine, reactive oxygen, and hypochlorous acid. However, according to a systematic review, the effects of topical antimicrobial treatments on PIs are not clear, and the quality of the evidence ranges from moderate to very low.⁷⁹

Signs of deep infection, such as increased erythema, foul odor, warmth, increased exudate, fever, new or increasing pain, and elevated white blood cell count, should be treated with systemic antibiotics, and wound care should be done using topical treatments similar to those used for local infections.⁷⁵ Other indicators, such as slow healing after two weeks of standard treatment, discoloration of granulation tissue to pale or dark tones instead of healthy red, and friable tissue, indicate possible infection in wounds.⁴⁰

In disseminated infection, such as cellulitis, microorganisms invade the surrounding tissue, spreading from a lesion, and the signs and symptoms extend beyond the wound edges. Disseminated infection can involve deep tissues, muscles, fascia, organs, or body cavities, with possible signs of increasing induration, lymphangitis, crepitus, wound dehiscence with or without satellite lesions, and widespread inflammation or erythema greater than 2 cm from the wound edge.⁷⁵ Systemic infection is the phase in which microorganisms spread throughout the body via the vascular or lymphatic systems, eliciting a host response. A local wound infection can also trigger the systemic inflammatory response through other pathways, such as toxin release or a dysregulated immune system. Symptoms may include malaise, lethargy or general nonspecific deterioration, fever/pyrexia, severe sepsis, septic shock, organ failure, and death.⁷⁵

Routine wound culture is not recommended when there is no suspicion of infection. However, when a clinical diagnosis of disseminated and systemic infection is made, an ulcer culture method is recommended to confirm the initial diagnosis, identify resident microorganism species, and determine effective antibiotics to treat the wound. Current

literature provides three laboratory techniques for diagnosing wound infections: deep tissue biopsy, needle aspiration, and swab culture. A blood culture should also be performed in the case of systemic infection.⁷⁵

Deep wounds or those with bone exposure are susceptible to osteomyelitis, which is better detected by magnetic resonance imaging or bone biopsy, and requires intravenous antibiotic therapy,¹ based on culture results.⁴⁰ However, clinical diagnoses related to PIs have been discussed. A systematic review found that no alternative diagnostic method (clinical, microbiological, or radiological) is reliable for diagnosing osteomyelitis associated with pelvic PIs.⁸⁰ Another systematic review⁸¹ describes osteomyelitis in the sacral region, which is the most affected area by PIs according to incidence studies.² In this review, bone biopsy remains the only accurate diagnostic method, but osteomyelitis is relatively rare in patients with stage 4 sacral PIs.⁸¹ Furthermore, it indicates that short-term antibiotics can treat acute soft tissue infections, with a duration of 2- to 6-weeks depending on the infection's depth; there is no evidence to support extending treatment beyond 6-weeks.⁸¹ More recently, a review explains that evidence remains inconclusive for microbiological and histological diagnoses, suggesting that bone biopsy remains limited for patient management.⁸² This highlights the importance of understanding patient frailty and the underlying evidence for bone biopsy in order to consider changes in clinical management and the risk-benefit ratio.

M (moisture): Assessment of the degree of exudation

One of the keys to wound care is maintaining the ideal moist environment, aiming to create a balanced setting that facilitates healing.⁸³ However, when a wound exhibits either excessive or insufficient exudate production, it can hinder the healing process and cause damage to the surrounding skin.¹

Considerations include the characteristics of the exudate regarding its quantity, color, odor, viscosity, potential constituents, and appearance.⁸⁴ Purulent, hemorrhagic-purulent, or seropurulent exudate may indicate infection. Additionally, color and odor can indicate microbial influence in the wound, including biofilm and infection.¹

Dressings are considered to have a unique potential for addressing issues related to exudate.⁸³ Selecting a dressing that manages the exudate from PIs and protects the peri-wound skin, as maceration and continuous contact with exudate hinder the healing process.⁴⁰ Viscous exudate requires different management than thin watery exudate, as products designed to handle thin exudate may become blocked by viscous exudate, reducing absorption and causing buildup in the dressing.¹ Low-viscosity exudate can be managed using a variety of absorbent dressings, including foams, calcium alginates, gelling fibers, superabsorbent dressings, multilayer dressings, polymer pads, and Negative Pressure Wound Therapy.¹

Low moisture levels can be treated with products that donate fluid to the wound, such as hydrogels and hydrocolloid dressings.¹

E (Edge): Assessment of the wound edge

Monitoring the epithelial margin guides the management approach to optimize the necessary conditions. The quality of the wound bed is crucial to facilitating epithelial advancement from the edges.¹

The edge needs to be assessed to see if it has hyperkeratotic tissue, epibole (rolled edge), or is not advancing, and the edges should be clean and level, as this facilitates epithelial migration.⁷⁰

R (Repair/Regeneration): Repair/Regeneration

The implementation of advanced therapies for repair should only occur once risk factors are addressed in difficult-to-heal wounds. Some experts limit the use of advanced therapies to wounds that have responded to standard treatment by less than 40%–50% in four weeks.¹

Different technologies can be selected based on their suitability for the wound and the patient's characteristics. These technologies include topical and systemic interventions (Fig. 2).¹ When epithelial advancement is slow, several alternatives can accelerate the process. In the field of regenerative medicine, based, for example, on tissue engineering, it could be an interesting option in patients with difficult-to-treat ulcers, such as patients with spinal cord injuries.⁸⁵ The findings from the systematic review suggest that cell-based therapies present a promising approach for improving PI outcomes, however, more extensive research is needed on this topic.⁸⁶

The latest technologies for regeneration include mesenchymal and epidermal stem cells, which can be applied to promote tissue regeneration; 3D bio-printing technologies to create biomimetic structures that facilitate healing; genetic therapy and gene editing to modify cellular behaviours; nanotechnology with nanomaterials used as drug carriers or to promote wound healing through controlled release of bioactive substances; and biomimetic scaffolds that develop acellular scaffolds mimicking the extracellular matrix to guide tissue regeneration.⁸⁷

Another therapy that has gained prominence is Platelet-Rich Plasma (PRP). However, it should be noted that it is still in the early stages of use, and possible variations need to be analyzed. A recent systematic review concluded that PRP stands out as a promising and safe therapeutic approach for injuries, but to improve the quality of the evidence, there is a need for new high-quality randomized clinical trials.⁸⁸

S (Social): Assessment of Social and patient-related factors

It encompasses overall health and well-being, including physical and psychological factors, and the impact on the patient's lifestyle.¹ Listening to and understanding the patient is key to treatment; involving them in their care and decision-making can improve outcomes and adherence.⁸⁹ The most negative impact on the quality of life of individuals with PIs occurs in the social dimension. PIs affect both patients and their caregivers by limiting their ability to carry out daily activities and making them more dependent on healthcare services and support environments.⁹⁰

The patient should be assessed holistically, including sleep, physical activity, and extrinsic factors such as family and health care facility support. Interdisciplinary actions are essential to alleviate potential problems and risks, particularly related to the proper management of odor and pain, which contribute to low self-esteem, depression, and social stigma.^{55,91}

Palliative wound care is a complex discipline that differs significantly from conventional wound treatment, with the primary goal being symptom relief and the provision of empathetic care by healthcare professionals.⁹² Factors that classify a wound as palliative include unmodifiable risk factors or medical conditions such as malnutrition with sarcopenia, inadequate perfusion, multisystem organ failure, immunocompromised states, anasarca, metastatic cancer, and a terminal prognosis that hinders normal healing processes.⁶⁹ A palliative approach can alleviate suffering, enhance quality of life, and reduce healthcare costs by avoiding futile and/or painful procedures and unnecessary expenses.⁶⁹

Education among the patient, family, and healthcare professionals is essential to promote understanding and define the desired care goals.⁹³

PW (Peri-wound): Assessment of the Peri-wound skin

Another current concept has defined the importance of the peri-wound area, even including it at the end of TIMERS as PW (peri-wound).⁵⁵ This area deserves attention, as it may have hyperkeratosis, erythema, maceration, eczema, xerosis, contact dermatitis (both allergic or irritant), or infection.^{67,94} Fig. 2 shows the main measures directed at each condition in this area.

Surgical approach

Surgical management is usually reserved for recalcitrant wounds or wounds with full-thickness skin loss and exposure of deeper structures such as muscle, fascia or bone (stage 3 and 4 – Table 2).^{55,95,96} Reconstructive surgery usually includes debridement of the wound, followed by filling the wound with new tissue. The surgical approach involves a multidisciplinary team, including the expertise of a plastic surgeon. A systematic review to assess the effects of different types of reconstructive surgery for treating PI, compared with no surgery or alternative reconstructive surgical approaches, included only one randomized clinical trial.⁹⁷ This trial included 20 participants with stage 4 ischial or sacral PI. The study compared two reconstructive techniques: conventional flap surgery and cone of pressure flap surgery, in which a large portion of the flap tip is de-epithelialized and deeply inset to obliterate dead space. The outcomes about complete wound healing, wound dehiscence, PI recurrence and wound infection were collected. The evidence for these outcomes as very low certainty. The authors concluded that there is very little randomized evidence on the role of reconstructive surgery in PI management, although it is considered a priority area. More rigorous and robust research is needed to explore this intervention.



Fig. 3 Marjolin's ulcer in a young paraplegic patient with a pressure injury in the ischial location for 15-years.

Indications for dressings and products for pressure injuries according to their classification

It is important to emphasize that the choice of any dressing or product should consider TIMERS, the location and size of the lesion, particularly in advanced therapies. Another consideration is the cost-effectiveness and making choices that are appropriate and consistent with the patient's social condition and treatment goals, with a focused approach whenever relevant to infection/biofilm, as many products are incompatible and should not be used on infected wounds.¹

Based on guidelines,^{7,55} the most used indications according to the classification of PIs were summarized in Table 2. An algorithm based on the Depth, Infection, and Perfusion (DIP) classification is also useful to clinicians in the initial evaluation, classification, and management of PI.^{95,96}

Prognosis and complications of pressure injuries

The occurrence of PIs is generally related to a prolonged period of hospitalization, and patients who develop them have a higher likelihood (22.5%) of not surviving.³⁹ Moreover, PIs are associated with various short- and long-term complications, including infection, malignant transformation (Marjolin's ulcer – Fig. 3), fistulas to nearby structures and organs, heterotopic ossification, systemic amyloidosis due to chronic inflammatory state (causing symptoms such as fatigue, weight loss, swelling, cardiac problems, renal dysfunction, neuropathy, and gastrointestinal issues), rhabdomyolysis due to prolonged pressure and ischemia, as well as recurrence of the PIs themselves⁹⁸ and even death.

The most common and severe complication of PIs is infection, which can include cellulitis, abscess, osteomyelitis, bursitis, septic arthritis, necrotizing fasciitis, sepsis, and even death. Often, it is caused by multiple microorganisms and exhibits resistance to various medications and antimicrobials, forming a biofilm, which hinders healing by preventing the migration of keratinocytes.⁷⁷

Table 2 Specifications and summary of some indications in managing Pressure Injuries (PIs) according to the classification by National Pressure Injury Advisory Panel⁷ and other guidelines and systematic review.^{55,95,96}

Summary – PIs classification	Exudate level	Treatment recommendations (remove and treat the cause)	Dressings, products and recommended measures
Stage 1 PI Non-blanchable erythema, intact skin	Absent	Avoid friction in the area when applying moisturizing creams and during bathing. Focus on pressure relief in the area and daily reassessment.	● Barrier film/cream when required; ● Five-layer foam dressings with or without silicone adhesive.
Stage 2 PI Superficial skin loss involving the epidermis/upper dermis.	Intact blister	Keep intact, protecting the area with an appropriate dressing. Depending on the blister's location, size, and characteristics, aspiration with an aseptic technique may be performed to prevent rupture and exposure to infection.	● Foam dressings with or without silicone adhesive; ● Collagen, or acrylic dressings
	Broken skin with minimal exudate	Promote treatment with a moist environment but with balance. Pay attention to signs of infection and the color of the exudate.	● Foam dressings with or without silicone adhesive ● Hydrocolloid, acrylic dressing, collagen/composite dressing
Stage 3 PI Full-thickness damage to the subcutaneous tissue, but not reaching the muscle fascia	Low/moderate exudate	Maintain moist treatment. Assess for necrotic tissue requiring debridement and stabilize viable tissues. Manage bacterial balance/biofilm.	● Hydrogel^a if autolytic debridement is required. ● Antimicrobial gels such as polyhexamethylene biguanide^a if local infection. ● Absorbent dressings for moderate exudation, such as foam dressings, gelling fibre^b
	High exudate	Increased exudate may be indicative of infection. Assess for necrotic tissue requiring debridement and stabilize viable tissues. Manage bacterial balance/biofilm. Protect edges with barrier cream products.	● Superabsorbent dressings, such as polymer foams, silver dressings (e.g., gelling fiber or foam dressings with silver^b) ● Alginate dressings^b ● Collagen dressings^b ● Negative pressure wound therapy.
Stage 4 PI Total loss of skin thickness affecting muscle and/or bone	Low/moderate exudate	Maintain granulation tissue. Assess for necrotic tissue requiring debridement. Manage bacterial balance/biofilm. Be attentive to osteomyelitis (exposed or palpable bone).	● Absorbent dressings for moderate exudation, such as foam dressings, gelling fibre^b ● Absorbent dressings for infection: foam dressings with silver^b, gelling fiber dressings with silver^b, PHMB gel^a, cadexomer iodine^a

Table 2 (Continued)

Summary – Pls classification	Exudate level	Treatment recommendations (remove and treat the cause)	Dressings, products and recommended measures
Non-classifiable PI Any wound completely covered by necrotic tissue with no visualization of the wound bed.	High exudate	Increased exudate may indicate of infection – be attentive to osteomyelitis (exposed or palpable bone). Assess for necrotic tissue requiring debridement and stabilize viable tissues. Manage bacterial balance/biofilm. Protect edges with barrier cream products	• High-absorption dressings, such as foams and silver ion dressings^b • Negative pressure wound therapy.
	Absent	Facilitate debridement (if the wound has the capacity to heal) or protect (keep the necrotic tissue dry if healing is not the goal of care of the wound is ischemic (DIP stages C). Instrumental debridement if there is adequate blood circulation and the patient is not anticoagulated. Combine debridement methods. Pay attention to patient pain.	• Below knee – aim to keep the wound dry until vascular assessment is determined. Apply povidone iodine 10%^a to the wound bed. Keep the wound dry until the vascular assessment is determined (exclude ischemic injury); after that, it is possible to perform surgical debridement • Above knee – consider an antimicrobial gel (polyhexamethylene biguanide)^a to aid in autolytic debridement • In case of mild bleeding, use calcium and sodium alginate dressing^a for hemostasis, or a hemostatic product. In case of severe bleeding seek help from a trained surgeon.
Deep Tissue PI Purplish, bruised, or blood-filled blister lesion in an area of bony prominence	Absent	Avoid friction in the area when applying moisturizers and during bathing. Focus on relieving pressure in the area and perform daily reassessment.	• Skin protectors • Barrier/film cream • Silicone foam dressings
	Superficial rupture with exudate (may occur days after the onset of the pressure injury)	Maintain moist treatment. Assess the necrotic tissue and proceed with caution when debriding. In cases of deep ischemia, avoid debridement in areas with compromised circulation; If necessary, do so gently and superficially, preserving viable tissue	Depending on the exudate: • Silicone foams for atraumatic coverage, or • Absorbent dressings for moderate exudation, such as gelling fiber and foam dressings.
	Blood blister	Inspect injury for improvement or deterioration and monitor capillary return; Aspiration with an aseptic technique may be performed to prevent rupture and exposure to infection	• Five-layer silicone foam dressing • Absorbent dressing if there is heavy exudate

Table 2 (Continued)

Summary – PIs classification	Exudate level	Treatment recommendations (remove and treat the cause)	Dressings, products and recommended measures
Medical Device-Related PI It has the shape of the device and follows the same classification as above, and the same treatment according to depth and location.	Exudate varies according to the stage of involvement and the phase of healing.	Control moisture. Focus on the ease of application and removal of the dressing. Allow assessment of skin condition. Evaluate for infection/biofilm.	• Treatment according to the location and stage of the pressure injury. • Combine wound coverage with protection of the medical device. • Include the use of cushions, coverings, or protective materials that not only prevent additional pressure in the area but also allow for easy and safe access to the device, minimizing the risk of contamination and infection
PI on mucous membranes Typically caused by medical devices on mucous membranes in areas such as the vaginal, rectal, urethral, and oral cavities.	Absent or exudative	Non-blanchable erythema is not visible on mucous membranes. Check for fluid accumulation. Reposition and adjust medical devices regularly to prevent prolonged pressure on a single point. Remove the device as soon as clinically possible. Assess for fungal/yeast infection.	Mucosa: • Carefully clean the lesion with water or saline and solutions appropriate for mucous membranes, avoiding irritants. • Apply solutions appropriate for the area. • Use topical/systemic antimicrobials as needed. Skin: • Superficial area on the nostril: keep the area protected and consider using gentle white paraffin. • If there is deeper tissue loss and exudate needs to be controlled, consider using a silicone foam dressing. • Necrotic tissue: keep intact and protect with a barrier dressing.

^a Interventions that require a secondary dressing, such as: rayon dressing with gauze pads and polyurethane films.

^b Interventions that require a secondary dressing, such as: adhesive foam dressing, gauze pads with polyurethane films.

Multidisciplinary team

Due to the broad impact, PIs require a multidisciplinary approach. As discussed, PIs are an adverse event that can occur due to various factors. Evidence-based knowledge of these risk factors is essential for all healthcare professionals, as optimal prevention and treatment can only be ensured through close and reliable collaboration.⁹⁹ Communication between the medical team and the nursing team is crucial to ensure awareness of conditions or symptoms relevant to the development of PIs, such as diabetes, hypoalbuminemia, anemia, and hypotension.⁹⁹ In addition to the medical and nursing teams, physical therapists are essential in treating PI by using techniques to improve mobility, reduce pressure on vulnerable areas with special beds and mobilization supports, and assist with self-care.⁷ Dietitians and other multidisciplinary team members are important for holistic care and attention to patients with PIs.⁷ The expertise of a plastic surgeon is needed for reconstructive surgical approaches such as local flaps for recalcitrant PI or those in stages 3 and 4. Dermatologists are essential to performing differential diagnoses and biopsies, recommending appropriate care for the surrounding skin, and indicating proper treatments and specialized dressings.¹⁰⁰

Final considerations

This review has expanded knowledge and evidence-based practices for adequately managing patients at risk and those with PIs, detailing current and innovative therapies and conventional ones.

Some key points of this review include: (1) The risk assessment for developing PIs should be structured, including a valid and reliable risk prediction scale, a thorough skin assessment, and a critical interpretation of the results; (2) The prevention bundles (risk assessment, moisture control, patient mobility, nutrition, and support surfaces) should be implemented together to impact patient outcomes better than individual interventions. (3) The first step in the care pathway for PIs is to relieve pressure in affected areas and prevent the development of injuries in new areas. (4) The acronym TIMERS is essential for facilitating efficient ulcer care, focusing on rigorous assessment of the wound bed, and implementing interventions to optimize the healing process. (5) PIs are associated with various short- and long-term complications, including infection, malignant transformation (Marjolin's ulcer), fistulas, rhabdomyolysis, as well as recurrence of the PIs themselves and even death.

Hopefully, it will serve as a decision-support tool for healthcare professionals and a practical guide for qualifications and studies in this critical and highly prevalent area.

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Does not apply.

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None declared.

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ORIGINAL ARTICLE

Clinicopathologic features and treatment outcomes of dermatofibrosarcoma protuberans: a 25-year retrospective study[☆]



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Abstract

Background: Dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous sarcoma characterized by slow growth, a high local recurrence rate, and low metastatic potential. **Objective:** To characterize the clinicopathological features and the treatment outcomes of patients diagnosed with DFSP.

Methods: Retrospective study of patients with a histopathological diagnosis of DFSP between 1997 and 2022.

Results: Data from 42 patients with DFSP were included. The majority were female (69%) with a mean age of 49.1 years. The trunk (52%) and extremities (40%) were the most common tumor sites. Classic histologic pattern was observed in 90% of cases, while rare variants, including fibrosarcomatous, pigmented, and myxoid subtypes, were also identified. Wide local excision was the primary treatment (95%), achieving clear margins in 71% of patients. Local recurrence occurred in 4.8% and adjuvant radiotherapy was employed in 19% of cases. Two patients developed pulmonary metastases with disease progression despite treatment with imatinib.

Study limitations: Retrospective study based on medical and pathological records.

Conclusions: Cutaneous DFSP in this series demonstrated clinicopathologic features consistent with those reported in the literature, including a predilection for the trunk and middle-aged females. Histologically, most cases exhibited the classic storiform pattern with strong CD34 positivity. Wide local excision was the primary treatment modality, with a relatively low recurrence rate compared to the literature, possibly influenced by the use of adjuvant radiotherapy in

[☆] Study conducted at the Unidade Local de Saúde Santa Maria, Lisbon, Portugal.

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select patients. Although uncommon, metastasis occurred in cases with recurrent disease and fibrosarcomatous transformation. Ongoing research into systemic therapies and molecularly targeted treatments is needed to improve outcomes in advanced DFSP.

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Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare tumor, occurring at a rate of 0.8 to 4.5 cases per million persons annually and, despite being the most common cutaneous sarcoma, it constitutes less than 0.1% of all malignancies and about 1.0% of all soft tissue sarcomas worldwide.^{1,2} It mainly affects young and middle-aged adults, with a peak of incidence between the second and fifth decades of age.³ Because DFSP is a slow-growing tumor, the diagnosis is often delayed for months to years.² Despite its slow growth and infrequent distant metastasis, it carries a high risk of local recurrence,^{4,5} emphasizing the importance of early diagnosis and appropriate treatment. This study aims to characterize the clinical and histopathological features of patients diagnosed with DFSP at a tertiary hospital over 25-years.

Methods

This was a single-institution, retrospective, observational study of patients diagnosed with dermatofibrosarcoma protuberans (DFSP) between January 1997 and December 2022. Eligible cases were identified through a search of the institutional electronic medical record system and pathology database. Patients were included if they had a biopsy-confirmed diagnosis of DFSP and received treatment at the academic tertiary care hospital during the study period. Cases lacking complete medical or pathological data were excluded. Clinical information was extracted from medical charts and included sex, age at diagnosis, tumor location, clinical presentation, history of previous malignancies, treatment modalities, surgical margin status, use of adjuvant therapy, and clinical outcomes, including recurrence and metastasis. Follow-up time was calculated from the date of diagnosis to the last recorded clinical visit or patient death. Histopathological data were reviewed from archived Hematoxylin and Eosin (H&E) – stained slides. Immunohistochemical staining for CD34 was reviewed when available. Descriptive statistics were used to summarize demographic, clinical, and pathological characteristics.

Results

A total of 42 patients with histologically confirmed dermatofibrosarcoma protuberans (DFSP) were included in this study (Table 1). The majority of patients were female (69%), and the mean age at diagnosis was 49.1-years (range: 22–78 years), with 55% of cases occurring in individuals under 50-years of age. Approximately 26% of patients had a prior history of other malignancies, most commonly breast cancer (10%) and melanoma (7%). The most frequent anatomical location of DFSP lesions was the trunk (52%), followed

Table 1 Patient demographics, clinical presentation, histopathological features, treatment, and outcomes.

Variable	No patients (%)
Age	
< 50 years	23 (55)
≥ 50 years	19 (45)
Mean (SD)	49.1 (±17.5)
Female sex	29 (69)
History of cancer	11 (26)
Location	
Trunk	22 (52)
Upper extremity	9 (21)
Lower extremity	8 (19)
Head and neck	3 (7)
Clinical feature	
Exophytic nodule	14 (33)
Plaque	8 (19)
Subcutaneous nodule	7 (17)
Not described	13 (31)
Clinical presentation	
Primary disease	40 (95)
Recurrent disease	2 (5)
Tumor size (cm)	
> 5	16 (38)
≤ 5	7 (17)
Not described	16 (38)
Lesion duration prior to diagnosis (years)	
> 5	8 (19)
≤ 5	7 (17)
Not described	27 (64)
Histopathological subtype	
Classic	37 (90)
Fibrosarcomatous	3 (7)
Pigmented (Bednar tumour)	1 (2)
Myxoid	1 (2)
COL1A1-PDGFB fusion protein	
Detected by FISH	2
Not performed	40
Treatment	
Wide local excision	40 (95)
Mohs micrographic surgery	2 (5)
Resection margins	
Free (R0)	31 (74)
Positive	11 (26)
Number of surgeries to achieve negative margins	
1	29 (69)
2	10 (24)
3	3 (7)
Adjuvant radiotherapy	8 (19)
Adjuvant systemic therapy	2 (5)
Distant metastasis	2 (5)
Death due to DFSP	2 (5)

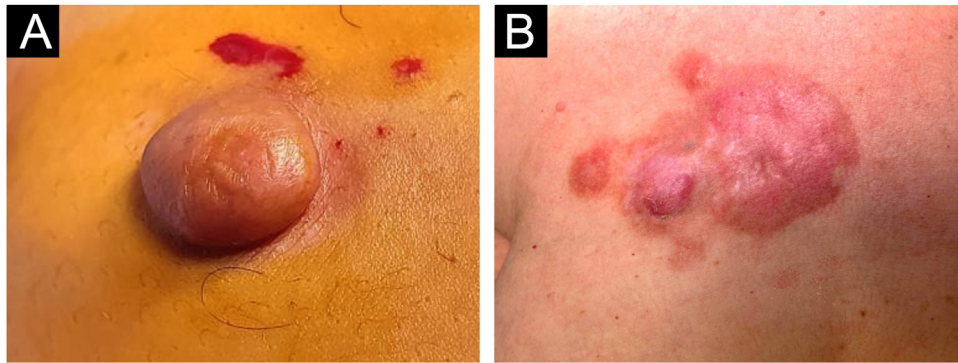


Fig. 1 Clinical presentation of dermatofibrosarcoma protuberans. (A) Solitary, firm, dome-shaped nodule with a smooth surface. (B) Irregular, violaceous plaque with multiple nodular components.

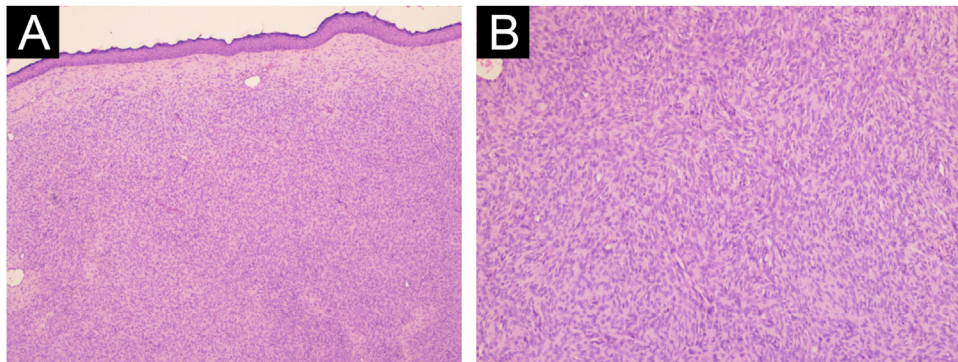


Fig. 2 Histologic features of classic-pattern dermatofibrosarcoma protuberans: uniform spindle cells arranged in a storiform pattern infiltrate the dermis and extend into the subcutaneous tissue (A – Hematoxylin & eosin, $\times 40$; B – Hematoxylin & eosin, $\times 100$).

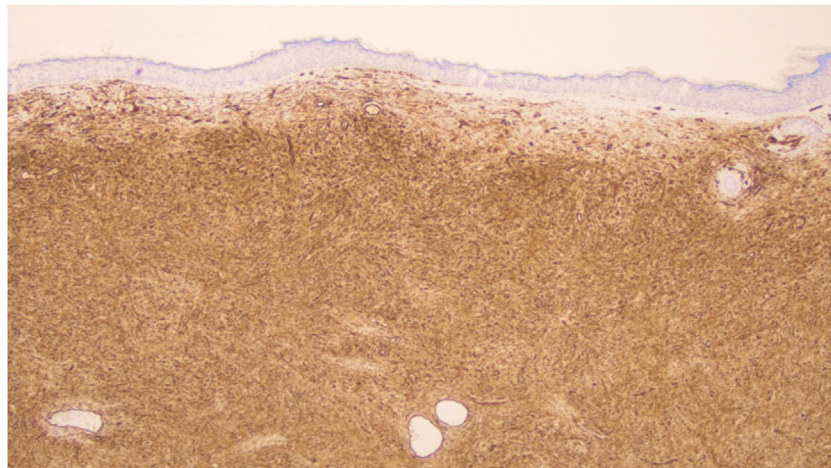


Fig. 3 Immunohistochemical staining for CD34 showing strong and diffuse positivity in tumor cells ($\times 40$).

by the upper and lower extremities (40%). The head and neck region accounted for a minority of cases (7%). Clinically, DFSP manifested most often as an exophytic nodule (33%) (Fig. 1A), but also as plaques (19%) (Fig. 1B) and subcutaneous nodules (17%). Most patients (95%) presented with primary DFSP, while only two cases involved recurrent disease at initial evaluation. The classical histopathologic pattern was observed in 90% of cases, characterized by a

storiform arrangement of uniform spindle cells infiltrating the dermis and subcutaneous tissue (Fig. 2). Immunohistochemical staining for CD34 showed strong and diffuse positivity in all cases (Fig. 3). Rare histologic variants were identified in 11% of cases, including fibrosarcomatous transformation (7%) (Fig. 4), pigmented (2%) (Fig. 5), and myxoid (2%) (Fig. 6) subtypes. Wide local excision (WLE) was the mainstay of treatment in 95% of cases, and clear resec-

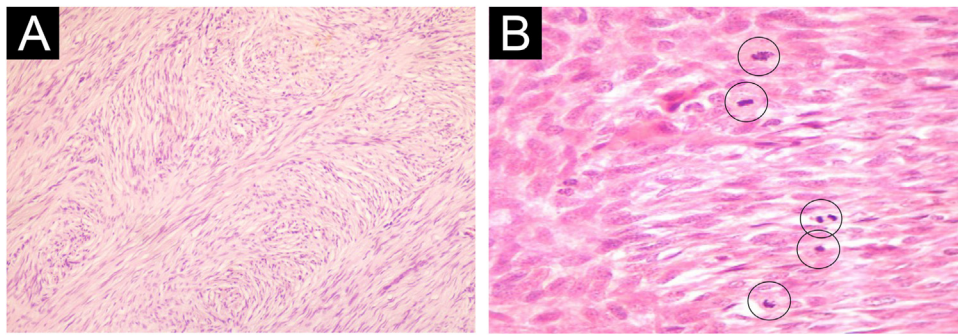


Fig. 4 Dermatofibrosarcoma protuberans with fibrosarcomatous transformation. (A) Spindle-shaped cells arranged in intersecting bundles with a herringbone pattern (Hematoxylin & eosin, $\times 100$). (B) Numerous mitoses are observed (highlighted with circles; Hematoxylin & eosin, $\times 400$).

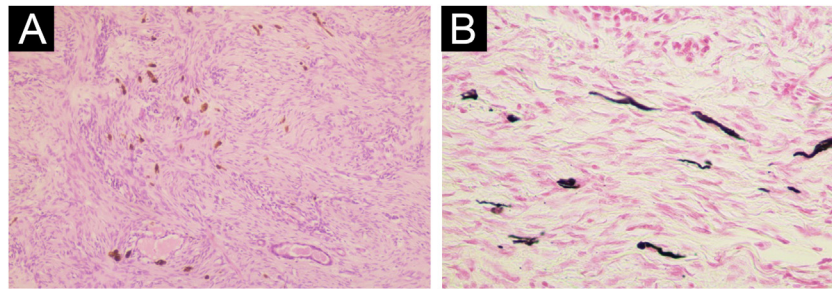


Fig. 5 Pigmented dermatofibrosarcoma protuberans (Bednar tumour). (A) Numerous pigmented dendritic cells interspersed among spindle cells, demonstrating heavy melanin deposition (Hematoxylin & eosin, $\times 100$). (B) The Fontana-Masson stain highlights the presence of melanin pigment within dendritic melanocytes interspersed among the spindle cell proliferation (Fontana-Masson, $\times 400$).

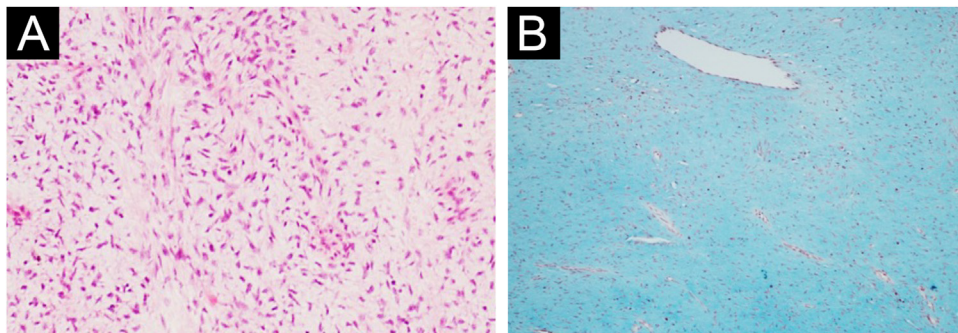


Fig. 6 Dermatofibrosarcoma protuberans with myxoid change. (A) Myxoid spindle cell neoplastic proliferation in the dermis (Hematoxylin & eosin, $\times 100$). (B) the prominent myxoid stroma, stains diffusely blue with Alcian blue (Alcian blue stain $\times 100$).

tion margins (R0) were achieved in 71% of patients. Among the three cases of fibrosarcomatous DFSP, the American Joint Committee on Cancer (AJCC) / Union for International Cancer Control (UICC) stages were IA (T1N0M0G1), II (T1N0M0G2), and IV (T1N0M1G3). Adjuvant radiotherapy was administered in 19% of cases, predominantly in those with close or positive surgical margins. During a mean follow-up period of 10.6-years (range: 1–22 years), four patients experienced recurrence: two presented with disease recurrence at diagnosis, and two developed local recurrence following surgical treatment. All recurrent cases occurred in male patients, three of whom were aged 50-years or older, two had a history of positive resection

margins, and the other two achieved complete resection with margins of 1 mm and 2 mm. One of these patients had fibrosarcomatous DFSP. Pulmonary metastases occurred in two patients – one with a history of multiple local recurrences and another with fibrosarcomatous transformation. Both were treated with imatinib mesylate, and one also received sunitinib malate. Both patients died from disease progression.

Discussion

Dermatofibrosarcoma protuberans (DFSP) is an uncommon, low-grade sarcoma of fibroblast origin.⁶ The predominance

of DFSP in females (69%) observed in this study aligns with some reports suggesting a slight female preponderance,⁷ although other studies report a more balanced gender distribution.⁵ The mean age of diagnosis at 49.1 years reflects the typical presentation in middle adulthood, although DFSP can occur at any age, including in pediatric populations.⁷

Patients with DFSP, especially females, had a 25% increased risk of developing a subsequent primary malignancy, with most of the increased risk owing to a greater than 21-fold increased risk of other non-epithelial skin cancer and a nearly 5-fold increased risk of soft tissue cancer.⁸ Approximately 26% of the studied patients had a history of other malignancies.

Clinically, DFSP presents as a slow-growing, firm, multilobular nodule or plaque that ranges in color from flesh-coloured to red and has irregular margins.⁹ Most DFSPs are localized on the trunk (40%–50%), followed by proximal extremities (30%–40%), and the head and neck (10%–15%).^{2,7} The clinical features of the studied patients were consistent with previous results, except for the location in the head and neck which was less frequent than in other series (7%).

Histologically, DFSP tumor cells present classically as uniform spindle cells arranged in a characteristic well-defined storiform pattern;⁶ they have minimal cytologic atypia, uniform nuclei, and absent-to-low mitotic activity.¹⁰ Strong CD34 positivity remains a hallmark diagnostic feature and serves to differentiate DFSP from benign entities such as dermatofibroma.² Rare histological variants were also observed in the present series. Fibrosarcomatous DFSP (FS-DFSP) is defined by the focal presence of areas with fascicles of spindle cells intersecting at acute angles in a typical "herringbone" pattern. In these areas, the mitotic activity is increased, and the cells show mild to moderate cellular and nuclear pleomorphism, and necrosis can be found.⁵ This subtype of DFSP is associated with a more aggressive clinical course, higher recurrence rates, and increased metastatic potential.^{6,11} Of the two cases with pulmonary metastasis, one exhibited the fibrosarcomatous variant.

More than 90% of DFSP cases are associated with a t(17;22)(q22;q13) translocation, resulting in the COL1A1-PDGFB fusion protein.⁷ Molecular testing, such as Reverse Transcription Polymerase Chain Reaction (RT-PCR) or Fluorescence In Situ Hybridization (FISH), is available to detect this translocation.² In the present study, FISH was performed on only two patients, as it was not available at the studied institution.

Complete resection is the primary treatment for DFSP. The modern options include wide local excision (WLE), Mohs micrographic surgery (MMS), and surgery followed by three-dimensional complete circumferential and peripheral deep margin assessment (or CCPDMA).¹⁰ Achieving clear margins is critical, as positive margins are a well-documented risk factor for local recurrence.⁹ Tumor cells tend to invade the subcutaneous tissue with irregular tentacle-like projections through septa and fat lobules. Therefore, local recurrences after excision with apparently wide margins are common.⁵ Some studies propose that MMS may result in lower local recurrence rates than WLE for DFSP. Notably, DFSP treated with WLE exhibits a recurrence rate that ranges from 10% to 60%,⁶ contrasting with the 1% recurrence rate observed with MMS treatment.^{12,13} However, MMS and its variants are

a time-consuming technique, and not widely diffused as a standard surgery procedure. For such reasons, several authors have proposed WLE (with at least 3 cm including the underlying fascia) as a valid therapeutic option to MMS.^{9,14} Most patients (95%) at the studied institution underwent WLE for treatment, as MMS is not available at the facility. The local recurrence rate after definitive therapy in the clinics was 4.8%, which is inferior to the literature data with WLE but higher than MMS. In the present series, this lower recurrence rate may be attributed to the approach of achieving wide surgical margins whenever feasible and the use of adjuvant radiotherapy for cases with narrow or positive margins.

Because DFSP is relatively sensitive to radiation, radiation therapy may be an important treatment option for inoperable tumors or when postoperative margins are positive, or for tumors with multiple recurrences.^{9,10} Radiotherapy has been suggested to reduce the risk of local recurrence after inadequate surgical resection in patients with narrow or positive surgical margins.¹⁵ Adjuvant radiotherapy was employed in 19% of the present cases, primarily for patients with positive resection margins. The authors hypothesize that this may have contributed to the lower recurrence rate after surgery observed in this series compared to the literature, regardless of WLE.

The clinicopathologic features reported in the literature as being associated with disease recurrence include a high-grade component (fibrosarcomatous change, increased cellularity, and high mitotic rate), close to a positive surgical margin, patient age > 50 years, a large tumor size (≥ 5 cm), male sex, and a location on the head, neck, or extremity rather than on the trunk.^{4,15,16} Since the authors recorded only four patients with recurrent disease, the capacity to characterize the impact of clinicopathologic features on recurrence after surgery is limited.

The variable time to recurrence (1–14 years) observed in this study underscores the importance of long-term follow-up for DFSP patients. European guidelines recommend follow-up examinations every 6-months for the first 5-years and at yearly intervals thereafter for up to 10-years. Surveillance strategies should include regular clinical examinations and MRI monitoring for patients with deeply invasive disease or a high risk of recurrence.^{6,17}

The overall risk for the development of metastatic disease is 5%, including 1% with regional lymph node metastasis and 4% with distant metastasis. The lung is the most common site of metastasis.² The two cases of pulmonary metastases highlight the clinical challenges of managing advanced DFSP. These cases suggest that recurrent disease and fibrosarcomatous transformation may increase the risk of metastasis. Tyrosine kinase inhibitors have shown promising response rates in patients with advanced or metastatic disease.² Both patients were treated with imatinib mesylate, a Tyrosine Kinase Inhibitor (TKI) targeting the PDGFB fusion protein.¹⁰ While imatinib has revolutionized the management of advanced and metastatic DFSP, resistance can develop, necessitating the exploration of alternative agents such as sunitinib or second-generation TKIs.¹⁸ Despite systemic therapy, both patients died due to disease progression, underscoring the need for continued research into novel therapeutic strategies, including immunotherapy and targeted molecular approaches.

This study has limitations, including its retrospective design and incomplete clinical data in some cases, especially those diagnosed further in the past. Additionally, the lack of MMS at the studied institution limited direct comparison with WLE outcomes.

Conclusion

Cutaneous DFSP in this series demonstrated clinicopathologic features consistent with those reported in the literature, including a predilection for the trunk and middle-aged females. Histologically, most cases exhibited the classic storiform pattern with strong CD34 positivity. Wide local excision was the primary treatment modality, with a relatively low recurrence rate compared to the literature, possibly influenced by the use of adjuvant radiotherapy in selected patients. Despite its generally favorable prognosis, the potential for late local recurrence and metastatic disease supports the need for vigilant, long-term follow-up. The adverse clinical course associated with advanced DFSP underscores the limited efficacy of current systemic therapies and highlights the critical role of early diagnosis, complete surgical excision, and adjuvant radiotherapy. Ongoing research into novel systemic and molecularly targeted treatments is essential to improve outcomes in late-stage DFSP.

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Mafalda Pinho: Data collection, analysis, and interpretation; manuscript writing; critical review of important intellectual content and the literature; and approval of the final version of the manuscript.

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Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Histological and immunohistochemical findings in recurrent nevi[☆]



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Abstract

Background: Recurrent nevi (RN) arise from the incomplete removal of a benign melanocytic lesion. They may present with clinical and dermoscopic characteristics similar to melanomas and are a potential mimic of neoplasia.

Objective: To describe histopathological and immunohistochemical findings of recurrent nevi, including BRAF immunoexpression.

Methods: A cross-sectional study was conducted on 58 recurrent nevi obtained from a previous prospective study. RN were submitted to histopathological and immunohistochemical analysis. The markers HMB-45, Tyrosinase, Ki-67, and BRAF V-600E were used.

Results: A trizonal pattern was observed in 84.5% of cases and is defined by the presence of junctional melanocytic proliferation, scar tissue, and residual dermal nests. Furthermore, architectural asymmetry (56.9%), lentiginous hyperplasia (75.9%), fibrosis (98.4%), lymphocytic infiltrate (96.5%), and melanophages (79.2%) were identified. Dropping off was observed in 1.7%, adnexal involvement in 22.3%, a pagetoid distribution in 30%, and cell atypia in 15%. HMB-45 and tyrosinase were expressed in a gradient and were identified in 98.3% and 91.4%, respectively. Ki-67 was positive in all cases, and the mean proliferative index was 2.83%. BRAF expression was positive in 72.4%.

Study limitations: Limited sample size, evaluation by a single dermatopathologist, targeted immunohistochemical profiling, and the lack of red counterstaining could be potential limitations of the study.

Conclusions: RN are characterized by architectural asymmetry and a trizonal pattern. Nuclear atypia and a pagetoid distribution may be observed. RN cells have a low proliferative index and are positive for HMB-45 and tyrosinase. BRAF expression occurs in most recurrences and is heterogeneous in RN melanocytes.

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Introduction

Recurrent nevi (RN) are pigmented lesions that arise after incomplete removal of a benign melanocytic lesion, usually an acquired melanocytic nevus.¹ They are more prevalent in females and young adults, with age being a predictor of recurrence.² The incidence of recurrence varies in the literature and is associated with the technique used to remove the primary lesion, with shaving being commonly associated with it.³

The genesis of recurrent nevi is not completely understood. Gougerot proposes the seeding of nevus cells during the surgical removal of the nevus.⁴ Schoenfeld and Pinkus suggest that, after partial excision of a nevus, nevus cells present at the dermal-epidermal junction and in the root sheath of the hair follicle would be transferred to the regenerative tissue and form a new junctional nevus.⁵ Cox and Walton propose that new junctional nevus cells are formed after stimuli induced by residual dermal nevus cells.⁶ Imagawa et al. describe junctional proliferative activity derived from hair follicles and eccrine sweat ducts.⁷

The recurrent nevus has clinical and dermoscopic similarities to melanoma.⁸ It presents as a pigmented lesion located over scar tissue, with irregular and asymmetrical contours and coloration that can range from light brown to black. The pigment respects the boundaries of the underlying scar, and the time to recurrence ranges from 6 to 12 months. In contrast, recurrent melanoma may extend beyond the scar boundaries, exhibit continuous growth, and the time to recurrence is generally longer than that of recurrent nevus.¹

The main dermoscopic features of recurrent nevus include heterogeneous pigmentation, globules, and segmental radial lines. Other possible findings include structureless areas, irregular striations, irregular pigmentary network, and starbursts.^{9–13}

In cases where examination of the primary lesion is not available and the diagnosis of melanoma cannot be ruled out, the lesion should be sent for histopathological analysis. Recurrent nevi may present with a trizonal pattern, consisting of junctional melanocytic proliferation over scar tissue and residual dermal nevus cells. Cytological atypia, pagetoid distribution, extension to the adnexa, and dermal inflammation are histological findings described in recurrent nevi and resemble those found in superficial spreading melanoma.^{4,14–17} This similarity led Kornberg and Ackerman, in 1975, to use the term “pseudomelanoma” for recurrent nevi.⁸ Immunohistochemical examination may be useful in helping to differentiate the two lesions.

Data on the immunohistochemistry of recurrent nevi are scarce and are assumed to be similar to common melanocytic nevi. The objective of this article is to describe the histopathological and immunohistochemical findings of recurrent nevi.

Methods

A cross-sectional study was conducted with 58 recurrent nevi obtained from a previous prospective study.² In this study, 224 common melanocytic nevi were removed using the shaving technique from 61 patients. All lesions were removed for aesthetic reasons or due to complaints of pruritus or dis-

comfort. The patients were followed for six months, and 58 nevi recurred. Recurrent lesions were excised and submitted to pathological and immunohistochemical examination. The project was approved by the institution's ethics committee, and all patients signed an informed consent form.

Anatomopathological and immunohistochemical examinations were evaluated by an experienced dermatopathologist. Histopathological analysis followed standard techniques and evaluated the following histological findings: architectural symmetry, trizonal pattern, residual nevus cells, lentiginous hyperplasia, pagetoid distribution, confluent melanocytic nests, dropping off, melanophages, fibrosis, inflammation, perineural and periadnexal involvement, mitosis, and nuclear atypia.

The immunohistochemical markers evaluated were: HMB-45, Tyrosinase, Ki-67, and BRAF V-600E. The automated Benchmark ULTRA[®] platform (Ventana Medical Systems, Tucson, Arizona) was used, and paraffin block samples were cut with a microtome set at 3 μ m. Each slide received a positive control, and deparaffinization was performed on the equipment using EZ PREP reagent. Antigen retrieval was performed using Ultra CC1, pH 9.0, at 95 °C for 64 minutes, followed by peroxidase blocking with the UltraView Universal DAB Inhibitor 3% H₂O₂ blocking reagent, present in the detection system. The following primary antibodies were used: anti-HMB-45, clone HMB45, dilution 1:100 (Cell Marque[®]), incubated for 32 minutes at 42 °C; anti-Ki67, clone 30-9 (Roche[®]), incubated for 16 minutes at 37 °C; and anti-Tyrosinase, clone T311 (Cell Marque[®]), incubated for 12 minutes at 37 °C. After primary antibody incubation, the reaction was detected with the Ultra View Universal DAB detection kit (multimers), using the Diaminobenzidine (DAB) chromogen present in the kit. The slides were counterstained with Mayer's hematoxylin, differentiated with Bluing reagent (Li₂CO₃ + Na₂CO₃), and examined after dehydration and mounting.

To process the slides for the BRAF antibody, antigen retrieval was performed at 100 °C, and the antibody used was anti-BRAF, clone VE1 (Roche[®]), incubated for 20 minutes at 36 °C. The antibody reaction was detected with the Optiview DAB detection system, using the DAB chromogen present in the kit, with the remaining steps being the same as described for the other markers.

Immunohistochemical expression was initially assessed by marker positivity, followed by marker expression assessment through nevus components.

A descriptive study was performed, with the data presented as frequency of occurrence.

Results

Clinical and epidemiological data on the primary lesions were presented in a previously published study.²

The histological findings are shown in Table 1.

The trizonal pattern was present in 84.5% of recurrent nevi (Fig. 1) and architectural asymmetry in 56.9%, characterized by asymmetry in the contours, size, and shape of nevus cell nests, distribution in the intraepithelial and dermal components, and inflammatory infiltrate.

Mild to moderate lentiginous hyperplasia was identified in 75.9%, fibrosis in 98.4%, and lymphocytic inflammatory

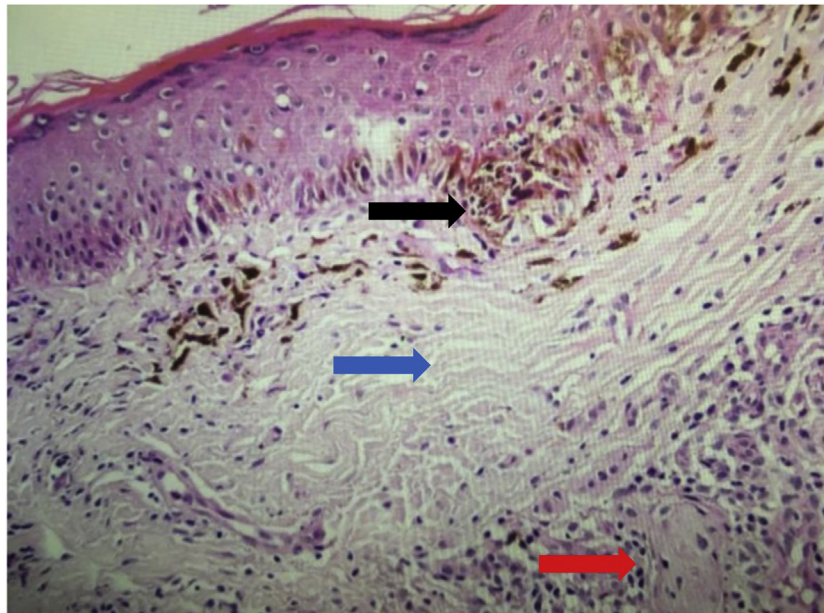


Fig. 1 Anatomopathological image of recurrent melanocytic nevus showing a trizonal pattern: lentiginous junctional component (black arrow), cicatricial dermal fibrosis (blue arrow), nests of nevus cells (red arrow; Hematoxylin & eosin, $\times 200$).

Table 1 Histological characteristics of recurrent nevi.

Histological findings	Number of lesions (%)
Trizonal pattern	49/58 (84.5%)
Architectural asymmetry	33/58 (56.9%)
Lentiginous hyperplasia	44/58 (75.9%)
Fibrosis	57/58 (98.3%)
Inflammatory infiltrate	56/58 (96.6%)
Dropping off	1/58 (1.7%)
Adnexal involvement	13/58 (22.3%)
Melanophages	46/58 (79.2%)
Pagetoid distribution	17/58 (29.3%)
Cell atypia	9/58 (15.5%)
Mitoses	0/58 (0%)

infiltrate in 96.5%, graded as mild and located in the superficial dermis in 65.5%. Adnexal involvement was identified in 22.3%, melanophages in 79.2%, and dropping off in 1.7%, defined as detachment of melanocytes from the epidermis into the scar tissue that separates the epidermal from the dermal component in the recurrent nevus.¹⁵

A pagetoid distribution was observed in 29.3% of the cases, which was classified as mild to moderate. Cell atypia was found in 15%, with no cases of marked atypia. No mitoses were observed in the sample.

Regarding the immunohistochemical markers, shown in [Table 2](#), HMB-45 was positive in 98.3% (57/58) and was expressed in a gradient, being strongly positive in the junctional component and with decreased staining in the deeper layers of the dermis ([Fig. 2](#)). Tyrosinase showed the same expression pattern as HMB-45 and was positive in 91.4% (53/58) of the cases. Ki-67 was positive in all recurrences and showed a staining index ranging from 1% to 8%, with a mean of 2.83% ([Fig. 3](#)). All lesions showed staining in the junctional component and only one lesion showed positiv-

Table 2 Immunohistochemical characteristics of recurrent nevi.

Immunohistochemical antibody	Number of lesions with positive expression
HMB-45	57/58 (98.3%)
Tyrosinase	53/58 (91.4%)
Ki-67	58/58 (100%)
BRAF V600E	42/58 (72.4%)

Table 3 BRAF expression in recurrent nevi.

Local of BRAF expression	n (%)
Junctional	7 (16.7%)
Compound	7 (16.7%)
Dermal	28 (66.7%)

ity in the dermal nests. BRAF positivity in nevi was 72.4% (42/58; [Table 3](#)). BRAF expression was observed in the junctional portion of seven lesions, in the dermal component of 28, and in both in seven lesions ([Fig. 4](#)).

Discussion

This study evaluated the histopathological and immunohistochemical characteristics of RN. The markers HMB-45 and tyrosinase were positive in most lesions and were expressed in a gradient. Recurrences showed a low proliferative index, as assessed by Ki-67, and immunohistochemical staining of the BRAF mutation occurred in 72.4%. Clinical and epidemiological data of recurrent nevi have been described in a previous study.²

Few studies have explored the histopathological findings of RN. In a sample of 175 recurrent nevi, Park et al. classified

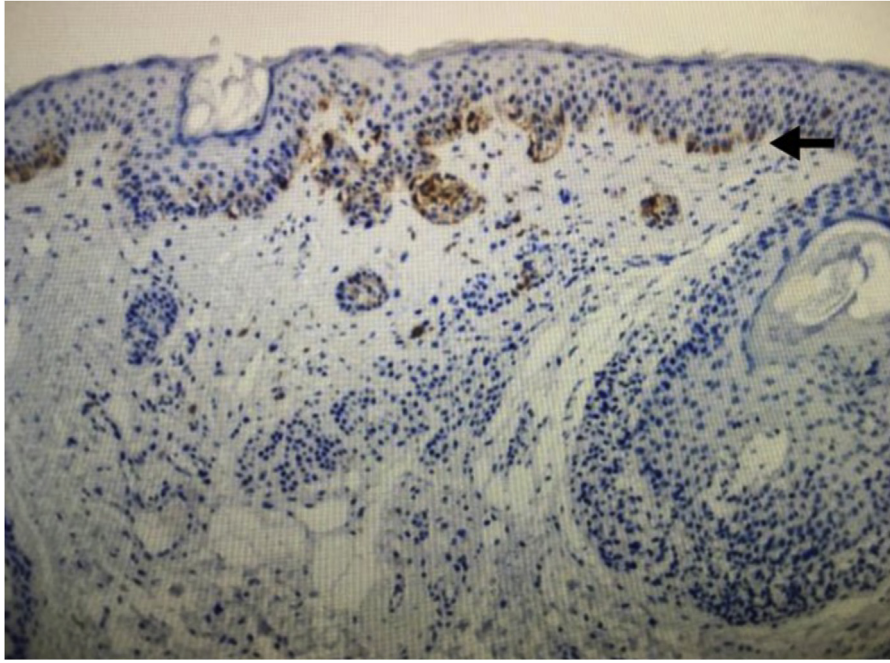


Fig. 2 Immunohistochemical analysis image of recurrent melanocytic nevus showing a gradient pattern: strongly positive expression in the junctional component (black arrow) and gradually decreasing expression in the deep components. (HMB-45 immunostaining $\times 100$).

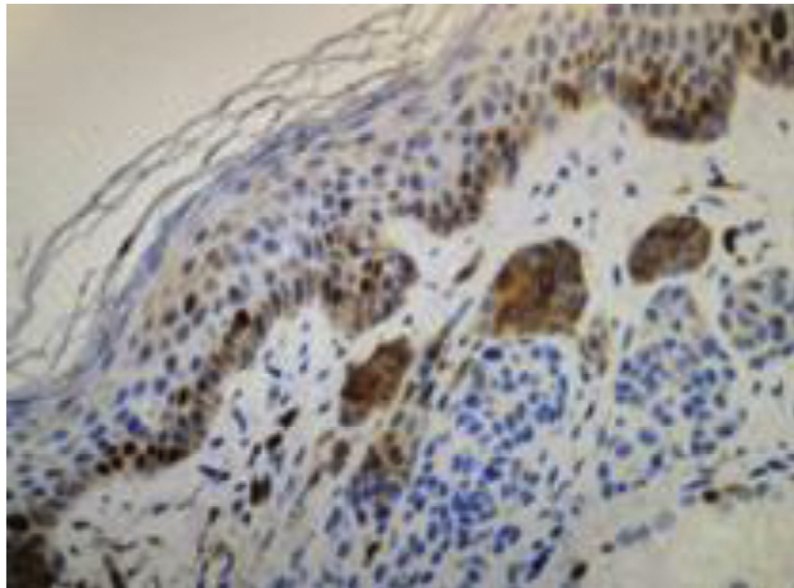


Fig. 3 Image of immunohistochemical analysis of recurrent melanocytic nevus showing staining for the Ki-67 antibody. (Ki-67 immunostaining $\times 200$).

them into four histological types: lentiginous, junctional, compound, and intradermal. Compound nevi show a trizonal appearance, consisting of junctional melanocytic proliferation, scar tissue, and residual dermal nests, and constituted 52% of their sample.¹⁵ The present study identified a trizonal pattern in 84.5%. Interestingly, in the present study, the majority of primary nevi (84.7%) were histologically classified as intradermal nevi and only 15.3% as compound nevi.² Park reports exaggerated junctional activity in their sample

and suggests that melanocytes located at the dermal-epidermal interface could give rise to recurrences, whether located in the eccrine glands, hair follicles, or adjacent skin.¹⁵ In the present sample (unpublished data), the margins were compromised in all primary lesions submitted to the shaving technique. These findings may suggest that perilesional melanocytes could repopulate the epidermis and that junctional activity in the recurrent nevus may be responsible for its formation. Botella-Estrada et al.¹⁸ eval-

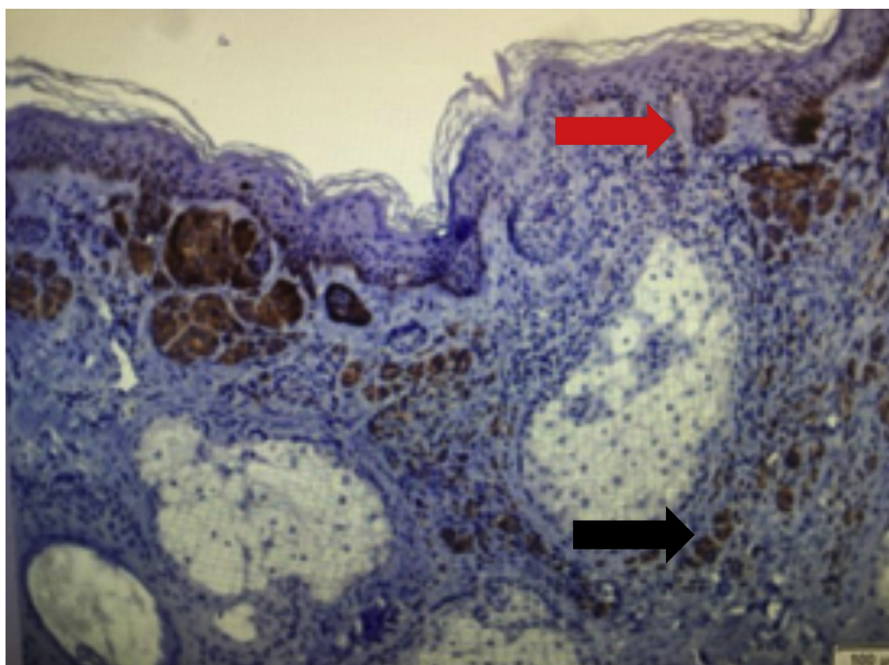


Fig. 4 Image of immunohistochemical analysis of recurrent melanocytic nevus showing the expression of the BRAF mutation in the junctional (red arrow) and dermal (black arrow) components (BRAF immunostaining $\times 100$).

uated pigmented lesions in scar tissue after excision of melanoma and non-melanocytic tumors. The authors found melanocytic hyperplasia in both scenarios and suggest that scar tissue acts by inducing melanocytes from the overlying epidermis. Although the authors state that this scenario is distinct from recurrent nevi, given the partial removal of the primary lesion in the latter case, one cannot exclude the effect of scar tissue on epidermal melanocytes. Further studies are needed to clarify the pathophysiology of recurrent nevi.

Regarding architectural symmetry, the present study observed asymmetry in 56.9%. In turn, Hoang et al. identified asymmetry in 46.6% of recurrent nevi. Adnexal involvement was identified in 22.3% of recurrent nevi. King et al. reported melanocyte extension into adnexal areas in 6% of cases, similar to Hoang's study. This difference can be explained by the location of the precursor nevi. The back was the most frequent anatomical site in the study by King (57%) and Hoang (33.3%).^{14,17} In the present study, the face was the site of highest frequency of recurrences (45.8%), followed by the back (22%).²

Park identified a marked pagetoid distribution in 3%, mild atypia in 30%, and moderate atypia in 12%.¹⁵ King et al. reported a pagetoid distribution in 6% and cell atypia in 26%, defined as the presence of hyperchromasia and enlarged nuclei. The authors observed that most recurrent nevi are easily recognizable histologically. However, RN that show flattening of the dermal-epidermal junction combined with a pagetoid distribution and adnexal involvement may be histologically indistinguishable from melanomas in late regression.¹⁴

Few studies have evaluated the immunohistochemical characteristics of recurrent nevi. Hoang et al. evaluated the expression profile of S-100, MART-1, HMB-45, tyrosinase,

and Ki-67 in 15 recurrent nevi. The authors found that HMB-45 and tyrosinase were positive in 90% of recurrent nevi, and the staining followed a gradient pattern, similar to that of acquired melanocytic nevi and in agreement with the present study.¹⁷

HMB-45 is a monoclonal antibody targeting the glycoprotein gp100, a component of the premelanosome, and it marks both activated and immature melanocytes. In benign lesions, the immunohistochemical staining pattern is similar to that of melanocyte maturation, i.e., a more strongly positive junctional component and progressively less staining as the lesion deepens into the dermis. Tyrosinase, in turn, is a cytoplasmic enzyme involved in melanin synthesis and is also expressed in a gradient in benign melanocytic lesions. The use of these markers can be a useful tool in differentiating recurrent nevi from melanoma, which shows diffuse staining.^{19,20}

When evaluating Ki-67 in recurrent nevi, it was observed that all were positive for this marker, with a mean proliferative index of 2.83%. All lesions showed positivity in their junctional component, except for one that showed positivity in dermal nests. The study by Hoang also identified low proliferative indices in recurrent nevi, both in the intraepidermal and dermal components.¹⁷ The present finding is consistent with the data on Ki-67 in melanocytic nevi.²¹ In benign melanocytic lesions, the proliferation index is generally below 5%, and staining predominates in the dermal-epidermal junction or superficial dermis. In melanoma, up to 50% of cells are stained, with diffuse and heterogeneous staining.²¹⁻²³

The use of immunohistochemical markers such as HMB-45 or tyrosinase, combined with Ki-67, can help differentiate recurrent nevi from melanoma. Uguen et al. used a panel of markers consisting of Ki-67, p16, and HMB-45 to differ-

entiate melanocytic nevi from melanoma. Ki-67 alone was the most effective marker for diagnosing melanoma, but it fails in cases of poorly proliferative melanomas.²⁴ Further studies evaluating the immunohistochemical characteristics of recurrent nevi are needed to define which markers are most effective in differentiating these lesions from melanoma.

The BRAF oncogene mutation was initially described in melanoma, and subsequent studies identified the mutation in melanocytic nevi. The high prevalence of the mutation in acquired melanocytic nevi suggests that the BRAF mutation is an initial event in melanocyte proliferation and nevus formation.²⁵ In melanoma, the BRAF mutation is associated with young age and intermittent sun exposure. In acquired melanocytic nevi, this mutation is associated with a globular dermoscopic pattern and growing nevi.²⁶ These findings may suggest that the BRAF mutation may be involved in melanocyte proliferation and the onset of recurrences. To the best of the authors' knowledge, this study is the first to describe the immunohistochemical expression of the BRAF mutation in recurrent nevi.

Investigating BRAF expression in recurrent nevi may help understand the phenomenon of recurrence, which has not yet been fully elucidated. In the present study, the mutation was expressed in 72.4% of recurrences, which is similar to the rates found in acquired melanocytic nevi in general.²⁷ It was also observed that in most recurrences (66.7%), BRAF immunoexpression was expressed only in the dermal component. This finding may suggest that recurrences may also originate from the proliferation of residual dermal melanocytes. In acquired melanocytic nevi, mutation expression occurs homogeneously throughout the nevus components.^{26,28} Furthermore, most recurrent nevi show heterogeneous BRAF immunoexpression, with isolated staining in the dermal or junctional component. These findings, combined with the observation of increased junctional activity in the recurrent nevus, may suggest that recurrences are polyclonal in origin and arise from cells that may or may not harbor the mutation.

The authors believe this study shows consistent data regarding the histopathological and immunohistochemical findings of recurrent nevi. However, it may have potential limitations, including: a small sample of recurrent nevi, analysis by only one dermatopathologist, use of a limited immunohistochemical panel to characterize recurrent nevi, and the lack of magenta counterstaining for BRAF expression analysis.

Conclusion

Recurrent nevi are primarily characterized by architectural asymmetry and a trizonal pattern. Atypical findings such as nuclear atypia and pagetoid distribution may be present in recurrent nevi, which may mimic melanoma both clinically and histologically. Immunohistochemistry can be of great assistance in their differentiation. In recurrent nevi, BRAF expression is present in most lesions and seems to occur heterogeneously among melanocytes. Further studies are needed to clarify the recurrence process and investigate its association with BRAF mutations.

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Renato Marchiori Bakos: Design and planning of the study; effective participation in research orientation; approval of the final version of the manuscript.

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Availability of research data

The entire dataset supporting the results of this study was published in the article itself.

Declaration of competing interest

None declared.

Editor

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ORIGINAL ARTICLE

Knowledge and attitudes towards psoriasis patients among adults: a cross-sectional study from Türkiye[☆]



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KEYWORDS

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Public awareness;
Stigmatization

Abstract

Background: Misconceptions about psoriasis can negatively influence attitudes toward people diagnosed with the condition as in other developing countries. Health literacy is known to be low, which may further exacerbate negative attitudes toward psoriasis patients.

Objectives: The study aimed to evaluate the attitudes and knowledge levels and associated factors regarding psoriasis among adults in a community-based sample.

Methods: This cross-sectional study was conducted among 715 individuals (aged ≥ 18 years) who presented to a university hospital.

Results: Approximately 60% of the participants in the study did not have sufficient knowledge about psoriasis, and approximately half of them had a negative attitude according to the attitude scale. A moderate negative correlation was found between the psoriasis knowledge score and the psoriasis attitude scale score. According to the multivariate linear regression model, predictors of a positive attitude toward psoriasis were identified as having an income-generating job (Beta; 95% CI: -1.812; -3.052 to -0.572), having heard of psoriasis in medical terminology (-3.946; -5.374 to -2.518), being aware of psoriasis (-3.961; -5.518 to -2.404), having a family member or close individual with a psoriasis diagnosis (-3.961; -4.637 to -1.694), and having an adequate knowledge level regarding psoriasis (-2.880; -4.072 to -1.687) ($F = 22.921$, $p \leq 0.001$, $R^2 = 0.206$).

Study limitations: Due to its cross-sectional design, causality could not be established. Additionally, the study was single-centered and based on self-reported data.

Conclusions: The most significant predictor of attitudes toward people with psoriasis was identified as knowledge adequacy.

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Introduction

Psoriasis is a chronic, immune-mediated inflammatory disease characterized by recurring flare-ups over a prolonged period.¹ Its prevalence varies globally, affecting 125 million people worldwide.^{2–4} Psoriasis patients often face a significant psychological burden that can surpass the physical symptoms.^{5,6} It is well-documented that there is an increased incidence of psychiatric disorders such as depression, suicidal ideation, anxiety, sexual dysfunctions, and alcohol dependency in affected individuals.^{7–10} Moreover, psoriasis patients often receive less social support and may experience greater stigmatization compared to individuals with other dermatological conditions, especially when lesions are located in visible areas such as the face, scalp, and hands.^{11–14} Social experiences, including exclusion, feelings of worthlessness, rejection, and difficulties in daily life, further exacerbate the impact of psoriasis on patients.

Given the high burden of psoriasis and its negative impact on quality of life, the World Health Organization (WHO) has classified it as a noncommunicable disease of particular importance. In line with WHO recommendations, psoriasis should be regarded with the same level of priority as cancer, cardiovascular diseases, diabetes mellitus, and chronic lung diseases in terms of health services. WHO also advocates for efforts to reduce the stigmatization associated with psoriasis and to raise awareness about the disease.¹⁵ Additionally, ensuring better access to guideline-based health services for individuals diagnosed with psoriasis is one of the requirements of the United Nations' 2015–2030 Sustainable Development Goals.¹⁶

Misconceptions about psoriasis can negatively influence attitudes towards individuals diagnosed with psoriasis.^{17,18} Studies conducted in different countries have revealed that a lack of knowledge about psoriasis leads to negative attitudes towards affected individuals.^{17,19–21} Health literacy in Türkiye, similar to other underdeveloped countries, is known to be low, and this may further exacerbate negative attitudes toward psoriasis patients.²² Moreover, identifying the factors that shape attitudes toward psoriasis is crucial, yet there are limited studies on this topic in these countries. This study aims to evaluate the attitudes, knowledge levels, and associated factors regarding psoriasis among adults in a community-based sample.

Methods

Study design and sample

This cross-sectional study was conducted on people aged 18 and over who applied to a university hospital (Eskişehir Osmangazi University Health, Practice and Research Hospital, Eskişehir, Turkey). The local ethics committee approved the study protocol (decision no: 2024/168). This study complies with the Declaration of Helsinki. The sample size of the study was calculated as a minimum of 683 people using the Epi Info program, taking the frequency of having knowledge about psoriasis as 20%, the margin of error as 3% and the confidence interval as 95%. All patients who applied to the hospital as outpatients during working days were included in the study group. 761 people who agreed to participate in

the study were reached. To avoid any discriminatory behavior during the study, a questionnaire was administered to 761 people, including 46 patients diagnosed with psoriasis. However, during data analysis, psoriasis patients were excluded, leaving a total of 715 individuals in the final study group.

Data collection

The questionnaire consisted of three sections. The first part included 17 closed-ended questions, covering the participants' sociodemographic characteristics (10 questions) and independent variables related to psoriasis (7 questions). The presence of physician-diagnosed chronic diseases was inquired about. Participants with diseases other than psoriasis were considered to have a chronic disease. The second part comprised 14 items with three response options ("Yes", "No", "I don't know") to assess participants' knowledge about psoriasis. The third part contained a tool designed to evaluate attitudes toward psoriasis. A 5-point Likert-type scale with 12 items was used to measure these attitudes. The validity of the tool was tested prior to data analysis, and a pilot study was conducted to ensure the clarity and acceptability of all items. Participants completed the questionnaire in approximately 10–15 minutes.

Data description

A higher total score on the knowledge questions indicated a greater level of knowledge about psoriasis. The Cronbach's alpha coefficient for the knowledge questions was calculated at 0.585. Participants who scored above 80% of the maximum possible score (33.6 points or higher out of a total score of 42) were considered to have an adequate knowledge level regarding psoriasis.²³ For the instrument measuring attitudes toward psoriasis, five items were reverse-coded. As the total score increased, it indicated a more negative attitude toward psoriasis. The possible total score on the scale ranged from 12 to 60.

Statistical analysis

Statistical analysis performed using SPSS Statistics v15 (SPSS Inc., Chicago, IL, USA) software program. The Cronbach's alpha coefficient, item-total correlation coefficient, and Exploratory Factor Analysis (EFA) were calculated to evaluate the validity of the attitude measurement tool (12 items) towards psoriasis. Cronbach's alpha coefficient of the items was found to be 0.875. Item-total correlation values were between 0.439 and 0.652. When the correlation matrix between the items was examined, it was seen that the correlation coefficient between any two items was not greater than 0.800, so it was accepted that there was no multicollinearity.

The Kaiser-Mayer-Olkin (KMO) test was calculated to evaluate the adequacy of the sample size for Factor Analysis: 0.867, Barlett test: 3607.5751; $p < 0.001$ was found, so the number of data collected was accepted as sufficient. The item analysis in the EFA of the measurement tool was performed using principal components analysis. The factor loading limit value was accepted as 0.40 (min-max:

0.609–0.873). It was found that the model explained 42.4% of the cumulative variance in one dimension. The significant difference between the item scores of the lower and upper 27% groups to evaluate the item discrimination of the scale showed that the discrimination feature of the measurement tool was sufficient ($p < 0.001$). The measurement tool was accepted as sufficiently valid as a result of the analyses, and the data were analyzed.

The conformity of measurable data to normal distribution was assessed using basic distribution criteria, graphs, and the Kolmogorov-Smirnov test. Since the measurement scores did not show normal distribution, Mann Whitney-U and Kruskal-Wallis tests were used in univariate analyses. Spearman correlation analysis was performed to determine the correlation between the scores of the measurement tools used in the study. Multivariate linear regression analysis was applied to determine the predictors associated with the psoriasis attitude scale score. The logarithm of the score was taken to make the psoriasis attitude scale score, which was previously the dependent variable, suitable for normal distribution. A multivariate model was created with variables showing a significance level of $p < 0.10$ in univariate analysis; $p \leq 0.05$ was accepted as the statistical significance value.

Results

Characteristics of the study group

Among the 715 participants in the study group, 398 (55.7%) were female and 317 (44.3%) were male. The mean age of the participants was 37.3 ± 13.5 years (range = 18–78). Seventy-seven percent of the participants had spent most of their lives in urban areas. Sixty-one percent of the participants were university graduates or had a higher level of education, and 53.8% of them were married.

Psoriasis knowledge questionnaire

Five hundred sixty-three (78.7%) of the participants stated that they had heard of psoriasis before, while 124 (17.3%) reported familiarity with the medical term ‘psoriasis’. The mean score on the knowledge questionnaire was 32.4 ± 3.7 (median = 33), with scores ranging from 20 to 41.

Only 284 participants (39.7%) in the study group had an adequate level of knowledge about psoriasis. According to the questionnaire, the most frequently correctly answered items were: ‘Psoriasis is an itchy disease’ (68.0%) and ‘Psoriasis is a disease that makes life difficult’ (67.3%). The least correctly answered items in the questionnaire were ‘Psoriasis is a disease that only affects the skin’ (22.9%) and ‘The symptoms of psoriasis may be decreased/regressed with sun exposure’ (26.0%). The distribution of responses to the psoriasis knowledge questionnaire in the study group is given in Fig. 1.

Psoriasis attitude scale

The mean score of the Psoriasis Attitude Scale was 30.2 ± 8.4 (median = 30), with scores ranging from 12 to 56. The

items with the highest positive attitudes towards psoriasis were ‘I can be a friend with someone who has psoriasis’ (75.7%) and ‘I would be uncomfortable working in the same workplace with someone who has psoriasis’ (69.1%). The items with the lowest agreement were ‘I can have a sexual relationship with someone who has psoriasis’ (36.2%) and ‘I would swim in the same swimming pool with someone who has psoriasis even if I knew they had rashes’ (32.9%). The distribution of responses to the Psoriasis Attitude Scale of the participants is given in Table 1.

The median scores of the Psoriasis Attitude Scale were higher among participants who lived in districts or villages, had lower levels of education, were not employed in income-generating jobs, had an income below the minimum wage, had not heard of psoriasis in either the local language or medical terminology, did not have family members or close relatives with psoriasis, and lacked adequate knowledge about psoriasis. In other words, these participants exhibited more negative attitudes. The distribution of the median scores on the Psoriasis Attitude Scale according to sociodemographic and psoriasis-related characteristics is given in Table 2.

A moderate negative correlation was found between the Psoriasis Knowledge Questionnaire scores and the Psoriasis Attitude Scale scores. The scatter diagram showing the correlation between the psoriasis attitude scale score and the psoriasis knowledge questionnaire in the study group is given in Fig. 2.

According to the multivariate linear regression model, factors that predicted a more positive attitude toward psoriasis included working in an income-generating job, having heard of psoriasis in both local and medical terminology, having a family member or close relative diagnosed with psoriasis, and having adequate knowledge about psoriasis. The multivariate model displaying the variables that may affect participants’ attitudes toward psoriasis is provided in Table 3.

Discussion

The present study demonstrated a moderate level of positive societal attitudes towards psoriasis, which were influenced by the participants’ knowledge levels. Attitude is defined as a fictional structure representing the degree of liking or disliking of an individual towards a certain attitude object. People’s attitude towards a certain attitude object (psoriasis patient) is the positive or negative views that develop towards that object as a result of the integration of thought, emotion and behavioral tendency. It is known that attitudes can be cognitive or affective.²⁴ The individual’s positive and negative information helps to make decisions about a subject. A positive societal attitude towards psoriasis patients is important as it can reduce the stigmatization of these individuals and lessen the psychological burden of the disease.

It is expected that an adequate level of knowledge about psoriasis in society will reduce misinformation and beliefs about the disease. In this study, the frequency of hearing about psoriasis before in the Turkish language was found to be 78.7% while the frequency of hearing about psoriasis as a term in medical terminology was found to be 17.3%. In the study conducted by Sommer et al., it was reported that 80%

Distribution of responses to psoriasis knowledge questionnaire

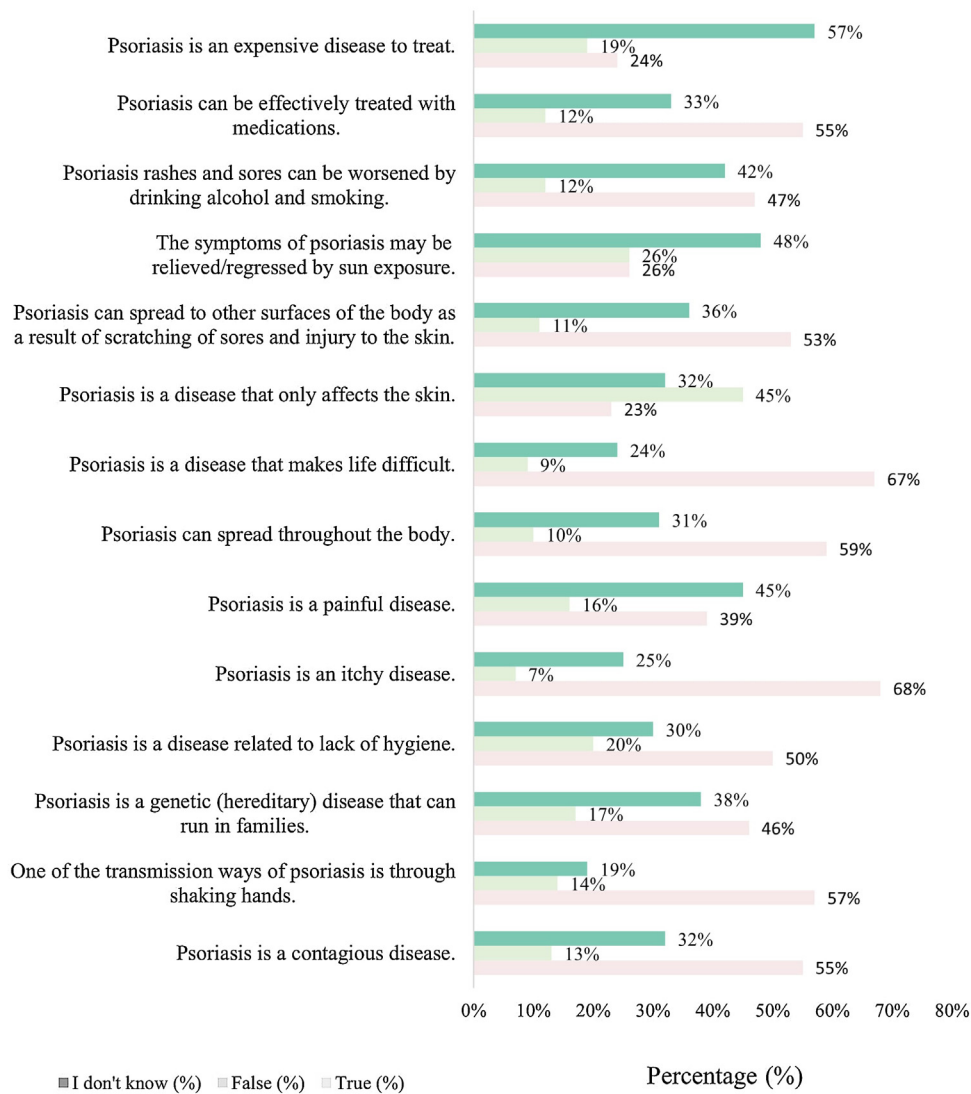


Figure 1 Distribution of responses to the psoriasis knowledge questionnaire in the study group.

of the participants had heard about psoriasis in the German language, while 20% of the participants had heard about the term "psoriasis".²⁰ In the study of Assiri et al., 79% of the study participants had heard about psoriasis in the Arabic language.²⁵ It is expected that diseases are known in the local language rather than by their medical terminology. This situation is important in terms of showing that efforts to increase psoriasis literacy in society should be based more on the use of the local language.

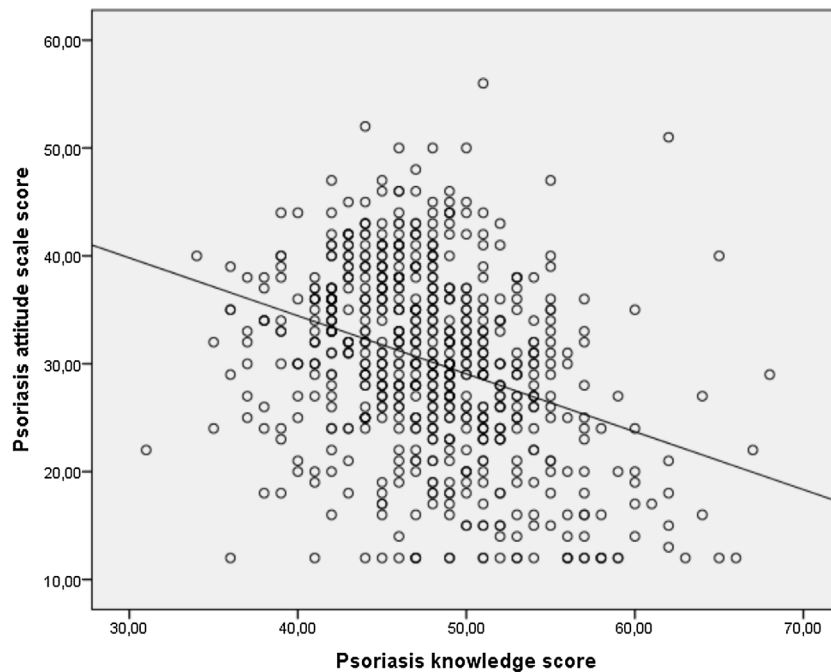
In the present study, approximately 60% of participants did not have an adequate level of knowledge about psoriasis. Misconceptions such as psoriasis being a contagious disease (45.8%), caused by a lack of hygiene (49.4%), or transmitted by shaking hands (43.4%) may contribute significantly to the stigmatization of patients. Similarly, a study by Halioua et al. in France reported that 62.4% of the general population lacked knowledge about psoriasis.²⁶ In a study by Alzolibani in Saudi Arabia, 45.6% of respondents were

unaware of whether psoriasis was contagious or not.¹⁷ These findings highlight that inadequate knowledge about psoriasis is a widespread issue across different societies.

Positive attitudes towards psoriasis can help reduce the severity of the disease by reducing psychological stress and improving treatment outcomes.^{27,28} First of all, the reliability and validity of the Psoriasis Attitude Scale were tested in this study. Based on these results, the Psoriasis Attitude Scale promised a reliable and valid measurement tool for the Turkish population.²⁹ It is noteworthy that 49.4% of the participants scored above the average on the Psoriasis Attitude Scale. Additionally, it was determined that they showed a moderately positive attitude towards psoriasis. In Malaysia, Yong et al. reported at least one misconception towards psoriasis in 64.6% of participants.³⁰ Similarly, in a study assessing the perception and stigmatization of people with psoriasis in Germany, it was reported that 59% of the general population had a negative attitude towards people

Table 1 The distribution of the participants' answers to the items related to the psoriasis attitude scale.

Attitude Items	Answers n (%)		
	Agree	Indecisive	Disagree
I would be uncomfortable sitting next to someone who has psoriasis. ^a	96 (13.4)	139 (19.4)	480 (67.2)
I shake hands with someone who has psoriasis.	390 (54.5)	190 (26.6)	135 (18.9)
I would eat with someone who has psoriasis in their home or in a different place.	404 (56.5)	171 (23.9)	140 (19.6)
If I had to marry someone with psoriasis, that would be fine with me.	258 (36.1)	263 (36.8)	194 (27.1)
I can have a sexual relationship with someone who has psoriasis.	219 (30.7)	237 (33.1)	259 (36.2)
I can be friends with someone who has psoriasis.	541 (75.7)	104 (14.5)	70 (9.8)
I would swim in the same swimming pool with someone who has psoriasis even if I knew they had rashes.	213 (29.8)	267 (37.3)	235 (32.9)
As an employer, encountering someone with psoriasis in the workplace would not be a negative factor in my hiring him/her.	456 (63.8)	167 (23.4)	92 (12.8)
I would not want someone with psoriasis to treat me if they have rashes or sores, even if they are a healthcare professional. ^a	145 (20.2)	187 (26.2)	383 (53.6)
I would be uncomfortable working in the same workplace with someone who has psoriasis. ^a	76 (10.6)	145 (20.3)	494 (69.1)
I would not allow my child to be in the same room with someone who has psoriasis. ^a	145 (20.3)	161 (22.5)	409 (57.2)
I would not allow my child to marry someone who has psoriasis. ^a	150 (21.0)	243 (34.0)	322 (45.0)

^a Negative items.**Figure 2** Scatter diagram showing the correlation between the psoriasis attitude scale score and the psoriasis knowledge score in the study group.

diagnosed with psoriasis.²⁰ The varied results in these studies may be explained by using different measurement tools in different cultural societies.^{20,30}

In the present study, when examining predictors of attitudes toward psoriasis, educational level and employment in an income-generating job were considered indicators of social status. The authors found that the attitude towards psoriasis was more negative in those participants with lower

educational levels. Low educational status may indirectly lead to an inadequate knowledge level and awareness about psoriasis. However, in a study by Almutairi et al., no significant difference was found between educational status and attitudes toward psoriasis.³¹ Other studies have also reported that people's attitudes towards psoriasis are not affected by higher educational levels.^{17,32} Additionally, in this study, a more positive attitude towards psoriasis was

Table 2 Comparison of scores obtained from psoriasis attitude scale statements in the study group according to sociodemographic and psoriasis related characteristics.

Sociodemographic Characteristics	Psoriasis Attitude Scale Items ScoreMedian (Min–Max)	Statistical Analysis p
Age group		
18–24 age	19 (12–34)	0.207
25–34 age	19 (12–34)	
35–44 age	18 (12–32)	
45 age and older	21 (12–35)	
Gender		
Male	20 (12–35)	0.968
Female	19 (12–34)	
Residence		
City center ^a	19 (12–35)	0.023
District ^a	21 (12–34)	
Village	21 (12–33)	
Education		
University ^a	18 (12–34)	<0.001
High school	21 (12–34)	
Primary school	20 (12–34)	
Marital status		
Married	20 (12–35)	0.532
Not married	19 (12–34)	
Income-generating employment status		
Currently working	18 (12–35)	<0.001
Not working ^a	21 (12–34)	
Family income status		
Minimum wage and below ^a	22 (12–35)	<0.001
More than minimum wage	19 (12–34)	
Presence of chronic disease ^b		
Present	20 (12–34)	0.908
Absent	19 (12–35)	
Hearing about “<i>sedef</i>” ^c		
Present	18 (12–35)	<0.001
Absent ^a	24 (12–32)	
Hearing about psoriasis in medical terminology		
Present	17 (12–34)	<0.001
Absent ^a	21 (12–35)	
Having psoriasis in the family/close relatives		
Present	17 (12–34)	<0.001
Absent ^a	21 (12–35)	
Knowledge level about psoriasis		
Adequate	17 (12–33)	<0.001
Not adequate ^a	21 (12–35)	
Total	19 (12–35)	

^a The category that makes the difference.^b Chronic diseases other than psoriasis.^c This word corresponds to psoriasis in the Turkish language.

found in those who worked in a job that generated income. In contrast, Assiri et al. reported that no significant difference was found between working in a job that generated income and attitudes towards psoriasis.²⁵ There are also other studies in the literature that reported no difference between working in a job that generated income and attitudes towards psoriasis.^{31,33} In fact, it can be expected that individuals' attitudes towards differences will be more positive as their interaction with their environment increases in their working lives. The different results presented in the

studies may be due to the differences in the educational systems and working environments in the countries and the differences in the measurement tools used.

The present study revealed that those who have a family member diagnosed with psoriasis showed a more positive attitude towards psoriasis. It is predicted that those who are exposed to such health conditions could empathize and also have a more positive attitude towards the situation. Numerous studies have shown that individuals with acquaintances who have skin diseases tend to have a more positive outlook

Table 3 Multivariate model showing variables affecting participants' attitudes towards psoriasis.

Variables	The Score of Psoriasis Attitude Scale Items			
	Unstandardized β	Standardized β	(95%CI)	p
Age group	-0.407	-0.304	-1.005-0.190	0.181
Living in rural area	0.301	0.519	-0.717-1.319	0.562
Lower educational status	0.953	0.086	-0.017-1.923	0.054
Working in a job that generates income	-1.812	-0.106	-3.052 - -0.572	0.004
Having heard of psoriasis in medical terminology	-3.946	-0.191	-5.374 - -2.518	<0.001
Having heard of "sedef"	-3.961	-0.178	- 5.518 - -2.404	<0.001
Having a family member/close relative diagnosed with psoriasis	-3.961	-0.147	- 4.637 - -1.694	<0.001
Having adequate knowledge about psoriasis	-2.880	-0.167	-4.072 - -1.687	<0.001
R ²		0.206		
F		22.921		<0.001

CI, Confidence Interval.

** This word corresponds to psoriasis in the Turkish language.

and a higher level of knowledge about the condition.^{20,33-35} It has also been reported that those who have a history of personal contact with a psoriatic patient have a more positive attitude towards the disease.¹⁷

Study limitations

The present study has several limitations. Due to its cross-sectional nature, a cause-and-effect relationship cannot be demonstrated. Besides, this study was conducted in a single center and relied on self-reported data from participants.

Conclusion

Approximately 40% of these participants had an adequate knowledge level about psoriasis, and about half showed a positive attitude according to the Psoriasis Attitude Scale. To assess the attitudes toward psoriasis, the authors tested the reliability and validity of the Psoriasis Attitude Scale. It can be used in future studies and may help establish standardization in measuring attitudes across different research. The present study revealed that the most significant predictor of attitudes toward psoriasis was the adequacy of knowledge. This finding suggests that educational interventions and efforts to raise public awareness about psoriasis, particularly by addressing common misconceptions, could play a crucial role in reducing stigmatization.

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Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None.

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ORIGINAL ARTICLE

Patient satisfaction as a quality indicator in dermatological care: cross-sectional study in two tertiary institutions with residency programs[☆]



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Abstract

Background: Patient satisfaction is a key indicator of healthcare quality and plays a crucial role in strengthening the physician-patient relationship. In dermatology, it contributes to greater treatment adherence and improved clinical outcomes, particularly in chronic skin conditions. However, limited studies have comprehensively evaluated the factors influencing satisfaction in outpatient dermatological settings, especially in academic institutions.

Objective: To identify factors associated with patient satisfaction during in-person dermatology visits at two tertiary care hospitals with postgraduate training programs and measure global satisfaction.

Methods: A cross-sectional analytical study was conducted using a structured survey assessing six domains of care: physician interaction, verbal and non-verbal communication, consult timing, privacy, teaching activity, and infrastructure. A multivariate logistic regression model was used to determine variables associated with overall satisfaction, adjusting for potential confounders.

Results: Most patients reported high satisfaction ([90.5%]), particularly with physician interaction. Key predictors of dissatisfaction included: inadequate bedside manner (AOR = 0.01 [95% CI 0.00–0.04], $p < 0.001$), discomfort during physical examination (aOR = 0.17 [95% CI 0.05–0.60], $p = 0.006$), presence of students during medical interview (aOR = 0.13 [95% CI 0.04–0.42], $p < 0.001$), and not use of white lab coat (aOR = 0.06 [95% CI 0.02–0.25], $p < 0.001$).

Study limitations: The cross-sectional design prevents causal inference, and subjective responses may be influenced by social desirability bias. Context-specific findings may limit generalizability.

[☆] Study conducted at the Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogotá, Colombia.

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Conclusions: Physician bedside manners, communication, and teaching dynamics significantly affect patient satisfaction. Targeted interventions in medical training and institutional policies may improve patient-centered care outcomes. Associations observed were statistically robust, minimizing the risk of spurious conclusions.

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Introduction

The World Health Organization (WHO) defines “quality” as the set of properties and characteristics that a system possesses to meet the needs of a population. Quality enables healthcare to achieve international health objectives.¹ The Panamerican Health Organization states that health services must meet optimal standards of safety, effectiveness, timeliness, efficiency, and equitable access to provide high-quality care, with individuals, families, and communities at the center of this approach.²

Considering the patient as the ultimate purpose of health service delivery, it is imperative to analyze their perception of the quality of care received. For this reason, various studies have been conducted aiming to quantify user satisfaction through different surveys and assessment tools.³ This allows stakeholders within the health system to identify areas for improvement in order to increase user satisfaction levels, understanding satisfaction as an indirect measure of quality that influences clinical outcomes.⁴ In order to provide high-quality healthcare, the measurement of patient satisfaction must be carried out across all levels of care and medical specialties, including dermatology.⁵ Dermatology is a specialty with a high demand for private healthcare services; therefore, it is important to assess and analyze patient satisfaction. Dermatology is a clinical specialty with a significant care component in terms of providing both outpatient and inpatient services. Therefore, conducting studies that quantify patient satisfaction will allow for a better understanding of patient needs, identification of key factors when evaluating healthcare, and incorporation of this assessment into institutional processes.⁶ Patient satisfaction is also a factor that impacts clinical outcomes; in patients with chronic diseases who require prolonged treatments, it has been shown that higher satisfaction is associated with greater adherence to the prescribed treatments and recommendations.⁴

Objective

General objective

To measure the overall satisfaction of patients attending the dermatology service (in-person) at two healthcare institutions with postgraduate dermatology training in Bogotá during the period from November 1, 2024, to April 16, 2025.

Specific objectives

1) To describe the sociodemographic characteristics of patients attended in the outpatient dermatology service

(in-person) at two healthcare institutions in terms of age, gender, education level, residence, socioeconomic status, health insurance affiliation, type of consult, and recruitment site. 2) To describe the characteristics of the outpatient dermatology service points of care (in-person) at two healthcare institutions in terms of availability of restrooms and examination gowns in the doctor’s office, personnel present during care, and specialists’ attire. 3) To quantify the prevalence of overall satisfaction and the different domains of satisfaction among patients attended in the outpatient dermatology service (in-person) at two healthcare institutions in terms of interaction with the physician, verbal language, non-verbal language, waiting times, privacy, teaching activities, and infrastructure. 4) To identify the aspects with the highest and lowest satisfaction levels within the evaluated domains among patients attended in the outpatient dermatology service (in-person) at two healthcare institutions. 5) To compare sociodemographic characteristics, consult aspects, and evaluate domains according to patient satisfaction among those attended in the outpatient dermatology service (in-person) at two healthcare institutions. 6) To determine the association between sociodemographic characteristics, consultation aspects, and evaluated domains with the overall satisfaction level of patients attended in the outpatient dermatology service (in-person) at two healthcare institutions. 7) To propose strategies to improve patient satisfaction levels in the outpatient dermatology service (in-person) at two healthcare institutions.

Methods

This is a cross-sectional observational study. The participating Institutions were private (Hospital Universitario San Ignacio) and public (Hospital Universitario La Samaritana) from Bogotá D.C, Colombia; the data collection period was from November 1, 2024, to April 16, 2025. All Patients who attended the outpatient dermatology service (in-person) were aimed to participate in the present investigation. The inclusion criteria were patients of any gender, aged over 18-years, and patients who had provided informed consent to participate in the questionnaire. The exclusion criteria were patients with cognitive disabilities, patients with visual impairments, patients with incomplete records (more than 20% missing data, i.e., 8 variables) or lacking information on the studied outcomes, patients with altered states of consciousness, and patients who completed the satisfaction survey but did not respond regarding consent to participate in the study. Given the descriptive nature of the study and the absence of a research hypothesis, no sample size calculation is required. Sampling will be convenience-based,

inviting all eligible patients who meet the criteria to participate immediately after their in-person dermatology visit.

A survey was designed and implemented through a server running the Research Electronic Data Capture (REDCap) web application in the period between May 2024 and April 2025 to collect and store data virtually. At the end of the dermatology consult, the attending physician will invite the patient to participate in the study. Upon affirmative response, the physician will send the patient a link (or QR code) via email directing them to the questionnaire created in REDCap. Upon accessing the link, the first document the patient is requested to complete is the informed consent form; once consent is provided, the quality survey begins.

Analysis plan

For descriptive analysis of qualitative variables, absolute frequencies and percentages will be used. For quantitative variables, measures of central tendency will be applied according to normality tests for each variable unless the sample size exceeds 30, in which case a normal distribution will be assumed, and the mean and standard deviation will be reported.

For bivariate analysis, two cohorts will be formed based on overall patient satisfaction: Satisfied (Overall satisfaction = Very satisfied or satisfied) and Not satisfied (Overall satisfaction = Neutral, Dissatisfied, Very dissatisfied). To analyze differences between groups for qualitative variables (gender, education, residence, socioeconomic status, health insurance affiliation, consult type, recruitment site, service point characteristics, and satisfaction domains), Chi-Square or Fisher's exact test will be applied, depending on sample size adequacy. For quantitative variables (age, number of persons in the doctor's office), Student's *t*-test or Mann-Whitney *U* test will be used based on normality tests, unless normality is assumed due to sample size, in which case only Student's *t*-test will be used.

To identify factors associated with overall satisfaction, a multivariate logistic regression model will be built, with the number of predictors depending on the number of events in each satisfaction category. For this analysis, satisfaction-related variables will be dichotomized as "Satisfied" (including Very satisfied or Satisfied responses) and "Not Satisfied" (Neutral, Dissatisfied, Very dissatisfied). Initially, univariate logistic regression will estimate crude Odds Ratios (ORs) for each variable. Variables meeting significance criteria will be selected as candidates for the multivariate model, which will be adjusted by backward selection.

A *p*-value less than 0.05 will be considered statistically significant. Analyses will be performed using R software (version 4.5.0) and RStudio.

Ethical considerations

According to Resolution 8430 of 1993, this research is considered minimal risk as it involves only the completion of a survey.⁷ The ethical principles of respect, beneficence, justice, and protection of human dignity will be observed.

Risks and benefits

To maintain participant confidentiality and ensure proper data handling, the following measures will be taken: data will be collected and stored on the REDCap platform, which offers a high level of security and is specifically designed for managing sensitive data in clinical and biomedical research. REDCap anonymizes the database by assigning a numeric code to each patient to protect confidentiality during statistical analysis. It also keeps a reversible coding record linking the survey responses to the informed consent to allow data validation if needed. Dissemination of study results will use anonymized data to protect patient confidentiality. This study was conducted after obtaining approval from the Institutional Ethics Committees of Hospital Universitario San Ignacio and Hospital Universitario La Samaritana. STROBE statement adherence points have been respected in the study design.

Results

Data were collected from a total of 437 patients who attended in-person dermatology visits at the two participating institutions. The data are summarized in Table 1.

The average age was 45.02 years (SD = 18.52), and 34.3% (150) were male. The most frequent educational level was secondary education (137 [31.4%]), followed by higher education (127 [29.1%]) and technical studies (62 [14.2%]). Approximately 40% (176) of the patients had postgraduate studies, and only a small percentage of patients didn't receive any kind of education (6 [1.4%]). Most patients lived in urban areas (369 [84.4%]) in socioeconomic level 1, 2 and 3 (349 [79.9%]).

In terms of overall satisfaction, 90.5% (395) of patients were satisfied with the care received (Very satisfied = 297 [68%], Satisfied = 99 [22.7%]). A small proportion of patients were neutral or dissatisfied with the care: 10 [2.3%] and 2 [0.5%], respectively. Only 6.6% (29) reported a high level of dissatisfaction.

The evaluated domains included physician interaction, verbal and nonverbal communication, consultant times, privacy, teaching activity, and infrastructure.

Patients were highly satisfied with the following aspects:

Domain 1: Medical history-taking (313 [71.6%]) – closely followed by physician behavior and physical examination;

Domain 2: Communication with the billing department (296 [67.7%]);

Domain 3: Physician wearing a white lab coat (272 [62.2%]);

Domain 4: Duration of the consult (246 [56.3%]);

Domain 5: Privacy during the consult (252 [57.7%]);

Domain 6: Presence of students during the consult (216 [49.4%]);

Domain 7: Comfort in the waiting room (223 [51%]).

Across the entire study, the item with the highest level of satisfaction was medical history-taking (313 [71.6%]), whereas the lowest was the taking of clinical photographs (190 [43.5%]).

Table 1 Sociodemographic and clinical characteristics of the study population.

Characteristic	Overall, n (%)	Hospital Universitario de la Samaritana, n (%)	Hospital Universitario San Ignacio, n (%)	p-value
Total (n)	437	345	92	
Age (years), mean (SD)	45.02 (18.52)	45.35 (18.63)	43.78 (18.19)	0.472
Male gender	150 (34.3)	119 (34.5)	31 (33.7)	0.984
Educational level				0.303
None	6 (1.4)	5 (1.4)	1 (1.1)	
Elementary School	56 (12.8)	49 (14.2)	7 (7.6)	
High School	137 (31.4)	112 (32.5)	25 (27.2)	
Technical	62 (14.2)	49 (14.2)	13 (14.1)	
Higher Education	127 (29.1)	93 (27.0)	34 (37.0)	
Postgraduate studies	49 (11.2)	37 (10.7)	12 (13.0)	
Urban residence	369 (84.4)	284 (82.3)	85 (92.4)	0.027
Socioeconomic stratum				
Stratum 1	66 (15.1)	65 (18.8)	1 (1.1)	
Stratum 2	104 (23.8)	90 (26.1)	14 (15.2)	
Stratum 3	179 (41.0)	150 (43.5)	29 (31.5)	
Stratum 4	72 (16.5)	36 (10.4)	36 (39.1)	
Stratum 5	16 (3.7)	4 (1.2)	12 (13.0)	
Health insurance scheme				0.011
Contributory	257 (58.8)	197 (57.1)	60 (65.2)	
Subsidized	81 (18.5)	73 (21.2)	8 (8.7)	
Private	63 (14.4)	44 (12.8)	19 (20.7)	
Special regimen	36 (8.2)	31 (9.0)	5 (5.4)	
Type of consult				0.149
First-time	249 (57.0)	203 (58.8)	46 (50.0)	
Follow-up	168 (38.4)	129 (37.4)	39 (42.4)	
Procedure	20 (4.6)	13 (3.8)	7 (7.6)	

Table 2 Highest- and lowest-rated aspects across domains.

Groups	Aspects with Highest Satisfaction (Very Satisfied)	Aspects with Lowest High Satisfaction	Aspects with Highest Dissatisfaction
Satisfied (n = 396)	Physician behavior (75.5%)	Interruptions during the consultation (50.8%)	Presence of students during consult (2.3%)
	Medical history-taking (75.3%)	Doctor's office temperature (47.5%)	Interruptions during the consultation (1.3%)
	Physical examination (72.7%)	Clinical photographs (46.2%)	Presence of students during history-taking (1.3%)
Not satisfied (n = 41)	Introduction with name and title (41.5%)	Clinical photographs (17.1%)	Physician Behavior (48.8%)
	Treatment explanation (41.5%)	Comfort of the waiting room (17.1%)	Physical examination (43.9%)
	Medical history-taking (41.5%)	Presence of students during history-taking (14.6%)	Medical history-taking (41.5%)
	Explanation of the disease (39%)		

Factors associated with patient satisfaction

Patients were divided in two groups according to satisfaction: Satisfaction group = 396 (Very satisfied and Satisfied) vs. No satisfaction group = 41 (Neutral, Unsatisfied, Highly unsatisfied). There were no differences in sociodemographic characteristics between groups, but there were statistically significant differences ($p < 0.001$) across all the domains. In the satisfied group, the aspects with the highest proportion

of high satisfaction were physician behavior (336 [75.5%]), medical history-taking (333 [75.3%]), and physical examination (323 [72.7%]). Among unsatisfied patients, the highest satisfaction was related to the physician's self-introduction with name and title (17 [41.5%]), while the highest levels of dissatisfaction were related to bedside manner, physical examination, and medical interview. Approximately one-third of patients in this group reported high dissatisfaction with the physician's tone of voice (2 [4.1%]), not use of a

Table 3 Factors most strongly associated with patient satisfaction.

Variable	Crude OR	[95% CI]	p-value	Adjusted OR	[95% CI]	p-value
Intercept				39.82	21.92–82.22	<0.001 ^a
Unsatisfactory bedside manner	0.01	0.00–0.03	<0.001 ^a	0.01	0.00–0.04	<0.001 ^a
Discomfort during physical examination	0.25	0.12–0.52	<0.001 ^a	25.76	4.46–190.04	0.001 ^a
Presence of students during the interview	0.11	0.05–0.21	<0.001 ^a	0.13	0.04–0.42	<0.001 ^a
Specialist not wearing a white lab coat	0.05	0.02–0.11	<0.001 ^a	0.06	0.02–0.25	<0.001 ^a

Model fit: AIC = 152.8, R^2 = 0.52, AUC = 0.897, Maximum VIF = 2.46.

^a Significant p-value < 0.05.

white lab coat (14 [34.1%]), body language (13 [31.7%]), and the appointment scheduling process (13 [31.7%]). Less than half of the group (190 [43.5%]) were highly satisfied with the clinical photographs, waiting room comfort, and the presence of students during medical interview (Table 2).

In the univariate logistic regression analysis, all variables were associated with overall satisfaction ($p < 0.05$). The final model (adjusted using backward selection) retained the variables with the strongest associations and clinical relevance.

After adjusting for the variables with the highest statistical significance, unsatisfactory bedside manner and the presence of students during medical interview decreased the likelihood of overall satisfaction (aOR = 0.01 [95% CI 0.00–0.04], $p < 0.001$; aOR = 0.13 [95% CI 0.04–0.42], $p < 0.001$, respectively). Likewise, specialists not using a white lab coat reduced the probability of satisfaction (aOR = 0.06 [95% CI 0.02–0.25], $p < 0.001$).

In conclusion, the probability of overall satisfaction was 39.82% when there was appropriate bedside manner, comfort during the physical examination, no students present in the doctor's office, and the specialist wore a medical gown (Table 3).

The model showed good explanatory power (R^2 = 0.52). The Hosmer-Lemeshow goodness-of-fit test could not be adequately calculated, possibly due to limitations in the number of observations.

Discussion

Measuring patient satisfaction in healthcare systems has become an important indicator of service quality, based on the premise that healthcare systems should be patient-centered.⁶

In dermatology, patient satisfaction plays an important role in the doctor-patient relationship, as it increases the likelihood of patient return and reduces claims of medical negligence and malpractice errors. Additionally, services with high satisfaction levels tend to be more productive, which positively impacts clinical outcomes by improving therapeutic adherence among patients with chronic skin diseases. Patient satisfaction is also an important factor when seeking international quality accreditations, such as The Joint Commission on Accreditation of Healthcare Organizations.⁴

Various international studies have been conducted to evaluate patient satisfaction levels in dermatology consult, both in-person and via telemedicine, encompassing clinical and cosmetic dermatology.^{6,8–15}

Below are the results of the present study compared with the existing literature, along with a list of recommendations for each evaluated domain.

Medical interaction

Bedside manner was one of the best-rated aspects. Dissatisfaction with bedside manner (even when the patient is comfortable during physical exam, there is no students present, and the physician wears a white lab coat) reduced the likelihood of overall satisfaction by 99% (aOR = 0.01 [95% CI 0.00–0.04], $p < 0.001$). It has already been established that respect, empathy, and effective communication between physician and patient are central elements in building patient satisfaction.^{16,17}

On the other hand, negative communication in the hospital environment, manifested as Rudeness, Disdain, and Aggression (RDA), is a recognized problem in healthcare systems that increases levels of stress, depression, and the intention to leave the profession among healthcare workers. It has also been associated with worse clinical outcomes, including mortality.¹⁸ Approximately 40% of physicians report that RDA significantly affects their workday, and 7% commit clinical errors for this reason, which can negatively impact patient satisfaction.¹⁶

Disrespectful behavior reduces the likelihood that patients will voice their concerns, ask questions, or even share relevant information. Poor communication skills reduce the probability that patients will understand the information and feel satisfied with the bedside manner.¹⁷

The hospital environment also affects physician behavior, especially since there is an institutional tendency to ignore problems of frustration, poor communication, and disrespect among healthcare professionals.^{18,19} These issues often occur in high-stress settings that can increase individual feelings of anxiety, insecurity, depression, aggression, narcissism, and even trigger a "survival mode" response that reduces empathy.¹⁶

Recommendations

- Establish an interdisciplinary committee (including administrative staff, physicians with varying levels of experience, and nursing personnel) to thoroughly analyze and clearly define disrespectful behavior among institutional staff and toward patients. This committee should provide a list of practical examples to help identify such behavior and specify a course of action when it is detected. A zero-tolerance policy should be imple-

mented, with interventions ranging from educational programs to disciplinary measures, accompanied by a non-retaliation policy to protect those who report misconduct. Evidence shows that these types of institutional policies increase the effectiveness of addressing these issues.²⁰

- Create a professional code of conduct that clearly defines the expected behavior for every member of the institution, to improve quality outcomes (without assuming that staff already know these expectations). Behavioral changes within a community often occur when a principle is collectively accepted as an absolute truth, for example, “Absolutely everyone deserves respect”.²¹
- Training in “agenda-setting”; this approach is based on allowing the patient to initially express all their concerns and then prioritizing and negotiating with them the most relevant issues to address during the consult or later if necessary.

Verbal and nonverbal communication

Voice tone had the lowest percentage of high satisfaction (214 [49%]), and speech speed, although minimal, was the most dissatisfying component in this domain (17 [3.9%]). Previous studies have reported that physicians who speak quickly may convey more information, demonstrate attentiveness and care toward the patient, and even appear more persuasive, which is generally perceived as a positive factor in patient satisfaction ($p < 0.01$). It has also been shown that high-pitched tones reduce patient satisfaction ($p < 0.001$). However, both tone and speech speed become less relevant when the physician possesses strong professional credentials (degrees, academic training, recognized employment, etc.).²¹ Dissatisfaction with the professional’s self-introduction with name and title was zero, compared to 66% (289) of patients who reported being highly satisfied in this area.

Non-verbal language was rated positively (272 [62.2%]). This aspect is positively associated with patients’ sense of well-being, self-esteem, and social processes, even in the absence of other comfort strategies.²² Gestures such as nodding, maintaining eye contact, eyebrow movements, as well as the amount and location of physical contact, also influence patient satisfaction. However, in the present study, only the absence of a white lab coat had a significant impact on satisfaction, reducing its likelihood by 93.7% (aOR = 0.06 [95% CI 0.02–0.25], $p < 0.001$).²³

Recommendations

- The physicians should introduce themselves by name and title to communicate their professional credentials, maintain a moderate-to-fast speaking pace, and avoid unnecessarily raising their voice when speaking with patients.
- It is advised to consistently wear a white lab coat during consult and to use gestures such as a light touch on the shoulder, forearm, or hand, or a handshake when greeting patients.

Consult timing

There was an adequate level of satisfaction with the 20-minute consult (246 [56.3%]). Previous studies have reported satisfaction rates as high as 74% with consults lasting as little as 12.1 minutes ($p < 0.001$, $r = 0.38$), with a 0.04-point increase in satisfaction for each additional minute of consult time ($p = 0.001$ [95% CI 0.01–0.06]).²⁴ A positive association has also been found in consultation lasting 9.85 ± 0.37 minutes ($p = 0.005$).

Efficient administrative processes – such as fast appointment scheduling, quick billing procedures, and effective communication with administrative staff – have been shown to increase patient satisfaction by 3.58 times (aOR = 3.59 [95% CI 2.36–5.42], $p < 0.001$).²⁵ Although waiting time typically impacts overall satisfaction, in this study population, it was not statistically significant. Despite average waiting times of up to 64 minutes, 57% of patients reported being satisfied ($p = 0.001$).

Recommendations

- Physicians should maintain the current consult duration (20-minutes) and ensure punctuality.
- The institution must provide the necessary tools and staff to facilitate appointment scheduling and billing procedures. Additionally, it should ensure effective communication between different teams (both medical and non-medical) to streamline care processes.

Privacy

Less than 50% (190) of patients reported being satisfied with privacy during the medical photographs. In the literature, most patients (79.2%) report satisfaction with medical photography, and many express contentment in contributing to research, particularly when institutional cameras are used. Taking photos with smartphones may cause distrust and be perceived as unprofessional, although one study reported a 79% acceptance rate for smartphone photography.²⁶

Privacy can influence a patient’s decision to allow physical examination or to share relevant information. In one study, 10% of patients declined a physical examination due to privacy concerns; closing doors or providing curtained areas increased the perceived privacy from 21% to 89%.²⁷

Recommendations

- Always close the door or use curtains to ensure patient privacy.
- Always use informed consent to take medical pictures, clearly explain to the patient the measures taken to ensure the security and confidentiality of the pictures, and communicate the purpose and academic value of the photographs.
- Whenever possible, use an institutional camera for a photograph.

Teaching activity

The participation of students during the clinical interview decreased the likelihood of overall patient satisfaction by 87% (aOR = 0.13 [95% CI 0.04–0.42], $p < 0.001$). In the review by Mol et al. (2011), the presence of students did not affect patient satisfaction and was actually associated with benefits such as longer consult times, more thorough examinations, and improved patient education.²⁸ Other studies have shown that patients report greater satisfaction when students are present, as they feel altruistic and believe they are contributing to the students' education.²⁸

Since the presence of students can limit a patient's willingness to share intimate or emotional issues, this may have influenced these results, particularly considering that many dermatological conditions are associated with feelings of stigmatization or embarrassment, often related to the anatomical location of the lesions.²⁷

Recommendations

- Always ask the patient, before starting the consult, whether they agree with the participation of students.
- Even if the patient authorizes student involvement, it may be advisable to ask the students to step out of the consult to allow the patient to discuss any intimate or emotional aspects.

Infrastructure

Paradoxically, discomfort during the physical examination was associated with a higher probability of overall satisfaction (aOR = 25.76 [95% CI 4.46–190.04], $p = 0.001$). Although this association may reflect a real phenomenon – for example, that patients perceive thorough, uncomfortable examinations as indicators of careful medical attention – it could also result from reporting bias or the limitations of sample size. Another possibility is that under conditions involving respectful bedside manner, presence of a physician wearing a white lab coat, and absence of students, discomfort becomes less relevant.

In patients with disabilities, studies have shown that 27% are not examined on the doctor's office table, which is associated with a lower likelihood of rating the physician's care and work positively (59% and 39%, respectively).²⁹

The size of the doctor's office is related to the patient's sense of privacy; small spaces where patients can overhear other conversations reduce satisfaction from 36% to 14%.

Recommendations

- At an institutional level, it is important to ensure that doctors' offices are either sufficiently spacious or provide adequate privacy so that clinical interactions cannot be overheard outside.

Study limitations

An important strength of this study is that it evaluates a wide variety of aspects related to healthcare, providing a comprehensive context to understand this phenomenon.

Additionally, the parameters of the multivariate regression model were adequate, suggesting that the variables used can discriminate between satisfied and dissatisfied patients.

However, several limitations must be considered, such as the cross-sectional nature of the study, which prevents establishing causal relationships. It is important to note that the measurement of satisfaction is subject to social biases, and the factors impacting it vary considerably across populations. For this reason, unusual outcomes, such as discomfort during physical exam, require verification through additional analyses, ideally using hierarchical models or sensitivity analyses.

Another limitation common to all studies evaluating satisfaction is the complexity of analyzing all possible factors related to satisfaction and appropriately measuring them to avoid collinearity issues. It is important to include aspects related to technology (virtual appointment scheduling, scheduling methods, preferred contact methods, use of medical instruments during consult, etc.), which are increasingly common in medical practice.

Analytical studies are recommended to assess the direction of causal relationships, as well as qualitative analyses to explore patients' subjective perceptions in depth, and even more so, experimental evaluations of educational interventions aimed at improving the relational competencies of physicians and students.

Conclusions

This study offers a comprehensive evaluation of patient satisfaction during dermatological consultations, examining various domains such as physician-patient interaction, verbal and non-verbal communication, waiting times, privacy, teaching activities, and infrastructure. Most patients reported high overall satisfaction with the medical interview, physician's behavior, and physical examination.

Statistical analysis showed significant differences between groups in all domains and identified key factors affecting patient satisfaction. Notably, unsatisfactory physician behavior, discomfort during the physical exam, the presence of students during the interview, and the lack of a white lab coat worn by the physician significantly decreased the likelihood of overall satisfaction.

The multivariate regression model demonstrated moderate explanatory power, supporting the clinical and statistical importance of the variables studied. However, limitations related to the cross-sectional design and the complexity of measuring satisfaction accurately – due to possible social biases and population differences – are recognized.

This study emphasizes the need for further analytical, qualitative, and experimental research to better understand patient perceptions, establish causal relationships, and evaluate interventions aimed at improving the relational skills of healthcare providers and medical students.

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Authors' contributions

Manuel Gahona: Conceptualization; Data curation; Resources; Writing-original draft.

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Daniela Chaparro: Conceptualization; Data curation; Writing-original draft.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Predictive factors for distant metastasis in early cutaneous melanoma: a 20-year experience of a Turkish tertiary referral hospital[☆]



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Abstract

Background: Melanoma is an aggressive skin cancer with a high metastatic potential and mortality risk. Identifying risk factors for distant metastasis is crucial for optimizing surveillance strategies. The authors aimed to evaluate the predictors of distant metastasis in early-stage cutaneous melanoma within a Turkish patient cohort.

Methods: A retrospective cohort study was conducted on patients with stage I–II melanoma, diagnosed between 2004 and 2024 at the Department of Dermatology, Dokuz Eylul University. A minimum follow-up period of five years was ensured. Demographic, clinical, and histopathological variables were analyzed for their association with distant metastasis using univariate and multivariate statistical models.

Results: Among 148 patients, distant metastasis occurred in 36 (24.3%) during follow-up. Multivariate analysis identified age (HR = 1.03 per year, $p = 0.050$), Breslow thickness (HR = 1.19 per mm, $p = 0.008$), ulceration (HR = 3.05, $p = 0.028$), and Lymphovascular Invasion (LVI) (HR = 4.20, $p = 0.002$) as significant independent predictors of distant metastasis. The risk was found to increase markedly, particularly after the age of 40. Additionally, the optimal cut-off value for Breslow thickness was determined to be 2.73 mm, with a sensitivity of 69% and a specificity of 71% based on ROC curve analysis.

Conclusion: Increasing age, Breslow thickness, ulceration, and LVI were identified as independent risk factors for distant metastasis in early-stage cutaneous melanoma. Notably, patients over 40-years and those with Breslow thickness >2.73 mm were at significantly higher risk. Further studies are warranted to validate these results and facilitate their integration into clinical practice.

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Introduction

Cutaneous melanoma is one of the most aggressive skin cancers, characterized by its high metastatic potential and significant mortality risk. Despite advancements in early detection and treatment, distant metastasis remains a critical factor influencing prognosis, often leading to poor survival outcomes. Identifying these risk factors is crucial for improving patient stratification, optimizing surveillance strategies, and developing targeted therapeutic approaches to mitigate the devastating impact of metastatic disease.¹

Current guidelines established by the American Joint Committee on Cancer (AJCC) emphasize the significance of Breslow thickness as the most important prognostic factor for the primary tumor, with ulceration status also serving as an independent prognostic factor.² However, investigating additional criteria that may predict patient prognosis has become increasingly important with recent advancements in melanoma treatment. Recent studies have demonstrated that several parameters, such as patient age, sex, anatomical location of the tumor, histological subtype, and specific histopathological features, are closely associated with distant metastasis and overall survival (OS).^{3–9} Nevertheless, the heterogeneity in study results in the literature emphasizes that the risk of distant metastasis in melanoma varies by geographic region, ethnicity, study design, and patient populations, highlighting the need for population-specific risk assessments and prognostic models.

There is a limited number of clinical and prognostic outcome studies reported from Turkey, and, to date, no long-term follow-up study has specifically addressed early-stage melanoma patients. This study aims to investigate clinical, demographic, and histopathological factors associated with distant metastasis in a cohort of Turkish patients with early-stage cutaneous melanoma. The findings are expected to provide novel insights and contribute to developing personalized management strategies for this population.

Methods

Ethics

The study received approval from the Local Ethics Committee and adhered to the guidelines outlined in the Declaration of Helsinki (Reference Number: 2025/03-05, Date: 22.01.2025).

Study population

The authors conducted a retrospective cohort analysis of cutaneous melanoma patients aged ≥ 18 years whose data were entered into the hospital registry system between 2004 and 2024 at the Department of Dermatology, Faculty of Medicine, Dokuz Eylul University. The sample size was determined by including all patients who met the inclusion criteria over a 20-year period at the studied institution, in order to enhance representativeness and avoid selection bias. The most recent diagnoses were made in 2019, ensuring a minimum follow-up period of five years for all surviving participants; however, patients who died due to

melanoma within this five-year period were also included in the study. Patients were excluded if they had discontinued follow-up, died from non-melanoma causes, had a history of hematologic or solid organ malignancies, or met any of the following criteria: melanoma in situ, multiple invasive primary melanomas, other aggressive skin cancers with the potential for distant metastasis (e.g., squamous cell carcinoma, Merkel cell carcinoma), extracutaneous melanoma, melanoma of unknown primary origin, metastatic cutaneous melanomas, melanomas arising from congenital nevi, or clinical or microscopic evidence of Lymph Node (LN) or distant metastases at the time of diagnosis. Following these criteria, the final cohort consisted of patients with Stage I to II melanoma classified by the AJCC 8th edition (Fig. 1).

Data collection

Demographic and clinical data, including age, gender, tumor location, radiological imaging results, and sentinel LN biopsy (SLNB) outcomes, were extracted from hospital records. Histopathology reports collected data on Breslow thickness (in millimeters), mitotic rate (in numbers), and presence of ulceration, regression, lymphovascular invasion (LVI), and tumor-infiltrating lymphocytes (TIL). Breslow thickness values were rounded as per AJCC 8th edition recommendations. The primary outcome was identifying prognostic factors for distant metastasis (Stage IV), while the secondary outcome focused on locoregional cutaneous or LN metastasis (Stage III).

Statistical analysis

Statistical analyses were performed using SPSS software (Version 24.0, SPSS, Inc., Chicago, Illinois). Missing or ambiguous data were categorized as “unknown”. Data normality was assessed using the Shapiro-Wilk test. Numerical variables were summarized as medians with interquartile ranges (IQR), while categorical variables were compared using χ^2 or Fisher’s exact tests in 2×2 tables when expected frequencies were < 5 . The Mann-Whitney *U*-test was used for nonparametric comparisons between groups. Survival analysis was conducted using Kaplan-Meier curves and the log-rank test to compare survival curves, censoring patients who did not experience the event of interest. Univariate Cox proportional hazards regression analysis was used to evaluate the effect of individual variables on survival. Variables found significant in univariate analysis were included in a multivariate Cox regression model to calculate Hazard Ratios (HRs), 95% Confidence Intervals (95% CIs), and p-values. Receiver operating characteristic (ROC) curve analysis was performed to assess prediction accuracy. A p-value < 0.05 was considered statistically significant, with adjusted p-values applied in log-rank tests as necessary.

Results

Patient demographics

The study cohort comprised 148 Caucasian patients, including 101 females with a median age of 48 (range: 19–83, IQR:

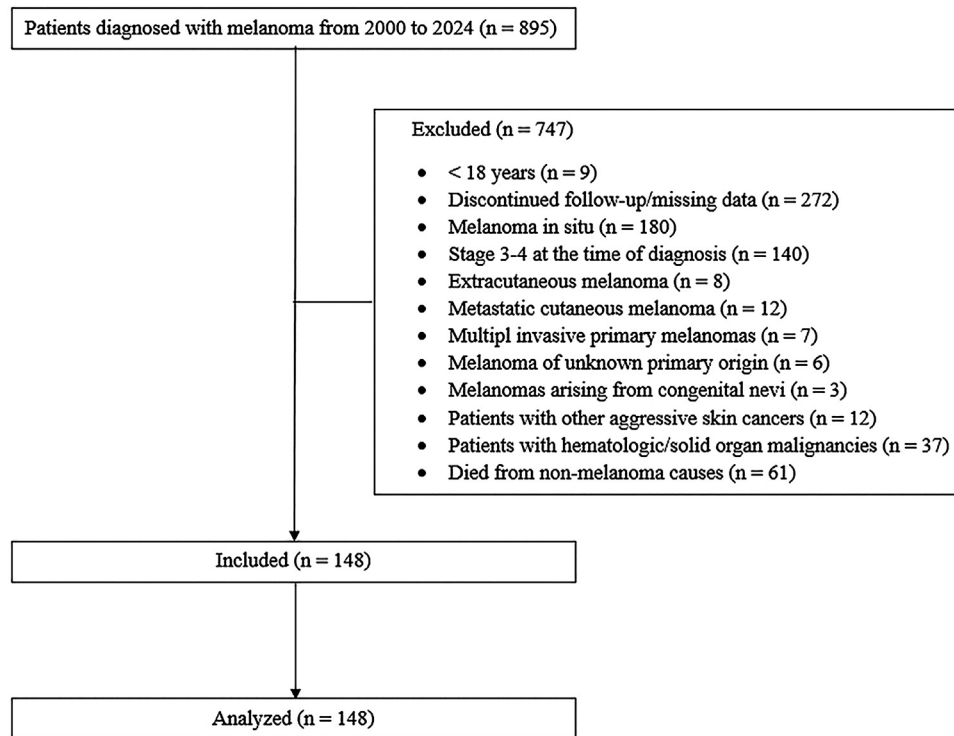


Fig. 1 STROBE diagram for the retrospective cohort study conducted between 2000 and 2024.

31–65 years) and 75 males with a median age of 57 (range: 18–86; IQR: 43–68 years). A statistically significant age difference was observed between genders ($p = 0.043$). [Table 1](#) presents a detailed summary of clinical and demographic data.

Rates and patterns of metastasis development in patients

During a median follow-up period of 7.0 years (IQR: 3–11 years), distant metastasis occurred in 36 out of 148 (24.3%) patients. Among these, 15 patients (10.1%) developed hematogenous metastasis only, 18 patients (12.2%) initially developed LN metastasis followed by hematogenous metastasis, and three patients (2.0%) experienced hematogenous metastasis before developing LN metastasis. 22 patients (14.9%) developed only locoregional cutaneous or LN metastasis ([Table 2](#)). The study cohort's 1-, 2-, and 5-year survival rates were 95.9%, 90.5%, and 60.8%, respectively.

Association of distant metastasis with clinical and demographic data

Distant metastasis was significantly more frequent in stage 2b and 2c melanomas compared to earlier stages ($p < 0.001$, HR = 12.18 [4.94–30.04]). In multivariate analyses, the only demographic factor significantly associated with distant metastasis was increasing age ($p = 0.050$, HR = 1.03 [1.00–1.05]). The categorical analysis of age groups also revealed significant differences ($p = 0.032$), indicating that this difference was due to an increased risk of metastasis

in individuals over 40-years of age compared to younger patients (adjusted $p = 0.006$, HR = 3.57 [1.38–9.24]).

Although not statistically significant in the overall analysis, the univariate analysis indicated that melanomas on the extremities were associated with a lower risk of metastasis compared to those in other anatomical sites ($p = 0.011$, HR = 0.26 [0.09–0.73]). Regarding melanoma histological subtypes, lentigo maligna melanoma (LMM) and superficial spreading melanoma (SSM) exhibited similar characteristics, whereas nodular melanoma (NM) and acral lentiginous melanoma (ALM) were associated with significantly higher rates of distant metastasis. However, the melanoma histological subtype did not retain its significance in multivariate analysis. The relationship between clinical, demographic, and histopathological variables and distant metastasis is presented in [Fig. 2](#), and the univariate and multivariate regression analyses are presented in [Table 3](#).

Association of distant metastasis with histopathological data

In univariate analysis, Breslow thickness, ulceration, LVI, and regression were significantly associated with distant metastasis. However, in multivariate analysis, LVI ($p = 0.002$, HR = 4.20 [1.67–10.57]), ulceration ($p = 0.028$, HR = 3.05 [1.13–8.20]), and Breslow thickness ($p = 0.008$, HR = 1.19 [1.05–1.35]) remained significant predictors, in order of their predictive value.

Categorical analysis of Breslow thickness showed a significant difference between the groups ($p < 0.001$). Detailed analysis revealed that this difference was due to an increased risk of metastasis in individuals with Bres-

Table 1 Clinical, demographic, and histopathological characteristics of patients at the time of diagnosis.

Parameter	n	%
Sex		
Female	73	49.3
Male	75	50.7
Age (years), median (quartiles)		3.00 (35.25–66.00)
< 40	44	29.7
40–60	49	33.1
> 60	55	37.2
Melanoma subtype		
SSM	83	56.1
NM	37	25.0
ALM	17	11.5
LMM	11	7.4
Localization		
Head and Neck	36	24.3
Trunk	51	34.5
Extremity	42	28.4
Acral	19	12.8
Stage		
Ia	49	33.1
Ib	18	12.2
Ila	28	18.9
Ilb	21	14.2
Ilc	32	21.6
Sentinel Lymph Node Biopsy		
Present	118	79.7
Absent	30	20.3
Breslow (mm), median (quartiles)		1.87 (0.72–4.00)
≤ 1	49	33.1
> 1–2	26	17.6
> 2–4	37	25.0
> 4	36	24.3
Ulceration		
Present	65	43.9
Absent	83	56.1
Mitosis rate, median (quartiles)		3.00 (1.00–11.00)
0	24	16.2
1–5	58	39.2
> 5	50	33.8
Unknown	16	10.8
LVI		
Present	19	12.8
Absent	107	72.3
Unknown	22	14.9
Regression		
Present	44	29.7
Absent	81	54.7
Unknown	23	15.5

SSM, Superficial Spreading Melanoma; NM, Nodular Melanoma; ALM, Acral Lentiginous Melanoma; LMM, Lentigo Maligna Melanoma; LVI, Lymphovascular Invasion; TIL, Tumor-Infiltrating Lymphocytes.

Table 2 Metastasis distribution in melanoma patients at the end of the study.

Parameter	n	%
Stage III	22	14.9
Stage IV	36	24.3
M-stage		
M1a	2	5.6
M1b	8	22.2
M1c	17	47.2
M1d	9	25.0

($p < 0.001$, AUC = 0.841) (Table 4). Fig. 3 shows the ROC curve of the Breslow thickness.

Association of regional LN metastasis with clinical, demographic, and histopathological data

In the univariate analysis, only ulceration ($p = 0.033$) and Breslow thickness ($p = 0.051$, borderline significance) emerged as significant predictors of LN metastasis. Additionally, patients with regional LN metastases had a significantly higher risk of developing distant metastasis ($p = 0.011$, HR = 2.42 [1.23–4.76]).

Discussion

In this study, the authors investigated the predictive parameters for distant metastasis in early-stage cutaneous melanoma within a cohort of Turkish patients who were followed for metastatic disease progression over 20 years in a dermatology setting at a reference university hospital. The present findings identified increasing age, greater Breslow thickness, ulceration, and LVI as independent risk factors for the development of distant metastases.

The clinicopathological characteristics of cutaneous melanoma in Turkish patients were first analyzed in an oncology clinic by Taş et al. in 2006. In this study including a total of 475 patients across localized, regional, and advanced disease stages, factors such as the nodular histological subtype, greater Breslow thickness, extensive invasion, the presence of ulceration, advanced stage, recurrence, male sex, older age, visceral recurrence, and high mitotic activity were found to be associated with poor OS in localized melanoma.¹⁰ In subsequent years, findings differed from earlier results, and the authors reported that while LVI was associated with metastatic disease, regression, patient age, tumor localization, and the ALM histological subtype were not.^{3,5,9–14} There are also several differences between these findings and those of previous studies. This is likely due to the fact that earlier studies excluded certain melanoma subtypes, such as LMM, and included patients at all disease stages who were followed in oncology clinics. Additionally, prognostic markers such as Breslow thickness, ulceration, regression, and LVI were often evaluated not only in early-stage patients but also in those diagnosed at advanced or metastatic stages.^{10–16}

Regarding studies worldwide, a Brazilian cohort identified male sex, nodular clinical and histologic subtype, Breslow thickness greater than 4 mm, and histologic ulcer-

low thickness > 2 mm compared to thinner melanomas ($p < 0.001$; HR = 11.08 [3.90–31.48]). In the ROC curve analysis, the optimal cut-off value for Breslow thickness in predicting distant metastasis was determined to be 2.73 mm

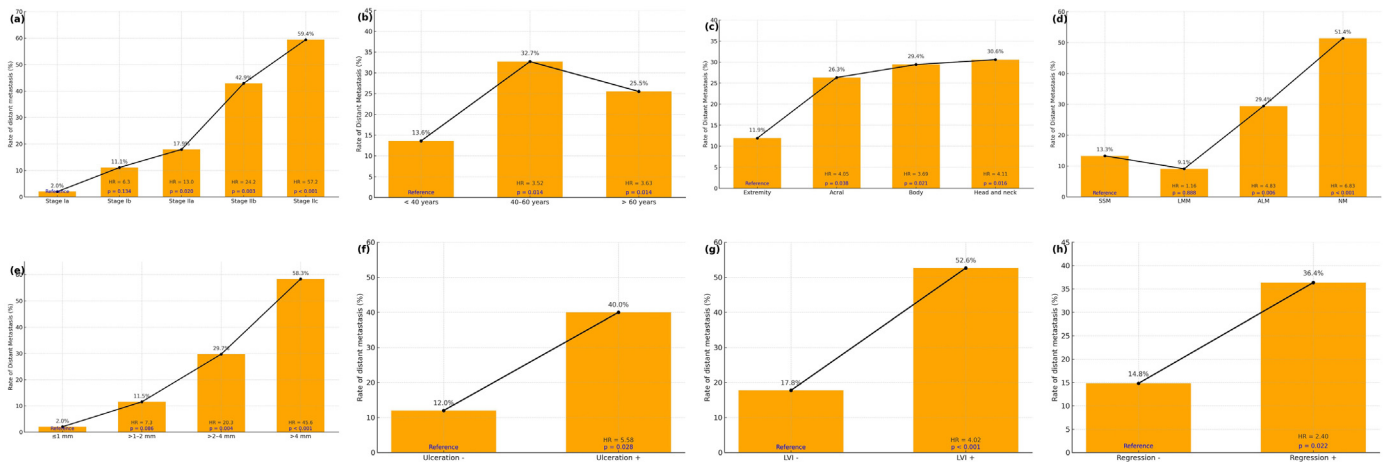


Fig. 2 Rates of distant metastasis and HR values observed in patients according to melanoma stage (a), age groups (b), melanoma localization (c), histological subtype (d), Breslow thickness (e), ulceration (f), lymphovascular invasion (g), and regression (h).

Table 3 Regression analysis of the relationship between clinical, demographic, and histopathological variables and distant metastasis.

	Univariate				Multivariate			
	p	HR	95% CI	χ^2 (Wald)	p	HR	95% CI	χ^2 (Wald)
Age at diagnosis (years, continuous)	0.015**	1.03	1.01–1.05	5.9	0.050**	1.03	1.00–1.05	3.9
Age at diagnosis (years)	0.032**			6.9				
< 40 (reference)		1.00						
40–60	0.014	3.52	1.29–9.63	6.0				
> 60	0.014	3.63	1.30–10.14	6.7				
Male Gender	0.321	1.41	0.72–2.76	1.0				
Localization	0.086			6.6				
Extremity (reference)		1.00						
Head and neck	0.016	4.11	1.31–12.96	5.8				
Body	0.021	3.69	1.22–11.13	5.3				
Acral	0.038	4.05	1.08–15.17	4.3				
Histologic subtype	< 0.001**			15.0	0.591			1.9
SSM (reference)		1.00				1.00		
NM	<0.001	6.83	2.98–15.66	20.6	0.681	1.23	0.45–3.36	0.2
ALM	0.006	4.83	1.57–14.89	7.5	0.367	0.49	0.10–2.33	0.8
LMM	0.888	1.16	0.15–9.29	0.0	0.734	1.44	0.18–11.91	0.1
Breslow (mm, continuous)	< 0.001**	1.28	1.19–1.39	39.1	0.008**	1.19	1.05–1.35	7.0
Breslow (mm)	< 0.001**			22.2				
≤ 1 (reference)		1.00						
> 1–2	0.086	7.27	0.75–70.26	2.9				
> 2–4	0.004**	20.28	2.61–157.35	8.3				
> 4	< 0.001**	45.64	6.10–341.47	13.8				
Ulceration (present)	< 0.001**	5.58	2.59–12.04	19.2	0.028**	3.05	1.13–8.20	4.9
Mitosis (present)	0.075	29.59	0.71–1233.61	3.2				
Regression (present)	0.022**	2.40	1.1–5.08	5.2	0.138	1.88	0.82–4.30	2.2
LVI (present)	< 0.001**	4.02	1.86–8.69	12.5	0.002**	4.20	1.67–10.57	9.3
TIL (present)	0.434	0.72	0.32–1.64	0.612				

SSM, Superficial Spreading Melanoma; NM, Nodular Melanoma; ALM, Acral Lentiginous Melanoma; LMM, Lentigo Maligna Melanoma; LVI, Lymphovascular Invasion; TIL, Tumor-Infiltrating Lymphocyte.

Table 4 Breslow thickness and roc curve analysis for distant metastasis.

Risk Factor	AUC (95% CI)	Cut-Off	p	Sensitivity	Specificity
Breslow thickness	84.1 (0.773–0.908)	2.7250	< 0.001	0.694	0.714

ROC, Receiver Operating Characteristic; AUC, Area Under the Curve.

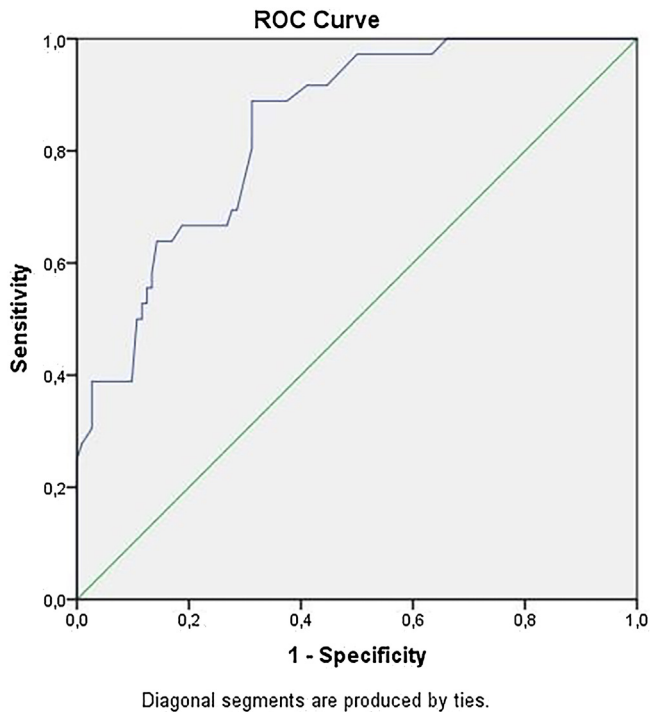


Fig. 3 Receiver operating characteristic curve showing the association of Breslow thickness with distant metastasis.

ation as prognostic factors for melanoma metastasis.¹⁷ Similarly, a Korean study reported that nodular histologic subtype, ulceration, and increased Breslow thickness were significant predictors of metastatic spread in primary cutaneous melanoma.¹⁸ A Taiwanese study focusing on stage I and II cutaneous melanomas demonstrated that a tumor thickness greater than 4 mm and the presence of ulceration were independent risk factors for hematogenous dissemination.¹⁹ Another study from Taiwan found that male sex, LVI, and positive LN status were prognostic indicators for both locoregional recurrence and distant metastasis.²⁰ In the US, a study reported that among patients with localized and regional disease, the relative risk of melanoma-specific mortality increased with advancing age at diagnosis, with this effect being more pronounced in women than in men.²¹ Finally, a recent meta-analysis investigating clinical and histological factors associated with distant metastasis in melanoma found that male sex, head and neck location (compared to the trunk), NM and LMM subtypes (compared to SSM), increased Breslow thickness, ulceration, and LVI were all significantly associated with a higher risk of distant metastasis. Conversely, the presence of regression was identified as a negative predictor of distant metastatic spread.⁹ The presence of differing results not only in national but also in international studies highlights the importance of conducting research in diverse clinical settings and across different ethnic and geographic populations, in order to enhance the evidence base regarding the progression and prognosis of early-stage melanoma.

In the studied cohort, age was the only independent demographic predictor of distant metastasis. This risk increased significantly, particularly in individuals over the age of 40. Although the highest metastasis rate was observed

in the 40–60 age group (32.7%), the > 60 age group had a higher HR (3.63 vs. 3.52), suggesting an earlier onset of metastasis in this population. These findings indicate that advanced age may be associated with a more aggressive disease course or reduced immune surveillance. In the studies by Taş et al., various age thresholds such as < 40, 40–60, ≥ 50 , ≥ 60 , and ≥ 75 -years were used to evaluate metastasis and OS. While some studies found no impact of age on prognosis, others associated older age with poorer outcomes.^{3,10–16} Numerous studies have shown that tumors in elderly patients exhibit greater Breslow thickness and a higher prevalence of ulceration and LVI, all of which are established prognostic indicators of aggressive disease and a heightened risk of distant metastasis.^{6,7,10} The underlying mechanisms behind the age-related differences in melanoma behavior are not fully understood but may involve a combination of biological and clinical factors. These include the decline in immune system efficiency associated with aging, impairing the body's ability to eliminate malignant cells; cumulative ultraviolet exposure over time, leading to a higher mutational burden and increased genomic instability in melanoma cells; the age-related decrease in melanin, a pigment that can inhibit melanoma cell proliferation; and delays in diagnosis due to reduced access to healthcare or differences in skin surveillance practices in elderly patients.^{22–24}

Breslow thickness measures the depth of tumor invasion and serves as a reliable indicator of the likelihood of metastatic spread and OS. The role of Breslow thickness in melanoma prognosis has been well-documented in both global and Turkish population studies.^{10,17,18} In the study by Taş et al., a Breslow thickness of > 2 mm was found to be a poor prognostic factor for OS and was also found to predict a shorter time to relapse in stage I–II patients.^{5,10,15} On the other hand, the results of another study by the same authors revealed that Breslow thickness had no impact on relapse-free survival or OS in elderly patients.³ In the study population, a Breslow thickness greater than 2 mm was significantly associated with distant metastasis in early-stage melanoma. In the ROC curve analysis, the authors found the optimal cut-off value to be 2.73 mm, with a sensitivity of 69% and a specificity of 71%. Although any cut-off point should be interpreted with caution and clinical decisions in patients with early-stage cutaneous melanoma should ideally be based on multiple selection criteria, the use of long-term follow-up data and the determination of an optimal Breslow cut-off value may serve as an initial reference for identifying patients at higher risk of developing distant metastases or for selecting candidates for adjuvant therapy in clinical practice.

In addition to Breslow depth, ulceration emerged as another critical prognostic factor for the risk of distant metastasis, conferring a 3.05-fold increased risk in the multivariate analysis. It was also identified as a predictor for LN metastasis. The erosion or destruction of the epidermis overlying the tumor generally reflects a more aggressive tumor biology and is indicative of a worse prognosis. Analyses of patients with LN metastases have shown that the absence of ulceration in the primary tumor is associated with a more favorable prognosis. In the literature, ulceration has also been identified as a strong predictor of LN metastasis and holds importance in patient selection for SLNB.²⁵ In

the eighth edition of the AJCC melanoma staging system, ulceration is considered the only histopathological parameter determining tumor stage apart from Breslow thickness.²

In this study, LVI was the strongest independent histopathologic predictor of distant metastasis, demonstrating a 4.20-fold increased risk in the multivariate analysis. Existing evidence suggests that the invasion of melanoma cells into lymphatic or blood vessels provides a pathway for tumor cells to access the circulation, facilitating their dissemination to distant sites and the formation of metastatic tumors.²² The definitive and prognostic role of LVI in localized cutaneous melanoma was associated with worse OS in previous studies conducted in Turkey, similar to findings observed in Western countries.^{9,23} In a meta-analysis of histological factors associated with distant metastasis, LVI was identified as a strong risk factor for distant metastasis, with an HR comparable to that of ulceration (2.86 vs. 2.05), suggesting the potential for wider applicability of these results.⁹

Although tumor location was not an independent prognostic factor in the multivariate analysis, it influenced metastatic patterns in the univariate analysis. Melanomas located on the extremities were associated with a significantly lower risk of distant metastasis compared to those on the trunk, head and neck, or acral areas. Previous studies have indicated that extremity melanomas predominantly develop locoregional recurrences, while axial melanomas tend to progress primarily with distant recurrences.⁴ It has been suggested that melanomas arising in chronically sun-exposed areas, such as the extremities, may exhibit increased melanin pigmentation, which is associated with more favorable biological behavior and reduced metastatic potential.²⁶ However, this hypothesis does not sufficiently account for the aggressive metastatic risk observed in melanomas of the head and neck, which is also chronically sun-exposed. In the present detailed analysis, head and neck melanomas were identified as the most common subtype and the earliest to develop distant metastases. Among the other subtypes, trunk melanomas showed a higher frequency of metastasis compared to acral melanomas (29.4% vs. 26.3%); however, the HRs suggested that acral melanomas may develop metastases earlier than trunk melanomas (4.05 vs. 3.69). In the studies conducted by Taş et al., tumor localization was generally not found to affect prognosis; however, in one of their studies, they reported that scalp melanomas were associated with poorer survival compared to melanomas at other sites.^{10,12,15} Recent studies have suggested that the anatomical site of the primary melanoma may also play a role in the age-related differences in metastatic risk. Melanomas located on the trunk and lower extremities have been associated with a higher risk of metastatic disease in older patients compared to those located on the head and neck.²⁷ Although these findings are conflicting, they highlight the importance of considering anatomical location in risk prediction, and further studies with larger sample sizes are needed to clarify these associations.

The histological subtype of melanoma also affected metastatic patterns in this study, with SSM and LMM associated with a better prognosis compared to NM and ALM. LMM showed the lowest frequency and latest onset of metastasis, whereas NM and ALM exhibited the highest risk and the most rapid progression to metastasis, respectively. The

relatively low rate of metastasis observed in LMM may be attributed to its characteristically slow and chronic course of progression. Although the high metastatic potential of NM is well known, the prognostic implications of ALM and plantar melanomas have been variably reported in the literature. Despite their aggressive features, previous studies found no correlation with nodal involvement, recurrence, distant metastasis, or poor survival outcomes.^{13,14} However, a recent meta-analysis identified the histologic subtype of the tumor as a strong predictor of metastasis, with NM, LMM, and ALM all showing an increased likelihood of developing distant metastasis compared to SSM (HR: 2.51, 1.87, and 1.47, respectively). Notably, a reduction in distant metastasis-free survival was found to be associated only with ALM.⁹ It remains uncertain whether these differences reflect true biological variation or are influenced by other factors such as delayed diagnosis and treatment due to anatomical localization, or by the effects of chronic pressure and trauma on tumor behaviour. However, the available evidence suggests that the inflammatory cells and other components within the tumor microenvironment can influence the ability of cancer cells to escape immune surveillance, promote angiogenesis, and facilitate invasion of the vasculature.^{13,14}

This study has certain limitations. The retrospective design and reliance on a single-center dataset may limit the generalizability of the findings. Additionally, while the study population represents a Turkish cohort, the relatively small sample size may not fully capture the variability across broader geographic or ethnic populations. On the other side, the strengths of this study include its long-term follow-up period, comprehensive data collection, and rigorous exclusion criteria, which ensured a homogenous cohort of early-stage melanoma patients. To assess the adequacy of the sample for multivariable analysis, a post-hoc power calculation based on observed metastasis rates was performed, and the power exceeded 85% confirming that the sample was sufficient for the study. By including all complete data, the authors aimed to reduce information bias and controlled for confounding effects using multivariate Cox regression analysis. Additionally, to the best of our knowledge, this study is the first to investigate the predictive value of clinical, demographic, and histopathological data on distant metastasis in Turkish patients with early cutaneous melanoma.

In conclusion, although each parameter may hold prognostic significance individually, the present study identified increasing age, greater Breslow thickness, ulceration, and LVI as independent risk factors for distant metastasis in early-stage cutaneous melanoma. Notably, the risk was significantly elevated in individuals over the age of 40 and in those with a Breslow thickness exceeding 2.73 mm. Nonetheless, further studies in this population are warranted to validate these findings, support their integration into clinical practice, and ultimately enhance patient outcomes.

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Data availability statement

The data of the study can be shared upon reasonable request.

Ethics statement

The authors confirm that the journal's ethical policies, as outlined on the journal's author guidelines page, have been adhered to. The study protocol was approved by the Local Ethics Committee, following the guidelines established by the Declaration of Helsinki. (Reference Number: 2025/03-05, Date: 22.01.2025).

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Authors' contributions

Ozlem Ozbagicvan: Approval of the final version of the manuscript, critical literature review, data collection, analysis and interpretation, effective participation in research orientation, intellectual participation in propaedeutic and/or therapeutic management of studied cases, manuscript critical review, preparation and writing of the manuscript, statistical analysis, study conception and planning.

Elif Kazaz: Approval of the final version of the manuscript, data collection, analysis and interpretation, manuscript critical review.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

The authors declare no commercial or financial conflicts of interest, including those related to the specific brands of materials used in this study.

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ORIGINAL ARTICLE

The efficacy of topical calcineurin inhibitor therapy for childhood vitiligo: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies[☆]



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KEYWORDS

Calcineurin inhibitor;
Child;
Phototherapy;
Tacrolimus;
Vitiligo

Abstract

Background: Topical calcineurin inhibitors (TCIs) are commonly used in the treatment of pediatric vitiligo; however, limited studies have specifically examined their efficacy in this patient population.

Objective: This study aims to evaluate the efficacy of TCI therapy in the treatment of childhood vitiligo.

Methods: A comprehensive search was conducted in MEDLINE, EMBASE, and Web of Science to identify prospective cohort studies and randomized controlled trials (RCT) evaluating the efficacy of TCI therapy for childhood vitiligo. The primary outcome was treatment success, defined as $\geq 50\%$ repigmentation. A meta-analysis was performed when appropriate. And the certainty of evidence was graded based on the GRADE (grading of recommendations assessment, development and evaluation) approach.

Results: Nine studies involving a total of 636 patients were included in this review. Five studies were included in the meta-analysis, and 2 RCTs met eligibility criteria with medium-quality results. The efficacy of TCI therapy for childhood vitiligo was comparable to that of topical corticosteroid (TCS) therapy (Risk Ratio [RR] = 0.70, 95% Confidence Interval [95% CI] 0.39–1.25). Additionally, low-certainty evidence indicates that the combination of TCI therapy with phototherapy demonstrated superior results compared to phototherapy alone (RR = 1.32, 95% CI 1.01–1.73).

Study limitations: The findings are based on a limited number of studies and patients.

[☆] Study conducted at the Department of Dermatology, Peking University Third Hospital, Beijing, China.

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Conclusion: TCI therapy for childhood vitiligo appears to be non-inferior to TCS therapy. Moreover, the combination of TCI and phototherapy may offer superior results compared to phototherapy alone; however, this conclusion should be interpreted with caution due to the low certainty of evidence as assessed by GRADE.

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Introduction

Vitiligo is a condition characterized by the loss of functional melanocytes, leading to depigmented skin macules and patches.¹ It can manifest at any age, with the prevalence of childhood vitiligo ranging from 0.0% to 2.16%, while adult vitiligo prevalence ranges from 0.0% to 2.28%.¹ Although vitiligo is generally considered an asymptomatic condition, a study indicates that nearly 30% of children with vitiligo experience itching and pain.² Childhood vitiligo can significantly impact not only the quality of life of affected children but also the emotional well-being of their caregivers.^{2,3} Vitiligo is a challenging dermatologic condition that imposes a substantial psychological burden on both patients and their families.

Despite the proven efficacy of topical corticosteroids (TCS) in childhood vitiligo, concerns regarding the side effects of corticosteroids are widespread.^{4–6} Tacrolimus ointment, a topical calcineurin inhibitor (TCI), has been shown to promote melanogenesis by modulating keratinocyte growth and stimulating melanocyte migration.^{7,8} Unlike TCS, long-term use of TCIs is associated with minimal side effects in patients with atopic dermatitis.⁹ According to the present research, there are a few systematic reviews combined with meta-analysis of TCI treatment for childhood vitiligo. Given this, it is crucial to evaluate the efficacy of TCIs specifically for childhood vitiligo, in order to establish evidence-based treatment protocols tailored to this population.

Methods

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.¹⁰ The authors have registered this systematic review in the PROSPERO database, and the registration ID is CRD42024629173.

Search strategy

Two reviewers (T.J. and W.W.) independently searched databases, which included MEDLINE, EMBASE, and Web of Science from all databases to November 25, 2024. Randomized controlled trials (RCTs) and prospective cohort studies were identified by the search, which used these terms: "child", "pediatric", "vitiligo", "tacrolimus", "pimecrolimus", "calcineurin inhibitor". Studies published online, in print, or in press were all included.

The search strategy is: 1) Pubmed: (child[Title/Abstract] OR pediatric[Title/Abstract]) AND vitiligo[MeSH Terms] AND (tacrolimus[Title/Abstract] OR

pimecrolimus[Title/Abstract] OR calcineurin inhibitors[MeSH Terms]); 2) Embase: ('child'/exp OR 'child'/ti,ab OR 'pediatric'/exp OR 'pediatric'/ti,ab) ; AND 'vitiligo'/exp AND ('tacrolimus'/exp OR 'tacrolimus'/ti,ab OR 'pimecrolimus'/ti,ab OR 'calcineurin inhibitors'/exp); 3) Web of Science: TS = (child*OR pediatric*) AND TS = (vitiligo) AND TS = (tacrolimusOR pimecrolimusOR calcineurin inhibitor)

Study selection

Two independent reviewers screened the titles and abstracts. If there were insufficient information in abstracts, the two reviewers would examine full-texts and resolve any differences by discussion. The inclusion criteria: 1) Participants were children (under 18 years old); 2) At least one group treated with TCI; 3) Diagnosis of vitiligo (including but not limited to non-segmental vitiligo, segmental vitiligo, and undetermined/unclassified vitiligo). The exclusion criteria: 1) Duplicate publication; 2) Papers with no available full texts; 3) Non-English papers.

Data extraction

Two reviewers independently performed data extraction. The template for extraction was built through the pilot extraction of three selected papers. The following data items included the last name of the first authors, country of studies, year of publications, number of participants/lesions, type of treatments, and duration of treatments. If studies were published by the same author, two reviewers would check whether the data overlapped or not.

Risk of bias assessment

The quality of the clinical trials has been assessed by two independent reviewers. Two reviewers assessed the risk of biases using the Cochrane Collaboration's quality assessment tool (ROB-2), which included the assessment of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.¹¹ The risk of biases of prospective cohort studies was assessed by the Newcastle-Ottawa Scale (NOS) within the Selection, Comparability, and Outcome categories.¹² Disagreements were resolved through the two reviewers' discussions.

Grading the certainty of evidence

The authors graded the certainty of evidence of relevant outcomes based on current GRADE guidance, which was

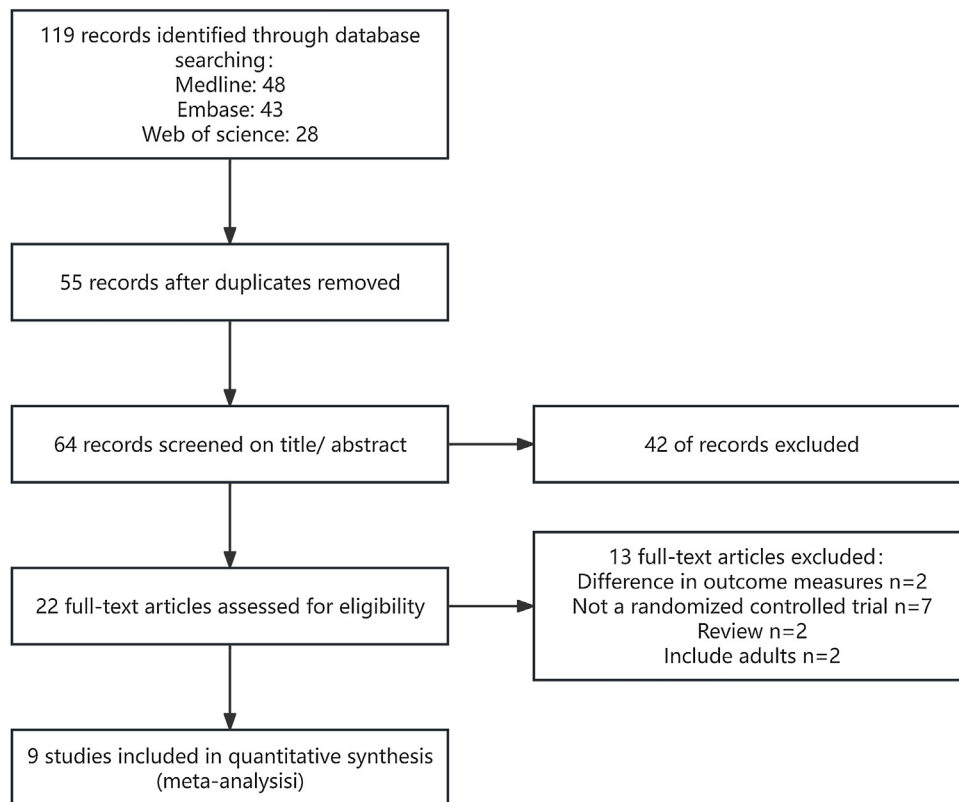


Fig. 1 Flow diagram of the identification of selected studies.

divided into four categories: high, moderate, low, and very low.¹³ This method was developed to grade the overall certainty of evidence.

Outcome measures

The primary outcome of interest was the extent of repigmentation, defined as 75% or greater. However, two studies used a threshold of 50% or greater repigmentation as the criterion for success.^{14,15} Given the limited number of studies included in the meta-analyses, the authors chose 50% or greater repigmentation as the main outcome for this review.

Statistical analysis

The authors used the Review Manager, Version 5.2, to perform the quantitative meta-analyses, using the Mantel-Haenszel ((M-H)) method and calculating the pooled Risk Ratio (RR) with the corresponding 95% Confidence Intervals (95% CI). A random-effects model would be used.

Results

Search results

A total of 9 articles were included in this review.¹⁴⁻²² The PRISMA flow diagram is presented in Fig. 1.

Description of included studies

A total of 9 articles, comprising 636 patients, were included in this review (Table 1).¹⁴⁻²² Of these, 5 studies involving 323 patients were included in the meta-analysis.^{15-17,19,20} The age range of the study population was unspecified in 2 studies,^{15,22} while the remaining studies included patients aged 2–18 years. Four studies compared the efficacy of TCI with TCS,^{14,15,17,20} three of which were included in the meta-analysis.^{15,17,20}

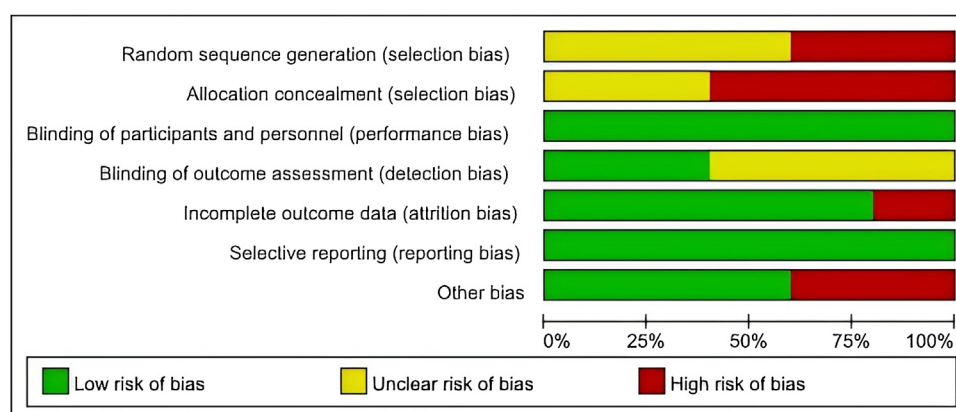
Six studies examined the effects of TCI combined with other treatments compared to monotherapy.^{15,16,18,19,21,22} Among them, three studies compared TCI combined with phototherapy to phototherapy alone.^{15,16,19} Two of these studies specifically compared tacrolimus combined with phototherapy to phototherapy alone,^{15,16} while the other two studies compared pimecrolimus combined with 308nm excimer laser treatment to excimer laser alone.^{15,19} Three studies were excluded from the meta-analysis.^{18,21,22}

Risk of bias assessment among included trials

Among the two prospective cohort studies, one received 4 points on the NOS,¹⁷ and the other received 6 points.¹⁶ According to the NOS criteria, studies scoring 7 or more points were considered high quality, while those scoring 3 or fewer points were classified as poor quality. Both studies were categorized as medium-quality studies. The results of the Randomized Controlled Trials (RCTs) are summarized in Figs. 2 and 3. All the studies in Fig. 3 presented at least one

Table 1 Characteristics of studies included in this review D, days; M, months; W, weeks.

Study			Sample Size		Intervention		Treatment duration
Author, year	Type	Country	Case	Control	Case	Control	
Alshiyab et al., ²¹ 2016	Randomized controlled trial	Jordan	25	25	0.1% Tacrolimus +308 nm excimer lamp	0.1% Tacrolimus	180 D
Alshiyab et al., ²² 2016	Randomized controlled trial	Jordan	25	24	0.1% Tacrolimus + pseudocatalase/superoxide dismutase gel	0.1% Tacrolimus	9 M
Dayal et al., ¹⁶ 2016	Open-label, prospective, clinical trial	India	20	20	0.03% Tacrolimus + NB-UVB	NB-UVB	24 W
Li et al., ¹⁵ 2018	Randomized controlled trial	China	77/74	82/78	0.1% Tacrolimus +308 nm laser / 1% Pimecrolimus +308 nm laser	Halometasone +308 nm laser / 308 nm laser	12 W
Ho et al., ¹⁴ 2011	Double-blind, randomized, placebo-controlled trial	Canada	31	30	0.1% Tacrolimus	0.05% Clobetasol propionate	24 W
Köse et al., ¹⁷ 2010	Open label, single-center, comparative trial	Turkey	20	20	1% Pimecrolimus	0.1% Mometasone	12 W
Farajzadeh et al., ¹⁸ 2009	Single-blind, randomized placebo-controlled study	Iran	60	60	1% Pimecrolimus + microdermabrasion	1% Pimecrolimus	10 D
Yang et al., ¹⁹ 2009	Single blinded, randomized study	China	48	48	1% Pimecrolimus +308 nm laser	308 nm laser	15 W
Lepe et al., ²⁰ 2003	Randomized double-blind trial	Mexico	20	20	0.1% Tacrolimus	0.05% Clobetasol propionate	8 W

**Fig. 2** Risk-of-bias graph.

domain with a high risk of bias, and this would lead to an overall risk of high risk.

Effect of interventions

TCI versus TCS

The TCIs used in these studies included 0.1% tacrolimus and 1% pimecrolimus, while the TCS included halometasone,

0.05% clobetasol, and 0.1% mometasone. A random-effects model was applied, revealing no statistically significant difference between TCS and TCI in promoting 50% or more repigmentation (Risk Ratio [RR = 0.70], 95% Confidence Interval [95% CI 0.39–1.25]) (Fig. 4A). Evidence for this was very low GRADE (Table 2). Another study not included in the meta-analysis also showed that TCS and TCI offered similar benefits.¹⁴

Table 2 Grading the certainty of evidence of topical calcineurin inhibitor versus topical corticosteroid.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsis- tency	Indirectness	Imprecision	Other con- sider- ations	TCI	TCS	Relative (95% CI)	Absolute		
>50% repigmentation												
3	Randomised Trials	Serious ^a	Serious ^b	No Serious Indirectness	Serious ^c	None	123/191 (64.4%)	90/122 (73.8%)	RR 0.7 (0.39 to 1.25)	221 fewer per 1000 (from 450 fewer to 184 more) 195 fewer per 1000 (from 396 fewer to 162 more)	ÅÅÅÅ VERY LOW	
							65%					

^a Lack of information on randomization of outcome measure.^b $I^2 > 50\%$.^c The population is small.**Table 3** Grading the certainty of evidence of topical calcineurin inhibitor and phototherapy combination therapy versus phototherapy alone.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Poly therapy	Mono therapy	Relative (95% CI)	Absolute		
>50% repigmentation												
3	Randomised trials	Serious ^a	No serious inconsistency	No serious indirectness	Serious ^b	None	159/219 (72.6%)	78/146 (53.4%)	RR 1.32 (1.01 to 1.73)	171 more per 1000 (from 5 more to 390 more)	ÅÅÅ LOW	
							57.7%				185 more per 1000 (from 6 more to 421 more)	

^a Lack of information on randomization of outcome measure.^b The population is small.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall risk
Dayal 2016	Red	Red	Green	Green	Green	Green	Green	Red
Köse 2010	Red	Red	Green	Yellow	Red	Green	Green	Red
Lepe 2003	Yellow	Red	Green	Green	Green	Green	Green	Red
li 2018	Yellow	Yellow	Green	Yellow	Green	Green	Red	Red
Yang 2009	Yellow	Yellow	Green	Yellow	Green	Green	Red	Red

Fig. 3 Risk-of-bias summary. Red ball, high risk; yellow ball, unclear risk of bias or some concerns; green ball, low risk.

In a prospective randomized trial of treating with pimecrolimus, the pimecrolimus group was less effective for treating facial and neck lesions 64.5% (20/31) and more effective for acral lesions 80.0% (4/5).¹⁵ Conversely, the tacrolimus group showed lower effectiveness for acral lesions 50.0% (3/6), but higher effectiveness for trunk lesions 88.2% (30/34).¹⁵ In an open-label, single-center, comparative trial, pimecrolimus was less effective on the extremities and trunk compared to the face.¹⁷ A double-blind randomized trial study suggested that most of the repigmentation occurred on the face in patients treated with topical tacrolimus.²⁰ Additionally, the study observed that TCS resulted in the development of a pigment island around the hair follicle, while the new pigmentation in the tacrolimus group showed a more uniform, centripetal pattern, mixing with the normal skin color.²⁰ In a double-blind, randomized, placebo-controlled trial, TCS and TCI had similar effects on vitiligo in children, both in facial and non-facial areas.¹⁴ Regarding adverse events, a total of 60 patients were included. In the TCS group, 8.3% (5/60) of patients experienced skin atrophy, 6.7% (4/60) had telangiectasia, while 8.3% (5/60) of patients in the TCI group reported burning sensations or pruritus.^{17,20}

TCI combined with the other treatment versus monotherapy

Three quantitative meta-analyses were conducted. The first meta-analysis included three clinical trials comparing the efficacy of TCI combined with phototherapy versus phototherapy alone (Fig. 4B).^{15,16,19} The TCI treatment included 0.1% tacrolimus, 0.03% tacrolimus, and 1% pimecrolimus, while the phototherapy treatments included the 308 nm excimer laser and Narrowband Ultraviolet B (NBUVB). The combination of TCI and phototherapy showed a significantly superior effect on childhood vitiligo (RR=1.32, 95% CI 1.01–1.73) based on the random-effects model. Evidence for this was low GRADE (Table 3).

The second meta-analysis included two clinical trials, comparing the efficacy of tacrolimus combined with phototherapy versus phototherapy alone (Fig. 5A).^{15,16} One study used 0.03% tacrolimus with NBUVB, and the other used 0.1% tacrolimus with the 308 nm excimer laser. The results showed no statistical difference between the two groups (RR=1.76, 95% CI 0.80–3.89), according to the random-effects pooling of the results. Evidence for this was very low GRADE (Table 4). The response was found to be more effective on the face and trunk than on the extremities in an open-label study.¹⁶ Adverse effects reported in this study included erythema in 10.0% (2/20) patients, blistering in 5.0% (1/20) patients, and pruritus in 5.0% (1/20) patients.¹⁶

The third meta-analysis involved two clinical trials comparing the combination of 1% pimecrolimus and 308 nm excimer laser treatment to 308 nm excimer laser alone for childhood vitiligo (Fig. 5B).^{15,19} The random-effects pooling revealed that the combination therapy had a significantly superior effect (RR=1.23, 95% CI 1.02–1.47). Evidence for this was low GRADE (Table 5). In a right/left comparative, single-blinded trial, of the 48 patients receiving the 308 nm excimer laser, 16.7% (8/48) experienced mild burning sensations, 6.3% (3/48) had blisters, and 14.6 (7/48) had pruritus.¹⁹ Some of these patients experienced worsened symptoms after using pimecrolimus.¹⁹

Three studies were not included in the meta-analysis.^{18,21,22} In these studies, TCI combined with microdermabrasion or with a 308 nm excimer lamp showed greater effectiveness than TCI alone.^{18,21} However, the combination of tacrolimus and topical pseudocatalase/superoxide dismutase gel did not appear to offer additional benefit.²²

Discussion

The systematic review provided the first child-specific evidence supporting two pivotal conclusions: 1) TCIs achieved comparable $\geq 50\%$ repigmentation rates to potent TCS (RR=0.70, 95% CI 0.39–1.25) with superior safety; 2) Efficacy was influenced by the anatomic site. The comparable efficacy between TCIs and potent TCS contrasted with data from both pediatric and adult studies.²³ This divergence likely stemmed from developmental differences in skin biology: children's thinner epidermis may enhance TCI penetration, potentially compensating for lower anti-inflammatory potency. Recent 2024 consensus treatment recommendations published in JAMA Dermatology identified TCIs applied twice daily as evidence-based first-line

Table 4 Grading the certainty of evidence of tacrolimus and phototherapy combination therapy versus phototherapy alone.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calci + exi	Exi	Relative (95% CI)	Absolute		
>50% repigmentation												
2	Randomised trials	Serious ^a	Serious ^b	No serious indirectness	Serious ^c	None	71/97 (73.2%)	49/98 (50%)	RR 1.76 (0.8 to 3.89)	380 more per 1000 (from 100 fewer to 1000 more)	ÅÅÅÅ VERY LOW	
								38.9%			296 more per 1000 (from 78 fewer to 1000 more)	

^a Lack of information on randomization of outcome measure.^b $I^2 > .50\%$.^c The population is small.**Table 5** Grading the certainty of evidence of pimecrolimus and 308 nm excimer laser combination therapy versus 308 nm excimer laser alone.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Poly	Mono	Relative (95% CI)	Absolute		
>50% repigmentation												
2	Randomised trials	Serious ^a	No serious inconsistency	No serious indirectness	Serious ^b	None	88/122 (72.1%)	74/126 (58.7%)	RR 1.23 (1.02 to 1.47)	135 more per 1000 (from 12 more to 276 more)	ÅÅÅÅ LOW	
								59.1%		136 more per 1000 (from 12 more to 278 more)		

^a Lack of information on the randomization of outcome measure.^b The population is small.

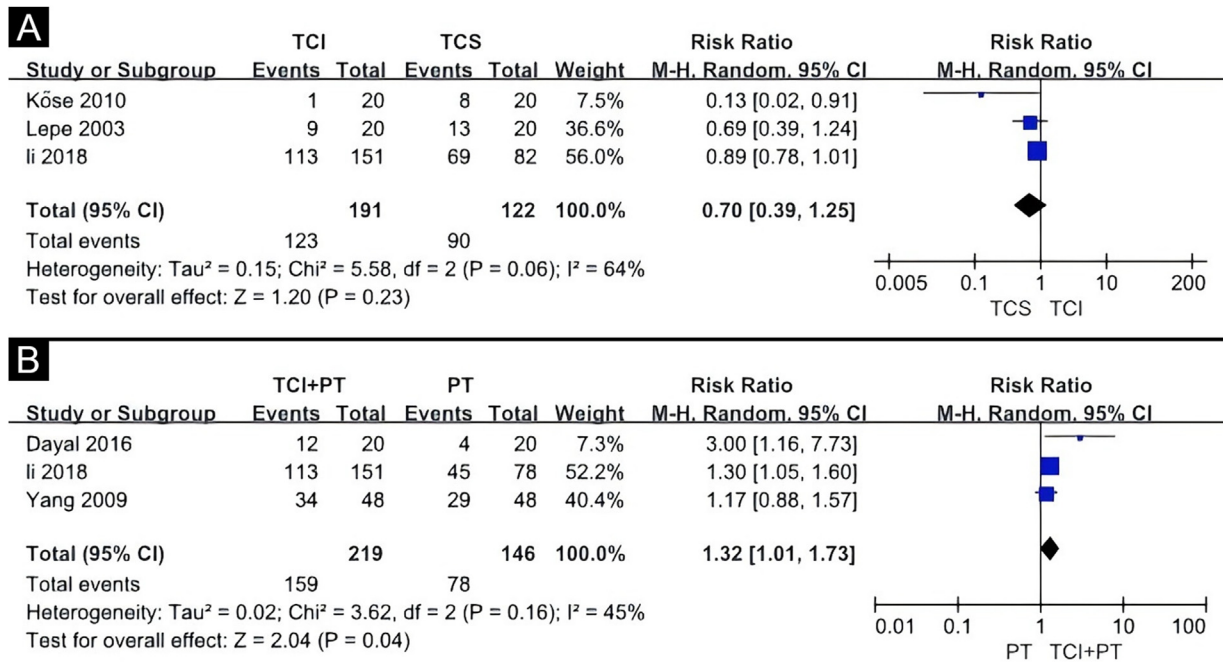


Fig. 4 Forest plot meta-analysis of repigmentation rate of topical calcineurin inhibitor versus topical corticosteroid (A), topical calcineurin inhibitor and phototherapy combination therapy versus phototherapy alone (B). CI, Confidence Interval; TCI, Topical Calcineurin Inhibitor; TCS, Topical Corticosteroid; PT, Phototherapy.

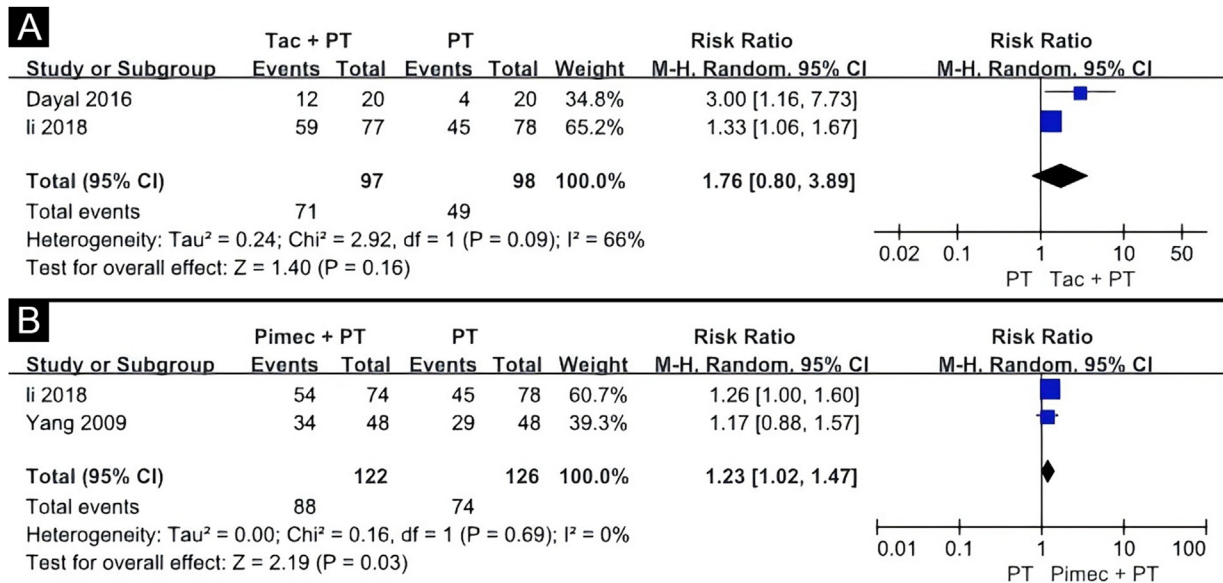


Fig. 5 Tacrolimus and phototherapy combination therapy versus phototherapy alone (A), pimecrolimus and 308 nm excimer laser combination therapy versus 308 nm excimer laser alone (B). Tac, Tacrolimus; Pimec, Pimecrolimus.

therapies for managing pediatric and adolescent vitiligo.²⁴ According to the present systematic review, both TCS and TCI demonstrated similar efficacy in treating childhood vitiligo ($RR = 0.70$; 95% CI 0.39–1.25). These findings supported the use of TCIs as first-line therapy for pediatric patients with vitiligo.

However, this review had several limitations. First, heterogeneity among the studies included in the meta-analysis remained a concern. Second, the sample sizes (both in terms

of the number of patients and lesions), follow-up durations, and the number of studies were relatively small. Third, the review might be limited by the risk of bias in the studies.

Most studies included in the analysis used 0.1% tacrolimus. However, it was challenging to obtain coverage in the U.S., as many insurance companies limit coverage to 0.03% tacrolimus for patients under 16 years of age. The authors did not find any literature comparing the efficacy of 0.03% tacrolimus and topical corticosteroids in children

with vitiligo. In a systematic review about atopic dermatitis, a comparison with a commonly used mild topical corticosteroid showed that 0.03% tacrolimus was more effective, while no significant differences were found between 0.03% tacrolimus and mid-potency corticosteroids.²⁵ It was hoped that future clinical studies would compare 0.03% tacrolimus with topical corticosteroids for the treatment of vitiligo in children.

Several other findings were reported in this systematic review: 1) The combination of TCIs with phototherapy showed some improvement in outcomes compared to phototherapy alone; however, the statistical significance was marginal, and the clinical relevance of this difference should be carefully considered; 2) Similarly, the combination of topical pimecrolimus with a 308 nm excimer laser showed slightly better results compared to excimer laser therapy alone. Despite these findings, the clinical significance of these improvements remains uncertain.

Tacrolimus (0.03%)+NB-UVB showed variable efficacy with face lesions exhibiting a good to excellent response (100%), compared to patches on the limbs (75%).¹⁶ Lesions on the face and neck (73.08%) were more affected than those on the limbs (63.64%) by 0.1% tacrolimus+NB-UVB.¹⁵ The limited efficacy in acral regions necessitated additional therapies (e.g., prolonged phototherapy sessions or surgical interventions or to improve the permeability of drugs), indirectly increasing cumulative costs due to sequential treatment failures.

The action of TCIs (such as tacrolimus) in vitiligo as: 1) TCIs downregulate proinflammatory cytokines, such as tumor necrosis factor, and induce anti-inflammatory cytokines, such as interleukin IL-10; 2) Promote the migration and proliferation of melanocytes and melanoblasts; 3) Induce melanogenesis through increasing tyrosinase expression and dopa oxidase activity; 4) Reduce oxidative stress and improved antioxidant capacity.^{26–28}

Initial treatment with TCIs might cause local irritation, erythema, burning sensations, and itching.²⁹ The risk of these side effects might be heightened in combination therapy. There were concerns about whether TCIs could increase the risk of cancer.³⁰ However, two studies did not find significant evidence linking TCI use with an increased risk of skin cancer or lymphoma.^{31,32}

While TCI formulations generally carried higher upfront costs compared to TCS, the observed lower rates of treatment-disruptive adverse events might result in long-term cost savings through improved adherence and reduced complication management. Regional pharmacoeconomic analyses would be needed to optimize formulary decisions.

Conclusion

In conclusion, TCI therapy for childhood vitiligo appears to be non-inferior to TCS therapy. Moreover, the combination of TCI and phototherapy may offer superior results compared to phototherapy alone; however, this conclusion should be interpreted with caution due to the low certainty of evidence as assessed by GRADE. TCI, or its combination with other treatments, is a promising option for pediatric patients with vitiligo. However, further clinical trials with

larger sample sizes and more rigorous methodologies are needed for a more comprehensive quantitative analysis.

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Authors' contributions

Tiande Jiang: Study design and conception, data collection, analysis and interpretation of data, statistical analysis, writing of the article, or critical review of important intellectual content, final approval of the final version of the manuscript.

Wengting Wu: Data collection, analysis and interpretation of data, and statistical analysis.

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Research data availability

The entire dataset supporting the results of this study was published in this article.

Declaration of competing interest

None declared.

Editor

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ORIGINAL ARTICLE

Vertical ex vivo dermoscopy in diagnosing and differentiating skin lesions[☆]



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Melanocytic nevus;
Keratoses seborrheic;
Hemangioma;
Acanthoma

Abstract

Background: Publications on vertical ex vivo dermoscopy of skin lesions are sporadic and present only as case reports.

Objectives: This study defines, describes, and determines the importance of structures visible by vertical ex vivo dermoscopy in the diagnosis of pigmented, benign skin lesions and their distinction between themselves, and in relation to other skin lesions.

Methods: The prospective, descriptive study was conducted in two University centers. Digital images of completely excised skin lesions, fixed in formalin before further processing, were evaluated dermoscopically. For the analysis of horizontal ex vivo dermoscopy, pattern analysis was used, while for the vertical section, a description of the visible structures was made.

Results: The research sample consisted of 80 benign pigmented skin lesions obtained from 73 patients. Histopathological diagnosis of the evaluated lesions included 59 nevi, 17 seborrheic keratoses, 3 angiomas and 1 clear cell acanthoma. Seborrheic keratosis had the most variable presentation on vertical ex vivo dermoscopy. By analyzing the vertical section of the evaluated skin lesions, the importance of vertical ex vivo dermoscopy in the diagnosis and/or differentiation of blue nevus, seborrheic keratosis and angioma from other skin lesions was noted.

Study limitations: Small number of analyzed lesions, and inclusion of Caucasian patients only.

[☆] Study conducted was carried out in two University Centers: at the Institute of Pathology, Faculty of Medicine, Belgrade, Serbia and the Department of Pathology, Faculty of Medical Sciences, University Clinical Centre of Kragujevac, Serbia.

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Conclusions: Vertical *ex vivo* dermoscopy can contribute to the distinction between different pigmented benign skin lesions, as well as to their differentiation from other skin lesions. Furthermore, vertical section enables more accurate assessment of additional, descriptive lesional characteristics.

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Introduction

Diagnosis of skin lesions primarily involves a clinical examination (inspection and/or palpation), which has been sufficient in most cases. However, due to global changes (migration of population, changed climatic conditions, appearance of new viruses), many skin lesions are no longer typical and easily recognizable. Application of dermoscopy as a supplementary method enables more accurate diagnosis, by visualizing additional morphological (pigment and/or vascular) criteria.^{1–3}

Dermoscopy was designed primarily for the diagnosis and differentiation of pigmented skin lesions. However, over time, the indication spectrum for the use of dermoscopy has expanded to include non-pigmented changes, primarily malignant. In the further course, the application of dermoscopy has been extended to inflammatory, parasitic, hair and nail diseases, capillaroscopy, so that today dermoscopy is an indispensable part of the clinical examination.^{1–5}

The further development of dermoscopy was aimed at the application of dermoscopy by doctors of other specialties, not only dermatologists. Numerous papers present *ex vivo* dermoscopy, which is a new type of application of standard *in vivo* dermoscopy on freshly excised tissue or tissue fixed in formalin.^{6–9} Despite the negative sides of *ex vivo* dermoscopy (poor image quality, loss of vascular structures, significant color changes), published papers show the usefulness of its application as an auxiliary method available to the pathologist (directing the tissue section by indicating the field of interest for the vertical section).^{5,8–11}

A few published papers describe vertical *ex vivo* dermoscopy, which involves the application of dermoscopy on a vertical section of excised, fresh or fixed tissue.¹² A vertical plane view can be useful to surgeons practicing Mohs micrographic surgery for mapping positive margins.¹³ Due to the possibility of easy sharing of mobile photos of marked positive margins with the surgeon, a possible application is suggested in cases where the Mohs laboratory is not included in the surgical area.¹³

The authors recently published results of vertical *ex vivo* dermoscopy analysis of malignant skin lesions, which provides diagnostic information that could be valuable in clinical practice.¹⁴ Herein is the second part of the investigation, describing the results of vertical *ex vivo* dermoscopy in benign pigmented skin lesions.

Materials and methods

After the approval of the institutional Ethics Committee, a prospective, descriptive study was conducted in the field of vertical *ex vivo* dermoscopy. The research included the

Table 1 Criteria for inclusion and exclusion of patients in the study.

Inclusion	Exclusion
• Completely surgically removed skin lesion • Good quality of dermoscopic photographs • A clear histopathological diagnosis • Clinically assessed pigmentation of benign lesions $\geq 50\%$	• Poor quality of dermoscopic images • Descriptive histopathological report • Clinically assessed pigmentation of benign lesions $< 50\%$

analysis of pigmented benign lesions collected during the study.

The experimental part of the research was carried out in two University centers: the service for pathological-anatomical diagnostics, University Clinical Center Kragujevac, Faculty of Medical Sciences in Kragujevac, and the Institute of Pathology of the Faculty of Medicine, University in Belgrade. The research included patients whose lesions were completely surgically excised and sent for histopathological verification in the period from September 1 to December 31, 2019. The study was postponed due to the epidemiological situation caused by the COVID-19 epidemic and continued from January 1 to April 1, 2022.

The criteria for inclusion and exclusion of patients are shown in Table 1. Demographic characteristics of patients and clinical data were collected by reviewing histopathological referrals and outpatient records of patients.

The research was performed on tissue material obtained after surgical removal of skin lesions, fixed in formalin before further processing according to the protocol. First, clinical images of the excised tissue were taken. After that, the contact surface of the dermatoscope was covered with a thin, transparent foil tightened with a rubber band for jars, to prevent cross-contamination.¹⁵ After the dermoscopic photography of the horizontal aspect of the skin lesion, a vertical section of the tissue was made, which was also photographed according to the same previously described protocol.

A mobile phone camera previously connected to a handheld dermatoscope (Dermlite 3DLN, California, USA) was used for digital clinical and dermoscopic images. Dermoscopic photographs of vertical tissue sections were taken at different magnifications with a mobile phone camera. All digital photos were electronically transferred and saved to a computer for further evaluation. For dermoscopic analysis of horizontal *ex vivo* dermoscopy, pattern analysis was applied, which determined the existence of dermoscopic

structures specific to the type of lesion.¹⁶ By analyzing *ex vivo* dermoscopic photographs of tissue on a vertical section, a description of the available visible structures was made.

Apart from demographic characteristics of patients (age, gender), independent variables of excised lesions were also evaluated, i.e., localization and diameter of included lesions, and expression of dermoscopic structures on digital photographs of horizontal and vertical aspects of excised skin tissue.

The obtained data were entered into an Excel (Microsoft Office 2016) database for further statistical processing.

Statistical analysis

A commercial software package (version 22.0, SPSS Inc., Chicago, IL) was used for statistical processing of the obtained results. Histopathological finding was the gold standard of the study. The descriptive statistics methods used in the analysis of the obtained results were:

- Absolute and relative numbers, n (%).
- Measures of central tendency (arithmetic mean – X, median – Med).
- Measures of variability (Standard Deviation – SD, interval of variation).

Results

Characteristics of patients and pigmented benign skin lesions

The research sample consisted of 80 benign, pigmented skin lesions obtained from 73 patients, with a predominance of the female gender F = 47 (64.4%), M = 26 (35.6%). The age of the patients ranged from 7 to 83 years (X 44, Med 43.5). The size of the lesions ranged from 1 mm to 25 mm (X 7 mm, Med 6 mm). The trunk was the location for 50% (40/80) of the lesions, while 23/80 (28.7%) of the lesions were localized on the extremities, and 17/80 (21.3%) on the head and neck region. Almost all included patients had one lesion (67/73, 91.8%), five patients had 2 lesions (5/73, 6.8%), while only one patient had 3 lesions (1/73, 1.4%).

Histopathological diagnosis of pigmented, benign skin lesions is shown in Table 2.

Description of benign pigmented lesions using vertical *ex vivo* dermoscopy

Melanocytic nevus

Among the included lesions, the most common were melanocytic nevi 59/80 (73.75%), and among them, intradermal nevi were the most frequent 32/59 (54.2%).

Intradermal nevus

Intradermal nevi clinically presented classical features in 12/32 (37.5%), in the form of variably elevated papules, smooth in 11/32 (34.4%), or with papillomatous surface in 9/32 (28.1%). Classic intradermal nevi in the form of soft, hemispherical-shaped, pigmented papules with the pres-

Table 2 Histopathological diagnosis of pigmented benign skin lesions.

Nevus	n=59
Common intradermal	32
Common epidermo-dermal (compound)	19
Dysplastic	6
Reed nevus	1
Blue nevus	1
Seborrheic keratosis	n=17
Acanthotic	7
Irritated	6
Hyperkeratotic	4
Angioma	3
Clear cell acanthoma	1
In total	n=80

ence of a variable number of terminal hairs, on horizontal *ex vivo* dermoscopy, showed brown/blue pigmentation in the homogeneous distribution (Fig. 1A), in a cobblestone pattern (Fig. 1B), or in the form of a network/pseudo-network.

On the vertical section, in more than half of classic intradermal nevi 7/12 (58.3%) pigmentation was presented in the form of a line that followed the rise of the nevus (Fig. 1C). A smaller number of classic intradermal nevi 5/12 (41.7%) on the vertical section showed a variable shade of brown and bluish-brown pigmentation throughout the thickness of the nevus with more developed vascularization (Fig. 1D).

Eleven intradermal nevi (34.4%) had a clinical presentation in the form of variably elevated pigmented papules. On horizontal *ex vivo* dermoscopy, their presentation was in the form of a homogeneous dark brown pigmentation (Fig. 2A). On the vertical section, these nevi showed pigmentation as continuous lines of variable thickness and length (Fig. 2B).

Papillomatous, intradermal nevi were slightly less frequent 9/32 (28.1%). On horizontal *ex vivo* dermoscopy, a cobblestone global pattern dominated (Fig. 2C). On a vertical section, they were presented in the shape of a mushroom with darker papillae and a whitish base interspersed with short, linear blood vessels (Fig. 2D).

Epidermo-dermal (compound) nevus

There were almost twice as many epidermal-dermal nevi as intradermal nevi, 19/59 (32.2%). Clinically, they were presented in the form of macules and papules with mostly smooth, less often papillomatous surfaces. The global presentation on horizontal *ex vivo* dermoscopy was highly variable – globular, homogenous, reticular, or parallel global pattern (Fig. 3A–B). However, despite the variable clinical and horizontal dermoscopic presentation, on vertical section, the structure was similar, in the form of a line recolored according to the depth of melanin (Fig. 3C–D).

Dysplastic nevus

Histologically confirmed dysplastic nevi were a total of 6/59 (10.2%). Clinically, dysplastic nevi were presented as pigmented macules or papules with positive ABCD criteria.

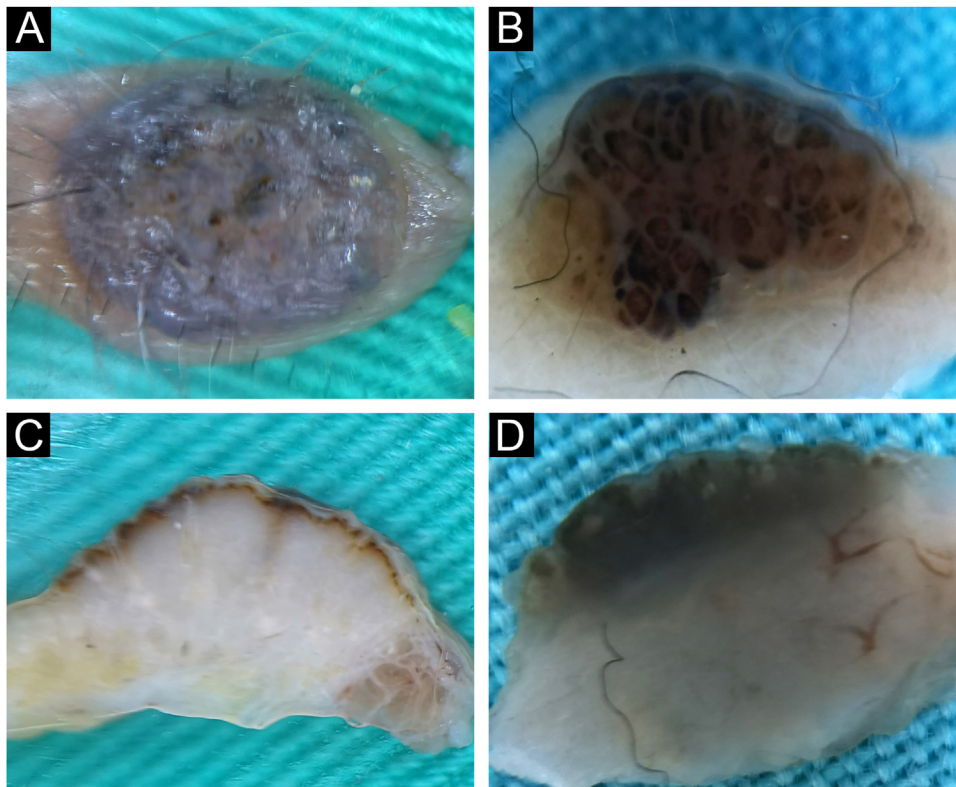


Fig. 1 Intradermal nevus. Horizontal *ex vivo* dermoscopy. Presentation as (A) dark blue homogeneous pigmentation. (B) Cobblestone global presentation. Vertical *ex vivo* dermoscopy. (C) Pigmentation in the form of a thin brown line extending above the whitish body with an indistinct lower border. (D) Pigmentation through the entire thickness of the nevus.

Dysplasticity was also confirmed by horizontal *ex vivo* dermoscopy by the general presence of chaos in the structure and color, with the presence of several criteria for the diagnosis of melanoma (Fig. 4A–B). Here, as well as with the epidermo-dermal nevus, despite the very different clinical and horizontal dermoscopic presentation, on the vertical section, the dermoscopic presentation was quite similar (Fig. 4C–D).

Blue nevus and Reed nevus

One blue nevus and one Reed nevus 1/59 (1.7%), were included in the research sample. The clinical and horizontal *ex vivo* presentation of the blue nevus was typical for this nevus (Fig. 5A). On the vertical section, the authors see the true depth of its spread (Fig. 5B).

Reed nevus was clinically presented as a dark pigmented macule, asymmetrical in shape. Horizontal *ex vivo* dermoscopy showed a homogeneous global pattern (Fig. 5C). On a vertical section, it had a similar presentation as a dysplastic nevus (Fig. 5D).

Seborrheic keratosis

A fifth of the analyzed benign lesions consisted of seborrheic keratoses 17/80 (21.25%), namely acanthotic type 7/17 (41.2%), irritated 6/17 (35.3%), and hyperkeratotic type 4/7 (23.5%). Clinically, acanthotic seborrheic keratoses presented as keratotic, pigmented papules. The majority of seborrheic keratoses of the acanthotic type showed clas-

sic characteristics of seborrheic keratosis on both horizontal and vertical *ex vivo* dermoscopy (Fig. 6A–B).

Irritated seborrheic keratoses did not have a specific clinical presentation. Also, the classical characteristics of seborrheic keratosis were less frequently manifested in both planes of *ex vivo* dermoscopy in the irritated type (Fig. 6C–D).

Hyperkeratotic seborrheic keratosis was clinically presented as a pigmented, hyperkeratotic papule/plaque. On horizontal *ex vivo* dermoscopy, a global cobblestone pattern was demonstrated, with no visible classic dermoscopic features of seborrheic keratosis. The presentation on the vertical section was more uniform in the form of hyperkeratotic epidermis and unchanged dermis.

Angioma

Out of a total of 80 benign lesions, angiomas were 3/80 (3.75%). The clinical presentation was in the form of bluish hemispherical/plane papules. On the horizontal section, the standard blue color of the angioma is visible with the absence of the specific lacunae (Fig. 7A–B). Darker pigmentation dominates on the vertical section compared to the horizontal plane, showing the true depth of its spread (Fig. 7C–D).

One out of three angiomas had a nonspecific finding on horizontal *ex vivo* dermoscopy (Fig. 7B), where differentially atypical blue nevus or melanoma cannot be excluded. However, a vertical section reveals structures that clearly indicate the diagnosis of angioma (Fig. 7D).

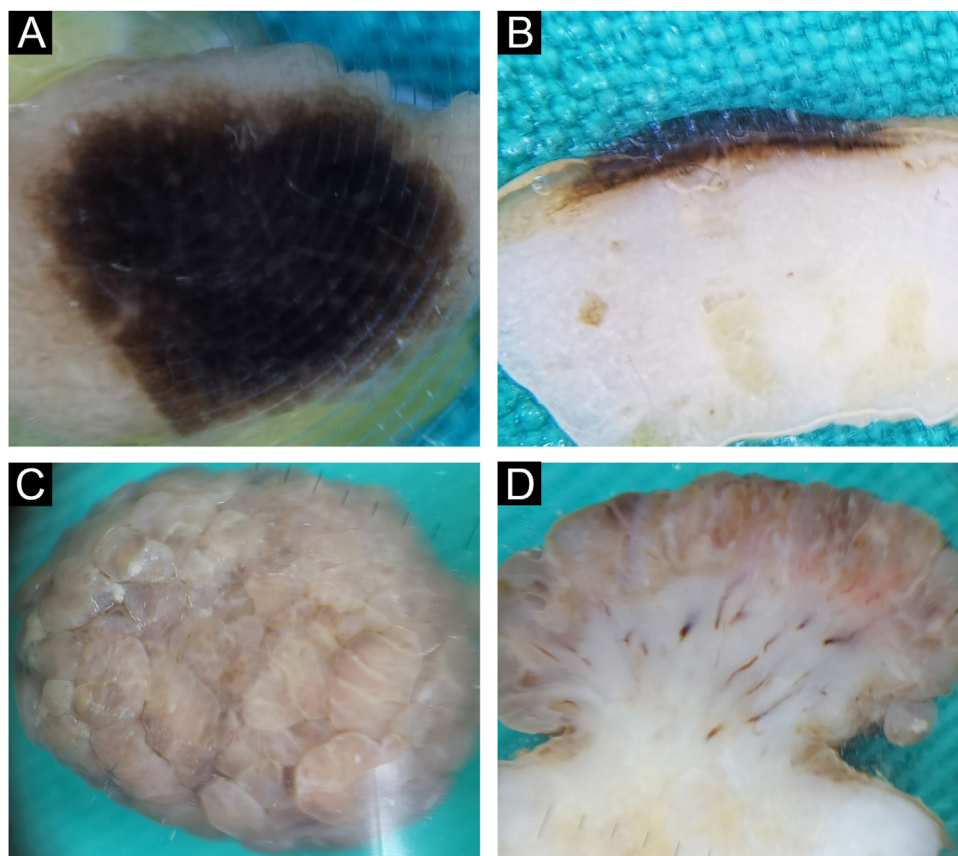


Fig. 2 Intradermal nevus. Horizontal ex vivo dermoscopy. (A) homogeneous global pattern. (C) cobblestone global pattern. Vertical ex vivo dermoscopy. (B) dark pigmentation in the form of a slightly curved line, without clear boundaries of the nevus body. (D) mushroom-shaped tumor, pigmentation of the upper third in the form of a strip of wavy surface with vascularized whitish body.

Clear cell acanthoma

Only one clear cell acanthoma was included in this study, 1/80 (1.25%). The clinical presentation was in the form of a bluish papule. Presentation on horizontal and vertical ex vivo dermoscopy was nonspecific.

Diagnosing and differentiating benign pigmented lesions using vertical ex vivo dermoscopy

During further research, the possibility of diagnosing and differentiating benign pigmented lesions using vertical ex vivo dermoscopy was established. In Figs. 7B, and 8A–B, the authors see pigmented lesions of non-specific findings on horizontal ex vivo dermoscopy. However, visible structures on the vertical section clearly indicate the diagnosis of angioma and seborrheic keratosis, respectively (Figs. 7D, and 8C–D).

In Fig. 9A–C, the authors see a seborrheic keratosis and a dysplastic nevus, which on a horizontal section meet the criteria for the diagnosis of melanoma. On the vertical section of both lesions, the authors see a similar presentation, with the presence of small, pigmented islands below the lower margin of the dysplastic nevus, which indicates a deeper than epidermal pigmentation, in contrast to the lower margin of seborrheic keratosis, which clearly limits epidermal pigmentation (Fig. 9B–D).

Also, the possibility of differentiation between benign and malignant lesions was investigated using vertical ex vivo dermoscopy. Fig. 10A–B shows a similar, inconclusive finding of both seborrheic keratosis and squamous cell carcinoma on horizontal ex vivo dermoscopy. In this case, the vertical section showed the involvement of skin layers and the depth of tumor extension (Fig. 10C–D).

Discussion

Despite numerous scientific papers confirming the utility of dermoscopy in daily practice, few papers have actually been published on ex vivo horizontal dermoscopy, while publications on ex vivo dermoscopy in the vertical plane include only sporadic case reports.^{17,18} Published papers on horizontal ex vivo dermoscopy show utility for pathologists,¹⁰ while for dermatologists and other clinicians involved in dermoscopy, the application of horizontal ex vivo dermoscopy does not provide any additional significant diagnostic information compared to in vivo standard dermoscopy. Moreover, a certain amount of diagnostic information is lost by interrupting the vascularization on the tissue section, which is the reason for its non-application in daily clinical practice.¹¹

Vertical ex vivo dermoscopy has been the least researched, which is why the main goal of this study was to define and describe the structures that can be seen on a

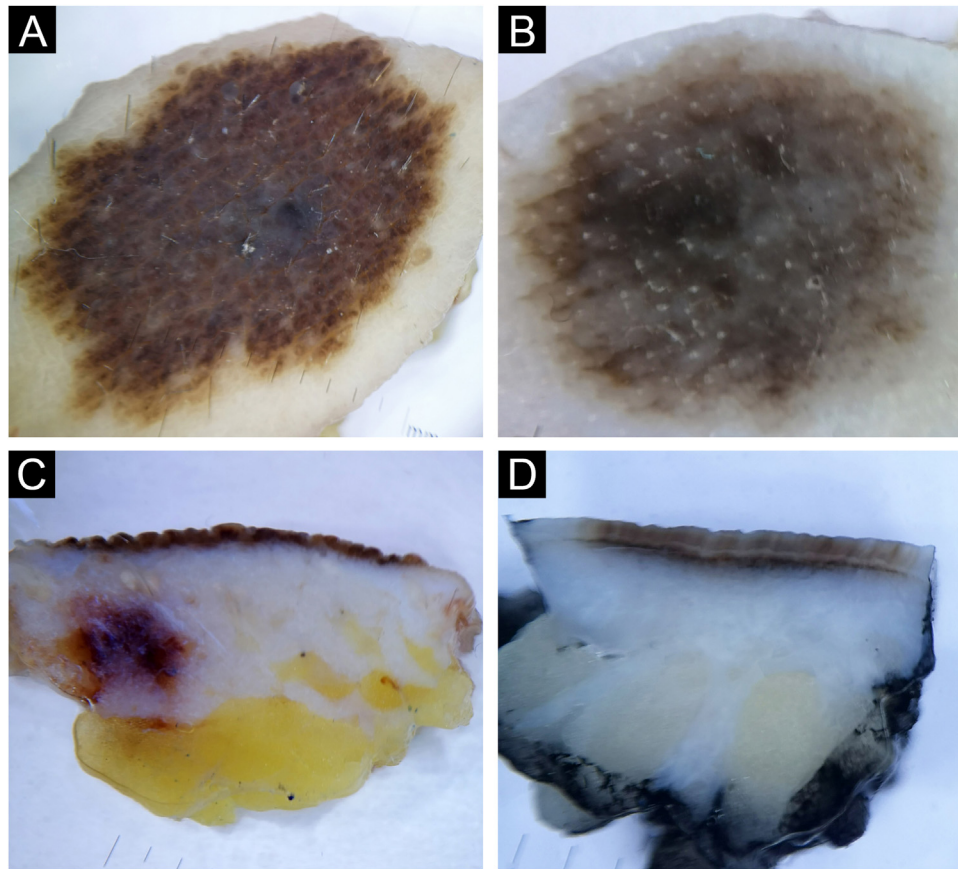


Fig. 3 Epidermo-dermal nevus. Horizontal *ex vivo* dermoscopy. (A) globular global pattern. (B) parallel furrow pattern (acral nevus). Vertical *ex vivo* dermoscopy. (C–D) linear pigmentation of different length, thickness, and color.

vertical section of the tissue and then to determine the possibility of the existence of additional characteristics that could be significant in diagnosis and/or differentiation of pigmented, benign skin lesions.

Diagnosis and differentiation of benign pigmented skin lesions

Melanocytic nevus

Clinical and dermoscopic diagnosis of a nevus is generally easy and does not require *ex vivo* dermoscopy. However, the authors were interested in whether, in rare cases of unclear diagnosis, vertical *ex vivo* dermoscopy can contribute to a more accurate diagnosis and/or differentiation of pigmented benign skin lesions. This study included the analysis of epidermo-dermal, intradermal, dysplastic nevi, and one blue and Reed nevus each.

On the vertical section of the nevus, different forms of pigmentation were seen. Intradermal papillomatous nevi had a unique form of pigmentation, which in the vertical plane presented the shape of a mushroom, made of vascularized whitish body, where the pigmentation covered the entire papillae. In all other evaluated nevi, on the vertical section, two basic forms of pigmentation were seen: superficial pigmentation, the different shape of which (flat, arcuate, hemispherical) follows the elevation of the nevus in the form of a line of variable thickness, length and shade

of color and pigmentation throughout the thickness of the nevus.

Pigmentations most often manifested different shades of the natural color of melanin, i.e., brown color. Visible colors on vertical *ex vivo* dermoscopy were correlated with the localization of melanin, i.e., darker shades of brown and black indicated the epidermal localization of melanin, while gray and blue indicated the dermal localization of the pigment. However, the blue nevus showed an exception to this rule when it comes to vertical dermoscopy. The blue color is visible clinically, on standard *in vivo*, as well as on horizontal *ex vivo* dermoscopy, on a vertical section, is dark brown to black throughout the thickness of the nevus (Fig. 7C–D). Also, apart from the blue nevus, one intradermal nevus showed a deviation from the rules of color and pigment localization on vertical dermoscopy. Visible blue pigmentation in the horizontal plane, on the vertical section, was presented as surface linear brown pigmentation (Fig. 1C).

Further analysis revealed the possibility of differentiating a blue nevus, in cases where clinically and by horizontal dermoscopy the authors see different shades of blue, as was the case with intradermal nevus (Fig. 1A) and Reed nevus (Fig. 5C). Both mentioned nevi, on vertical *ex vivo* dermoscopy, had a different presentation compared to the blue nevus. Superficial, darker, linear pigmentation was seen in the intradermal and Reed nevus (Figs. 1C, and 5D), while in the blue nevus, the spread of dark pigmentation made it

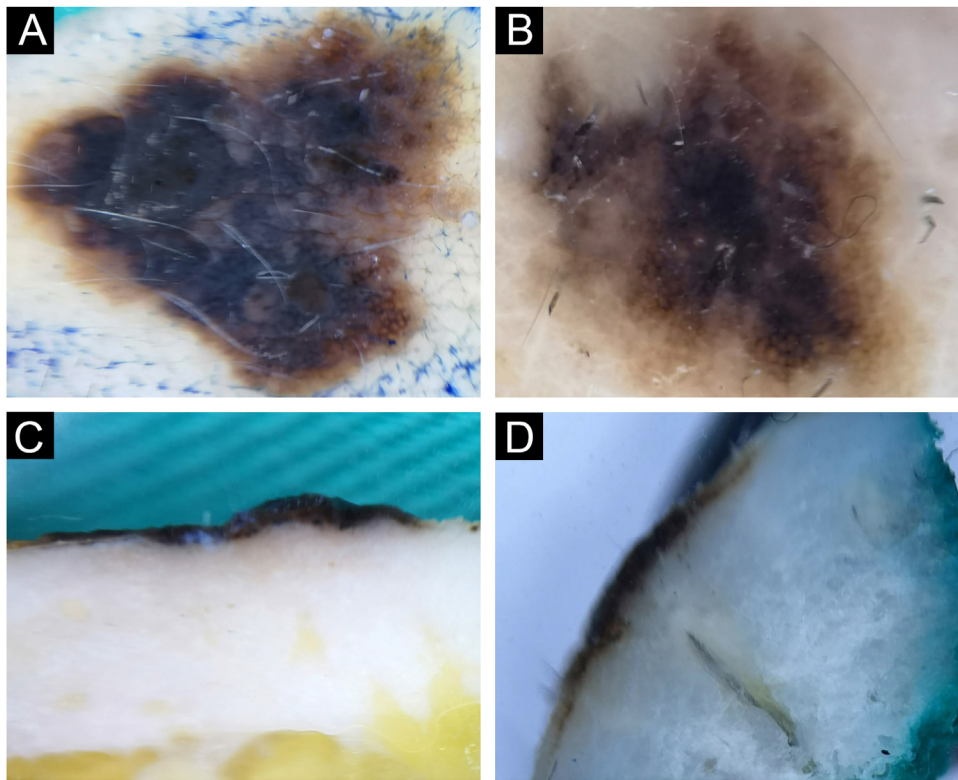


Fig. 4 Dysplastic nevus. Horizontal ex vivo dermoscopy. (A–B) Predominance of darkly pigmented homogeneous global pattern with conspicuous presence of one or more dermoscopic features of melanoma. Vertical ex vivo dermoscopy. (C–D) Superficial, thin, linear dark pigmentation.

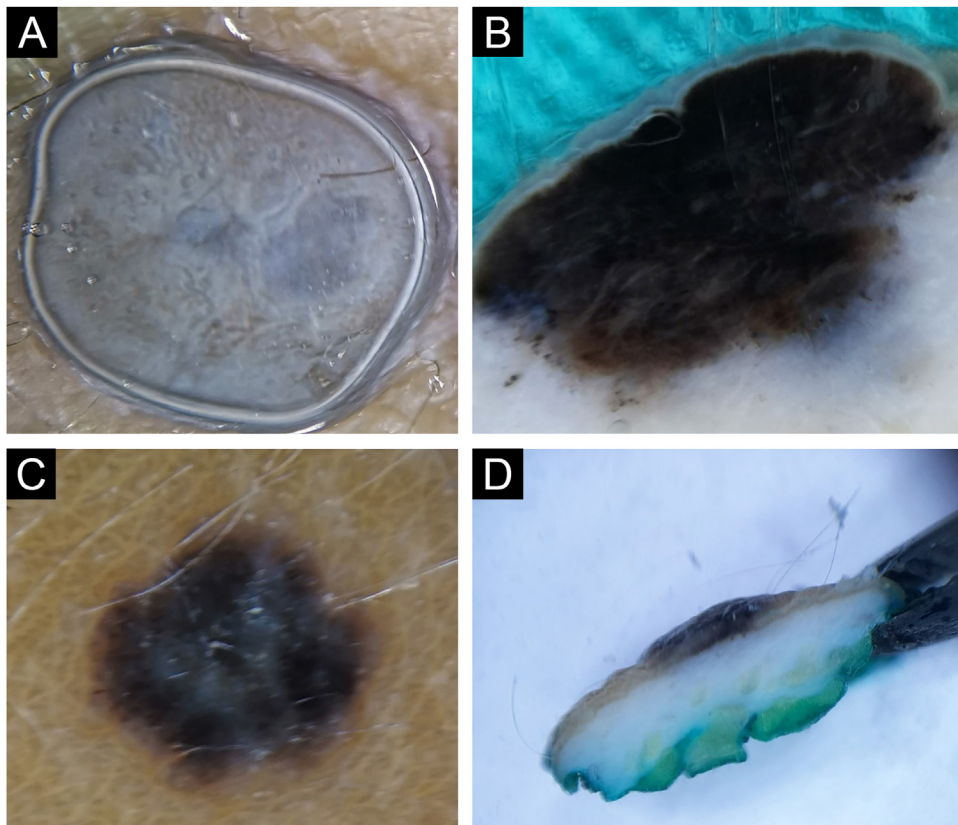


Fig. 5 Blue (A–B) and Reed (C–D) nevus. Horizontal ex vivo dermoscopy. (A) Homogeneous blue global presentation. (C) Homogeneous global pattern, asymmetric shape, irregular edges, and blue-whitish veil in the central part. Vertical ex vivo dermoscopy. (B) Visible deep, homogeneous, dark pigmentation with an irregular lower margin. (D) Linear, superficial dark pigmentation.

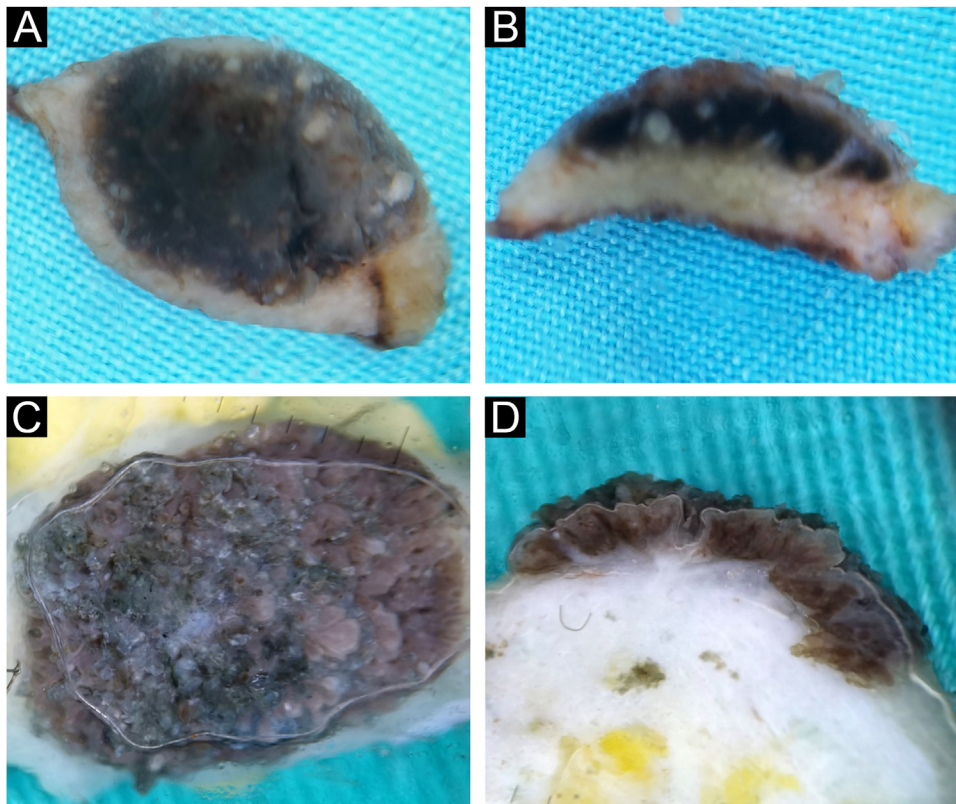


Fig. 6 Seborrheic keratosis, acanthotic type (A–B) and irritated (C–D). Horizontal *ex vivo* dermoscopy. (A) Milia-like cysts, clear demarcation, homogeneous pigment background. (C) Pronounced hyperkeratosis and papillomatous surface. Vertical *ex vivo* dermoscopy. (B) Thickened epidermis, milia-like cysts, dark pigmentation filling the epidermis. (D) Absence of milia-like cysts, brown, thickened wavy epidermis.

possible to see the true depth of its spread, which significantly contributes to its differentiation (Fig. 5B) compared to the other two nevi.

By reviewing the literature, the authors did not find any reports of vertical *ex vivo* dermoscopy of melanocytic nevi, so the authors could not compare the findings. However, the authors came across a report of vertical *ex vivo* dermoscopy of an acral melanoma. Maia et al. showed a vertical *ex vivo* dermoscopy of acral melanoma, where melanin, located within intermediate ridges, was clearly visible, reaffirming the parallel pattern of ridges and the diagnosis of acral melanoma.¹² Although the present study did not include acral melanoma, but a nevus, the authors compared the findings with the aim of establishing the possibilities of differentiation of the biological nature of acral melanocytic proliferations. In acral regions, determining the location of melanin is of vital importance in differentiating acral malignancies from benign proliferations. In cases of more intense pigmentation, it is more difficult to determine whether the pigment is in a groove or a ridge, so in some cases, it is used to cover the lesions with pen ink, which remains in the grooves after wiping with alcohol, which makes it easier to distinguish ridges from grooves.¹⁹

Horizontal *ex vivo* dermoscopy of the acral nevus included in the study (Fig. 3B–D), could not exclude acral melanoma due to the presence of several criteria for melanoma (presence of multiple colors, interruption of the

parallel groove pattern in the central part and in places on the periphery, general asymmetry of colors and structures. On vertical *ex vivo* dermoscopy, the authors could clearly see parallel brown, narrow lines within the thickened epidermis, with a wider lighter space between them, indicating furrow pigmentation and not ridge pigmentation as in melanoma, thus allowing their differentiation. Certainly, this finding should be confirmed by further research that would include only plantar melanocytic proliferations.

Seborrheic keratosis

Seborrheic keratoses generally do not present a diagnostic problem in daily clinical practice. However, in rare situations, especially when they are pigmented and irritated, seborrheic keratoses require further diagnostics. This study included the analysis of acanthotic, hyperkeratitic, and irritated seborrheic keratoses.

Acanthotic seborrheic keratoses mostly had a classic presentation on horizontal *ex vivo* dermoscopy, with the manifestations that are also seen on standard *in vivo* dermoscopy (comedo-like openings, milia-like cysts, clear limitation).^{4,13} On the vertical section, the tumor tissue was limited to the epidermis, with the recognition of the same typical characteristics of seborrheic keratosis, but hyperkeratotic and irritated seborrheic keratoses less frequently showed their typical characteristics, both in the horizontal and vertical planes. Of the dermoscopic features of sebor-

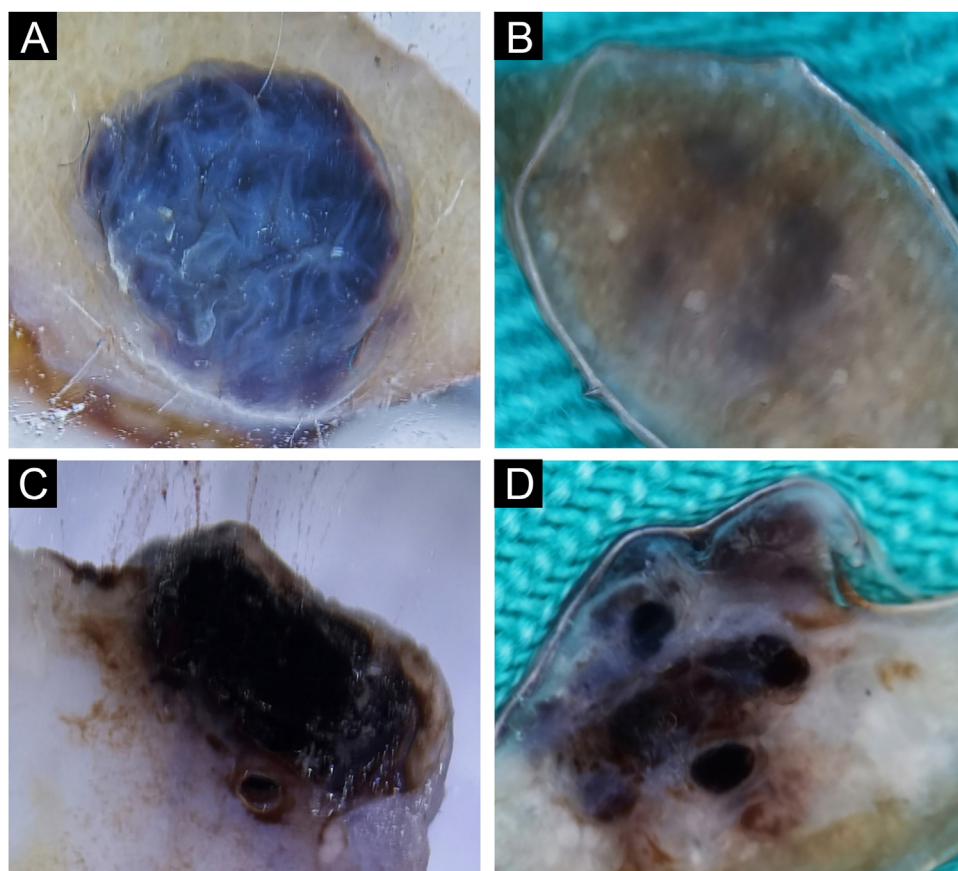


Fig. 7 Angioma. Horizontal *ex vivo* dermoscopy. (A) Typical presentation as homogeneous dark blue pigmentation. (B) Atypical presentation as asymmetric, homogeneous light blue pigmentation. Vertical *ex vivo* dermoscopy. (C) Deep homogeneous indigo-black pigmentation, irregular in shape. (D) Typical lacunae and deep homogeneous indigo dark background.

rhic keratosis, milia-like cysts were identically presented on vertical sections as well as on horizontal dermoscopies.

Further analysis included the possibility of diagnosis and differentiation of seborrheic keratoses in unclear cases, with variable contribution of vertical *ex vivo* dermoscopy. In the case of inconclusive findings of horizontal dermoscopy in irritated seborrheic keratoses, with a vertical section, the authors encountered characteristics that indicated the diagnosis of seborrheic keratoses (involvement of only the epidermis, clear limitation of the pigmented island, regular shape and edges, presence of typical features). However, in the case of acanthotic seborrheic keratoses, where the differential diagnosis of horizontal *ex vivo* dermoscopy included dysplastic nevus/melanoma, the finding of the vertical section suggested melanocytic lesion as well (dysplastic, intradermal nevus, in situ melanoma) and not seborrheic keratosis (Fig. 9B).

Nevertheless, vertical *ex vivo* dermoscopy in certain cases of hyperkeratotic lesions can contribute to the differentiation of seborrheic keratoses from invasive SCC. In Fig. 10, the authors see a similar presentation of seborrheic keratoses and invasive SCC on horizontal *ex vivo* dermoscopy. However, on a vertical section, epidermal hyperkeratosis without changes in the dermis clearly distinguishes seborrheic keratosis from invasive SCC, in which,

in addition to epidermal hyperkeratosis, the authors also see deep involvement of the dermis and subcutis by tumor tissue.

The authors believe that in cases of unclear diagnosis, especially in cases that include skin malignancy in the differential diagnosis, it is worth allocating a little more time for a vertical section and analysis. If the authors find typical characteristics of seborrheic keratosis, vertical *ex vivo* dermoscopy can help us in diagnosis, and if they are absent, the authors can look at the depth of infiltration in order to differentiate between benign and malignant proliferations. Certainly, there is also a scenario where the authors will not receive any significant additional information.

Angioma

Typical angiomas are easily diagnosed by clinical examination, while standard dermoscopy increases the certainty of the diagnosis. However, in rare cases, angiomas can be atypical, when they require further diagnostics. Two of the three evaluated angiomas, on horizontal *ex vivo* dermoscopy, showed typical bluish pigmentation interspersed with lighter short lines. Typical angiomas on vertical section presented as homogeneous, deep, dark brown pigmentation instead of the expected blue color visible on horizontal dermoscopy.

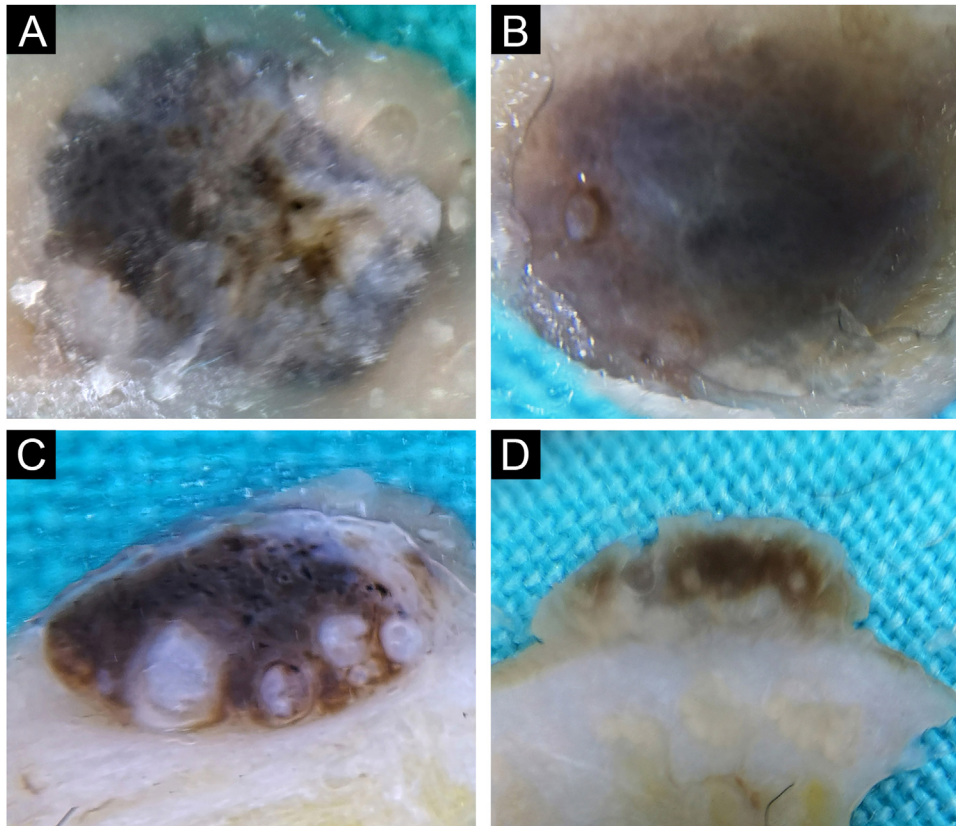


Fig. 8 Irritated seborrheic keratosis. Horizontal *ex vivo* dermoscopy. (A) Whitish fields, blue-white veil, asymmetry of color and shape. (B) Non-specific blue-brown pigmentation. Vertical *ex vivo* dermoscopy. (C–D) Epidermal involvement, striking milium-like cysts, clear regular margins.

Of the dermoscopic characteristics of angioma, lacunae are identically presented on vertical section as well as on horizontal dermoscopy.

When it comes to angiomas, the authors do not recommend vertical *ex vivo* dermoscopy as a routine analysis. However, one angioma in this study did not have the typical dermoscopic finding of an angioma in the horizontal plane, and given the partial bluish pigmentation of an asymmetric shape, the differential diagnosis included an atypical blue nevus, possibly melanoma. Analysis of the vertical plane revealed lacunae, easily visible, typical dermoscopic characteristics of angioma² in the form of dark, oval, clearly limited globules. In this case, vertical *ex vivo* dermoscopy contributed to the diagnosis of angioma and its differentiation from atypical melanocytic lesions.

Clear cell acanthoma

This study included only one clear cell acanthoma, which is also rarely diagnosed in daily clinical practice. Due to the variable clinical morphology, it is diagnosed mainly histologically. It is most often presented as a red papule on the lower extremities, while pigmentation is rarely seen.²⁰ The dermoscopic image of clear cell acanthoma is dominated by the vascular pattern, where the blood vessels are in the form of dots/globules with a characteristic linear or serpen-

tine arrangement reminiscent of a string of pearls on a pale reddish background.²⁰

The finding of horizontal *ex vivo* dermoscopy of the analyzed acanthoma was atypical, inconclusive in the form of homogeneous bluish pigmentation that indicated an atypical blue nevus or angioma in the differential diagnosis. On a vertical section, the acanthoma was presented as a slightly arched, brown pigmentation with increased vascularization in the central part of the whitish tumor tissue.

Although dermoscopy in both planes did not contribute to the diagnosis of clear cell acanthoma, in cases of unclear diagnosis, the authors' recommendation is to perform an additional analysis of the vertical section, as it may contribute to narrowing the differential diagnosis. In this case, the authors can rule out blue nevus and angioma by dermoscopic analysis of the vertical section, which shows deep pigmentation in contrast to the superficial pigmentation seen in clear cell acanthoma. It should be noted that the distribution of punctate blood vessels like a string of pearls is not pathognomonic for clear cell acanthoma, but can be seen, among others, in pigmented seborrheic keratosis. In this case, a vertical examination can allow us to confirm or exclude seborrheic keratosis due to the presence or absence of dermoscopic characteristics of seborrheic keratosis.

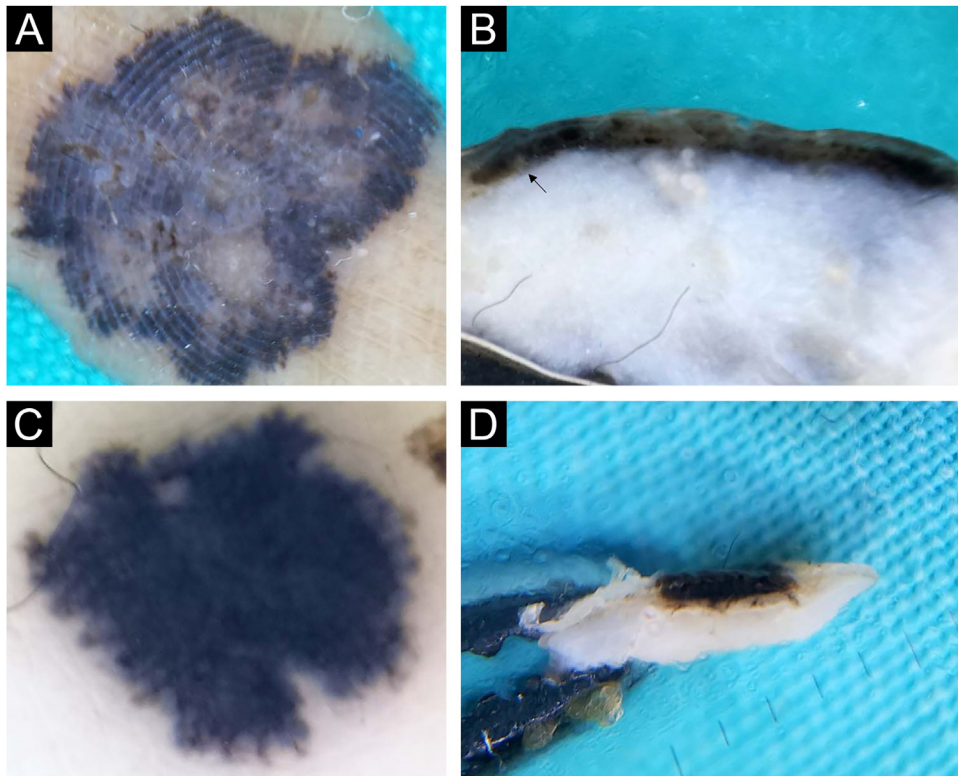


Fig. 9 (A-B) Seborrheic keratosis, acanthotic type. (C-D) Dysplastic nevus. Horizontal *ex vivo* dermoscopy. (A-C) Numerous pseudopods along the periphery of the tumor with indigo blue pigmentation interspersed with whitish structures. Vertical *ex vivo* dermoscopy. (B) Lesion confined to the epidermis, pigmentation in the form of a line with a regular lower margin and the presence of one milia-like cyst (arrow). (D) Superficial, dark homogeneous linear pigmentation with tiny islands of pigmentation protruding from the lower margin.

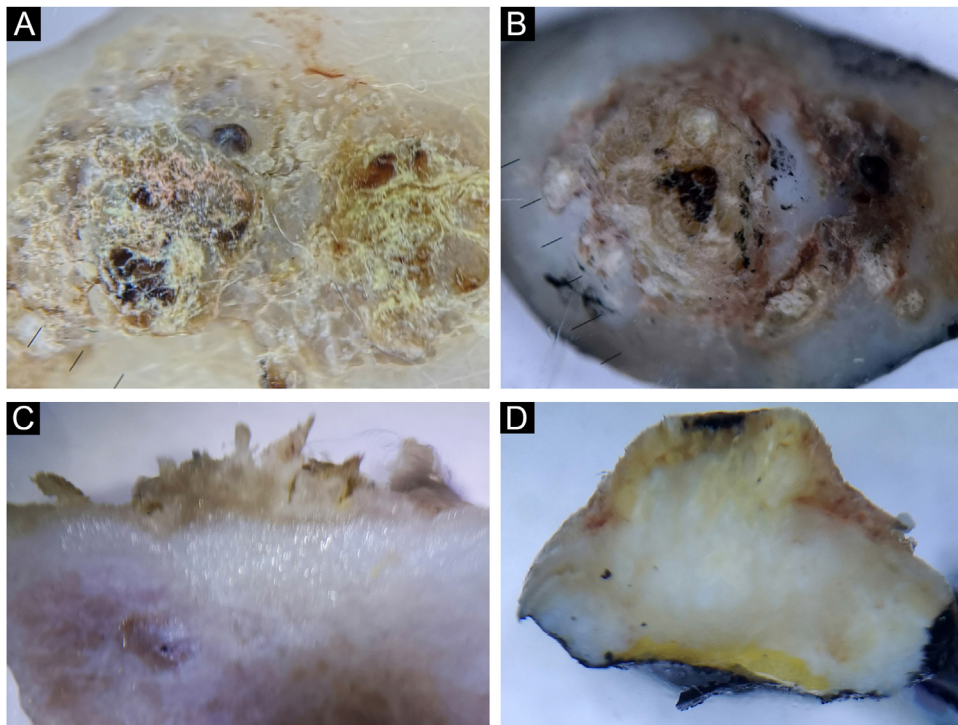


Fig. 10 (A-C) Seborrheic keratosis, hyperkeratotic type. (B-D) Invasive squamous cell carcinoma. Horizontal *ex vivo* dermoscopy. (A-B) Visibility of whitish structures, crusts, yellowish scales. Vertical *ex vivo* dermoscopy. (B) Involvement of the epidermis alone, in the form of whitish hyperkeratosis of an irregular surface, with normal dermis. (D) Hyperkeratosis of the epidermis under which there is a whitish tumor body infiltrating the dermis and the subcutaneous fat.

As the authors expected, due to the rarity of the literature review, we did not come across a description of vertical *ex vivo* dermoscopy of clear cell acanthoma.

Conclusions

In conclusion, vertical *ex vivo* dermoscopy provides instant insight into significant descriptive characteristics of skin lesions. Using this technique, the possibility of diagnosis and/or differentiation of blue nevus, seborrheic keratosis, and angioma from other pigmented skin lesions was established, as well as distinguishing hyperkeratotic seborrheic keratosis from invasive squamous cell carcinoma.

It should be emphasized that the resolution of vertical *ex vivo* dermoscopy is not sufficient for evaluating changes at the cellular level or detecting narrow tumor infiltrates.

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Authors' contributions

Mirjana Popadić: Study concept and design; data collection, or analysis and interpretation of data; statistical analysis; writing of the manuscript or critical review of important intellectual content; critical review of the literature.

Dimitrije Brasanac: Data collection, or analysis and interpretation of data; critical review of the literature; final approval of the final version of the manuscript.

Danijela Milošev: Data collection, or analysis and interpretation of data.

Ana Ravić Nikolić: Critical review of the literature; final approval of the final version of the manuscript.

Slobodanka Mitrović: Data collection, or analysis and interpretation of data; critical review of the literature; final approval of the final version of the manuscript.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

The authors declare no conflicts of interest. The funder had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Luciana P. Fernandes Abbade.

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REVIEW

Efficacy and safety of nemolizumab in prurigo nodularis: a systematic review and meta-analysis of randomized controlled trials[☆]



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Abstract

Background: Prurigo nodularis (PN) is a chronic, debilitating inflammatory skin disorder characterized by persistent itching, firm pruritic nodular lesions, and evidence of frequent scratching, like excoriation, and lichenification. Nemolizumab, a monoclonal antibody targeting IL-31, has shown significant improvements in skin lesions, itching, and sleep disturbances by reducing type 2 immune responses in PN.

Objectives: Evaluate the efficacy and safety of nemolizumab in treating PN by systematically analyzing randomized controlled trials (RCTs). **Methods:** The authors conducted a systematic review and meta-analysis by searching Pubmed, Embase, Cochrane Central and Scopus for RCTs comparing nemolizumab to placebo for PN. Statistical analysis used R Studio 4.3.2.

Results: Three trials, involving 630 patients, were included. Nemolizumab significantly reduced pruritus at week-4 (MD = −32.04; 95% CI: −38.47, −25.62) and at week-16 (MD = −347.34; 95% CI: −1039.71, 345.04). Investigator's Global Assessment (IGA) success favored Nemolizumab at week-16 (RR = 3.50; 95% CI: 2.18, 5.63). No significant differences were observed in adverse events (RR = 1.10; 95% CI: 0.97, 1.25) or serious adverse events (RR = 0.77; 95% CI: 0.43, 1.39). Nemolizumab also significantly reduced neurodermatitis.

[☆] Study conducted at the Universidade de Santo Amaro, São Paulo, SP, Brazil; Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil; Universidade de Passo Fundo, Passo Fundo, RS, Brazil; Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, RS, Brazil; Universidade Federal do Piauí, Teresina, PI, Brazil.

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Study limitations: Limitations include variability in treatment duration, small sample sizes, and the lack of direct comparisons with other biologics.

Conclusion: Our meta-analysis shows that Nemolizumab significantly improves pruritus, IGA success rates, and PAS > 75% in treating patients with moderate to severe PN. Its safety profile is favorable, with no significant differences in adverse events compared to placebo. These findings support Nemolizumab as a viable treatment for moderate to severe PN.

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Introduction

Prurigo nodularis (PN) is a chronic, debilitating inflammatory skin disorder characterized by persistent itching, firm pruritic nodular lesions, and evidence of frequent scratching, like excoriation and lichenification. It is considered a relatively uncommon illness, impacting 72 out of every 100,000 people in the United States, and primarily affects middle-aged to older adults, women, and individuals of African descent.^{1,2} The condition can also affect patients' mental and emotional health, being strongly linked to mental health issues, including depression, anxiety, and inclinations toward self-harm or suicidal thoughts.³

PN pathogenesis has been linked to an intense inflammatory response in the skin, with dense dermal infiltrates and cell release mediators such as Interleukin (IL)-13, other cytokines, and neuropeptides, which contribute to inflammation and intense pruritus. Neural dysregulation is also evident, with increased dermal innervation and elevated Nerve Growth Factor Receptor (NGFR) and PGP-9.5 density. At the same time, the epidermis lacks NGFR-positive fibers and has reduced PGP-9.5 fibers, likely due to repetitive scratching. Dysregulated neuropeptides, including elevated levels of substance P and calcitonin Gene-Related Peptide (CGRP), further contribute to PN pathogenesis. Substance P activates neurokinin-1 receptors, while CGRP drives neurogenic inflammation, regulates eosinophils and mast cells, disrupts opioid receptor expression, and intensifies pruritus.^{4,5}

Therapies for PN are limited, with dupilumab and the recently approved nemolizumab being the only systemic treatments approved by the US Food and Drug Administration (FDA).^{6,7} Other available pharmacological interventions are off-label, although there is notable variation in treatment regimens, therapeutic aims, and safety/effectiveness. Interleukin-31, a cytokine that elicits itch sensation, is significantly increased in PN patients in comparison with healthy individuals; therefore, blocking interleukin-31 presents a highly promising therapeutic strategy for addressing the disease.^{5,7}

Nemolizumab, a humanized monoclonal antibody, disrupts IL-31 by binding to the IL-31 receptor α subunit and blocking receptor activation signaling. This reduces type 2 immune responses in PN, easing the disease's underlying inflammation and symptoms.⁸ Current clinical studies have shown significant improvements in skin lesions, itching, and sleep disturbances with Nemolizumab treatment.^{1,9,10}

A previous network meta-analysis has assessed the efficacy of treatment choices for PN, including nemolizumab,

although it incorporated only one randomized controlled trial (RCT) assessing nemolizumab.¹¹ Nilforoushadeh et al. conducted a systematic review on interleukin-31 inhibitors for PN treatment, yet they did not perform a meta-analysis to provide a more precise estimate of effect size and included a broader range of study designs, such as cohort studies.¹² While these studies have provided valuable insights into the efficacy and safety of Nemolizumab, there is a need for a comprehensive synthesis of the latest available data to better understand the benefits and risks of this agent in patients with PN. Our meta-analysis fills this gap by including three high-quality RCTs, enabling a more precise evaluation of the efficacy and safety of nemolizumab in prurigo nodularis. By focusing solely on RCTs, the authors provide a clearer, evidence-based understanding of the treatment's benefits and risks, crucial for guiding clinical practice and future research.

Therefore, this meta-analysis aims to systematically review and synthesize the available evidence on the efficacy and safety of Nemolizumab in patients with PN.

Methods

This systematic review and meta-analysis were conducted in accordance with the protocols established by the Cochrane Collaboration and adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The study protocol was pre-registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identification number CRD42024626990.

Search strategy and Data extraction

The authors systematically searched databases, including PubMed, Embase, Scopus, and Cochrane Central Register of Controlled Trials, from inception to December 12, 2024, following the PRISMA Statement guidelines and the Cochrane Collaboration Handbook for Systematic Reviews of Interventions. The following search terms were employed: "nemolizumab", "prurigo nodularis", and "prurigo". The complete search strategy is available in the [Supplementary Material](#).

Two authors (ACPV and KKH) independently extracted data on study characteristics, interventions, and outcomes of interest. Any discrepancies were addressed through consensus among the authors.

Outcomes evaluated included: Percent change from baseline in Peak Pruritus Numerical Rating Scale (PP-

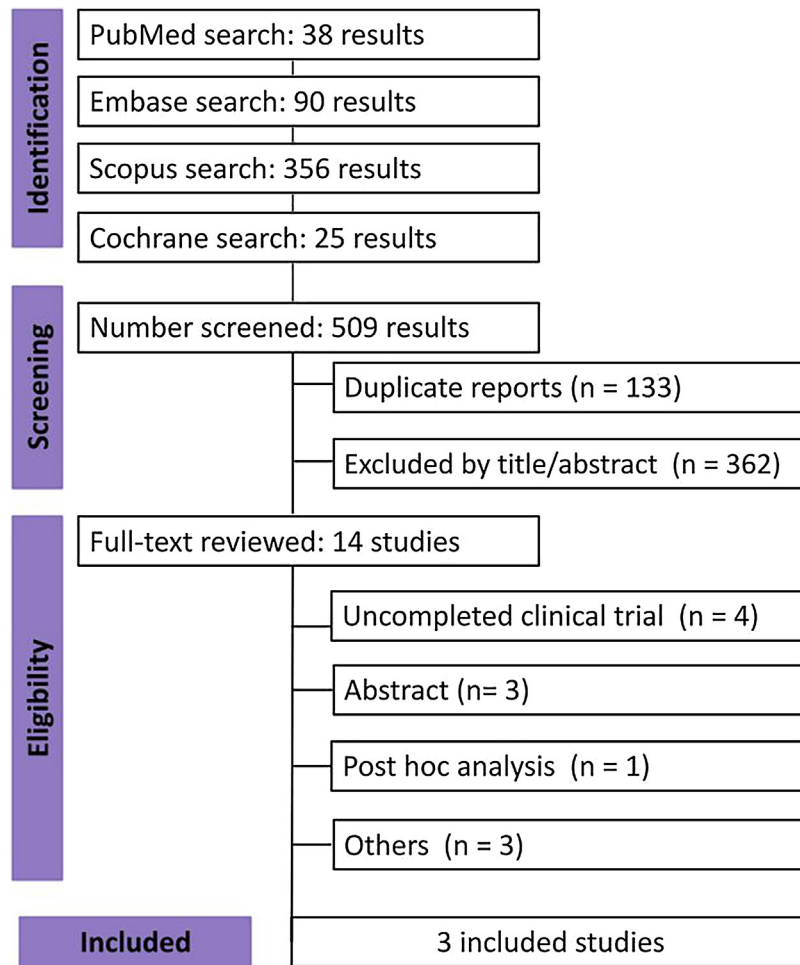


Fig. 1 PRISMA search flow diagram.

NRS) at 4-, 12- and 16-weeks, Investigator's Global Assessment (IGA) success at 12-weeks, Prurigo Activity Score (PAS) >75% healed pruriginous lesions at 12- and 16-weeks, adverse events (AEs), serious adverse events (SAEs), any adverse events leading to discontinuation, alopecia, cardiac disorders, contact dermatitis, dry skin, eczema, peripheral edema, gastrointestinal disorders, infections and infestations, injection related reaction, musculoskeletal and connective tissue disorders, nervous system disorders, neurodermatitis, rash, rosacea, urticaria.

Eligibility criteria and study selection

Two reviewers (ACPV and GCGC) independently screened the articles for inclusion, with any discrepancies resolved by consensus. Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: 1) RCTs; 2) Comparing Nemolizumab therapy with placebo; 3) Reporting at least one clinical outcome such as PP-PRS or adverse events. Exclusion criteria included: 1) No control group; 2) Not reporting outcomes of interest; 3) Non-randomized designs; 4) Studies only available in abstract form; 5) Post hoc analysis; 6) Uncompleted clinical

trials; 7) Studies involving concomitant corticosteroid use.

Quality assessment

Two authors (ACPV and GCGC) assessed the quality of the included studies. As suggested by Cochrane, risk of bias was assessed using the Cochrane Risk-of-Bias tool for randomized trials (RoB-2).

Statistical analysis

This systematic review and meta-analysis were performed and reported following the Cochrane Collaboration Handbook for Systematic Review of Interventions and PRISMA Statement guidelines. Standardized Mean Differences (SMD) with 95% Confidence Intervals were used to compare continuous outcomes. The authors assessed heterogeneity with I^2 statistics and the Cochran Q test; p-values < 0.10 and I^2 > 25% were considered significant for heterogeneity. Statistical analysis was performed using R Studio 4.3.2.

Table 1 Baseline characteristics of included studies.

Study, Year	Eligibility Criteria	Treatment Duration	Patients (n) NEMO/PB	Age ^a (years) NEMO/PB	Female (%) NEMO/PB	Weight ^a (kg) NEMO/PB	Weekly average PP-NRS score ^a NEMO/PB	DLQI ^a NEMO/PB
Ständer et al. 2024 (Olympia 1) ¹⁰	Adults with PN $\geq$ 6 months, severe pruritus (PP-NRS $\geq$ 7 in the week prior to baseline), $\geq$ 20 bilaterally distributed nodules (upper/lower limbs or trunk), and IGA $\geq$ 3.	24 weeks	190/96	57.5/57.6	57.9/58.3	87.1/80.8	8.5 /8.4	17.1/16.9
Kwatra et al. 2023 (Olympia 2) ¹	Adults $\geq$ 18 with PN $\geq$ 6 months, severe pruritus (PP-NRS $\geq$ 7 in the week prior to baseline), $\geq$ 20 bilaterally distributed nodules (arms, legs, or trunk), and IGA score of 3 or 4.	16 weeks	183/91	53.7/50.8	61.7/60.4	79.7/80.8	8.5/8.4	16.5/17.1
Ständer et al. 2020 ⁹	Adults with PN and severe pruritus (mean score $\geq$ 7 for $\geq$ 6 months), $\geq$ 20 bilateral nodules on the upper limbs, with or without trunk/lower limb.	12 weeks	34/36	59.7/52.4	55.8/61.1	81.6/80.3	8.4/8.4	16.9/15.8

PN, Prurigo Nodularis; PP-NRS, Peak Pruritus Numerical Rating Scale (0 = none, 10 = worst itch); IGA, Investigator's Global Assessment (0–4; higher scores = more severe prurigo nodularis); NEMO, Nemolizumab; PB, Placebo; DLQI, Dermatology Life Quality Index (0–30; higher scores = more quality of life impairment).

^a Mean or median.

Results

Study selection and baseline characteristics

As shown in Fig. 1, the initial search identified 509 results. After eliminating duplicate records and ineligible studies based on title and abstract, 14 studies remained for full-text review based on the inclusion criteria. Of these, three studies were included in this systematic review and meta-analysis, comprising 630 patients. Among these, 407 (65%) patients received Nemolizumab, while 223 (35%) were given a placebo. Follow-up periods ranged from 16 to 32 weeks.

The mean age of participants varied from 50.8 to 59.7 years, with a mean weight ranging from 79.7 to 87.1 kg. Study and patient characteristics are summarized in Table 1.^{1,9,10}

Dose and duration of nemolizumab therapy

In Ständer et al. 2024, the trial included a screening period of 1- to 4-weeks, a 24-week treatment phase, and an 8-week follow-up. Participants were randomized to receive subcutaneous injections of nemolizumab monotherapy or matching placebo every 4-weeks for 24-weeks. Patients weighing < 90 kg received an initial dose of nemolizumab, 60 mg, fol-

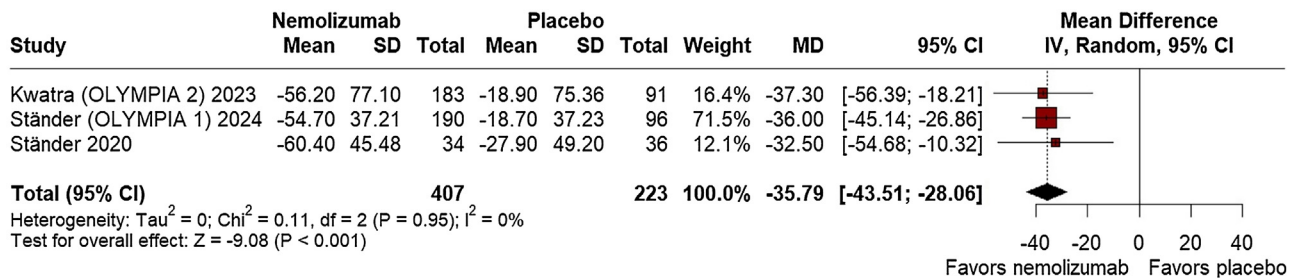


Fig. 2 Percent change from baseline in peak pruritus numerical rating scale at 16 weeks.

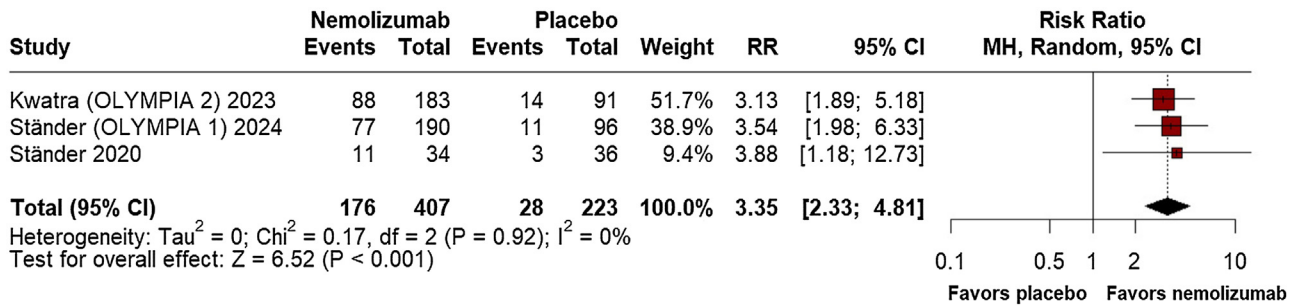


Fig. 3 Investigator's Global Assessment (IGA) success rates at 12 weeks.

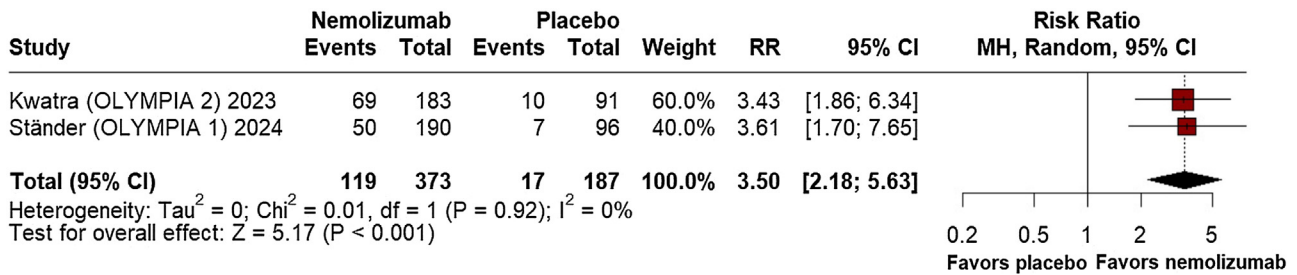


Fig. 4 Investigator's Global Assessment (IGA) success rates at 16 weeks.

lowed by 30 mg every 4-weeks, while those weighing ≥ 90 kg received 60 mg of nemolizumab every 4-weeks.

In Kwatra et al., the study featured a screening period of 1- to 4-weeks, a 16-week treatment phase, and an 8-week follow-up. Patients were randomized to receive subcutaneous injections of nemolizumab or matching placebo, with those weighing <90 kg receiving an initial dose of 60 mg (administered as two 30 mg injections) followed by 30 mg every 4-weeks, and those weighing ≥ 90 kg receiving 60 mg (two 30 mg injections) every 4-weeks.

The Ständer et al. 2020 study featured a 12-week treatment phase and follow-up visits at weeks-16 and -18. Patients were randomized to receive nemolizumab at a dose of 0.5 mg per kilogram of body weight or placebo, with subcutaneous injections administered at baseline, week-4, and week-8. Rescue therapy for pruritus was allowed from day-29 onward, with topical therapies permitted while continuing nemolizumab or placebo, and systemic therapies requiring discontinuation of the study drug.

Pooled analysis of all studies

Regarding efficacy outcomes, nemolizumab demonstrated a significant percent change from baseline in the Peak Pruritus Numerical Rating Scale Least Squares (LS) Mean at week-4 ($MD = -32.04$; 95% CI: $-38.47, -25.62$; $p \leq 0.001$; $I^2 = 0\%$; Supplement Fig. S1), favoring the intervention. At week-12, however, no significant difference was observed between the groups ($MD = -347.34$; 95% CI: $-1039.71, 345.04$; $p = 0.325$; $I^2 = 0\%$; Supplement Fig. S2). By week-16, nemolizumab again showed considerable improvement in pruritus reduction ($MD = -35.79$; 95% CI: $-43.51, -28.06$; $p \leq 0.001$; $I^2 = 0\%$; Fig. 2). Investigator's Global Assessment (IGA) success rates consistently favored nemolizumab at week-12 ($RR = 3.35$; 95% CI: 2.33, 4.81; $p \leq 0.001$; $I^2 = 0\%$; Fig. 3), with a significant relative increase at week-16 ($RR = 3.50$; 95% CI: 2.18, 5.63; $p \leq 0.001$; $I^2 = 0\%$; Fig. 4).

In terms of the proportion of patients achieving PAS > 75 , the results at week-12 favored nemolizumab ($RR = 3.35$; 95%

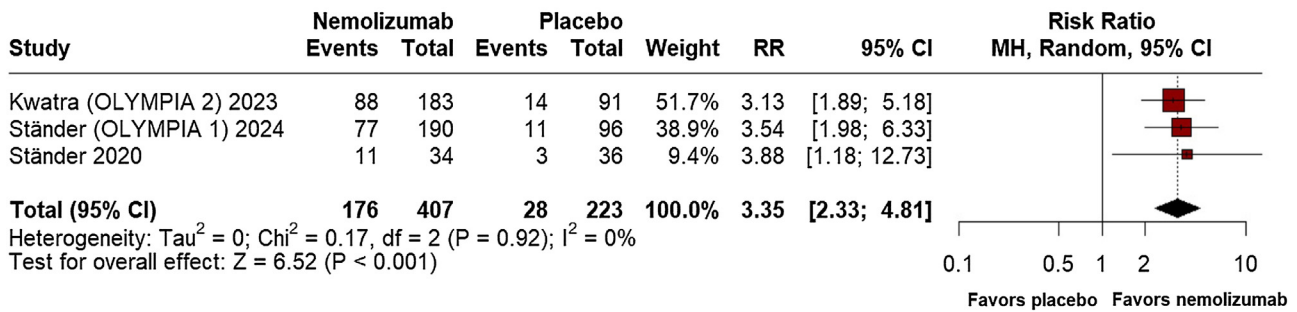


Fig. 5 Prurigo Activity Score (PAS) >75% healed pruriginous lesions at 12 weeks.

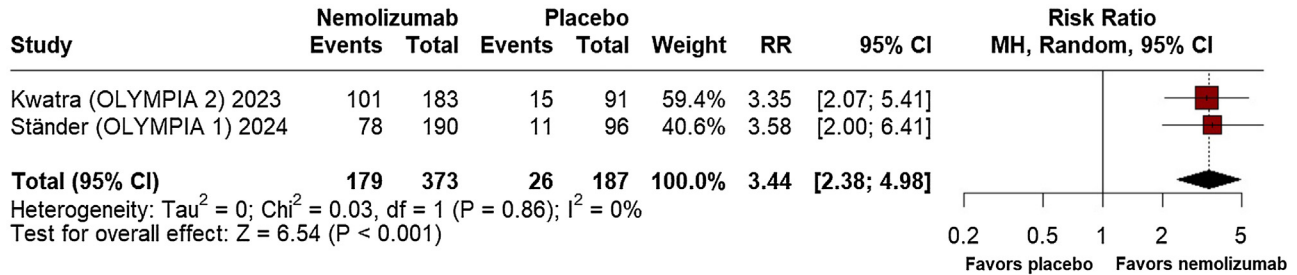


Fig. 6 Prurigo Activity Score (PAS) >75% healed pruriginous lesions at 16 weeks.

CI: 2.33, 4.81; $p \leq 0.001$; $I^2 = 0\%$; Fig. 5), while at week-16, nemolizumab demonstrated superior outcomes (RR = 3.44; 95% CI: 2.38, 4.98; $p \leq 0.001$; $I^2 = 0\%$; Fig. 6).

For safety outcomes, there was no significant difference between nemolizumab and placebo in the overall incidence of AEs (RR = 1.10; 95% CI: 0.97, 1.25; $p = 0.125$; $I^2 = 0\%$; Fig. 7) or SAEs (RR = 0.77; 95% CI: 0.43, 1.39; $p = 0.385$; $I^2 = 0\%$; Fig. 8). The proportion of patients discontinuing the study due to AEs was also not significantly different (RR = 1.09; 95% CI: 0.46, 2.54; $p = 0.849$; $I^2 = 0\%$; Supplement Fig. S3), and injection-related reactions were infrequent and not significantly different between groups (RR = 2.31; 95% CI: 0.38, 14.02; $p = 0.364$; $I^2 = 0\%$; Supplement Fig. S4).

Specific adverse events, such as peripheral edema (RR = 1.54; 95% CI: 0.40, 6.00; $p = 0.530$; $I^2 = 0\%$; Supplement Fig. S5), urticaria (RR = 1.94; 95% CI: 0.31, 12.19; $p = 0.479$; $I^2 = 0\%$; Supplement Fig. S6), contact dermatitis (RR = 3.62; 95% CI: 0.64, 20.35; $p = 0.145$; $I^2 = 0\%$; Supplement Fig. S7), and other dermatological conditions including eczema, alopecia, rash, rosacea, and dry skin, were not significantly different between groups (Supplement Figs. S8–S12). Interestingly, nemolizumab showed a significant reduction in neurodermatitis compared to placebo (RR = 0.50; 95% CI: 0.32, 0.80; $p = 0.004$; $I^2 = 11\%$; Supplement Fig. S13).

Other system-related AE, such as cardiac disorders (RR = 0.56; 95% CI: 0.14, 2.20; $p = 0.411$; $I^2 = 0\%$; Supplement Fig. S14), gastrointestinal disorders (RR = 0.89; 95% CI: 0.48, 1.65; $p = 0.707$; $I^2 = 19\%$; Supplement Fig. S15), and skin and subcutaneous tissue disorders (RR = 1.03; 95% CI: 0.79, 1.35; $p = 0.89$; $I^2 = 0\%$; Supplement Fig. S16), were not significantly different. Infections and infestations (RR = 0.98; 95% CI: 0.66, 1.44; $p = 0.899$; $I^2 = 0\%$; Supplement Fig. S17), musculoskeletal and connective-tissue disorders (RR = 1.48; 95% CI: 0.89, 2.46; $p = 0.132$; $I^2 = 0\%$; Supplement Fig. S18), nervous system disorders (RR = 1.10; 95% CI: 0.65, 1.84;

$p = 0.730$; $I^2 = 0\%$; Supplement Fig. S19), and respiratory, thoracic and mediastinal disorders (RR = 0.93; 95% CI: 0.29, 3.01; $p = 0.3839$; $I^2 = 0\%$; Supplement Fig. S20) also showed no significant differences.

These findings provide a comprehensive overview of the efficacy and safety profiles of Nemolizumab, highlighting its potential benefits in reducing pruritus and improving IGA success rates. It also has a favorable safety profile with no major safety concerns compared to the placebo.

Quality assessment

The risk of bias assessment for each RCT included in this meta-analysis was conducted using the RoB-2 tool, and all studies were deemed as low risk of bias (Fig. 9).

Domain 1 (Randomization Process) demonstrated a low risk of bias across all studies. The allocation sequence was reported as random, baseline differences between intervention groups did not indicate issues with randomization, and the allocation sequence was adequately concealed until participants were enrolled and assigned to interventions.

Domain 2 (Deviations from Intended Interventions) showed that participants were likely unaware of their assigned interventions during the trials, rated as "Probably No" for all studies. Carers and intervention providers were also unaware of participants' assigned interventions, rated as "No". Additionally, all studies employed an appropriate analysis to estimate the effect of assignment to intervention, rated as "Yes".

Domain 3 (Missing Outcome Data) was assessed as low risk, as all studies reported data for all or nearly all randomized participants.

In Domain 4 (Measurement of Outcomes), the methods used to measure outcomes were deemed appropriate, with

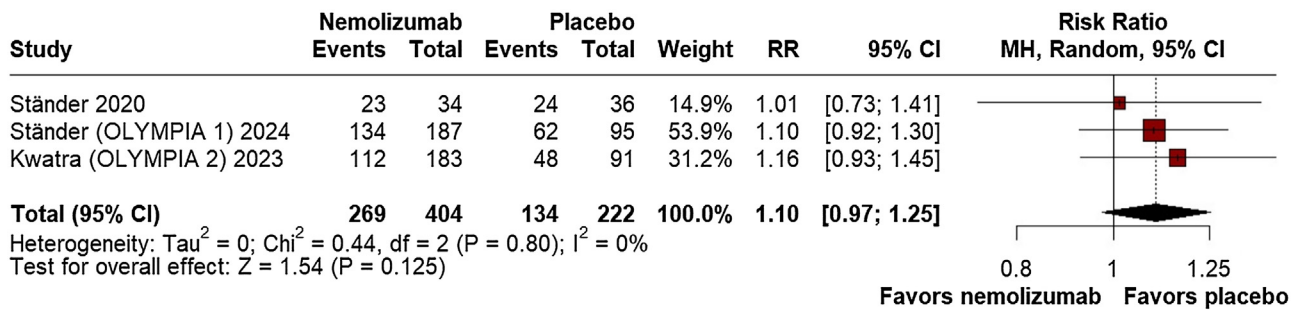


Fig. 7 Adverse Events (AEs).

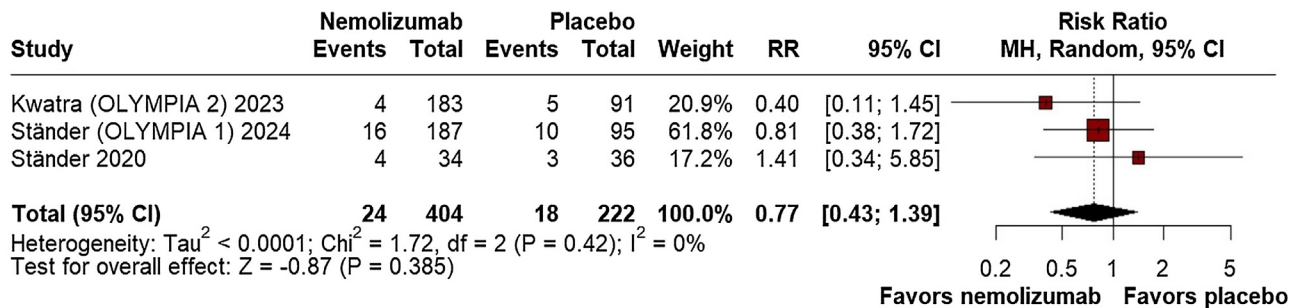


Fig. 8 Serious Adverse Events (SAEs).

		Risk of bias domains				
		D1	D2	D3	D4	D5
Study	Ständer 2024 (OLYMPIA 1)					
	Kwatra 2023 (OLYMPIA 2)					
	Ständer 2020					
		Domains:				
		D1: Bias arising from the randomization process.				
		D2: Bias due to deviations from intended intervention.				
		D3: Bias due to missing outcome data.				
		D4: Bias in measurement of the outcome.				
		D5: Bias in selection of the reported result.				
		Judgement				
		Low				

Fig. 9 Risk of Bias assessment of included studies.

no evidence of differences in measurement or ascertainment between intervention groups. Outcome assessors were likely unaware of the intervention received by participants, rated as "Probably No" for all studies.

Finally, Domain 5 (Selection of the Reported Result) revealed that the data were analyzed according to a pre-specified plan finalized before unblinded outcome data were available, rated as "Yes" for all studies. There was no evidence of selective reporting from multiple eligible outcome measurements or analyses, rated as "No" for all studies.

Discussion

This systematic review and meta-analysis of three RCTs, including 630 patients, compared nemolizumab with placebo for prurigo nodularis. The main findings were: 1)

Nemolizumab significantly improved pruritus, with greater reductions in the Peak Pruritus Numerical Rating Scale at weeks-4, -12, and -16, higher IGA success rates at week-12, and superior outcomes in PAS > 75% healed lesions at week-16; 2) While no significant differences were observed in the incidence of overall or serious adverse events between groups, nemolizumab significantly reduced neurodermatitis compared to placebo. Other safety outcomes showed no substantial differences, reinforcing the favorable safety profile of nemolizumab.

Nemolizumab is a monoclonal antibody that targets the Interleukin-31 Receptor A (IL-31RA).¹³ IL-31, a cytokine associated with itching and the pathophysiology of prurigo nodularis, is crucial in T-helper 2 skin inflammation by promoting the production of IL-4 and IL-13. Furthermore, IL-31 triggers itch sensation in the peripheral nervous system

by interacting with sensory nerve fibers. Through inhibiting IL-31, nemolizumab interrupts the neuroimmune-driven itch-scratch cycle, suppresses inflammation, enhances epithelial function, and strengthens the skin barrier. Nemolizumab has also been seen to suppress keratinocyte proliferation post-treatment.^{8,14}

The management of prurigo PN is determined by disease severity. Mild PN is typically managed with topical treatments such as corticosteroids, calcineurin inhibitors, and antihistamines. However, moderate-to-severe PN often requires systemic interventions due to its significant impact on quality of life and the often inadequate response to topical therapies alone.¹⁵ In the trials included in the present study, only patients with moderate-to-severe PN were enrolled, highlighting that nemolizumab is most effective for individuals with this level of severity.

Nemolizumab (Nemluvio®) has been approved by the US Food and Drug Administration (FDA) for subcutaneous injection to treat adults with prurigo nodularis.⁶ It is recommended for subcutaneous dosage only. For adults weighing less than 90 kg, the initial dose is 60 mg (administered as two 30 mg injections), followed by 30 mg every 4-weeks, and for adults weighing 90 kg or more, the initial dose is 60 mg (administered as two 30 mg injections), followed by 60 mg every 4-weeks.¹⁶

This medication is contraindicated in patients who have known hypersensitivity to nemolizumab-IL-31 or any of the excipients. Data on its use during pregnancy or breastfeeding is insufficient. However, it was detected in the breast milk of monkeys following subcutaneous doses up to 25 mg/kg once every two weeks during organogenesis to parturition. Additionally, the safety and effectiveness of nemolizumab (Nemluvio®) have not been established in pediatric patients, being only approved for adults over 18, with limited data on individuals aged 65 or older.^{16,17}

In this meta-analysis, superior efficacy outcomes were observed in the nemolizumab group compared to placebo at week-16, including a significant reduction in pruritus and higher IGA success rates. Statistically significant differences were evident for pruritus reduction as early as week-4, with nemolizumab showing considerable improvement. By week-12, patients receiving placebo had achieved a greater PAS > 75 score, but by week-16, success rates favored nemolizumab.

The present findings support the use of nemolizumab as an effective and safe treatment option for prurigo nodularis, aligning with previous research on biologics targeting the IL-31 pathway. For instance, Sofen et al. demonstrated similar efficacy with vixarelimab, another IL-31 inhibitor.¹⁸ A network meta-analysis comparing different treatments for PN to placebo, including vixarelimab, dupilumab, serlopitant, nalbuphine, and nemolizumab, showed that nemolizumab has the potential to improve pruritus and skin lesions in PN patients.¹¹ While dupilumab is considered an excellent choice for treating PN, nemolizumab appears to have better results in reducing the extent and severity of skin lesions. Furthermore, Brooks et al., a review on nemolizumab, showed that when compared to dupilumab, nemolizumab performs similarly, further emphasizing its potential as a key treatment option.¹⁴

Moreover, the analysis of adverse outcomes revealed no significant differences in the overall incidence of AEs or

SAEs, indicating favorable safety data for nemolizumab. Although peripheral edema, worsening of eczema were observed in the Olympia 1, Olympia 2, and Stander et al. 2020 trials, as well as in other studies investigating atopic dermatitis, the meta-analysis showed no significant difference between groups.^{1,9,10,19–22}

In the present study, nemolizumab showed a significant reduction in neurodermatitis compared to placebo. This may be explained by the common features between neurodermatitis, also known as lichen simplex chronicus, and PN. Both conditions are characterized by epidermal hyperplasia, orthokeratosis, and hypergranulosis, resulting from repetitive scratching and rubbing of the skin.²³ Nemolizumab, by targeting specific pathways of pruritus and inflammatory responses, breaks this itch-scratch cycle, reducing pruritus.¹³

This meta-analysis has several strengths, including the rigorous design of the included trials, which were randomized, placebo-controlled, and double-blinded, and consistent findings that enhance the reliability of the results. However, there are some limitations. One is the variability in treatment duration, as Ständer et al. 2020 report outcomes only up to 12 weeks and provide fewer outcome measures compared to other trials. This inconsistency poses challenges for robust statistical analysis. Additionally, the follow-up periods in the included studies are relatively short, restricting the ability to evaluate long-term disease management, which is crucial given the chronic nature of PN. To address these limitations, future research should prioritize longer follow-up periods to better assess the long-term efficacy and continued effectiveness of Nemolizumab.

Another limitation is the relatively small sample sizes in the included studies. Although placebo-controlled comparisons are valuable, the lack of direct head-to-head comparisons with other biologics limits the ability to position Nemolizumab precisely within the broader therapeutic landscape. Furthermore, all three included trials were industry-sponsored, raising concerns about potential selective reporting, where positive outcomes may be emphasized, and negative or inconclusive results could be underreported or unpublished. Due to the limited number of studies, a formal assessment of publication bias, such as funnel plot analysis or a statistical test, was not performed. Such analyses are typically unreliable with a small sample size, as they lack the statistical power necessary to detect bias.²⁴

Notwithstanding these challenges, this systematic review and meta-analysis offers a comprehensive overview of the most robust evidence regarding the use of Nemolizumab for PN treatment.

Conclusion

The meta-analysis provides strong evidence for the efficacy of Nemolizumab in treating PN, demonstrating significant improvements in pruritus reduction, IGA success rates, and PAS > 75%. Additionally, the safety profile of Nemolizumab was favorable, with no significant difference in the incidence of adverse events or serious adverse events compared to placebo. These findings support the use of Nemolizumab as an effective and safe treatment option for PN.

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Authors' contributions

Ana Carolina Putini Vieira: The study concept and design; critical review of literature; data collection, analysis and interpretation; preparation and writing of the manuscript; final approval of the final version of the manuscript.

Maria Antônia Costa Cruz Akabane: Data collection, analysis and interpretation; statistical analysis; preparation and writing of the manuscript; final approval of the final version of the manuscript.

Gianna Carolinne Graff Caletti: Critical review of literature; final approval of the final version of the manuscript.

Kélen Klein Heffel: Data collection, analysis and interpretation; final approval of the final version of the manuscript.

Amanda Tauana Oliveira e Silva: The study concept and design; preparation and writing of the manuscript; effective participation in research orientation; manuscript critical review; final approval of the final version of the manuscript.

Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

The authors have no conflicts of interest that are directly relevant to the content of this article.

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.2025.501210>.

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REVIEW

The history of Teledermatology and its evolution, practical aspects, and prospects in Brazil[☆]



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Abstract Teledermatology services in Brazil have a rich history, with several ongoing projects boosting academic research and providing efficiency gains by reducing waste, humanizing healthcare, and ensuring greater quality and speed in patient assistance. Reviewing the fundamentals and history of Teledermatology, along with the continuing evolution of Telemedicine services in Brazil and its practical aspects and future prospects, might bring better comprehension of how to further develop and improve these services.

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Introduction

Fundamentals and history of Teledermatology

Although strongly associated with technological innovations in the areas of information technology and telecommunications in recent decades, especially the Internet, the history of medicine with remote support actually dates back to probably even before the Middle Ages.¹ In ancient times, for example, sending letters via ships or horse-mounted messengers containing clinical information, hand-drawn

pictures, and even urine samples to doctors or healers requesting a report with expert opinion could already be considered a rudimentary form of health services provided remotely.

The authors can take as a reference that the use of technologies in the provision of health services probably began with the invention of the stethoscope by the French physician René-Théophile-Hyacinthe Laennec in 1819. Although it still required the physical presence of the physician, for the first time in History, it was possible to make clinical and diagnostic inferences without the need for direct contact with the patient during physical examination.²

The incorporation of new technologies for the provision of remote health services over time occurred with the advent of increasingly sophisticated forms of communication: starting in the 19th century with the expansion of mail services, moving on to the creation and large-scale imple-

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mentation of the telegraph, and later telephone, radio and closed-circuit television networks, culminating in the global computer network – the Internet, created in 1969 – providing a high-speed, worldwide connection experience never seen before.³

The modern term Telemedicine has been associated with the idea of using electronic technologies (devices and telecommunications) to provide medical services remotely, having gained important meaning because of the war efforts during the Cold War and the Space Race, a time when many pioneering technological advances were achieved by government and military agencies and were later incorporated into the civil and health sectors.⁴ With all the innovation brought about by computerization and the development of high-speed and stable Internet connections, written and visual information began to circulate globally in practically real time.

In the field of Dermatology, it is very difficult to separate telemedicine from the significant advances in digital images (photographs and videos), especially since the last decade of the 20th century, which have made it possible to generate visual information with ease and increasingly higher resolutions at progressively lower costs.

Although controversial, the invention of photography is often attributed to the Frenchman Joseph Nicéphore Niépce, who in 1826 managed to obtain the oldest permanent photograph still in existence,⁵ leading mankind towards a new era as for the first time there was a shift from artistic drawing to realistic or real and reproducible documentation with the same characteristics under the same conditions. The process has been perfected ever since, but it took more than a century until the first digital processing of a photograph was carried out by the US government space agency, the National Aeronautical and Space Administration (NASA), in the mid-1960s, when cameras and transmitters were attached to a lunar probe in order to transmit analog video/image signals.⁶ Technological advances were gradually implemented in cameras, leading to the creation of the first digital camera prototype by Steven Sasson in 1975, at the time a young engineer working for Kodak. Despite being innovative, Sasson's invention was not met with enthusiasm by Kodak's own executives, which eventually led to the company's bankruptcy in 2012.⁷

It was only in the early 1980s that these technologies became more popular, with the initial milestone being the commercialization of the Mavica analog models produced by Sony in 1981. The first professional digital camera was released by Kodak in 1991, allowing images with up to 1.3 megapixels of resolution. However, the extremely high prices until the early 1990s made widespread access to these machines prohibitive. The revolution in popular access to digital cameras occurred only approximately 30-years ago, in mid-1995, when Apple's QuickTake 100 and Kodak's DC 40 models were launched at prices below the US\$1,000.00 barrier.⁸

Closely following the evolution of digital cameras, smartphones (cell phones with advanced features and personal computer resources) have also shown rapid development in terms of processing capacity and production/capture of high-resolution images. The first smartphone with a built-in digital camera was the J-SH04 model produced by Sharp and launched in Japan in November 2000.⁹ Since then,

new models equipped with more powerful digital cameras and extra versatile features are released at competitive prices yearly. The development of digital cameras attached to smartphones was extremely important for Telemedicine since images with higher resolution, combined with appropriate Digital Photography techniques, allow for a greater level of detail, making them suitable for clinical assessment (Fig. 1).¹⁰

According to data obtained by the 28th Annual Survey on the Use of Information Technology carried out by the Getúlio Vargas Foundation (FGV), the estimated number of smartphones in Brazil at the end of 2017 was 208 million devices, which means 1 smartphone per inhabitant in the country.¹¹ Easy access to mobile devices with increasingly greater processing and image generation power has led to a significant increase in the use of these devices in the digital world, cloud data processing and social networks. At the same time, in the medical field, there has been an increase in application tests on several areas, including Ophthalmology,¹² Dermatology,^{13,14} Plastic Surgery,¹⁵ Endocrinology,¹⁶ Neurosurgery¹⁷ and Radiology,¹⁸ being applied in a versatile way as a means of remote screening, diagnosis, prevention and post-operative follow-up. Images of clinical cases are often shared on messaging apps or social networks such as WhatsApp® (Meta Platforms Inc, Menlo Park, California, USA) for discussion with other medical colleagues¹⁹ or through smartphone apps created especially for this purpose.

Due to the widespread, often informal, use of smartphones as everyday tools and sometimes in applications that could be associated with Telemedicine, some fundamental aspects such as patient data privacy, legal support for doctors and healthcare institutions, data security and storage, and medical education in Telemedicine and digital photography techniques still need to be better discussed and consolidated.²⁰ As smartphones are portable devices that can easily be lost, compromised, or stolen, healthcare professionals need to become increasingly aware of the responsibility of carrying patients' private and sensitive data on their personal devices.

Dermatology may be a medical specialty prone to the use of Telemedicine because of its large visual component, and a growing application of Teledermatology has been noted on a global scale over the years.²¹ Multiple studies have corroborated the clinical effectiveness,^{22,23} cost-benefit,^{24,25} high satisfaction rates^{21,26} and reduced waiting times for specialized dermatological evaluation in health systems^{23,27} through the incorporation of Teledermatology, showing potential applicability with high rates of sensitivity and diagnostic agreement in relation to the traditional clinical examination in several skin pathologies in both outpatient and hospital settings.^{13,26,28} Due to the high prevalence of skin cancers and their significant economic impact on public and private health systems in several countries,^{29,30} Cutaneous Oncology in particular has been the focus of much of the Teledermatology studies.^{14,22,27,31–34}

The evolution of Telemedicine in Brazil

Telemedicine has been regulated in Brazil by the Federal Council of Medicine (CFM) since 2002, through Resolution

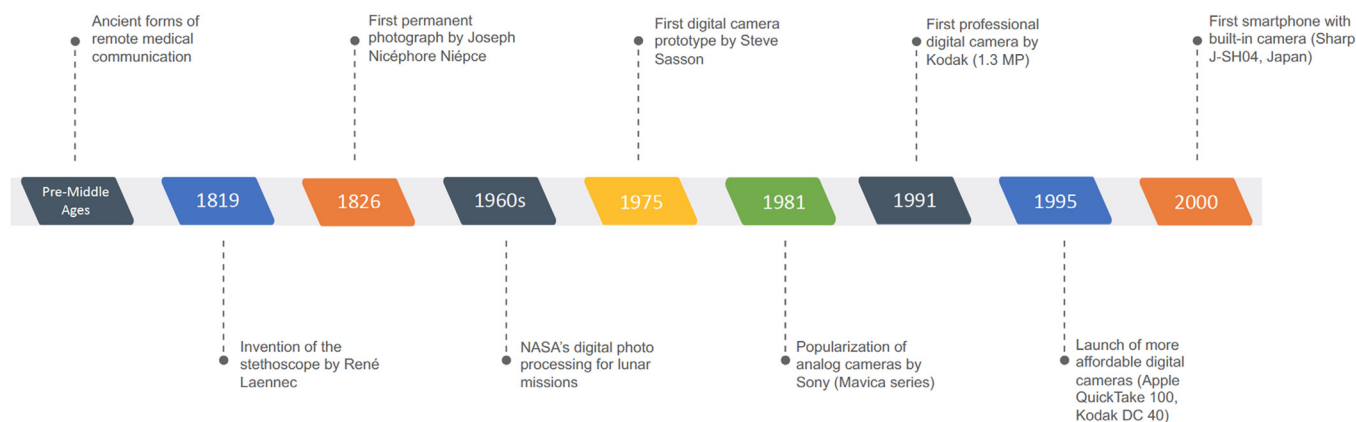


Figure 1 Evolution of remote medical communication and imaging until the smartphone era.

1643/2002,³⁵ which already provided for the teleinterconsultation modality. In 2011, the Brazilian Ministry of Health proposed the use of Telemedicine resources to solve problems in the Primary Care level of its public Unified Health System (SUS), through the publication of Ordinance n° 2,546 of October 27, 2011,³⁶ which defined the concept of Second Formative Opinion, a source of information originated through teleconsultations that deal with issues relevant to the SUS and with the possibility of answering questions and needs of other health workers, aiming to increase the resolution capacity in similar cases or situations.

Since 2020, the Brazilian Ministry of Health has established the National Health Data Network (RNDs) through Ordinance n° 1,434 of May 28, 2020,³⁷ a strategic program targeting digital transformation of healthcare in the country aiming to promote interoperability to enable the exchange of information and data sharing between the different sites within the Health Care Network, allowing the transition and continuity of care in the public and private sectors.

Brazilian legislation regarding Telemedicine progressed significantly during the COVID-19 pandemic, culminating in Resolution n° 2314/2022³⁸ of the CFM, which definitively regulates Telemedicine, defining this practice as a medical act, as a form of medical services mediated by communication technologies, defining clearly seven different telemedicine modalities (Table 1).

In the same year, Ordinance Office of the Minister/Ministry of Health n° 1,348 of June 2, 2022³⁹ was published, which provides for Telehealth actions and services within the scope of the SUS, with the objective of regulating and operationalizing the use of information and communication technologies in remote assistance, education, research, prevention of diseases and injuries, management and promotion of citizen health, and also Law n° 14,510 of December 27, 2022,⁴⁰ which authorizes and regulates the practice of Telehealth throughout the national territory.

Due to the restrictions on mobility caused by the pandemic, the Brazilian Society of Dermatology (SBD), aiming at the safe practice of remote evaluations that had increased dramatically, published in 2021 the first version of the Manual of Good Practices in Teledermatology, in addition to organizing a series of webinars on the subject, seeking training and continuing medical education of specialists. This

manual had a second version published in 2022⁴¹ containing an update in accordance with CFM resolution n° 2314/2022.³⁸

Therefore, despite being fully authorized and regulated only recently, Telemedicine and, by extension, Teledermatology, have been a widely debated topic in Brazilian society due to its high relevance and potential impact, advantages highlighted even more in the context of social isolation imposed during the COVID-19 pandemic.

Methods

A literature review search strategy was performed on the PubMed® platform, maintained by the National Library of Medicine (Bethesda, Maryland, USA) and which gathers records from the MEDLINE database, using the terms "Dermatology" AND "Brazil". All abstracts were analyzed, and only unique published articles reporting on Teledermatology projects developed and executed in Brazil were included in the analysis after reading of the full-text articles and confirmation of pertinence.

Results

The research strategy returned 39 original published and indexed scientific articles, of which 28 report on Teledermatology projects developed and executed in Brazil (Fig. 2).

Of these, 08 articles describe the results of Teledermatology projects conducted by Hospital Israelita Albert Einstein (HIAE)⁴²⁻⁴⁹ in partnership with the Municipal Health Department of São Paulo. In July 2017, the city of São Paulo, through its Municipal Health Department, agreed in a partnership with the Telemedicine service of the HIAE with the aim of significantly reducing the waiting list for dermatological care, where dermatologists from HIAE would remotely analyze the needs of patients based on clinical information and photographic images of skin lesions collected by nurses from SUS health units in the capital of São Paulo – if any additional diagnostic or surgical procedure was necessary, HIAE was responsible for providing a referral network and its own infrastructure with mobile units to meet the demand.⁵⁰

Other published studies present results from projects where primary care professionals benefit from specialized

Table 1 Telemedicine modalities and Telehealth definitions established in Brazil.

	Definition
Teleconsultation	A non-face-to-face medical consultation, mediated by Digital, Information and Communication Technologies (DICTs), with the doctor and patient located in different spaces.
Teleinterconsultation	Exchange of information and opinions between physicians, with the help of DICTs, with or without the presence of the patient, for diagnostic or therapeutic, clinical or surgical assistance.
Telediagnosis	The medical act at a distance, both geographically and/or temporally, with the transmission of graphs, images and data for issuing a report or opinion by a qualified specialist physician in the area related to the procedure, in response to the request of the attending doctor.
Telesurgery	Surgical procedures are performed remotely, using robotic equipment and mediated by safe interactive technologies.
Telemonitoring or medical televigilance	The act performed under the coordination, indication, guidance and supervision of a doctor for remote monitoring or surveillance of health and/or disease parameters, through clinical evaluation and/or direct acquisition of images, signals and data from equipment and/or devices attached or implanted in patients at home, in specialized chemical dependency clinic, in a long-term care facility for the elderly, in a clinical or home hospitalization regime or in the transfer of patients until their arrival at a health establishment.
Teletriage	The act performed by a physician with evaluation of the patient's symptoms, remotely, for outpatient or hospital regulation, with definition and direction of the patient to the appropriate type of assistance needed or to a specialist.
Teleconsulting	An act of consultancy mediated by DICTs between physicians, managers and other professionals, with the purpose of providing clarifications on administrative procedures and health actions.
Telehealth	Method of providing health services remotely, through the use of information and communication technologies, which involves, among others, the secure transmission of health data and information, through texts, sounds, images or other appropriate forms.

remote assessment through partnerships with university and/or reference services: from the Santa Catarina Telehealth project, the largest Teledermatology initiative in Brazil detailed further in this article, there are 7 articles published;^{51–57} from the Mobile Prevention Unit of the Hospital do Amor, in the city of Barretos, 3 articles;^{58–60} from the Telecare Network in Minas Gerais, 1 article;⁶¹ from the Alfredo da Matta Hospital Foundation (FUHAM) in Amazonas, 1 article;⁶² from the Amaral Carvalho Cancer Hospital, in the city of Jaú, 1 article;⁶³ and from the Rio Grande do Sul Telehealth project, 1 article.⁶⁴ The results of a national survey applied to members of the Brazilian Society of Dermatology (SBD) were also published,⁶⁵ a study led by a research team from the State University of Campinas (UNICAMP). However, despite these initiatives, there are still a lot of opportunities for expansion of Teledermatology in Brazil, since according to information available on the Brazilian Open Data Portal⁶⁶ there are currently around 38,000 Primary Care Units operating in Brazilian territory.

Many studies have already addressed the pedagogical importance of Teledermatology for medical education in academic environments.^{67,68} At the University of São Paulo Faculty of Medicine (FMUSP), the institution where the remaining 5 published articles^{13,28,69–71} were developed, some academic pilot projects involving Tele-education for non-medical workers have already been developed with promising results - online training platforms for the prevention of venereal diseases targeting beauty salon employees⁷⁰ and a Distance Education (EAD) system for the training and education of non-medical health professionals in screening of skin lesions with malignant potential,⁷¹ in addition to a website offering organized content for training in early recognition of melanoma by first-year medical students.³¹ Two other studies, involving physician participants, studied the application of asynchronous Teledermatology: one evaluated its role in supporting clinical diagnosis of leprosy performed by primary care physicians, with promising and low-cost results;²⁸ the other assessed its application

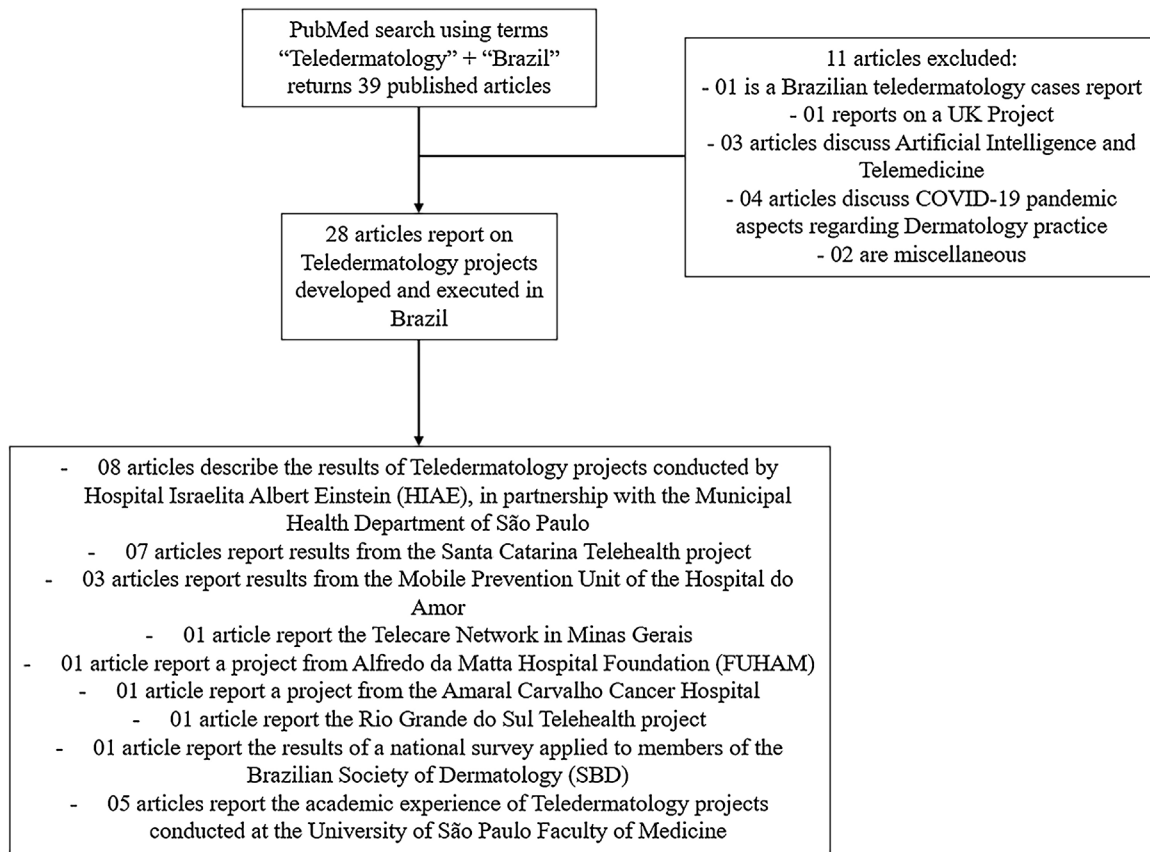


Figure 2 Summary of the PubMed research results regarding Teledermatology studies in Brazil.

through smartphones to discuss cases of patients admitted to a reference hospital and evaluated by Dermatology residents.¹³

In this same institution, in 2001, an Internet-based dermatological consultation system (cyberambulatory) called “Telederma” was developed, where dermatology residents registered patients’ records containing clinical data and digital photographs of skin lesions so that they could later be evaluated by more experienced dermatologists. In order to maintain the academic aspect of this virtual outpatient clinic, fundamentals of Problem-Based Learning and Evidence-Based Medicine were incorporated through an electronic tutor (cybertutor), with the online provision of diagnostic guidelines, bibliographic references, a database on drug interactions, didactic classes taught by FMUSP professors, and performance evaluation methods of participating physicians.^{69,72} In mid-2003, this same cyberambulatory would be used in the training of residents in Sanitary Dermatology in the specialized service for Sexually Transmitted Infections (STI) of the Geraldo de Paula Souza School Health Center, led at the time by Prof. Dr. Luiz Jorge Fagundes.

Regarding analysis of the factors involved in the use of photographs for dermatological diagnosis, a study conducted at FMUSP made it possible to identify that the systematization and implementation of dermatological tele-propaedeutics should be analyzed under a set of classifications of the types of skin lesions and their clinical relevance, forming a matrix, demonstrating that in

several situations additional clinical information is necessary. It concluded that skin diseases with clinically atypical or moderately typical lesions and with palpable morphology (e.g., infiltrated lesions, subcutaneous tumors) are more difficult to diagnose with the aid of digital photography alone, with clinical data and additional information being of fundamental importance to increase diagnostic accuracy. Furthermore, the systematic implementation of Teledermatology allowed improvement in remote diagnostic performance comparable to in-person assessment.⁷³

Discussion

Practical aspects

A great example of how to bring Teledermatology to practice, integrated with existing health systems, is the main and largest Brazilian initiative with the incorporation of Teledermatology into the regulatory process of the SUS in the state of Santa Catarina, which has been in non-stop operation since October 2013. In a continental-sized country like Brazil, with several economic disparities within its national territory and a large variance regarding access to quality healthcare within different regions of the country, if most of the Primary Care Units are integrated in a nationwide Teledermatology project such as the one running in

Santa Catarina, the impact on healthcare delivery and cost-efficiency could be huge.

The use of Teledermatology in the state of Santa Catarina, located on the Southern region of Brazil, was formalized with Resolution 366/CIB/13 from August 22, 2013,⁷⁴ issued by the State Bipartite Health Management Committee (CIB/SC), which approved the use of Telediagnosis in Dermatology for risk assessment and regulation of patient flow originating from Primary Care services within the medical specialty of Dermatology. Consequently, ever since, in Santa Catarina, patient triage and referrals via the Brazilian National SISREG System began officially to be conducted through Telemedicine.

The platform was developed by the Federal University of Santa Catarina (UFSC) and is used as a tool for both triaging patients with skin diseases and for risk assessment by the State Health Department of Santa Catarina (SES-SC). The Teledermatology reports issued through the platform are part of the decision-making process for Primary Care physicians and support the regulatory physician in referring patients to specialized services.

This service is well-established, with over 300,000 Teledermatology examination reports conducted until 2024, and is currently present in 15 other federative units through a national program.^{75,76} Furthermore, the implementation of the Teledermatology tool has been able to reduce both direct and indirect costs to the Brazilian Public Healthcare System through a decentralized infrastructure for patient triage with access to risk classification, aiding in the appropriate referral of patients, reducing travel expenses, queues, wait times, and also eliminating unnecessary intermediary appointments.⁷⁷

In the USA, by 2017, among the 40 nationally active teledermatology programs, 70% provided direct-to-patient care, and 72% used store-and-forward models only.⁷⁸ As for the United Kingdom National Health Service (NHS), since October 2018, all General Practitioners in England are required to use the NHS e-Referral Service (e-RS), a mostly asynchronous physician-to-physician platform, to refer to consultant-led new outpatient appointments.⁷⁹ Despite global changes prompted by the COVID-19 pandemic caused synchronous models (primarily video visits) to supplant asynchronous models (store-and-forward or shared digital photographs) as the predominant modality of teledermatology care in various locations,⁸⁰ in the published Brazilian teledermatology projects asynchronous models still largely prevail, possibly due to the synchronous models technological barriers, as they require greater infrastructure to achieve optimal video quality and accessibility.

Yearly, Internet access in Brazil is increasing rapidly, especially in rural areas, where homes with Internet access increased from 35.0% to 81.0% between 2016 and 2023,⁸¹ which might also increase access to teledermatology services in remote areas. This is specially beneficial considering that the number of Brazilian medical school graduates is rapidly increasing – from 2020 to 2022, graduated physicians increased by 8.6%, an over five-fold difference compared to the population growth on the same period of only 1.6% – but the number of Dermatology residents decreased by 30.9% between 2018 and 2021,⁸² leading to a proportional lack of specialists – therefore, teledermatology has a great potential to increase access to specialized opinion to non-

specialist physicians, in order to improve proper healthcare access.

Future prospects

Exciting future prospects regarding Teledermatology which still requires further studies, but in fields where Brazilian institutions definitely have the potential and opportunity to develop, include application of Teledermatology services with an academic approach involving medical residents and the determinant factors that impact telemedicine usage and training among physicians in-training; integration of Telemedicine within smart homes and its potential impacts on the general population and Lifestyle Medicine;⁸³ and the integration of Artificial Intelligence (AI) and Teledermatology, which has already been showing promising signs on improving risk assessment, diagnostic accuracy and quality control, but still present some gaps such as proper regulation and standardization, development of position statements and guidelines, and also clarification on civil and ethical aspects of its usage.^{84,85} Rapidly advancing projects such as DermAI keep continuously developing novel deep learning techniques to improve automated classification of skin lesions.⁸⁶

Although AI-powered Teledermatology widespread populational initiatives still lack, Edge Health, a specialist UK healthcare analytics consultancy, was commissioned by Health Innovation East Midlands (one of 15 organizations across England acting together as the innovation arm of the NHS) to carry out an independent evaluation of the effectiveness of a pilot tested across University Hospitals of Leicester (UHL) sites starting from March 2022.⁸⁷ This collaborative project was designed to respond to the local need for improved patient access to dermatology diagnostics, notably skin cancer, using a Skin Analytics AI-powered Teledermatology solution called DERM. Their preliminary October 2023 report confirmed that the pilot led to a reduction in referrals, freeing up 1450 outpatient appointments, and there was also a clinical time saving of 263 minutes per 100 patients, with a cost-benefit ratio of 1.05 (for each pound invested in the AI-powered solution, the health system received £1.05 in benefits).

Conclusion

In view of these data and the vast potential for expansion of Teledermatology services in Brazil, especially Teleinterconsultation assisted with AI, which has strategic potential for streamlining processes and efficiency gain not only from an economic point of view, but also as a way of humanizing care by reducing waste and ensuring greater quality and speed in assistance, it is extremely important that Teledermatology keep advancing to provide better patient experience and training for future professionals, including dermatologists and other physicians and health care workers.

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Authors' contributions

Kevin Yun Kim: Conceptualization; data curation and analysis; writing original draft; critical review of literature; final approval of the manuscript.

Chao Lung Wen: Conceptualization; critical review of important intellectual content; effective supervision and research orientation; critical review of literature; final approval of the manuscript.

Cyro Festa Neto: Conceptualization; critical review of important intellectual content; effective supervision and research orientation; critical review of literature; final approval of the manuscript.

Research data availability

Does not apply.

Conflicts of interest

None declared.

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SPECIAL ARTICLE

Highlights of the Brazilian Society of Dermatology's Brazilian Consensus on Psoriasis[☆]



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Abstract The 2024 Brazilian Consensus on Psoriasis and Treatment Algorithm of the Brazilian Society of Dermatology (SBD, *Sociedade Brasileira de Dermatologia*) comes four years after the release of the last Consensus, published in 2020. This new consensus now includes 43 chapters and has the participation of 85 professionals from across Brazil, including dermatologists and rheumatologists working in university hospitals, research centers, and public and private health-care systems. The concept of Cumulative Life Course Impairment (CLCI), the inclusion of new biologics approved in Brazil after 2020, the update on psoriasis treatment in specific situations (such as pregnancy and surgery), and the discussion on "Response Predictors" are examples of updates addressed in this Consensus. The updated treatment algorithm used experts' responses through the Delphi method and, among other modifications, removed acitretin from the plaque psoriasis treatment sequence, defined treatment lines for choosing immunobiologics in both adult and pediatric populations, and included spesolimab and cyclosporine as first-line treatments for generalized pustular psoriasis. Finally, the new Consensus addresses the place of small molecule inhibitors in the algorithm and discusses future treatment options for plaque psoriasis.

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[☆] Study conducted at the Department of Dermatology, Hospital das Clínicas, Universidade de São Paulo, São Paulo, SP, Brazil; Hospital Moinhos de Vento, Porto Alegre, RS, Brazil; Dermatology Clinic, Santa Casa de Misericórdia, São Paulo, SP, Brazil; Instituto Bahiano de Imunoterapia, Salvador, BA, Brazil.

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** The members of the Brazilian Consensus Working Group on Psoriasis of the Brazilian Society of Dermatology are listed in [Appendix A](#).

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The Brazilian Consensus on Psoriasis 2024 and Treatment Algorithm of the Brazilian Society of Dermatology (SBD) comes four years after the release of the last "Brazilian Consensus on Psoriasis 2020,"¹ a period during which significant advances and innovations in the study of psoriasis were made, making updating the topic essential.

To develop this new work,² which now includes 43 chapters, the authors relied on the participation of 85 experts from across Brazil, including dermatologists and rheumatologists from a wide range of regions (Fig. 1) and working in university hospitals, research centers, and public and private healthcare systems.

Among the updates to the 2024 Consensus, the authors highlight the introduction of the concept of CLCI (Cumulative Life Course Impairment), which characterizes the set of factors detrimental to the lives of patients with psoriasis resulting from stigma and physical and psychological disability, as well as different coping strategies.³ Furthermore, the inclusion of new biological drugs and small molecules, such as bimekizumab, brodalumab, spesolimab, tildrakizumab, and deucravacitinib. The new Consensus also highlights specific situations such as neoplasms, surgeries, and other procedures. It also innovates with the discussion of "Response Predictors" to contribute to and personalize psoriasis treatment and optimize results for each patient.

This Consensus maintained the Delphi methodology adopted in the 2020 consensus,¹ which facilitates decision-

making by seeking to standardize approaches to controversial issues in the literature.^{4,5} For this purpose, two rounds of questions were conducted, with anonymous participation from 80 and 76 authors, respectively, in each round. To ensure data validity, important criteria were adhered to, such as an adequate number of participants, representation from different regions of the country, the inclusion of experts from both the public and private healthcare systems, and the consistency of opposing questions in the same round. These measures help reduce potential biases. The consensus was considered reached when, for each question, at least 70% of voters assigned a score higher than 7 (Fig. 2).

Finally, this Consensus updates the psoriasis treatment algorithm. For this purpose, the experts' responses were taken into consideration, and through the Delphi method, they reached an agreement on significant modifications compared to the 2020 Consensus. Among the new features of the updated severe psoriasis treatment algorithm, the authors highlight the removal of acitretin from the plaque psoriasis treatment sequence, with its use being reserved only for special situations. Deucravacitinib was also included in the treatment sequence, and treatment lines were defined for the selection of immunobiologics. Anti-interleukin biologics were placed in the first-line position in relation to anti-TNF drugs. The treatment of psoriasis in the pediatric population was also included in the algorithm, with first- and second-line biologic treatments being defined. The

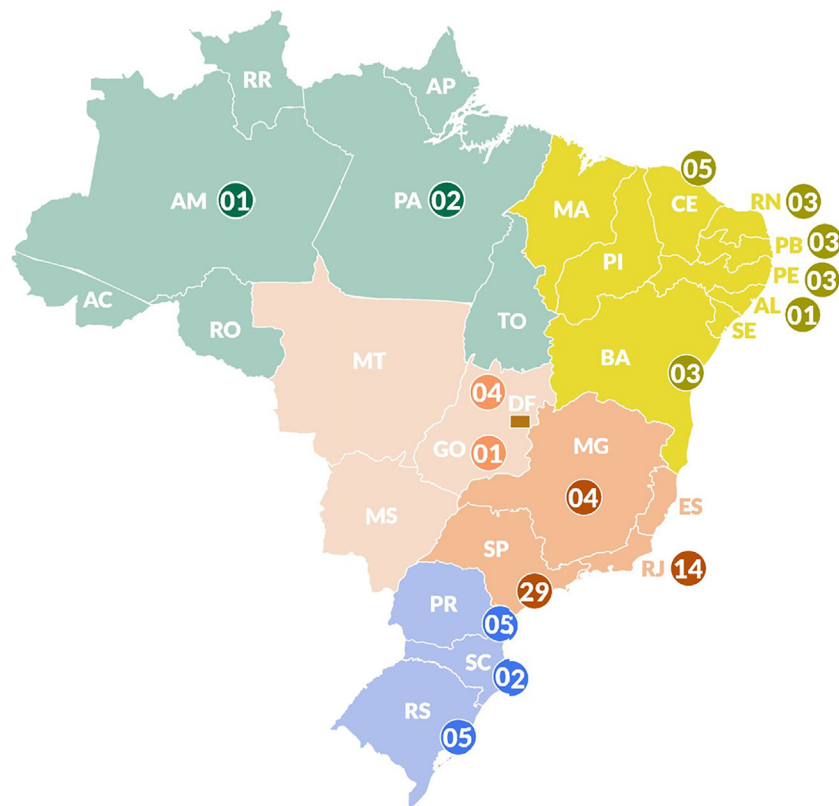


Fig. 1 Distribution of the 85 specialists participating in the Brazilian Psoriasis Consensus 2024 according to the different states of Brazil.

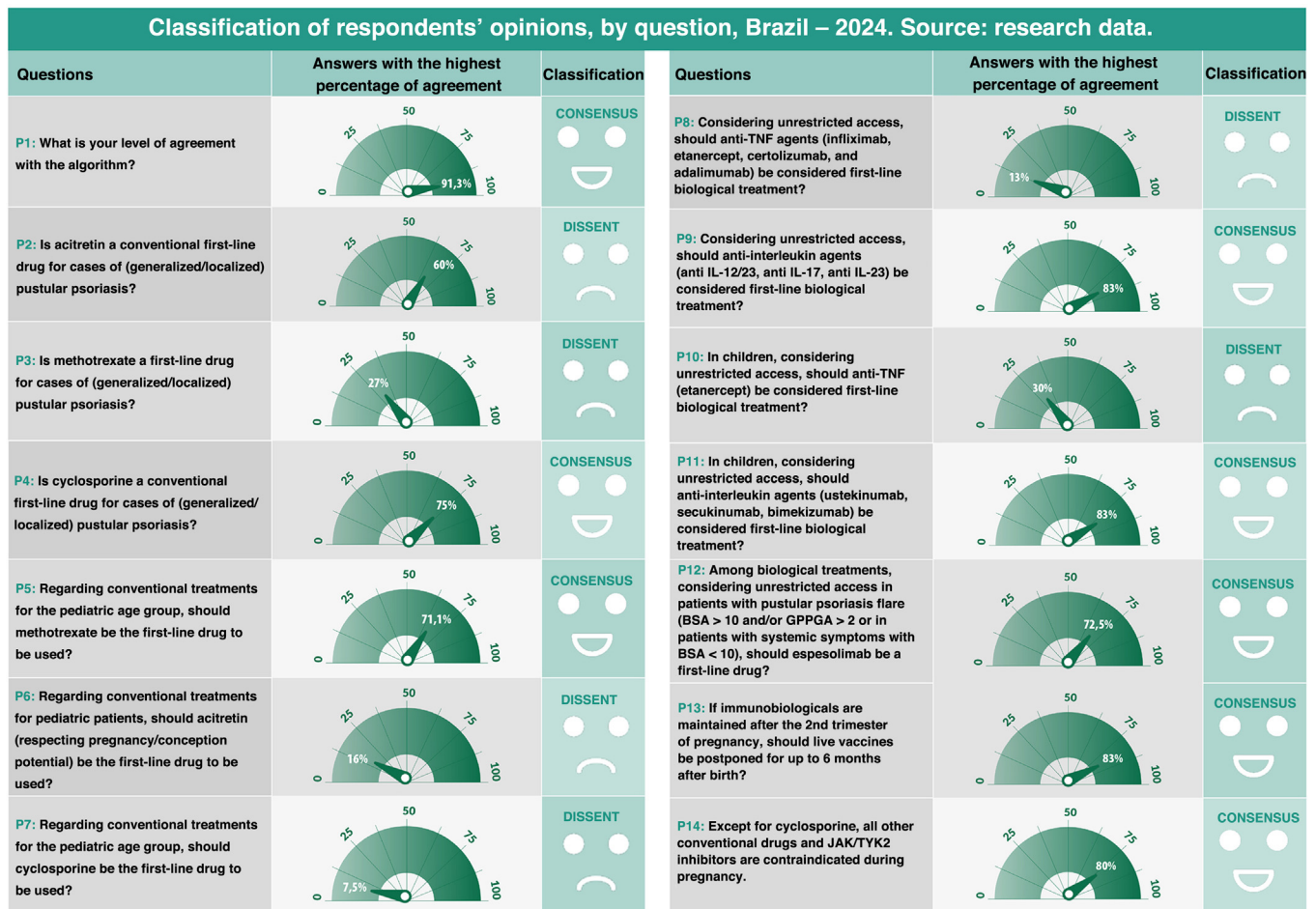


Fig. 2 Classification of respondents' opinions, by question, Brazil – 2024. Source: research data.

algorithm (Fig. 3) includes a treatment sequence for flares-ups of generalized pustular psoriasis, with spesolimab and cyclosporine in the first-line therapy in this situation.

In addition to the recently approved targeted therapies described in the new Brazilian Psoriasis Consensus, new pathophysiological pathways have been targeted for blocking with biologics and small molecules, offering new future therapeutic perspectives.

Recently, pivotal studies involving the use of an oral peptide antagonist of interleukin receptors involved in the inflammatory cascade of psoriasis promise to offer another innovative, potentially effective, and safe treatment line for the management of this immune-mediated dermatosis. The outlook for interventions in psoriasis seems promising, the safety profile of new treatments has proven satisfactory, and the debate about a possible cure for psoriasis is more current than ever.⁶⁻⁸ Future updates to this consensus are therefore mandatory, allowing the discussion of increasingly effective and safe measures in the management of patients with psoriasis.

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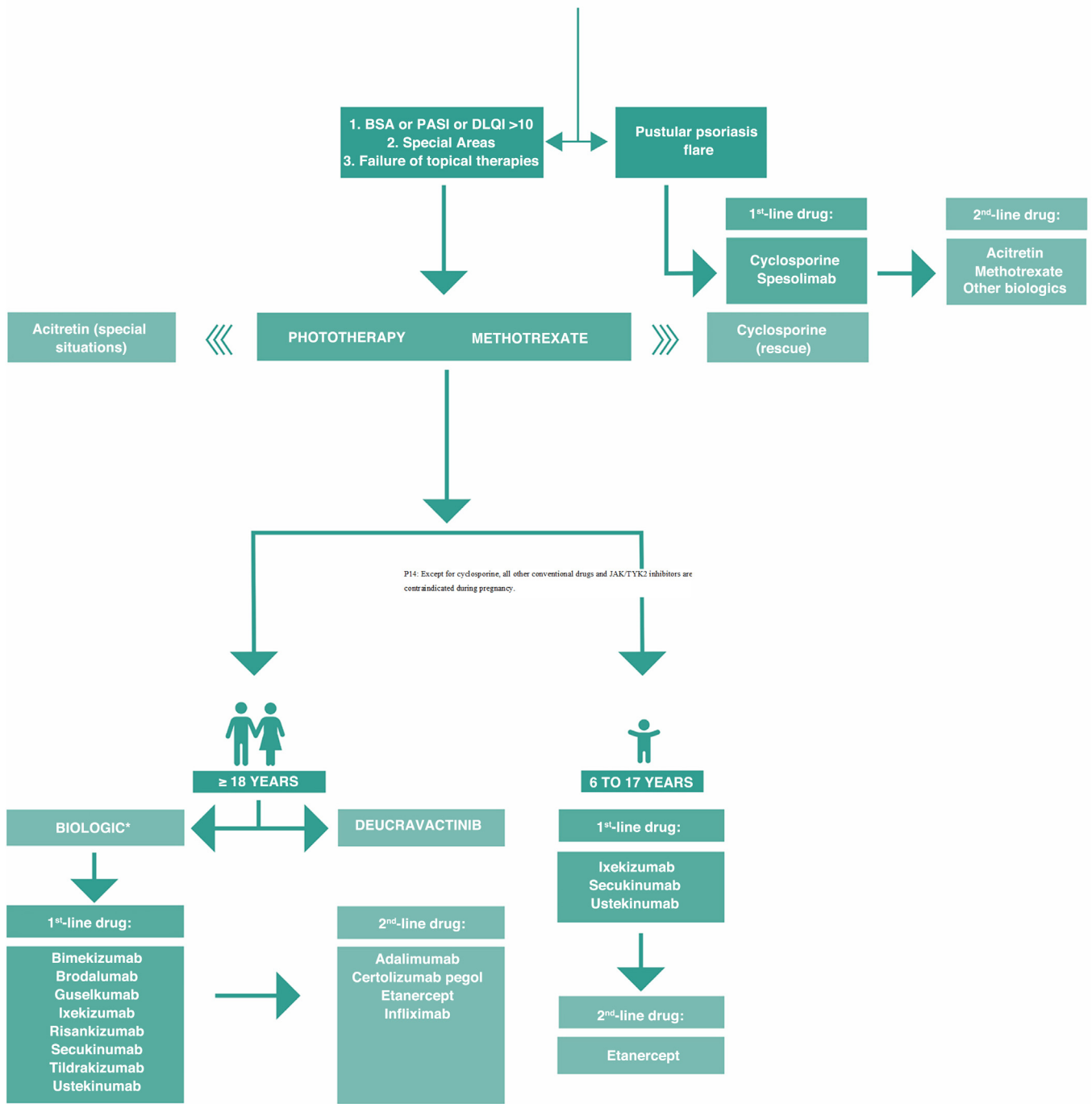
André V.E. de Carvalho: Data curation; original draft; review and editing.

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Psoriasis with indication for systemic therapy?



***Medications approved in Brazil in alphabetical order**

Fig. 3 Treatment algorithm for severe psoriasis of the Brazilian Society of Dermatology.

Funding

Brazilian Society of Dermatology.

Research data availability

The entire dataset supporting the results of this study was published in this article.

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Conflicts of interest

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LETTER – RESEARCH

Circular excision *versus* fusiform excision in the treatment of non-melanoma skin cancer: clinical trial on aesthetic and oncological outcomes[☆]

Dear Editor,

Skin cancer is the most common malignant neoplasm in Brazil and worldwide.^{1–3} Several therapeutic modalities are available; however, excision with margins recommended in the literature is the gold standard for treatment.^{3–5} Elliptical or fusiform excision is the most commonly used in clinical practice, mainly due to its practicality.^{6,7} However, studies show that this approach can sacrifice a large area of healthy skin by removing three to four times more tissue than the original tumor size, resulting in long and often unsightly scars.^{6,8} In contrast, the literature proposes circular excision as an alternative, with the potential to preserve a larger tissue area, resulting in shorter scars and better alignment with skin tension lines.^{6,8} Given this scenario, the present study aims to compare the fusiform and circular excision techniques in the treatment of low-risk basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), evaluating the length and final scar orientation, with an emphasis on aesthetic and oncological outcomes.

A clinical trial was conducted with 67 patients undergoing surgical excision of lesions suspected of non-melanoma skin cancer, evaluated clinically and dermoscopically by dermatologists with at least five years of training and clinical experience. All patients underwent circular excision, with the material subsequently being sent for conventional histopathological analysis.

Patients ≥ 18 years of age with primary lesions suspected of BCC or SCC, with a diameter ≤ 2 cm, located on the trunk or limbs, were included. Patients < 18 years of age, with recurrent lesions, lesions > 2 cm, located on the head, neck,

acral, or genital regions, or without clinical and dermoscopic criteria for BCC or SCC were excluded.

The primary outcome was the size of the scar obtained by circular excision and its final orientation. The secondary outcome was the difference between the planned fusiform excision diameter and the final scar size. The sample size calculation was based on the Hudson-Peacock study,⁶ estimating that at least 63 patients would be needed to detect a 21% difference in scar length with 95% confidence and a 10% margin of error.

The procedure consisted of: 1) Asepsis with 2% chlorhexidine disinfectant and 0.5% alcohol; 2) Circular marking of the lesion with recommended margins; 3) Delimitation of a theoretical zone with a 3:1 length-to-width ratio; 4) Measurement of the zone with a millimeter ruler; 5) Local anesthesia with an anesthetic solution of 20 mL of 2% lidocaine diluted in 20 mL of 0.9% saline and 0.02 mL of epinephrine 1:1000; 6) Excision with a 15-blade scalpel; 7) Hemostasis with electrocautery and tissue dissection; 8) Correction of "dog ears" when necessary; 9) Suturing with simple stitches and Mononylon; 10) Measurement of the final scar with a millimeter ruler and photographic record; 11) Comparison between the length and orientation of the final scar with the recommended fusiform design. The steps are outlined in **Figs. 1 and 2**.

Clinical, demographic, and surgical data were recorded on a standardized form and transferred to a spreadsheet (Microsoft Excel®). Categorical variables such as sex, age, comorbidities, lesion location, histopathological diagnosis, and final scar orientation were analyzed using the chi-square or Fisher's exact test. Ordinal variables such as age, lesion size, planned fusiform excision diameter, final scar size, and the difference between the fusiform excision size and the final scar size were evaluated using ANOVA or Kruskal-Wallis tests, according to normal or non-normal distribution, respectively. Normality was assessed using the Shapiro-Wilk test.

After histopathological analysis, 63 of the 67 lesions were confirmed as BCC or SCC. Four lesions were excluded due to alternative diagnoses. All removed lesions had neoplasia-free margins. The final sample consisted of 32 women (50.8%) and 31 men (49.2%), with a mean age of 65.3 years. Most lesions were located on the trunk (63.5%). Their diameter ranged from 0.4 to 2.0 cm, with a mean of 1.1 cm. The additional margin used was 0.4 cm for suspected BCC

[☆] Study conducted at the Hospital Universitário Pedro Ernesto, Departamento de Dermatologia, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

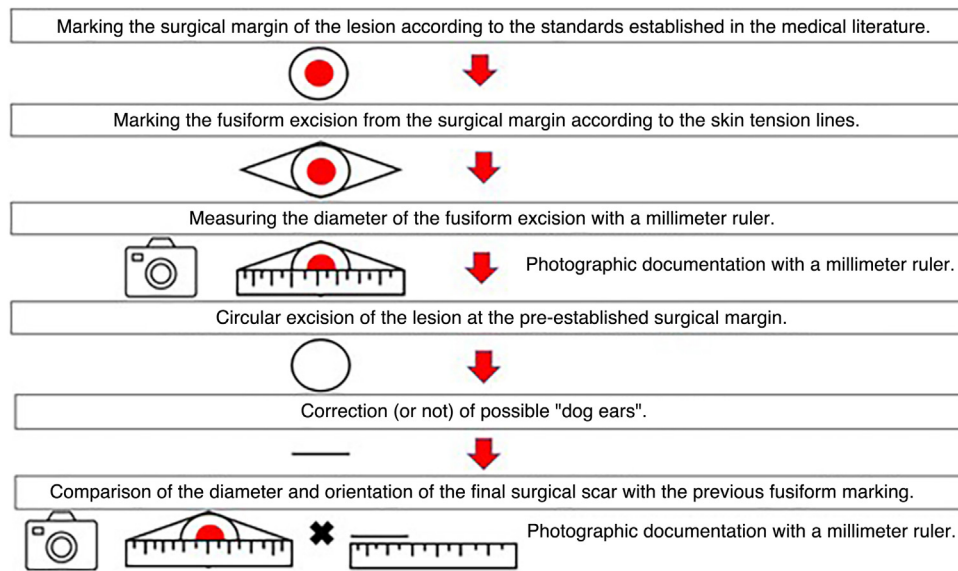


Figure 1 Stages of the surgical procedure.

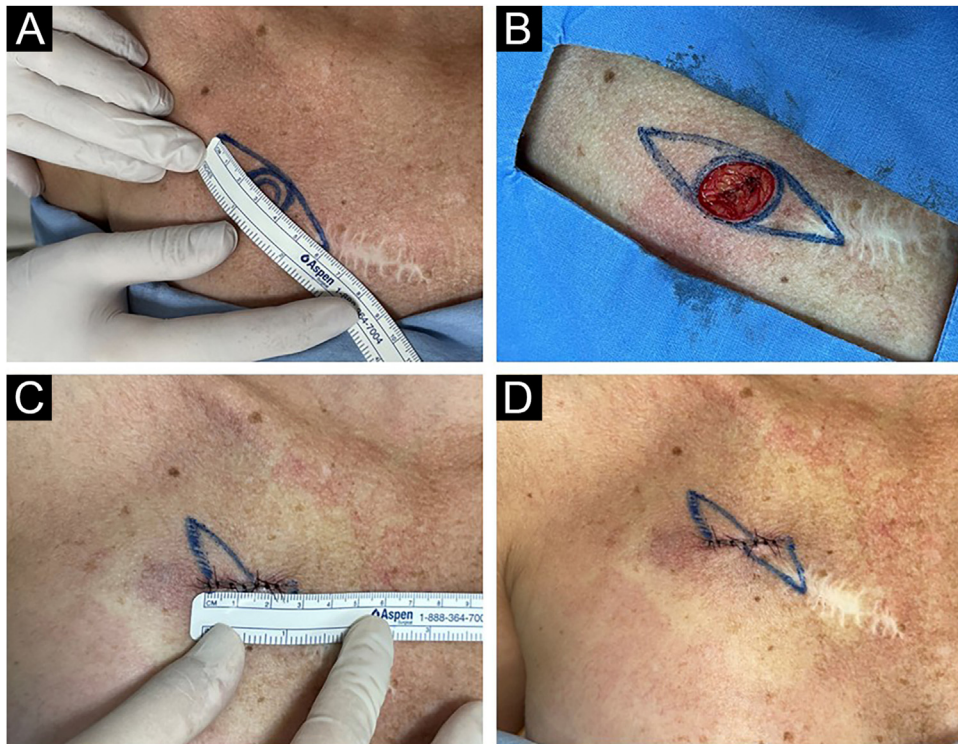


Figure 2 Clinical photographs of the surgical procedure steps. (A) Marking and measuring the fusiform excision diameter from the 0.4cm circular margin of the lesion according to the skin tension lines. (B) Surgical defect after excision of the lesion at the circular margin. (C) Measurement of the final scar for comparison with the programmed fusiform excision diameter. (D) Final scar: smaller and with a different orientation than the fusiform design.

and 0.5 cm for SCC. The mean theoretical zone length was 5.5 cm, while the final scar length was 3.1 cm, representing a mean reduction of 2.4 cm (43.6%). This reduction was observed in 100% of cases. In 32 cases (50.8%), correction of "dog ears" was necessary, 14 unilateral and 18 bilateral, and the remaining 49.2% did not require correction. In 30.2% of surgeries, there was a change in scar orientation, result-

ing in better alignment with skin tension lines. These data are shown in [Table 1](#).

The results of this study reinforce that circular excision is an effective alternative to the fusiform technique in the treatment of low-risk BCC and SCC. The reduction in scar length (43.6%) observed in all cases demonstrates that it is possible to preserve healthy tissue without compromising

Table 1 Comparative analysis of variables with correction of “dog ears”.

	Total	Number of corrected ears			p-value
		0	1	2	
Characteristics		n = 31	n = 14	n = 18	
Sex, n (%)					
Female	32 (50.8%)	15 (48.4%)	8 (57.1%)	9 (50.0%)	0.801
Male	31 (49.2%)	16 (51.6%)	6 (42.9%)	9 (50.0%)	
Age (ordinal)					
Mean (Standard deviation)	65.3 (14.4)	66.4 (11.7)	66.4 (19.2)	62.7 (14.9)	0.664
Median (Interquartile Interval)	67 (17)	69 (15)	66 (21)	64 (14)	0.676
Minimum; Maximum	29; 92	29; 89	30; 92	29; 85	–
Age (categorical), n (%)					
< 60	18 (28.6%)	6 (19.4%)	5 (35.7%)	7 (38.9%)	0.573
≥ 60	45 (71.4%)	25 (80.6%)	9 (64.3%)	11(61.1%)	
Histopathological diagnosis, n (%)					
Basal cell carcinoma	49 (77.8%)	26 (88.9%)	11 (78.6%)	12(66.7%)	0.389
Squamous cell carcinoma	14 (22.2%)	5 (11.1%)	3 (21.4%)	6 (33.3%)	
Lesion location, n (%)					
Limbs	23 (36.5%)	10 (32.3%)	4 (28.6%)	9 (50.0%)	0.364
Trunk	40 (63.5%)	21 (67.7%)	10 (71.4%)	9 (50.0%)	
Lesion size (cm)					
Mean (Standard deviation)	1.1 (0.4)	1.0 (0.4)	1.2 (0.4)	1.1 (0.5)	0.322
Median (Interquartile Interval)	1.0 (0.6)	0.9 (0.6)	1.2 (0.5)	1.0 (1.0)	0.286
Minimum; Maximum	0.4; 2.0	0.4; 2.0	0.5; 1.8	0.4; 2.0	–
Diameter: programmed fusiform excision (cm)					
Mean (Standard deviation)	5.5 (1.4)	5.2 (1.3)	5.5 (1.5)	5.8 (1.6)	0.350
Median (Interquartile Interval)	5.5 (1.5)	5.0 (2.0)	6.0 (2.0)	6 (2.5)	0.522
Minimum; Maximum	3.0; 9.0	3.0; 8.0	3.0; 8.0	3.4; 9.0	–
Final size: scar (cm)					
Mean (Standard deviation)	3.1 (1.0)	2.5 (0.7)	3.6 (0.9)	3.8 (1.0)	<0.001
Median (Interquartile Interval)	4.0 (1.7)	2.4 (1.0)	3.5 (1.2)	4.0 (0.9)	<0.001
Minimum; Maximum	1.4; 6.0	1.4;4.1	2.3; 5.0	1.5; 6.0	–
Programmed fusiform excision diameter – Final scar size (cm)					
Mean (Standard deviation)	2.4 (1.1)	2.7 (0.9)	2.0 (1.1)	2.0 (1.1)	0.024
Median (Interquartile Interval)	2.5 (1.5)	2.5 (1.5)	2.3 (2.0)	1.8 (2.0)	0.367
Minimum; Maximum	0.2; 5.0	1.1;5.0	0.2;3.7	0.2; 5.0	
Final scar orientation, n (%)					
Same	44 (69.8%)	22 (71.0%)	10 (71.4%)	12 (66.7%)	0.938
Different	19 (30.2%)	9 (29.0%)	4 (28.6%)	6 (33.3%)	

oncological cure, considering that all margins were free of neoplasia.

Compared with the literature, the results were superior to those of the studies by Hudson-Peacock and Lawrence, Seo et al., and Lee et al.^{6,8,9} In these studies, scar reduction ranged from 21% to 35%, with an improvement in the final wound orientation.

The reduced need for “dog ears” correction in about half of the cases is another favorable factor, reducing surgical time and tissue trauma. Furthermore, the possibility of realigning the final scar with skin tension lines in one-third of cases may contribute to a better aesthetic and functional result.

The study has limitations, such as the lack of a control group with true fusiform excision and the exclusion of lesions > 2 cm, which tend to form larger defects, leading to greater tension during closure, which could alter

the outcome. Furthermore, the lack of subjective aesthetic evaluation and long-term follow-up are factors to be considered in future studies to validate and expand the findings.

Therefore, circular excision proved to be a safe and effective technique with significant aesthetic advantages in the treatment of low-risk non-melanoma skin cancer. Its application resulted in smaller and, in many cases, better-oriented scars, without compromising oncological treatment, representing a viable alternative to the fusiform technique.

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Availability of research data

The entire dataset supporting the results of this study was published in the article itself.

Conflicts of interest

None declared.

Editor

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LETTER – RESEARCH

Cohort study on the survival of methotrexate and acitretin treatment in patients with plaque psoriasis: experience from a single center[☆]

Dear Editor,

Psoriasis is an inflammatory, immune-mediated, multifactorial, chronic disease of universal occurrence.¹ An estimated 125 million individuals are affected worldwide, with five million of them in Brazil alone.^{2,3}

Its treatment is based on topical active ingredients for mild cases; however, phototherapy, systemic drugs such as cyclosporine, methotrexate (MTX), acitretin (ACT), immunobiologicals, and small molecules are reserved for moderate and severe forms.³

As with other chronic diseases, continuity of therapy is an important aspect in the remission of clinical manifestations. The duration of use of a medication, known as therapeutic survival, is an indicator of its overall effectiveness, reflecting aspects such as adherence, side effects, cost, access, and patient and physician satisfaction.^{4,5}

In Brazil, MTX and ACT are first-line therapies for the treatment of moderate to severe psoriasis, available through the Brazilian Unified Health System (SUS, *Sistema Único de Saúde*). However, to date, there are no studies addressing the survival of these drugs in our population or the factors that affect treatment continuity.

With these objectives in mind, a real-world study was conducted with a bidirectional cohort design, based on the analysis of medical records of patients with psoriasis vulgaris who used MTX or ACT as systemic monotherapy at the public psoriasis outpatient clinic of Hospital das Clínicas, FMB-Unesp (Botucatu, SP). The protocol was approved by the institutional ethics committee, and data collection included the analysis of medical records of patients treated between January 2012 and July 2024. Survival curves were estimated using the Kaplan-Meier method, and comparisons between groups were performed using the log-rank test. The



effect size was expressed as a Hazard Ratio (HR) with a 95% Confidence Interval.⁶

A total of 274 patients and 346 treatment cycles were evaluated, including 200 MTX treatments and 146 ACT (Table 1). The distribution of ACT treatments showed a prevalence of older age and more elderly patients (≥ 60 years). A higher frequency of patients with arthritis was observed in the MTX group ($p < 0.05$). ACT was also preferred in the three patients with psoriasis vulgaris associated with pustular palmoplantar psoriasis.

Considering the survival curve (Fig. 1), the estimated median survival for MTX in the sample was 25 (95% CI 22–29) months and for ACT, 32 (95% CI 22–43) months ($p = 0.010$). The survival rates for MTX were 67%, 32%, and 21%; and ACT was 81%, 39%, and 30% after 1, 3, and 5 years, respectively.

Table 2 analyzes survival according to the main covariates. Dyslipidemia was associated with a lower risk of discontinuing treatment with ACT (HR = 0.6) or MTX (HR = 0.5). Late onset of psoriasis (age ≥ 60 years) was associated with a lower risk of discontinuing treatment with MTX (HR = 0.7).

Treatment discontinuation occurred in 86.5% of MTX cases and in 78.8% of ACT cases (Table 3). Treatment failure was the main cause of treatment discontinuation with both MTX (34.5%) and ACT (30.8%).

When comparing treatments initiated before 2020 in relation to those initiated after 2020, the median survivals of patients using MTX were 29 and 12 months ($p < 0.01$), respectively, whereas in patients who initiated the use of ACT before 2020 and after 2020, the median survival values found were 40 and 19 months ($p = 0.025$).

The median survival times for MTX and ACT in the population treated at the psoriasis outpatient clinic of Hospital das Clínicas, FMB-Unesp (Botucatu, SP) were slightly higher than the medians reported in the literature (12 to 21 months), demonstrating greater adherence to these treatments in Brazil.^{5–9} This may be explained by the limited availability of more effective treatments, such as immunobiologicals, through the SUS (Unified Health System).

As expected, the main cause of discontinuation of MTX and ACT treatments was treatment failure. In one of the studies, the main reason for discontinuation of MTX treatment was gastrointestinal adverse effects, even with folic acid administration in 99% of patients.⁵ On the other

[☆] Study conducted at the Department of Dermatology, Faculty of Medicine, Universidade Estadual Paulista, Botucatu, SP, Brazil.

Table 1 Demographic and clinical data of the sample of patients with psoriasis vulgaris, with registered visits between January 2012 and July 2024 at the psoriasis outpatient clinic of Hospital das Clínicas of FMB-Unesp (Botucatu, SP), undergoing treatment with methotrexate or acitretin.

Variables	Methotrexate	Acitretin
n	200	146
Female sex, n (%)	97 (48.5)	57 (39.0)
Age, (in years) mean (SD)	55.0 (13.8)	60.2 (14.5) ^a
≥ 60 years, n (%)	87 (43.5)	80 (54.8) ^a
Ethnicity, n (%)		
White	179 (89.5)	128 (87.7)
Brown	15 (7.5)	11 (7.5)
Black	6 (3.0)	6 (4.1)
NA	– (–)	1 (0.7)
Level of schooling, n (%)		
Illiterate	16 (8.0)	12 (8.5)
Elementary School	97 (48.5)	78 (54.9)
High School	51 (25.5)	30 (21.1)
Higher Education	18 (9.0)	14 (9.9)
NA	18 (9.0)	12 (8.2)
Weight, (in kg) mean (SD)	81.2 (17.7)	80.8 (16.9)
≥ 100 kg, n (%)	32 (16.0)	24 (16.4)
Clinical form, n (%)		
Vulgaris	200 (100)	146 (100)
Psoriatic arthritis	54 (27.0) ^a	19 (13.0)
Nail	48 (24.0)	37 (25.3)
Guttate psoriasis	9 (4.5)	7 (4.8)
Inverse psoriasis	10 (5.0)	7 (4.8)
Palmoplantar pustular	– (–)	3 (2.1) ^a
Hyperkeratotic palmoplantar psoriasis	16 (8.0)	20 (13.7)
Scalp	92 (46.0)	58 (39.7)
Others	8 (4.0)	12 (8.2)
Age of onset of psoriasis, (in years) mean (SD)	37.2 (14.9)	40.2 (17.6)
< 30 years, n (%)	60 (30.8)	42 (29.6)
≥ 60 years, n (%)	12 (6.2)	23 (16.2) ^a
Family history of psoriasis, n (%)	24 (12.1)	15 (10.4)
Comorbidities, n (%)		
Arterial hypertension	78 (39.0)	63 (43.2)
Diabetes mellitus	62 (31.0)	39 (26.7)
Depression / Anxiety	46 (23.0)	31 (21.2)
CVD	14 (7.0)	16 (10.9)
Dyslipidemia	86 (43.0)	75 (51.4)

CVD, cardiovascular diseases; NA, Not available.

^a $p < 0.05$ (Methotrexate × Acitretin).

hand, two other studies found that treatment failure was the main cause of discontinuation of MTX treatment.^{8,9} In the dermatology service of FMB-Unesp, it is common to prescribe oral folic acid at a dose of 5mg/week for patients using MTX, which could help minimize the gastrointestinal effects of MTX, as well as conversion to injectable MTX. Shalom et al. (2015) also observed that the use of oral MTX and folic acid supplementation would be protective factors against the termination of MTX treatment.⁷

The percentage of patients who achieved adherence to MTX and ACT treatments by the end of the third and fifth years of treatment, with a greater superiority in adherence for ACT (30%) compared to MTX (21%) at the end of the fifth year, highlights the importance of these drugs in the

long-term treatment of patients with moderate to severe psoriasis in Brazil, where access to new therapies is limited due to availability through the SUS.

Finally, the observation of longer survival rates for both drugs in patients enrolled before 2020 may reflect both the availability of more effective treatments (e.g., anti-IL-23 and anti-IL-17), but also the establishment of more rigorous endpoints for disease control, such as PASI 75-100. Therefore, changes in survival rates also reflect the changing psoriasis treatment flowchart.³

A national series showed median survival of less than two years for infliximab and etanercept, while adalimumab showed approximately three years, suggesting that MTX and ACT have survival rates quite comparable to anti-TNF agents.¹⁰

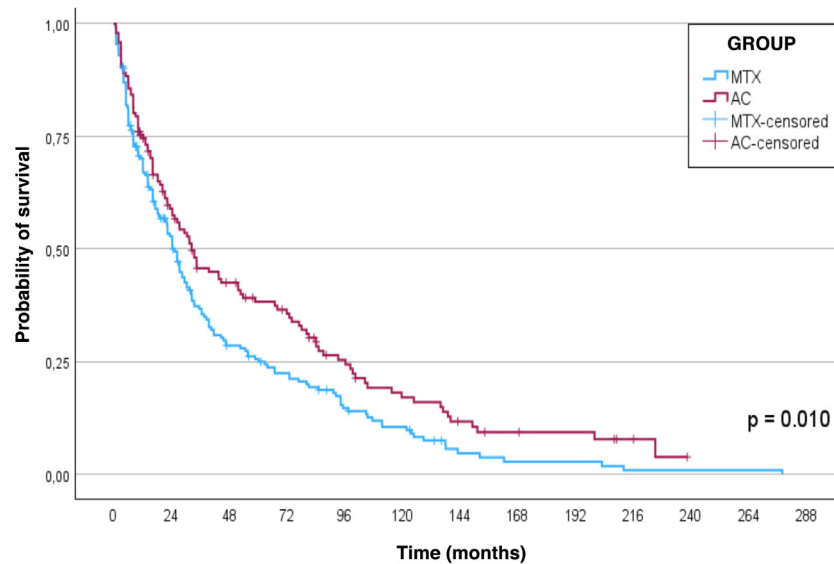


Fig. 1 Survival functions (Kaplan–Meier curve) for treatments with methotrexate and acitretin in patients with psoriasis vulgaris treated at the psoriasis outpatient clinic of the Hospital das Clínicas of FMB-Unesp (Botucatu, SP), from January 2012 to July 2024.

Table 2 Hazard Ratio of variables associated with survival of treatments with methotrexate and acitretin in patients with psoriasis vulgaris treated at the psoriasis outpatient clinic of Hospital das Clínicas of FMB-Unesp (Botucatu, SP), from January 2012 to July 2024.

Variables	Methotrexate		Acitretin	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex (female)	1.1 (0.8–1.5)	0.616	0.9 (0.7–1.4)	0.773
White ethnicity	0.6 (0.4–1.0)	0.061	0.7 (0.4–1.4)	0.112
Schooling (Higher Education)	1.4 (0.8–2.4)	0.213	1.2 (0.6–2.1)	0.619
Family history	1.1 (0.7–1.8)	0.645	0.7 (0.4–1.3)	0.299
Age (≥ 60 years)	0.7 (0.5–0.9)	0.015	1.0 (0.7–1.4)	0.912
Weight (≥ 80 kg)	1.2 (0.9–1.6)	0.271	1.1 (0.8–1.6)	0.615
Age at onset (< 30 years)	1.1 (0.8–1.5)	0.695	0.8 (0.5–1.1)	0.182
Age at onset (≥ 60 years)	1.1 (0.5–2.2)	0.856	1.1 (0.6–1.9)	0.743
Psoriatic arthritis	1.1 (0.8–1.6)	0.480	1.5 (0.9–2.5)	0.087
Nail psoriasis	1.3 (1.0–1.9)	0.095	0.8 (0.5–1.3)	0.416
Depression / Anxiety	0.9 (0.6–1.3)	0.564	1.1 (0.7–1.7)	0.713
Diabetes mellitus	0.9 (0.7–1.3)	0.690	1.1 (0.7–1.7)	0.625
Arterial hypertension	0.8 (0.6–1.1)	0.102	0.9 (0.6–1.2)	0.432
Dyslipidemia	0.5 (0.4–0.7)	< 0.001	0.6 (0.4–0.8)	0.003

HR, Hazard Ratio (95% confidence interval - CI) for treatment discontinuation.

This study has limitations related to its reliance on medical records, lack of objective metrics (e.g., PASI score), and loss to follow-up, especially during the pandemic.

In conclusion, the median therapeutic survival for methotrexate was 25 months, and for acitretin, 32 months, and the main cause of treatment discontinuation was treatment failure. The data obtained reinforce the role of these drugs in the management of moderate to severe psoriasis

in public health services, especially in settings with limited access to advanced therapies.

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Table 3 Causes of permanent discontinuation of methotrexate or acitretin treatments in patients with psoriasis vulgaris treated at the psoriasis outpatient clinic of the Hospital das Clínicas de FMB-Unesp (Botucatu, SP), from January 2012 to July 2024.

Variables	Methotrexate, n (%)	Acitretin, n (%)
Cases	173 (86.5)	115 (78.8)
Therapeutic failure	69 (34.5)	45 (30.8)
Emergence of contraindication	27 (13.5)	13 (8.9)
Age > 65 years	3 (1.50)	–
Time of use/Accumulated dose	8 (4.0)	–
Pregnancy	4 (2.0)	1 (0.7)
Infections	7 (3.5)	1 (0.7)
Comorbidities	6 (3.0)	1 (0.7)
Arthritis/arthralgia	–	10 (6.8)
Loss to follow-up	28 (14.0)	15 (10.3)
Adverse effect	37 (18.5)	32 (22.0)
Laboratory alteration	15 (7.5)	18 (12.3)
Mucocutaneous symptoms	–	12 (8.3)
Gastrointestinal symptoms	20 (10.0)	2 (1.4)
Headache	1 (0.5)	–
Pneumonitis	1 (0.5)	–
Clinical improvement	18 (9.0)	21 (14.4)
Poor adherence	7 (3.5)	3 (2.1)
Cost	7 (3.5)	–
Shortage	–	6 (4.2)
Death	1 (0.5)	1 (0.7)
Others / NA	12 (6.0)	5 (3.4)

NA, Not available.

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Authors' contributions

Hélio Amante Miot: Design and planning of the study; analysis and interpretation of data; statistical analysis; drafting and editing of the manuscript; critical review of the literature; critical review of the manuscript; approval of the final version of the manuscript.

Luciane Donida Bartoli Miot: Design and planning of the study; analysis and interpretation 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.

Maria Cecília Valsechi Belli: 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.

Christina de Castro Brommonschenkel: Design and planning of the study; collection of data; analysis and interpretation of data; statistical analysis; drafting and editing of the manuscript; critical review of the literature; critical review of the manuscript; approval of the final version of the manuscript.

Availability of research data

The entire dataset supporting the results of this study was published in the article itself.

Conflicts of interest

None declared.

Editor

Sílvia Alencar Marques.

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LETTER - RESEARCH

Dietary antioxidant intake in women with facial melasma: a cross-sectional study[☆]



Dear Editor,

Melasma is a chronic, multifactorial pigmentary dermatosis that exclusively affects sun-exposed areas (with lesions predominantly on the face) and is more prevalent in women in the period between menarche and menopause. Genetic predisposition, exposure to ultraviolet radiation (UVR), and hormonal stimuli are its main triggers. However, other factors, such as exposure to environmental pollution, heat, sleep deprivation, and chronic conditions such as depression, can aggravate systemic oxidative stress, potentially contributing to the genesis and progression of melasma.¹

Systemic oxidative stress is prominent in patients with melasma. Concurrently, the administration of oral antioxidants, such as pycnogenol, enhances the clearing effect of topical treatment.²

Chronic exposure to UVR, especially type A, induces both cell and systemic oxidative stress, contributing to the sustained melanogenesis observed in melasma.¹ There is a negative correlation between the clinical severity of melasma and plasma glutathione (GSH) levels, as well as increased levels of components of the intracellular antioxidant defense enzyme system, such as superoxide dismutase (SOD) and GSH-peroxidase.³ Furthermore, individuals with melasma have higher plasma concentrations of malondialdehyde, a byproduct of lipid peroxidation that is a marker of cell damage.⁴

In the context of antioxidant defense mechanisms, in addition to the enzyme system (such as SOD and GSH-peroxidase), the importance of non-enzymatic antioxidants obtained through diet stands out. These include compounds present in foods rich in beta-carotene, vitamins C and E, ellagic acid, bioflavonoids, catechins, isoflavones, lycopene, omega-3 fatty acids, polyphenols, resveratrol, selenium, zinc, and cysteine.

To date, no study has systematically evaluated dietary aspects in individuals with melasma. To fill this gap, a cross-sectional study was conducted to investigate dietary patterns, with a specific focus on the intake of antioxidant-rich foods, in women with facial melasma compared to those without the condition.

After approval by the institutional ethics committee (CAAE 26390419.7.0000.5515), 194 adult women of child-bearing age (aged 18 to 49) were included and divided into two groups: 97 with facial melasma (diagnosed by a dermatologist) and 97 controls. Participant recruitment occurred from September 2023 to January 2024. Matching was performed by age, and women with concomitant facial dermatoses were excluded. Sampling was consecutive, among patients treated at the Presidente Prudente Regional Hospital, and was conducted after informed consent was obtained.

The main study outcome measure was the adapted Food Frequency Questionnaire (FFQ), which was administered to participants to assess their weekly consumption of 41 types of foods (Supplementary Material). The data obtained were converted to grams, and from this, energy, macronutrient, and micronutrient values were calculated using the Nutritional Data System for Research (NDSR) software. Dietary patterns were analyzed based on their components, extracted using the PLS (Partial Least Squares) method, using data scaled by standard deviations.⁵ All dietary intake assessments were processed and analyzed by a nutritionist (TCF).

In addition, demographic data, adherence to photoprotection, smoking status, and oral antioxidant supplementation were collected. Nutrients were compared between groups using the Mann-Whitney (exact) test, with significance set at $p \leq 0.01$. Sample size was calculated to detect a minimum difference of 20% in nutrient intake between groups, with an alpha of 0.01 and a beta of 0.1.

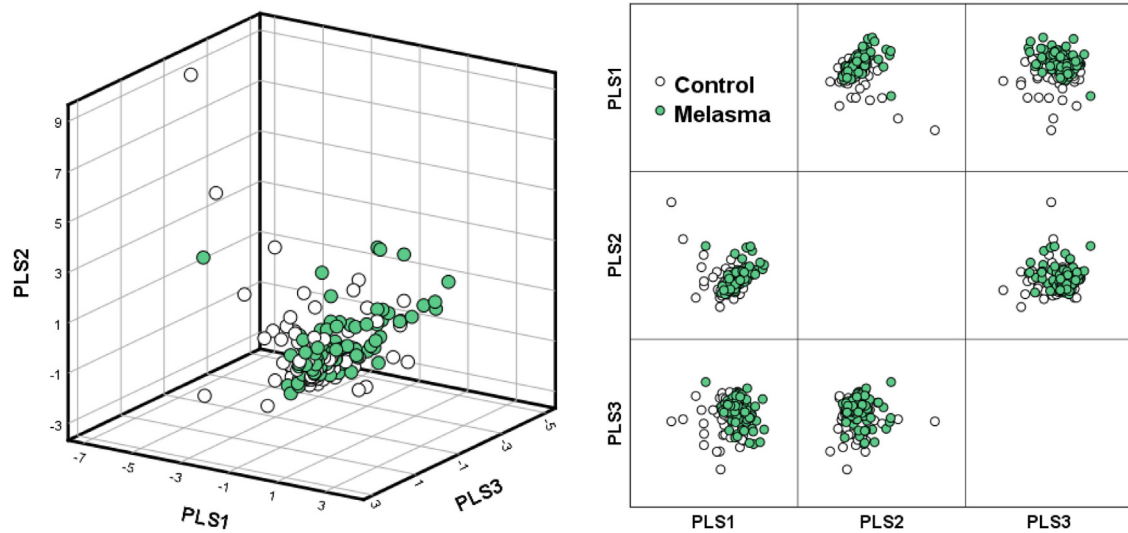
There were no differences between the groups in age, phototypes, age at menarche, smoking status, number of children, adherence to sunscreen, contraceptive use, or oral antioxidant supplementation (Table 1).

The diet in both groups was monotonous, and the most commonly consumed foods per week in both groups were milk, cheese, oranges, tomatoes, coffee, and white meat. No celiac disease or vegetarians were found in the sample. Extraction of three PLS components based on the

[☆] Study conducted at the Hospital Regional de Presidente Prudente Doutor Domingos Leonardo Cerávolo, Presidente Prudente, SP, Brazil

Table 1 Main demographic data of women with melasma and controls.

Variables	Melasma	Control	p-value ^a
<i>n</i>	97	97	–
Age (years) – mean (sd)	38 (7)	37 (9)	0.162
Phototype (Fitzpatrick) – <i>n</i> (%)			0.035
I–II	37 (38)	50 (52)	
III	44 (45)	39 (40)	
IV–V	16 (17)	8 (8)	
Family member with melasma – <i>n</i> (%)	58 (60)	20 (21)	<0.001
Regular use of sunscreen – <i>n</i> (%)	73 (75)	63 (65)	0.158
Age at menarche (years) – mean (sd)	12 (1)	12 (1)	0.916
Time of melasma (years) – median (p25–p75)	8 (5–15)	–	–
Number of children – median (p25–p75)	1 (0–2)	1 (0–2)	0.243
Uses oral contraceptive – <i>n</i> (%)	33 (34)	39 (40)	0.458
Current smoker – <i>n</i> (%)	9 (9)	2 (2)	0.058
Use of oral antioxidant – <i>n</i> (%)	18 (19)	10 (10)	0.152

^a Bivariate analysis.**Fig. 1** Dietary patterns of participants regarding the 41 foods investigated. Loading according to the three PLS (partial least squares) components (*n* = 194).

dietary patterns formed by the 41 foods studied explained the variance of only 20% of the groups, without implying adequate separation between the melasma group and controls (Fig. 1). Furthermore, no differences were observed between the two groups regarding the consumption of macro and micronutrients, including dietary antioxidants (Table 2).

Despite the oxidative microenvironment in the upper dermis, the causes of systemic oxidative imbalance in melasma patients are not understood, and the results of this study demonstrated no differences in dietary antioxidant consumption in these patients.

The eating habits of the urban Brazilian population are unbalanced, characterized by low food variability, high caloric intake of carbohydrates such as rice and pasta, and consumption of ultraprocessed foods, but low intake of fiber and micronutrients.⁶ The study participants did not exhibit eating habits that differed from those of the urban Brazilian population.

Research on dietary patterns and their association with health outcomes is important but has been little explored systematically in the dermatological literature. It is also important to highlight that understanding the nutritional components of a diet influences not only the body's nutritional aspects but also the composition of the intestinal microbiome, the effects of xenobiotics, and the overall epigenetic control exerted by certain foods.⁷

There are no robust studies in the literature that have investigated the increased consumption of antioxidant-rich foods in other dermatoses. Specifically in rosacea, studies with zinc supplementation have shown conflicting results and methodological limitations, resulting in insufficient evidence to recommend its clinical use. A review of the literature on dietary supplements showed that, in patients with vitiligo, only oral vitamin D replacement is recommended in cases of proven deficiency, although there is still no consensus on the ideal dose to promote repigmen-

Table 2 Nutritional data of participants' diets, reported in one week (n = 194).

Nutrients	Melasma			Control			p-value ^a
	Median	p25	p75	Median	p25	p75	
Energy(kcal)	18,164	12,396	25,836	21,110	13,309	29,083	0.208
Protein (g)	920	635	1,418	1,204	715	1,878	0.023
Carbohydrate (g)	2,392	1,292	3,618	2,332	1,365	3,224	0.608
Lipids (g)	441	328	666	598	335	952	0.021
Saturated lipids (g)	163	71	311	223	86	407	0.053
Monounsaturated Lipids (g)	116	61	168	173	81	282	0.024
Polyunsaturated Lipids (g)	53	32	100	61	33	124	0.258
Cholesterol (mg)	2,427	1,564	4,815	3,240	1,799	7,157	0.063
Fiber (g)	438	235	745	384	251	735	0.924
Sodium (mg)	13,817	7,736	30,341	19,383	11,864	33,522	0.039
Calcium (mg)	13,744	7,575	20,338	14,368	8,832	23,694	0.205
Iron (mg)	107	63	207	133	75	217	0.213
Zinc (mg)	95	63	140	124	70	156	0.055
Vitamin A (mcg)	11,617	5,259	23,800	10,542	4,818	24,518	0.967
Vit. B1 (mg)	20	11	28	21	13	34	0.273
Vit. C (mg)	4,586	1,895	9,793	3,678	1,523	7,917	0.220
Vitamin E (mg)	82	45	166	105	45	182	0.467
Vitamin B6 (mg)	29	20	46	34	21	44	0.419
Vitamin D (mg)	23	9	65	34	9	98	0.103
Potassium (mg)	52,573	32,826	77,674	55,828	35,776	78,289	0.675
Magnesium (mg)	4,774	2,987	7,318	5,491	3,142	7,981	0.257
Selenium (mg)	878	508	1,570	1,044	568	2,234	0.086
Folate (mg)	4,388	2,099	6,665	3,899	2,323	6,163	0.627

^a Bivariate analysis.

tation. The use of *Polypodium leucotomos* is also indicated, as long as it is combined with phototherapy, and shows evidence of increased repigmentation, especially in exposed areas. Supplementation with vitamins C and B12, vitamin E, antioxidant mixtures, and *Ginkgo biloba* still has insufficient evidence for routine recommendation.⁸

A Chinese study involving 150 cases and 150 controls identified alcohol intake as a risk factor (Odds Ratio=20.5) and soft drink consumption as a protective factor (Odds Ratio=0.04) for the development of melasma. However, these factors have not been adequately investigated from a pathophysiological perspective.⁹ And, despite being a common demand of patients, there are still no validated associations between dietary aspects and the onset of melasma. In this study, no differences in dietary patterns were identified when comparing women with melasma and the control group.

To date, evidence suggests oral supplementation with antioxidants (such as pycnogenol) as an adjunct to treatment.¹⁰ In the context of specific dietary intake, it is hypothesized that soy may exacerbate melasma due to its estrogen-like action; however, there is no data on a critical amount for this outcome.¹¹

Studies related to dietary patterns have limitations related to participant recall, food recall, and the monotony of urban populations' diets. However, sample homogeneity, such as that of these participants from a single center, strengthens internal validity when exploring factors linked solely to diet. The lack of observational association does not mean that dietary interventions are ineffective; how-

ever, different study designs are required to confirm this. Finally, studies exploring the intestinal microbiome may suggest dietary interventions for melasma.

In conclusion, neither dietary patterns nor dietary antioxidant consumption is associated with the development of melasma in Brazilian women.

Authors' contributions

Ana Cláudia Cavalcante Espósito: Design and planning of the study; analysis and interpretation 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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Hélio Amante Miot: Design and planning of the study; analysis and interpretation of data; statistical analysis; drafting and editing of the manuscript; critical review of the literature; critical review of the manuscript; approval of the final version of the manuscript.

Approval by the Ethics Committee

This project was approved by the Ethics Committee of Universidade do Oeste Paulista CAAE: 26390419.7.0000.5515 (UNOESTE).

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Availability of research data

The entire dataset supporting the results of this study was published in this article.

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.2025.501218>.

Conflicts of interest

None declared.

Editor

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LETTER - RESEARCH

Pediatric melanoma in Brazil: an analysis of mortality[☆]



Dear Editor,

Cutaneous melanoma in children and adolescents is a rare condition, accounting for 1% to 3% of all pediatric malignancies and approximately 1% to 4% of all melanoma cases.¹ The global incidence is estimated at 2 to 5 new cases per million people annually, with an average annual increase of 2% over the past few decades.²⁻⁴ However, recent data from the United States show a decreasing trend in new melanoma cases since 2006, particularly among adolescents.³ In the United States, 79% of cases in recent decades have been

diagnosed in adolescents, while only 0.3% to 0.4% occur during the first decade of life.⁵

The risk factors, clinical presentation, and prognosis differ significantly among neonatal melanoma, childhood melanoma, and adult melanoma.⁶⁻⁸ Despite its rarity, pediatric melanoma is the most common skin cancer in children and a crucial diagnosis in pediatric oncology and dermatology, as melanocytic lesions are among the most frequent reasons for dermatological consultations in this age group.^{7,9}

Given its uncommon occurrence, the literature on pediatric melanoma remains limited, with most knowledge derived from single-institution studies or small regional cancer registries. Here, the authors describe mortality associated with melanoma in the pediatric population of Brazil.

Distribution of melanoma deaths in the pediatric population in Brazil from 2008 to 2023 by year

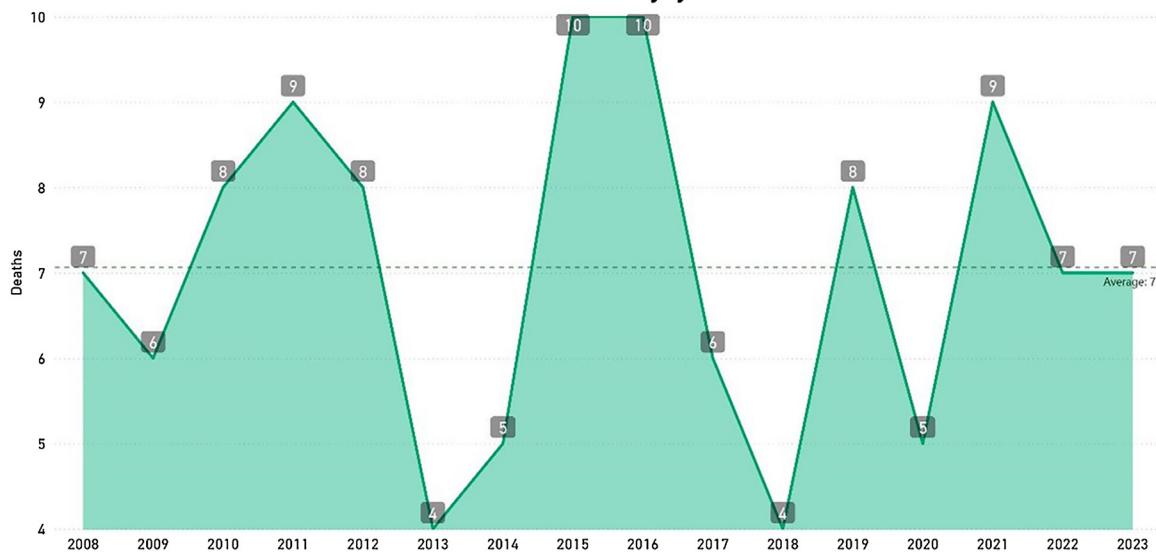


Fig. 1 Distribution of melanoma deaths per year in the pediatric population in Brazil from 2008 to 2023. The number of deaths peaked in 2015 and 2016, with 10 deaths per year. Other years with relatively high numbers were 2011 and 2021, with 9 deaths each. Most years showed relatively low and consistent numbers of deaths, ranging from 4 to 8.

[☆] Study conducted at the Centro de Diagnósticos Anatómopatológicos, Joinville, SC, Brasil.

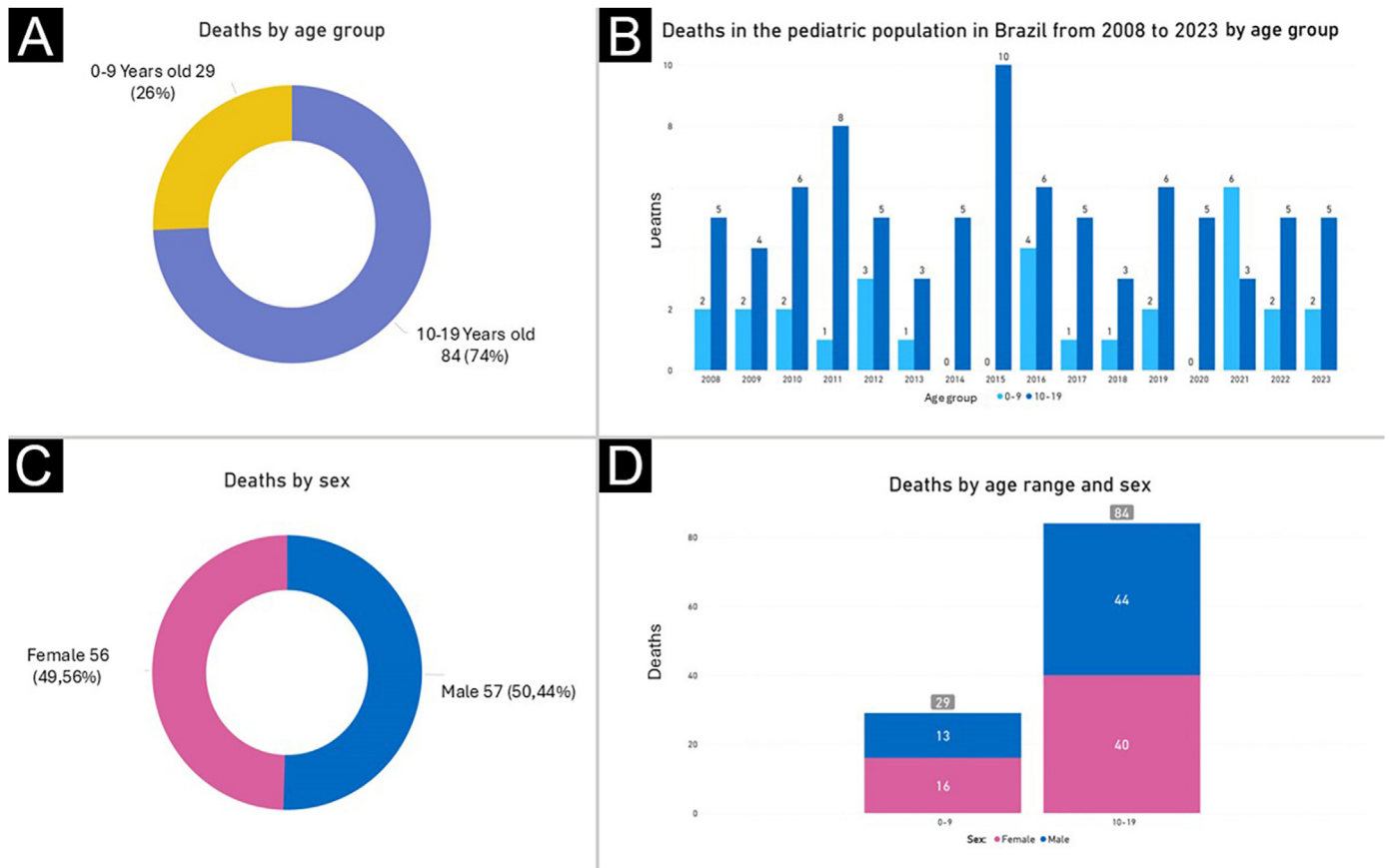


Fig. 2 Distribution of melanoma deaths in the pediatric population in Brazil from 2008 to 2023, by age and sex. (A) Overall distribution of deaths by age group, with the 0–9 years group representing 26% of total deaths (29 deaths), while the 10–19 years group accounts for 74% (84 deaths). (B) Distribution of deaths by age group over the years. The 10–19 years group, represented in dark blue, frequently shows higher numbers of deaths than the 0–9 years group (light blue). However, distinct peaks were observed in specific years. In 2015, the 10–19 years group recorded the highest number of deaths, with 10 deaths, while in 2021, the 0–9 years group had the highest number of deaths, with 6 deaths. Although the 10–19 years group has a generally higher prevalence of deaths, the annual variations in the 0–9 years group suggest a non-linear distribution of deaths over the years. (C) Overall distribution of deaths by sex, with 49.56% of deaths occurring in females (56 deaths) and 50.44% in males (57 deaths). (D) Number of deaths by age group and sex, with 13 (45%) deaths in males and 16 (55%) in females in the 0–9 years age group (totaling 29 deaths), and 44 (52%) deaths in males and 40 (48%) in females in the 10–19 years age group (totaling 84 deaths). These data indicate a generally balanced distribution of deaths between the sexes, with a slight predominance of females in the 0–9 years age group and a nearly equal distribution in the 10–19 years age group.

The authors carried out a retrospective, descriptive exploratory analysis of melanoma mortality in the Brazilian pediatric population, using nonidentifiable national registry data from the Mortality Information System (SIM), provided by the Department of Informatics of the Brazilian Unified Health System (DATASUS). Consolidated data from 2008 to 2022, including preliminary data from 2023, were analyzed. The processing and coding of mortality data followed the official documentation provided by DATASUS, and gathered from the official File Transfer Protocol (FTP) address (<ftp.datasus.gov.br>), with the needed data decompression and conversion from dbc (compressed 'XBASE' database) into comma-separated values. The inclusion criteria established were underlying causes classified under group C43 of the International Classification of Diseases (ICD-10) and age at death between 0 and 19 years and 364 days. The variables extracted from SIM reflect the Death Certificate (DO), and

for this research, they include year and date of death, date of birth, age at death, gender, race, federal unit, underlying cause, and items A, B, C, and D from the DO. Data collection was carried out on 09/24/2024, based on the latest publicly available version. Demographic information and population indices were obtained through the Application Programming Interface (API) of the Brazilian Institute of Geography and Statistics (IBGE), integrating census data and official population estimates. The average mortality rate was calculated for the total pediatric population (0 to 19 years) and for the age groups of 0 to 9 years and 10 to 19 years, using data from IBGE between 2008 and 2023. To calculate the annual mortality rate, the number of deaths was divided by the total population, and the result was multiplied by 100,000. To obtain the average mortality rate, the annual mortality rates were accumulated, and the total was divided by the

Deaths by region

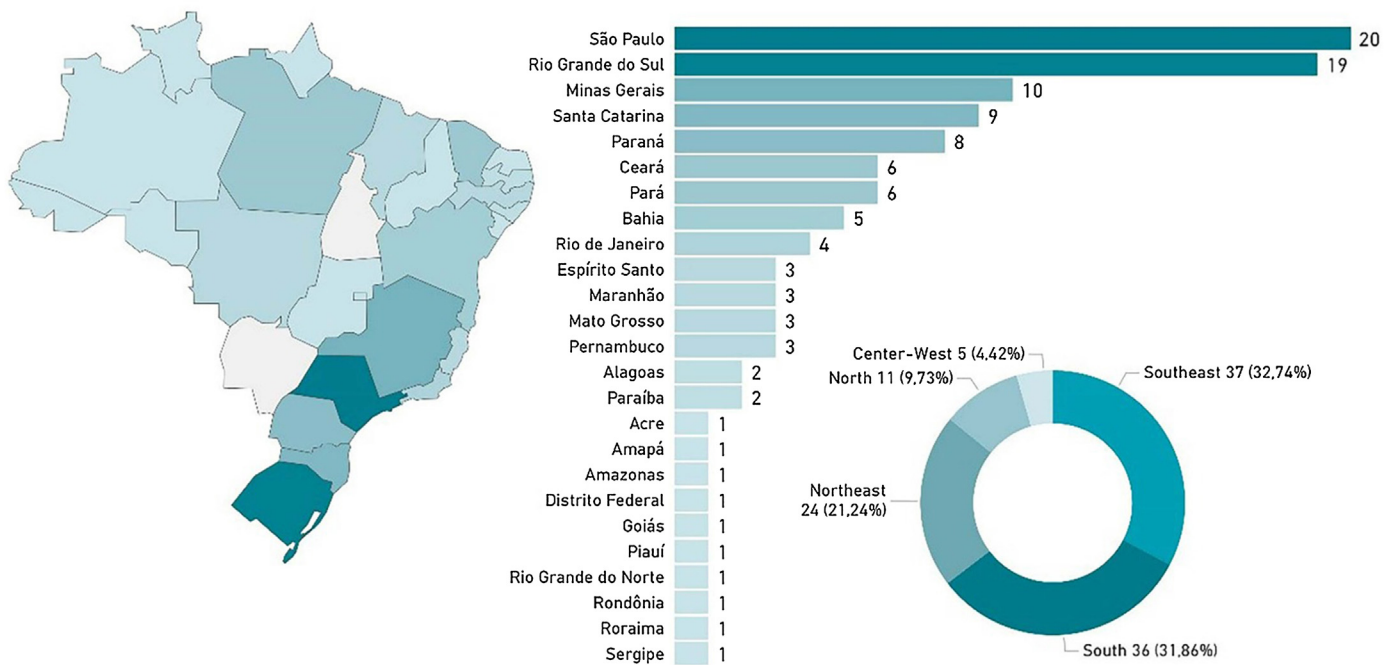


Fig. 3 Distribution of melanoma deaths in the pediatric population in Brazil from 2008 to 2023, by state and region. The map on the left shows the geographic distribution of melanoma deaths, with states reporting the highest numbers of deaths represented in darker green. The bar graph in the center presents the total number of deaths by state and the Federal District, with São Paulo (20 cases) and Rio Grande do Sul (19 cases) at the top of the graph. The pie chart in the lower left shows the distribution of deaths by region, with the southern (36 cases, 31.86%) and southeastern (37 cases, 32.74%) regions reporting the highest numbers of deaths, followed by the northeast (24 cases, 21.24%), northern (11 cases, 9.73%), and central western regions (5 cases, 4.42%). The darker green colors in all three graphs indicate the areas with the highest number of deaths.

16 years of the period. Power BI was used for the creation of graphs.

A total of 113 cases of melanoma-related deaths in pediatric patients in Brazil were identified from 2008 to 2023, corresponding to 0.01% of all deaths in the pediatric population. Fig. 1 shows the distribution of deaths per year. The distribution of deaths by age per year shows a predominance in the adolescent population (84, which corresponds to 74%), compared to children (29, or 26%) (Fig. 2). The average mortality rate was 0.011367 per 100,000 inhabitants for the total pediatric population (0 to 19 years), with 0.00613 for the 0 to 9 years age group and 0.014785 for the 10 to 19 years age group.

There was a small predominance in the male population (50.44%). However, when analyzed by age group, there were more deaths among females in children and among males in adolescents (Fig. 2D). These findings indicate the need for equitable attention to both sexes in prevention and early diagnosis strategies. The authors also analyzed the distribution of death cases for each region and state in Brazil. Results showed a predominance of deaths from pediatric melanomas in the southeast (32.74%) and southern (31.86%) regions and in the states of São Paulo ($n = 20$) and Rio Grande do Sul ($n = 19$) (Fig. 3 and Fig. 4). There was also a higher number of records in the white-skinned population, followed by the mixed-race (brown) population (Fig. 4). These find-

ings may be related to population density, better quality of notification data, easier access to health services and the higher proportion of light-skinned individuals, who are generally at greater risk for melanoma. The Brazilian phenotypic distribution exhibits considerable heterogeneity across latitudes. In the states of Santa Catarina and Rio Grande do Sul, 89% of the urban population has fair skin.¹⁰

The main limitations of the present study are related to the retrospective nature of the database and the analysis conducted on raw data, which were not adjusted for the population. The national data did not provide important histopathological features such as histological subtype, presence of ulceration, and staging. In addition, the results were based on secondary data, and the actual number of deaths by melanoma in this age group might be higher. Furthermore, data considering the distinct clinical forms of pediatric melanoma were not available.

In summary, this study reports deaths from melanoma in the pediatric population in Brazil, highlighting the need for specific strategies for prevention, early diagnosis, and treatment. The clinical management of pediatric melanoma is challenging and lacks specific guidelines, making it crucial to ensure access to clinical trials and new therapies that can alter the natural history of advanced melanoma. Future studies should preferably include data on predisposing conditions, such as xeroderma pigmentosum or congenital

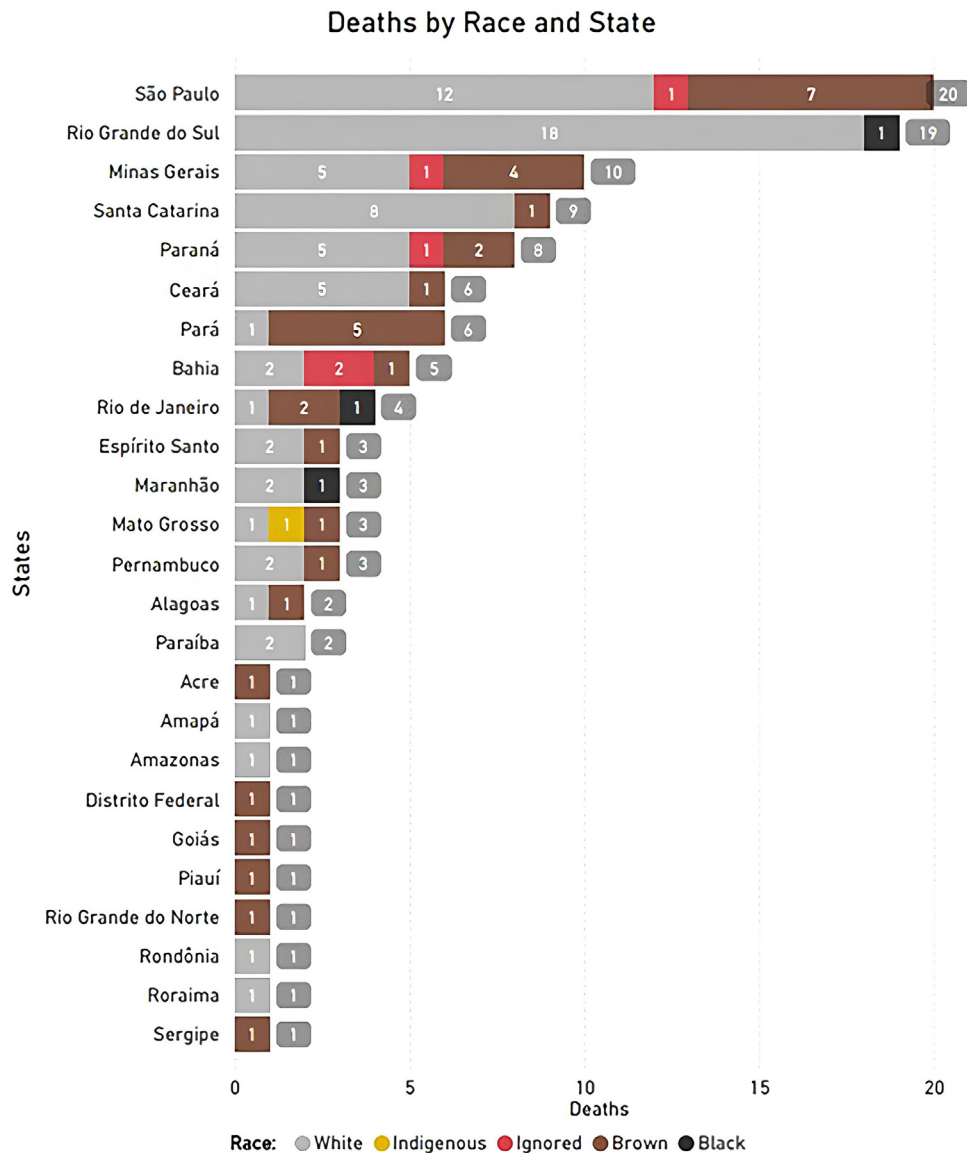


Fig. 4 Distribution of melanoma deaths in the pediatric population in Brazil from 2008 to 2023, by race and state. The bar graph presents the number of deaths by state and race, with the following color coding: gray for white, yellow for indigenous, red for ignored (unknown), brown for brown (mixed-race), and black for black. The data indicate that white children represent the majority of deaths, with São Paulo, Rio Grande do Sul, and Santa Catarina showing the highest numbers in this group. Black and indigenous children show fewer deaths, with only a few states reporting cases. Brown (mixed-race) children also account for a significant portion of deaths, with a more even distribution across various states.

melanocytic nevi, to enhance the understanding of the underlying etiology and improve risk stratification strategies in this vulnerable population.

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Research data availability

The entire dataset supporting the results of this study was published in this article.

Conflicts of interest

None declared.

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LETTER - RESEARCH

Reduction in chromium sensitization: a retrospective analysis from 2010 to 2024 in a dermatology allergy service[☆]



Dear Editor,

Among the agents most often involved in allergic contact dermatitis (ACD) are metals, especially chromium (Cr), found in cement, leather, cleaning products, and cosmetics.¹ Potassium bichromate (PB) is the compound used as a marker of Cr sensitization in patch tests (PT). Previous studies have shown Cr sensitization rates ranging from 12% to 47%, with a downward trend following regulations in European countries.² In Brazil, although specific legislation is still lacking, clinical observations suggest a progressive decrease in cases.

A retrospective study was conducted in a dermatology allergy outpatient clinic between 2010 and 2024, including 1,599 patients with suspected ACD who underwent PT. The battery of tests recommended by the Brazilian Group for Studies on Contact Dermatitis (GBEDC, *Grupo Brasileiro de Estudos em Dermatite de Contato*) was applied to the patients' back. The PT readings were taken at 48 and 96 hours, with the latter being considered for analysis. Patients were grouped by five-year periods: 2010–2014 (group A), 2015–2019 (group B), and 2020–2024 (group C). Sex, occupation, dermatosis location, and positive PT for PB were analyzed, with statistical analysis using the chi-square (χ^2) test.

Among the 1,599 patients tested, 111 (6.9%) tested positive for PB. The frequency was 11.4% in group A; 5.6% in group B; and 3.6% in group C, with a statistically significant difference between the periods ($p < 0.05$), indicating a consistent reduction over the years (Table 1). Although most cases occurred in men, no statistically significant difference was observed between the periods in terms of sex ratio, suggesting a uniform reduction between men and women (Table 2).

Table 1 Patients tested in the period 2010–2024 and frequency of positive tests for Potassium Bichromate (PB).

Group	Tested patients	PB (+)	PB (–)
A (2010–14)	544	62	482
B (2015–19)	557	31	526
C (2020–24)	498	18	480
Total	1599	111	1488

$$\chi^2 = 23.57/p < 0.0001.$$

Table 2 Distribution of patients with positive patch test to potassium bichromate, according to sex. Period 2010–2024.

Period/Sex	Male	Female	Total
A (2010–14)	45 (72.5%)	17 (27.5%)	62
B (2015–19)	20 (64.5%)	11 (35.5%)	31
C (2020–24)	11 (61%)	7 (39%)	18
Total	76 (68.5%)	35 (31.5%)	111

$$\chi^2 = 1.283/p > 0.05.$$

The main dermatitis location were the hands (81% of cases), followed by the upper limbs (42%), trunk and head (16% each), lower limbs (14%), and feet (10%; Table 3). Among the cases with plantar involvement, eight were associated with the use of leather footwear, a material that may contain Cr in its manufacture. The occupation most frequently associated with Cr positivity was mason (46%), followed by homemakers (30.5%), office workers (11%), mechanics, and retirees (4.5% each; Table 4).

During the analyzed period, 78 masons were treated, with a decreasing distribution over the years (Table 5; $p < 0.001$). The frequency of positive PB tests among masons also showed a significant reduction ($p < 0.006$). Of the total number of masons, 27 tested negative for PB (Table 6).

These findings indicate a progressive reduction in chromium sensitization in the population over the past 15 years. This trend is in line with what has already been observed in European countries after the implementation of restrictions on Cr content in cement and leather, as established by European Directive 2003/53/EC, which limits hexavalent chromium to 2 ppm in cement.^{3,4} In Brazil, although such regulation does not yet exist, a 2009 study detected levels above the European limit in national cement

[☆] Study conducted at the Dermatology Clinic, Santa Casa de São Paulo, São Paulo, SP, Brazil

Table 3 Distribution of contact dermatitis to potassium bichromate according to location. Period 2010–2024.

Location/Period	UULL ^a	Hands	LLLL ^b	Feet	Trunk	Cephalic segment
A (2010–2014)	23	48	5	8	7	13
B (2015–2019)	12	24	6	3	6	5
C (2020–2024)	11	18	4	0	5	0
Total ^c	46 (42%)	90 (81%)	15 (14%)	11 (10%)	18 (16%)	18 (16%)

^a Upper limbs.^b Lower limbs.^c Value greater than the number of patients with positive BP tests, as some patients had more than one location.**Table 4** Distribution of patients with positive patch tests to potassium bichromate, according to profession. Period 2010–2024.

Profession/Period	Mason	Homemaker	Mechanic	Office worker	Retired	Other	Total
A (2010–14)	36	16	4	4	1	1	62
B (2015–19)	12	12	0	4	2	1	31
C (2020–24)	3	6	1	4	2	2	18
Total	51	34	5	12	5	4	111

Table 5 Number of treated masons. Period 2010–2024.

Period	Masons	Non-masons	Total
A (2010–14)	49	495	544
B (2015–19)	19	538	557
C (2020–24)	10	488	498
Total	78	1521	1599

$$\chi^2 = 30.89/p < 0.001.$$

Table 6 Distribution of masons treated in each group and the presence of positive PB tests. Period 2010–2024.

Period	Mason PB+	Mason PB–	Total
A (2010–14)	36	13	49
B (2015–19)	12	7	19
C (2020–24)	3	7	10
Total	51	27	78

$$\chi^2 = 14.76/p < 0.006.$$

samples.⁵ Despite this, our data suggest a real decrease in sensitization, possibly influenced by factors such as improved working conditions, greater use of Personal Protective Equipment (PPE), replacement of contaminating materials (e.g., refractory bricks used in kilns used in cement manufacturing),^{6,7} and the removal of Cr from cleaning products, detergents, and cosmetics.⁸

The predominance of masons and homemakers among those sensitized reflects direct exposure to Cr present in cement and household products, respectively. The reduction in consultations among masons and the positivity rate in this population suggests that preventive measures may be more effectively implemented, albeit informally, in the construction sector. The anatomical distribution of lesions, particularly on the hands, is consistent with the occupational exposure pattern.^{9,10}

In summary, this study shows a consistent reduction in chromium sensitization over the past 15 years, even in the absence of specific national regulations. The observed trend

may be the result of a combination of factors, including changes in industrial processes, substitution of materials, and increased awareness among employers and workers about the risks of allergic contact dermatitis. These data reinforce the importance of preventive measures and regulations that limit the presence of allergens in materials for professional and household use.

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Availability of research data

The entire dataset supporting the results of this study was published in the article itself.

Conflicts of interest

None declared.

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LETTER – RESEARCH

Rosai-Dorfman disease: an infrequent entity with heterogeneous presentation. Case series of six patients[☆]



Dear Editor,

Rosai-Dorfman disease (RDD) or sinus histiocytosis with massive lymphadenopathy is a rare, benign histiocytic lymphoproliferative disorder with a prevalence of 1:200,000, most frequently in children and young adults. RDD is classified into classical or nodal (57%) and extranodal (43%) forms. The cutaneous presentation is the second most frequently affected extranodal site (10%). The cutaneous-only subtype known as cutaneous Rosai-Dorfman disease (CRDD) is uncommon (3%), does not present systemic or lymphonodal involvement, and is a diagnosis of exclusion. Histopathology is characterized by large histiocyte proliferation with pale cytoplasm, hyperchromatic nucleus, and prominent nucleolus, usually accompanied by multiple plasma cells. A key finding is emperipolesis, where intact inflammatory cells are engulfed by histiocytes, differentiating it from phagocytosis. Immunohistochemical (IHC) staining typically reveals S100+, CD68+, and CD11a- histiocytes. Less frequent markers include CD163+, CD14+, and CD207-.¹⁻³

Complementary investigation includes laboratory and imaging studies. Magnetic resonance imaging (MRI) is preferred for initial staging in pediatric patients, while adults benefit from positron emission tomography – computed tomography (PET-CT).^{2,4} Treatment varies depending on the presence of skin or systemic involvement, with highly variable responses.^{4,5}

Prognosis depends on systemic/nodal involvement. Nodal or cutaneous disease can remit spontaneously in 20%–50% of cases. The prognosis is less favorable in multisystemic disease, with mortality of 7% to 12%.⁴

The aim of this communication is to describe six cases of cutaneous RDD seen at a Chilean public hospital, highlighting its heterogeneous clinical presentation and the importance of accurate recognition for appropriate management.

[☆] Study conducted at the Hospital San José, Independencia, Santiago, Chile.

Case 1

A 61-year-old man presented with an asymptomatic single lesion on the dorsum of four months of evolution. Examination revealed a brown exophytic tumor, with a sessile base and smooth and soft surface in the interscapular area (Fig. 1A). No other findings were detected. The dermatoscopic image of the lesion described in this case can be seen in Fig. 1-B. Systemic workup excluded extracutaneous involvement, supporting a diagnosis of CRDD.

Case 2

A 54-year-old man was referred for multiple lesions of four-months of evolution, associated with little pain and pruritus, night sweats, weight loss, and general malaise. On physical examination: multiple erythematous-violaceous exophytic tumors with a rough, hyperkeratotic surface and well-defined borders, of variable sizes (ranging from 10 to 40 mm), located in the bilateral lumbar region, left dorsal area, left shoulder, and right lower extremity. Bilateral firm inguinal lymphadenopathy was noted. The clinical and dermatoscopic image of the largest lesion can be seen in Fig. 2. Complementary studies confirmed nodal involvement, consistent with systemic RDD.

Case 3

A 60-year-old man. Consulting by the appearance of multiple lesions three-months old, located on the face, anterior and posterior trunk. On examination: multiple rounded, erythematous-violaceous plaques, well circumscribed, irregular surface, with whitish punctiform areas. Lesions on the anterior trunk (sternal area), left cheek, and middle/lower dorsum. In addition, an irregular plaque of 30 × 20 mm, formed by multiple confluent erythematous papules of 2–4 mm, grouped on an irregular erythematous-violaceous background, was found in the right axilla (Fig. 3). The imaging studies showed systemic involvement.

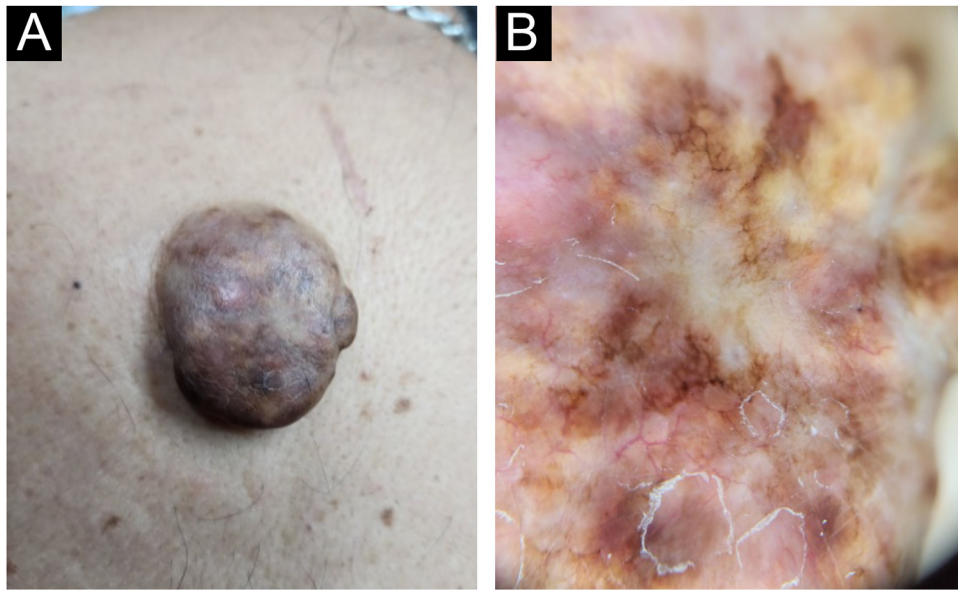


Figure 1 Clinical and dermatoscopic images of case 1 [extranodal cutaneous RDD]. (A) Single skin lesion on the medial dorsum. (B) Dermatoscopic image: disorganized white-yellowish areas and pigmentary network patches on a red-milky background, with telangiectatic vessels.

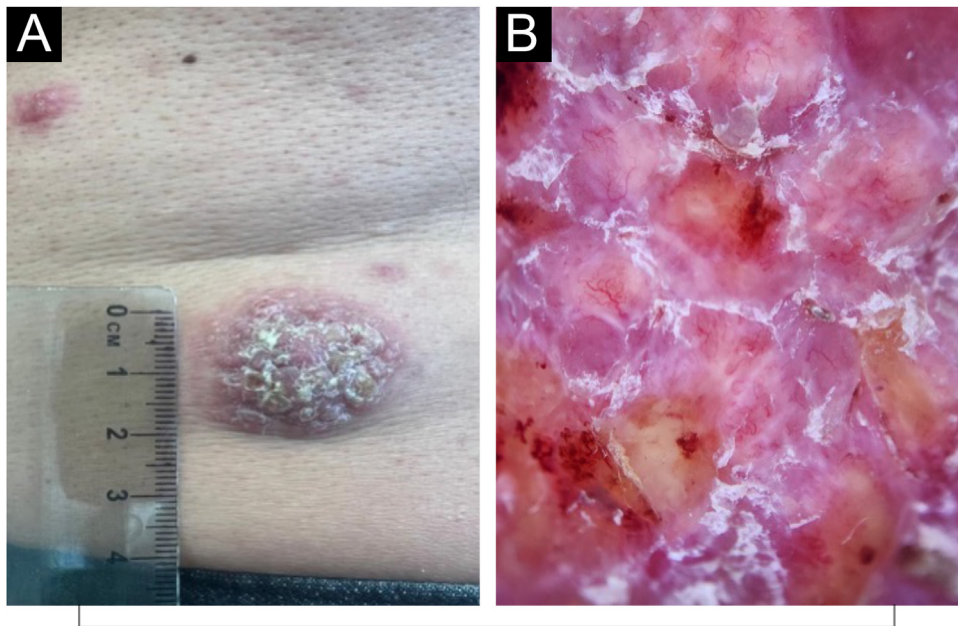


Figure 2 Clinical and dermatoscopic images of case 2 [systemic RDD]. (A) Lumbar lesion. (B) Dermatoscopic image: unstructured yellowish areas surrounded by milky-red regions associated with in focus arborizing vessels, whitish scales, and some intracorneal hemorrhagic crusts.

Case 4

28-year-old woman. Referred from the breast pathology unit (BPU) due to an increase in volume of the left breast, of unspecified evolution time (at least 6-months), and whose study by BPU was negative. On physical examination: subcutaneous nodule of indurated consistency,

partially mobile, approximately 40 mm, painless, evident to deep palpation. The overlying cutaneous surface showed a few faint pink-colored papules of 1–2 mm, with a slightly erythematous-violaceous background (Fig. 4A). There were also ipsilateral axillary lymph nodes. Extension studies excluded systemic involvement, supporting the diagnosis of exclusively cutaneous disease.



Figure 3 Clinical images of Case 3 [systemic RDD]. (A) Facial lesions. (B) Axillary lesions.

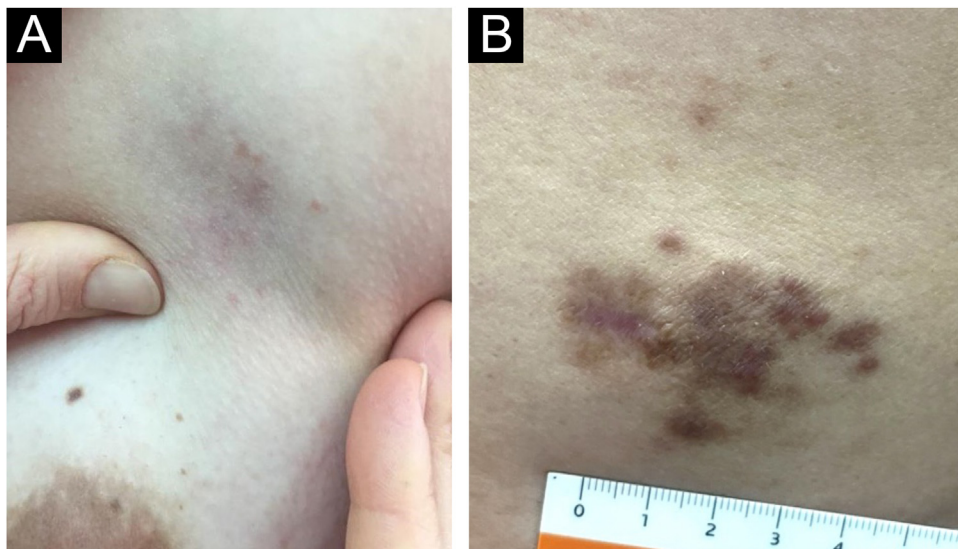


Figure 4 Clinical images of case 4 and 5 [Extranodal cutaneous RDD]. (A) Case 4. Single skin lesion on left breast (subcutaneous nodule evident to deep palpation). (B) Case 5. Dorsal lesion.

Case 5

A 48-year-old man, with a history of arterial hypertension presented with two asymptomatic skin lesions on the dorsum and abdomen, of four-months of evolution. Physical exam showed a 5 × 3 cm subcutaneous firm and poorly defined nodule on the right dorsum, with erythematous-violaceous macules grouped on the skin surface (Fig. 4B). Additionally, a subcutaneous mass of 10 × 10 cm was found in the right iliac fossa. PET-CT shows no evidence of systemic involvement, supporting the diagnosis of exclusively cutaneous disease.

Case 6

A 34-year-old man with a history of arterial hypertension. He consulted due to multiple palpable subcutaneous nodules on the dorsum of eight-months of evolution, preceded by sudden dysphonia six-months earlier (interpreted as recurrent laryngeal nerve palsy), without findings in the neck and chest Computed Tomography (CT). In a second chest CT scan, requested after the appearance of skin lesions, a mediastinal mass compressing the path of the recurrent laryngeal nerve was observed. Cutaneous metastasis of an undetermined primary tumor was suspected.

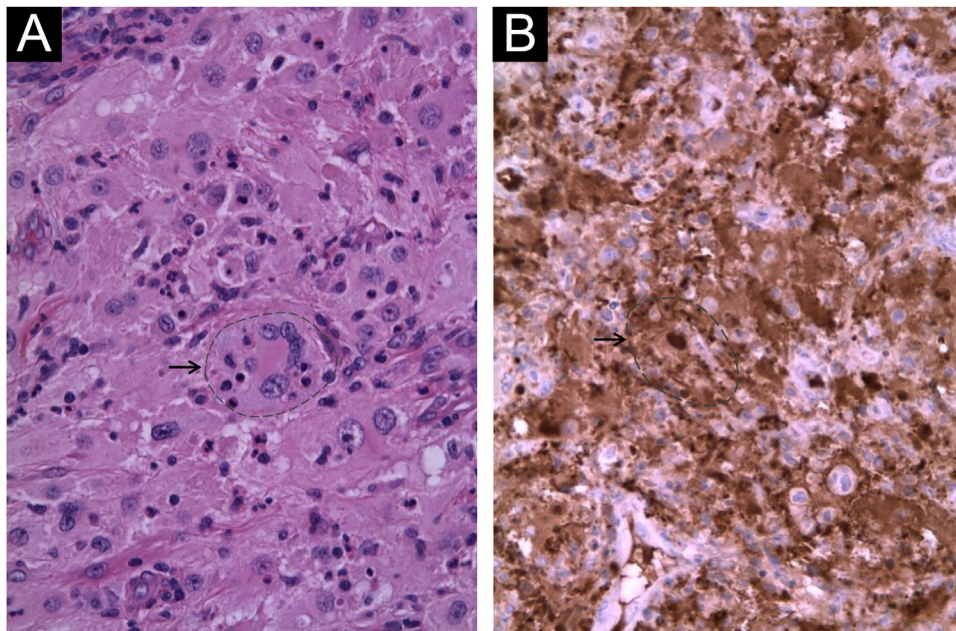


Figure 5 Histopathological images of case 2. (A) Hematoxylin and eosin (20 $\times$, case 2). Foamy histiocytes with pale eosinophilic cytoplasm and emperipolesis, accompanied by lymphocytes, neutrophils, plasma cells and eosinophils. (B) Immunohistochemistry (IHC) positive for S100 in histiocytes (20 $\times$, case 2), especially notable in the central histiocyte of the image, which shows the phenomenon of emperipolesis. Emperipolesis is indicated by the arrow and the dashed line in both figures.

In the six cases described, skin biopsy was performed, and all reported a dermal histiocytosis with morphological and immunohistochemical findings compatible with RDD. Histopathology with hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) of one of the lesions from case 2 can be observed in Fig. 5. The complementary study determined that cases 2, 3 and 6 had systemic involvement, and were referred to the hematology-oncology service, with partial response during the first months of oncology treatment. Cases 1, 4 and 5 had exclusively cutaneous involvement, which were successfully managed with a surgical approach by dermatology.

The diagnosis of RDD can be challenging, requiring a high degree of suspicion due to its rare and heterogeneous presentation, which often leads to a wide spectrum of differential diagnoses. The diagnosis is confirmed by histopathological biopsy. However, the clinical and histopathological features of the lesions alone cannot predict whether there is extracutaneous involvement. Therefore, a complementary laboratory (including complete blood count, liver function, and coagulation and urine test) and imaging studies are essential to assess systemic involvement, disease extent, and associated disorders.

This miniseries of cases aimed to highlight the diverse and atypical dermatological manifestations of an uncommon disease and thus provide tools that contribute to its proper recognition, as these manifestations may represent the initial sign of a pathology with potential systemic involvement.

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Conflicts of interest

None declared.

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LETTER – CLINICAL

Granulomatous filler reaction treated with adalimumab: a case report and literature review[☆]



Dear Editor,

Dermal fillers (DF) are one of the most common procedures performed by dermatologists, and their use continues to grow yearly.¹ The materials used as DF include hyaluronic acid, calcium hydroxylapatite, poly-L-lactic acid, silicone, and polymethylmethacrylate (PMMA).²

There is no consensus on the definition of early and late adverse reactions concerning time. Mild adverse events associated with DF, as classified by the World Health Organization (WHO), include swelling, bruising, and erythema at the injection site.³ These effects are generally self-limited and do not require significant medical intervention. In contrast, moderate adverse events such as mycobacterial infections and granulomatous inflammatory reactions often require medical treatment.³

Some fillers have specific approaches for granuloma treatment, although evidence of their effectiveness varies depending on the type of filler used.⁴ Surgical extraction is rarely recommended, not only due to the possibility of filler migration but also because of significant anatomical limitations. Fillers are often present in the musculoaponeurotic system or near critical structures such as vessels, nerves, or glands, which may render excision unfeasible.⁵ In severe or recalcitrant cases, Tumor Necrosis Factor- α (TNF- α) inhibitors such as etanercept and adalimumab – typically reserved for serious, treatment-resistant complications – have been employed with success.^{6–9}

We present the case of a woman with a severe delayed granulomatous filler reaction with response to adalimumab and perform a review of TNF- α inhibitors used in these complications.

A 58-year-old woman presented to the dermatology clinic with an eight-year history of recurrent facial swelling. The

patient's symptoms started after receiving cosmetic filler injections in the face with an unknown material by a general practitioner. At the initial examination, the patient presented with painful facial edema, erythema, and the presence of inflammatory subcutaneous nodules in the cheeks and lips (Fig. 1). The patient had received treatment with methotrexate and hydroxychloroquine for 2-years, colchicine for 1-year, and antibiotics, including doxycycline and minocycline, for 6-months without improvement. She had been employing intramuscular dexamethasone every two weeks for more than five years with irregular control. Skin biopsies showed a chronic inflammatory infiltrate composed of histiocytes and lymphocytes. Abundant translucent micro-vacuoles of silicone-like material were found inside the histocytes. Histopathology was consistent with a foreign body granuloma (Fig. 2). Ziehl-Neelsen, Gram, and PAS staining were negative. The histocytes were CD68 positive and S-100 negative. Skin biopsy cultures for bacteria, mycobacteria, and fungi were performed twice. All cultures were negative. PCR on skin biopsies was performed for the detection of *Mycobacterium tuberculosis* and atypical mycobacteria, which were also negative. A computed tomography was performed, which revealed right-sided facial edema, inflammation, and the presence of soft-tissue foreign bodies embedded in the subcutaneous tissue. No abnormalities in bones, the oral cavity, pharyngeal mucosal, or facial muscles were identified. Subcutaneous adalimumab 40mg every two weeks was prescribed following an 80mg loading dose. After six weeks, the patient referred complete improvement of her symptoms with full regression of subcutaneous nodules and inflammation. At the twelve-month follow-up, she continues to receive adalimumab every two weeks with complete disease control. At the 18-month follow-up, an ultrasound was performed to evaluate the DF. The ultrasound revealed in the lips and subcutaneous tissue of the malar and periorbital regions the "snowstorm" sign, which is compatible with silicone filler (Fig. 3).

The long-term safety of adalimumab has been well established in other conditions. Annual monitoring with tuberculosis, hepatitis B, and C testing is necessary. We plan to continue treatment for at least two years and, depending on the clinical response, modify the dosage every 3-weeks.

We performed a literature review on the use of TNF- α inhibitors and adverse reactions to DF on December 20, 2024, through PubMed with the following search strategy:

[☆] Study conducted at the Rheumatology Department, University Hospital "Dr José Eleuterio González," Autonomous University of Nuevo León, Monterrey, México.



Fig. 1 Adverse reaction to dermal filler. (A and B) Facial edema, erythema, and subcutaneous nodules in the cheeks, lips, and eyelids. (C) Patient at the one-year follow-up after starting treatment with adalimumab.

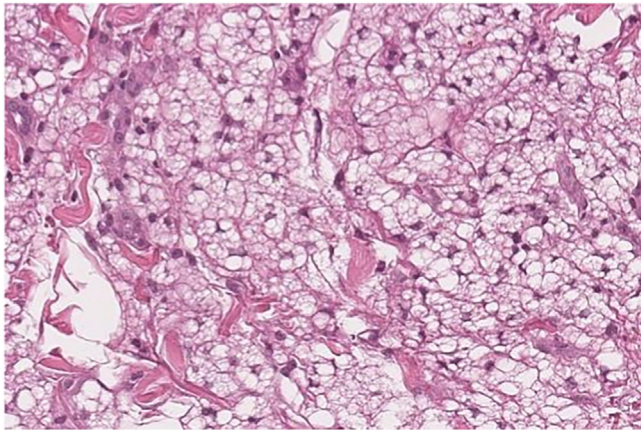


Fig. 2 Granulomatous inflammation with lymphocytes and foamy histiocytes with abundant vacuoles (Histopathology with Hematoxylin & eosin; $\times 40$).

(adalimumab OR etanercept OR "TNF alpha inhibitors" OR "TNF inhibitors") AND (silicone OR "hyaluronic acid" OR granuloma OR dermal filler OR cosmetic).

Out of the 336 retrieved records, we identified six cases that presented an adverse reaction due to DF and were treated with a TNF-alpha inhibitor (Table 1). One of the cases full texts could not be retrieved from electronic records, and five cases were included in our analysis. The ages of the patients ranged from 36 to 78 years-old.⁶⁻⁹ In regards to DF composition, all cases reported the use of silicone fillers.⁶⁻⁹ Three patients had injections in the calves and buttocks area, and two patients had injections in the facial area.⁶⁻⁹ Three patients were treated with adalimumab 40mg subcutaneously every two weeks, and two patients with etanercept 25mg subcutaneously twice a week.⁶⁻⁹ In most cases, the time to improvement after starting the TNF- α inhibitor ranged from 1–2 months with full regression at subsequent follow-up.⁷⁻⁹

Pasternack et al.⁹ presented two patients with erythema, edema, pain, and functional limitations after silicone injections in the calves and buttocks. Initial antibiotic treatments showed only mild improvement, but etanercept therapy produced a significant regression of symptoms within two weeks. Guhan et al.⁸ reported two women with silicone granulomas in the buttocks. The first case responded to

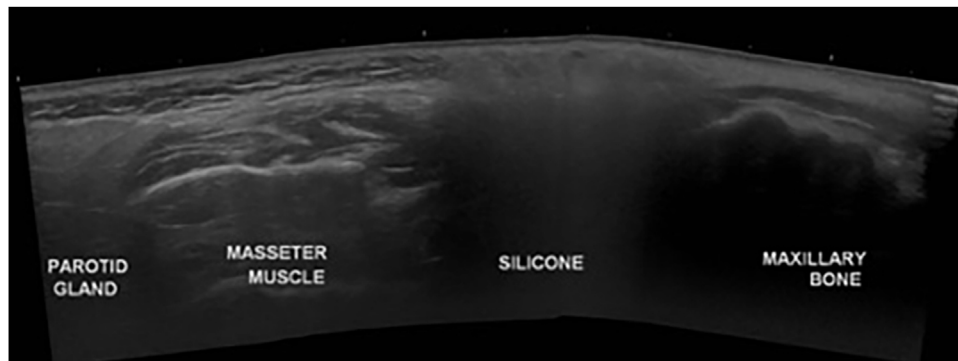


Fig. 3 Transverse panoramic ultrasound image of the right cheek with the characteristic "snowstorm" sign between the masseter muscle and maxillary bone.

Table 1 Articles included in the literature review of anti-TNF alpha inhibitors and adverse reactions to dermal fillers.

Author	Year	Age	Sex	Anti-TNF therapy used	Posology	Material used	Area injected	Time of response after treatment	Time to develop lesions	Adverse Reaction	Failed treatment	Follow up time and outcomes
Pasternack et al. ⁹	2005	47	Woman	Etanercept	25 mg sub-cutaneously twice a week	Silicone	Calves and Buttocks	1 month	10 years	Erythema, swelling, induration, and tenderness of the anterior legs and ankles in the calves and buttocks	-Piperacillin and tazobactam -Trimethoprim and sul-famethoxazole. -Amikacin and imipenem -Linezolid -Minocycline	2 months and regression of lesions
Pasternack et al. ⁹	2005	37	Woman	Etanercept	25 mg sub-cutaneously twice a week	Silicone	Buttocks	1 month	5 months	Erythema and edema of the posterior left leg and tender, sub-cutaneous nodules with overlying induration of the buttocks	-NSAIDs -Hydrocodone -Minocycline	2 months and complete remission
Guhan et al. ⁸	2021	36	Woman	Adalimumab	40 mg every 2 weeks after an 80 mg loading dose	Silicone	Buttocks	2 months	3 years	Violaceous to pink, slightly indurated plaques on the bilateral buttocks	-Cephalexine - Betamethasone Dipropionate 0.05% - Hydroxychloroquine -Minocycline	2 months and complete remission

Table 1 (Continued)

Author	Year	Age	Sex	Anti-TNF therapy used	Posology	Material used	Area injected	Time of response after treatment	Time to develop lesions	Adverse Reaction	Failed treatment	Follow up time and outcomes
Silverberg et al. ⁶	2022	78	Woman	Adalimumab	40 mg every 2 weeks	Silicone	Cheeks and glabella	Not mentioned	18 years	Erythematous, tender plaques on cheeks, and forehead	-Prednisone -Triamcinolone acetonide -Doxycycline -Cyclosporine -Mycophenolate mofetil	14 months and complete remission
de la Torre Gomar et al. ⁷	2023	63	Woman	Adalimumab	40 mg every 2 weeks after an 80 mg loading dose	Silicone	Lips	1 month	20 years	Facial angioedema and subcutaneous erythematous nodules located on the forehead and cheeks.	-Prednisone -Allopurinol -Triamcinolone acetonide -Loratadine -Hydroxychloroquine -Dapsone	26 months and complete remission
Current Report	2024	58	Woman	Adalimumab	40 mg every 2 weeks after an 80 mg loading dose	Unknown	Cheeks and lips	2 weeks	8 years	Painful facial edema, erythema, and the presence of inflammatory subcutaneous nodules in the cheeks and lips	-Methotrexate -Colchicine -Hydroxychloroquine -Doxycycline -Minocycline	12 months and complete remission

antibiotics, while the other showed no improvement with antibiotics, hydroxychloroquine, or topical steroids. The second patient experienced complete remission after 10-weeks of adalimumab therapy. Silverberg et al.⁶ presented a case of silicone injections in the cheeks and glabella that led to bilateral indurated plaques on the buttocks. The patient initially responded to prednisone but experienced a flare during tapering. Treatments with triamcinolone, doxycycline, cyclosporine, and mycophenolate mofetil were ineffective, but administration of adalimumab was effective in the resolution and regression of the lesions after 14-months. de la Torre Gomar et al.⁷ described a patient with facial angioedema and subcutaneous erythematous nodules who showed no improvement after treatment with prednisone, allopurinol, triamcinolone, loratadine, and hydroxychloroquine. Therapy with adalimumab led to a response within a month.

The underlying immune mechanisms of granulomatous reactions to DF are not well known. The granulomatous response to biomaterials varies depending on their permanence and specific properties. Permanent, non-biodegradable materials typically induce a more persistent foreign body reaction due to their resistance to degradation, leading to sustained macrophage activity. In contrast, biodegradable materials are gradually resorbed and tend to elicit a less prolonged inflammatory response. Furthermore, the frequency and severity of granuloma formation are influenced by factors such as surface morphology and material fragmentation, with irregular or particulate biomaterials provoking stronger inflammatory reactions.¹⁰

The inability to phagocytose large foreign particles may result in chronic inflammation and granuloma formation. These granulomas are composed of macrophages and lymphocytes that secrete pro-inflammatory cytokines, including TNF-alpha, interferon-gamma, and interleukin 12. Additionally, fillers may act as adjuvants, amplifying the innate immune response and triggering the release of Th1 inflammatory cytokines. Permanent fillers, such as liquid silicone and polymethylmethacrylate, are highly susceptible to chronic inflammation, infections, abscess formation, and migration, even years after injection. In contrast, non-permanent fillers like hyaluronic acid are generally safer but can still cause granulomatous reactions. It is crucial to rule out underlying infections by bacteria, mycobacteria, or fungi in all cases of chronic reaction to dermal fillers.¹¹ When the substance is unknown, it is essential to determine whether it was compounded and identify the professional responsible for the procedure.

TNF-alpha inhibitors act by blocking circulating cell-bound TNF. Through this mechanism, it has an inhibitory action on macrophages and may aid in controlling granuloma formation.¹¹ After this patient failed to respond to multiple treatments (steroid, methotrexate, hydroxychloroquine, colchicine, and antibiotics), the use of a TNF-alpha inhibitor was employed as an alternative, previously reported to be effective in a few case reports.⁶⁻⁹ Rarely, these drugs may present paradoxical granuloma formation, and this should be considered by clinicians. Granulomatous reactions due to non-permanent fillers such as hyaluronic acid may resolve spontaneously or be treated with other treatment options, including hyaluronidase or, in select cases, surgery. The effect of TNF-alpha inhibitors on non-permanent fillers is

not well known, and further research is needed to determine the best treatment strategy.

As a limitation, our literature review comprises five case reports, which are insufficient to draw definitive conclusions regarding the overall efficacy of TNF-alpha inhibitors in managing granulomatous reactions to DF. Further research is necessary to determine the long-term safety and efficacy of TNF-alpha inhibitors in such cases.

In conclusion, we report a patient with a one-year follow-up and remission of granulomatous inflammatory reaction due to DF successfully treated with adalimumab. Managing these lesions can be challenging, and physicians should consider TNF- α inhibitors as a possible treatment for recalcitrant cases.

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Max Oscherwitz: Statistical analysis and interpretation of data.

Rodolfo Franco-Márquez: Histopathological analysis and figure preparation.

Dionicio Ángel Galarza-Delgado: Supervision and final approval of the manuscript.

Jesús Alberto Cárdenas-de la Garza: Study design, corresponding author, and manuscript revision.

Research data availability

Does not apply.

Conflicts of interest

None declared.

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LETTER – CLINICAL

Intravascular large B-cell lymphoma: presentation with generalized dendritic-type telangiectasias. A diagnostic challenge[☆]

Dear Editor,

Intravascular lymphoma is an extremely rare disease with diverse and atypical clinical manifestations, making early diagnosis challenging and impacting the prognosis.¹

We present the case of a 70-year-old female patient with a history of cervical cancer treated with surgery, brachytherapy, and radiotherapy, who presented with a two-year history of progressive edema in both lower extremities, associated with multiple generalized telangiectasias (Fig. 1), significant weight loss, episodes of fever up to 38 °C, and night sweats. Laboratory tests revealed hemoglobin of

8.7 g/dL, MCV 94 fL, leukocytes 3,240 μ L with neutrophil predominance, platelets 144,000 μ L, ESR 48 mm/h, uric acid 6.2 mg/dL, LDH 662 U/L (RI: 125–220), ALP 246 U/L (RI: 40–150), GGT 135 U/L (RI: 9–36), normal transaminases and bilirubin levels, and vitamin B12 at 1360 pg/mL, with normal renal function, calcium, and phosphorus levels. β 2-microglobulin was elevated (3.74 mg/L). Protein electrophoresis showed a monoclonal peak in the gamma region, with an IgM kappa monoclonal component and lambda light chain on immunofixation. Computed tomography (CT) of the chest, abdomen, and pelvis showed no significant pathological findings. Doppler ultrasound of the lower extremities revealed subcutaneous edema. Bone marrow biopsy was normal. A skin biopsy was performed, identifying large atypical lymphoid cells with prominent nucleoli within small vessels (Fig. 2). Immunohistochemistry was positive for CD20, PAX-5, MUM-1, and Bcl-2 and negative for CD3, Bcl-6, CD10, CD56, CD30, CD34, and cytokeratins (Fig. 3). A diagnosis of intravascular large B-cell lymphoma (IVLBCL)

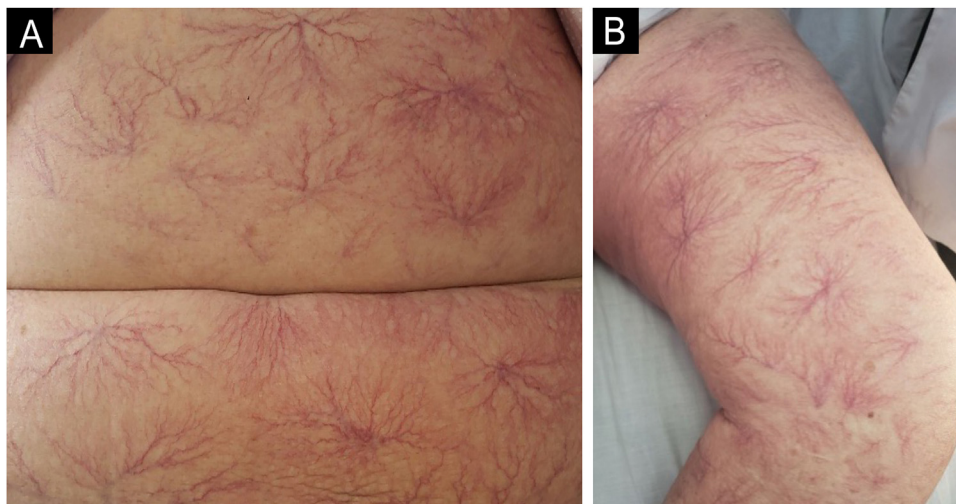


Figure 1 Clinical images. Multiple generalized dendritic type telangiectasias on the abdomen (A) and thigh (B).

[☆] Study conducted at the Hospital Dr. Sótero del Río, Puente Alto, Santiago, Chile.

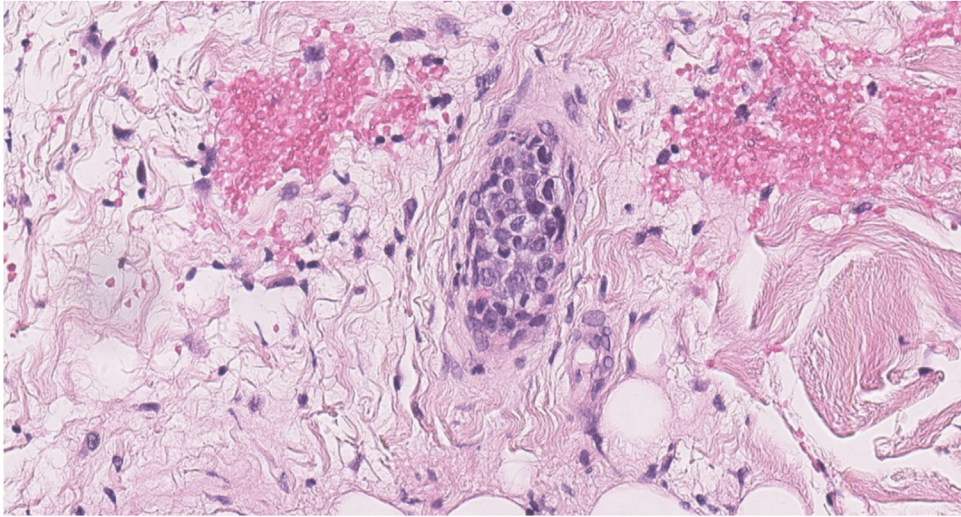


Figure 2 Atypical intravascular lymphoid population with monomorphic, uniformly enlarged cells with prominent nucleoli (Hematoxylin & eosin, $\times 400$).

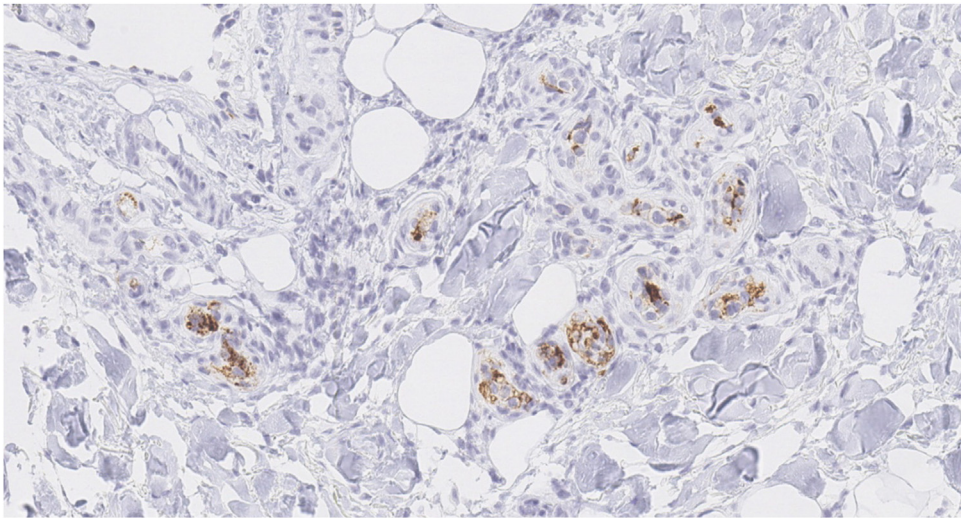


Figure 3 Immunohistochemistry showing hyperchromatic cells showing positive immunohistochemical staining with the CD20 B-cell marker ($\times 400$).

was established. The patient was initiated on the R-CHOP chemotherapy regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). A marked reduction in cutaneous telangiectasias – estimated at approximately 60% – was noted following the first cycle. Intrathecal methotrexate was also administered due to the presence of pathological mononuclear cells in moderate quantity in the cerebrospinal fluid, which subsequently cleared. The patient remains under multidisciplinary follow-up by hematology and dermatology, exhibiting a favorable clinical response after six cycles of R-CHOP, with only sparse residual telangiectasias noted on the chest.

Intravascular lymphoma is a rare type of extranodal non-Hodgkin lymphoma (<1% of cutaneous lymphomas), characterized by the proliferation of neoplastic lymphocytes in the lumen of small vessels, described in 1959 as “endotheliomatosis and reticuloendotheliosis”.² An inci-

dence of 0.09 per 1 million inhabitants was reported in the USA between 2000–2013.³ The average age of presentation is 70-years, with no gender differences.^{2,3} 85% originate from B-cells (IVLBCL) and 15% from NK or T-cells.⁴ Two clinical variants are described: the “Asian” variant, associated with multi-organ involvement and hemophagocytosis, and the “Western” variant, associated with skin lesions and central nervous system involvement.^{5,6} Clinical presentation is variable, including the presence of B-symptoms (55%–85%) without associated lymphadenopathy, neurological symptoms (39%–76%), and skin lesions (17%–39%) with erythematous-violet indurated plaques and nodules that simulate panniculitis, associated with edema. Its presentation as dendritic-type telangiectasias is very rare, with only 24 reported cases.^{1–6}

Due to its variable and nonspecific symptoms, the diagnosis tends to be delayed, leading to a poor prognosis,

with a median survival of 46.1% at 5-years.³ In cases of timely treatment with R-CHOP, the survival rate is 66% at 24-months, making it a potentially curable disease with chemotherapy.^{3,5} If there is CNS involvement, methotrexate or cytarabine is recommended.⁵ In certain cases, an autologous stem cell transplant should be considered.^{2,5}

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Research data availability

Does not apply.

Conflicts of interest

None declared.

Editor

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.abd.2025.501221>.

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LETTER – CLINICAL

Linear syringocystadenoma papilliferum: an unusual presentation in the inguinal region[☆]

Dear Editor,

Syringocystadenoma Papilliferum (SCAP) is a benign adnexal tumor characterized by apocrine differentiation.¹ It often manifests at an early age, with approximately 50% of cases identified at birth, and 15%–30% emerging during puberty.² While most SCAPs develop de novo, up to 40% have been reported to arise from a pre-existing sebaceous nevus.³

The histogenesis mechanisms underlying SCAP remain unclear. Genetic studies have identified mutations in the HRAS gene in SCAPs associated with sebaceous nevi, and RAS and BRAF mutations in sporadic lesions.¹

SCAP occurs predominantly on the head and neck region, accounting for 75% of reported cases.³ Other less common sites include the arms, chest, axilla, scrotum, perineal, and inguinal regions.² Clinically, SCAP manifests in three forms: solitary nodule, plaque, and linear type, with the latter being extremely rare.² This paper presents an unusual case of a congenital, de novo SCAP with a linear configuration located in the inguinal region.

A 29-year-old female presented with a history of several pink lesions on the right inguinal region since birth. Physical examination revealed multiple pink dome-shaped papules with central umbilication and some exhibiting surface erosions, arranged in a linear configuration (Fig. 1). Dermoscopy showed pink papillomatous structures with erosions, white rosettes, white circles, yellowish crusts, and telangiectasias (Fig. 2). Suspecting an adnexal tumor based on clinical and dermoscopic findings, an incisional biopsy was performed. Histopathological analysis revealed hyperkeratosis and acanthosis of the epidermis, with invaginations of tubular-papillary structures lined by a bilayer of cuboidal epithelium, exhibiting focal stratification and some evidence of apical secretion by decapitation. Numerous plasma



Fig. 1 Clinical image. Multiple pink dome-shaped papules with central umbilication and some with erosions on the surface, arranged in a linear plaque.

cells were noted in the stroma. No evidence of cellular atypia was observed (Fig. 3).

The diagnosis of linear syringocystadenoma papilliferum was made on a comprehensive assessment of clinical, dermoscopic, and histopathologic findings. The patient subsequently underwent a complete tumor excision, and the diagnosis was confirmed by the definitive histopathological results.

The linear presentation of SCAP is extremely infrequent, with only 22 cases reported in the literature.^{2–4} The head and neck are the most commonly affected regions, accounting for 8 of these 22 cases. Notably, only two cases have been documented in the inguinal region.^{2,3}

Most cases of linear SCAP are de novo occurrences. Only two cases have been associated with Jadassohn's sebaceous nevus,^{2,5} two with hidrocystoma and cystadenoma,^{2,6} and one with apocrine tubular adenoma.²

Dermoscopic findings described in SCAP include red exophytic papillary structures with central umbilication,

[☆] Study conducted at the Department of Dermatology, Faculty of Medicine, Universidad del Desarrollo, Clínica Alemana, Santiago, Chile.



Fig. 2 Dermoscopy image ($\times 10$): Pink papillomatous structures with erosions (black arrows), white circles (blue arrows), yellowish crusts (yellow arrows), and telangiectasias (green arrow).

ulceration, hairpin vessels, polymorphous vessels, and comma vessels. Additional features may include white circles, crusts, yellowish scales, and pink-white globular structures.^{2,3} The circle umbilicated structures might correspond to the open pseudocystic spaces of SCAP, but further studies are needed to validate these findings.

The differential diagnosis includes molluscum contagiosum, warts, epidermal nevi, lymphangioma circumscriptum, basal cell carcinoma, and other adnexal neoplasms. Therefore, clinical and dermoscopic features are crucial techniques to identify this tumor.

Malignant transformation of SCAP is rare. Most documented cases correspond to syringocistoadenocarcinoma papilliferum,⁷ although other malignancies such as ductal carcinoma have also been reported.⁸ There are no reports of malignant transformation specifically associated with lineal SCAP.³

This report presents a new and exceptional case of linear SCAP located in an atypical region, with distinctive clinical and dermoscopic findings. Although the malignant transformation of linear SCAP has not been described in the literature, it is prudent to perform a complete excision. This approach is warranted as non-linear SCAP has the potential to develop secondary malignancies.

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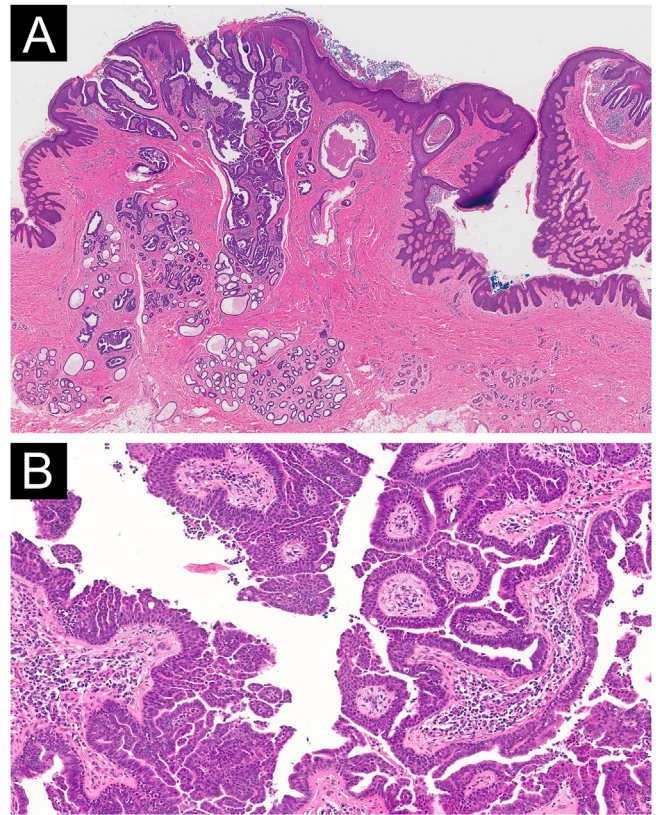


Fig. 3 (A) Histopathological image (Hematoxylin & eosin, $20\times$): Epidermal and dermal tumor. The epidermis shows hyperkeratosis and acanthosis with invaginations composed of papillary projections. (B) Histopathological image (Hematoxylin & eosin, $100\times$): Tubulo-papillary structures lined by a bilayer cuboidal epithelium with focal stratification and some evidence of apical secretion by decapitation. The tumoral stroma contains numerous plasma cells. No cellular atypia was observed.

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Research data availability

Does not apply.

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None declared.

Editor

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LETTER - CLINICAL

Melanoacanthoma of the nipple: two cases with unique clinical presentations[☆]



Dear Editor

Melanoacanthoma is a rare pigmented variant of seborrheic keratosis that mimics melanoma, posing a diagnostic challenge.¹ While commonly found on sun-exposed areas, its occurrence in the nipple-areola complex is rarely reported.^{2,3} We present two cases in young female patients with prior UV exposure, emphasizing the need for clinical awareness and the role of dermoscopy and biopsy in diagnosing pigmented lesions in uncommon sites.

A 27-year-old female presented with a progressively enlarging, darkly pigmented lesion on the left nipple, first noted a year ago. She had a history of full-body tanning bed exposure two years prior. Examination revealed two irregularly bordered hyperpigmented patches (1.5 cm and 1 cm) on the nipple-areola complex (Fig. 1A). Dermoscopy showed a pigmented background with circular structures (Fig. 1B). Histopathology confirmed melanoacanthoma with basal melanin hyperpigmentation, epidermal acanthosis, and elongation of rete ridges (Fig. 2A). Superficial cryotherapy was applied in four sessions over three months, resulting in partial regression, with no progression observed at six months of follow-up (Fig. 2B).

A 34-year-old female presented with irregular pigmentation on the right areola, which developed during the second trimester of pregnancy. She had a history of full-body tanning bed exposure one year prior, consisting of six sessions. Examination revealed a 3 cm hypopigmented patch with irregularly pigmented plaques (Fig. 3A). Dermoscopy demonstrated a pigmented background with circular structures and V-shaped linear pigmentation (fish-scale-like pattern) (Fig. 3B). Histopathology confirmed melanoacanthoma, showing epidermal acanthosis, rete ridge elongation, basal layer hyperpigmentation, superficial dermal edema, melanin incontinence, and perivascular lymphocytic infiltration (Fig. 4A). Over five years of follow-up,

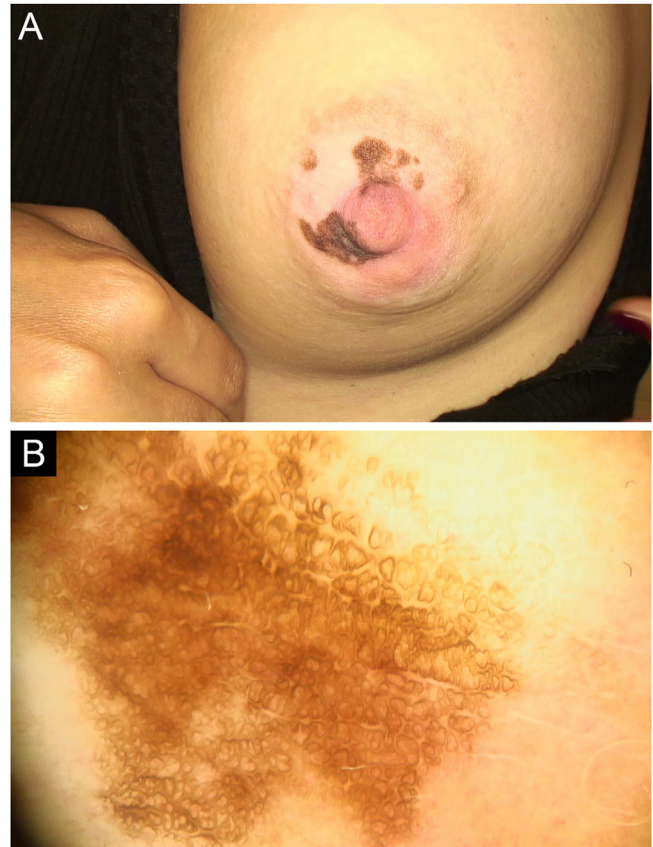


Fig. 1 (A) Two irregularly bordered hyperpigmented patches on the nipple-areola complex in the first patient. (B) Dermoscopic image showing a pigmented background with circular structures forming a ring pattern in the first patient.

the lesion exhibited partial depigmentation without treatment, with no progression observed (Fig. 4B).

Melanoacanthoma is a heavily pigmented variant of seborrheic keratosis, commonly found on the head, neck, and trunk, with a predilection for older individuals.¹ Its occurrence on the nipple-areola complex is extremely rare, with only two previously reported cases.^{2,3} Proposed etiological factors include FGFR3 mutations, ultraviolet exposure, and hormonal influences such as pregnancy or estrogen therapy.³ Despite being a non-sun-exposed area, both of our patients

[☆] Study conducted at the Faculty of Medicine, Kocaeli University, Kocaeli, Turkey.

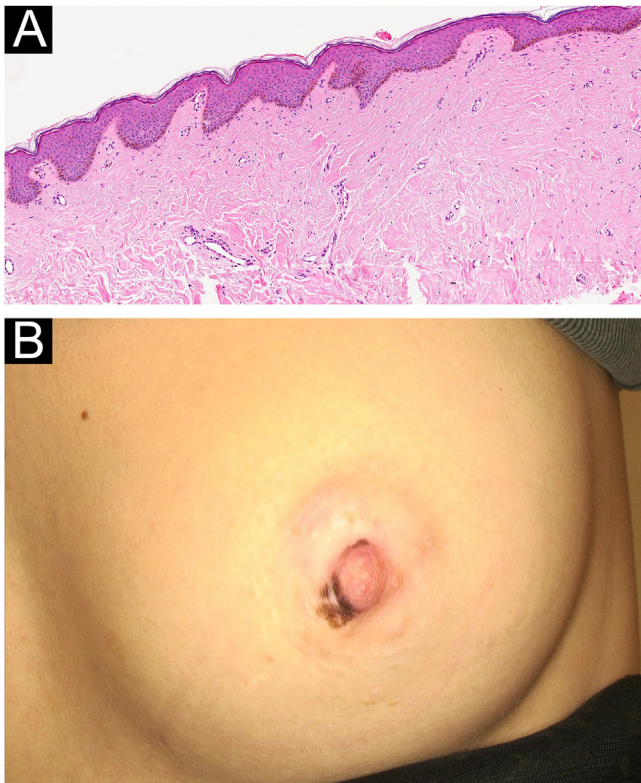


Fig. 2 (A) Histopathological findings of the first patient: basal melanin hyperpigmentation, epidermal acanthosis, and elongation of rete ridges (Hematoxylin & eosin, $\times 10$). (B) Partial regression of the lesions after four sessions of superficial cryotherapy in the first patient.

had a history of tanning bed use, and one developed the lesion during pregnancy.

Differential diagnoses include nevoid hyperkeratosis, seborrheic keratosis, and melanoma.^{2,4} Various patterns, including the starburst appearance, ridges, fissures, comedo-like openings, hairpin vessels, and sharp demarcation, have been described, along with melanoma-specific features such as a blue-white veil and atypical dots.¹⁻⁵ In our cases, dermoscopy revealed circular structures, which had not been previously described in melanoacanthoma but have been observed in other benign lesions like labial melanotic macules.⁶

Histopathology remains essential for confirming melanoacanthoma, showing basaloid keratinocyte proliferation and scattered dendritic melanocytes. Given the aesthetic and functional considerations of the nipple-areola complex, biopsy should be carefully planned.^{2,3} Most cases do not require treatment unless symptomatic; cryotherapy resulted in partial regression in one of our patients.¹

These cases emphasize the importance of considering melanoacanthoma in the differential diagnosis of pigmented lesions in the nipple-areola region and highlight the need for dermoscopic and histopathologic evaluation for accurate diagnosis. The presence of circular structures expands its known features, and the history of UV exposure in both patients suggests a potential role in its pathogenesis.

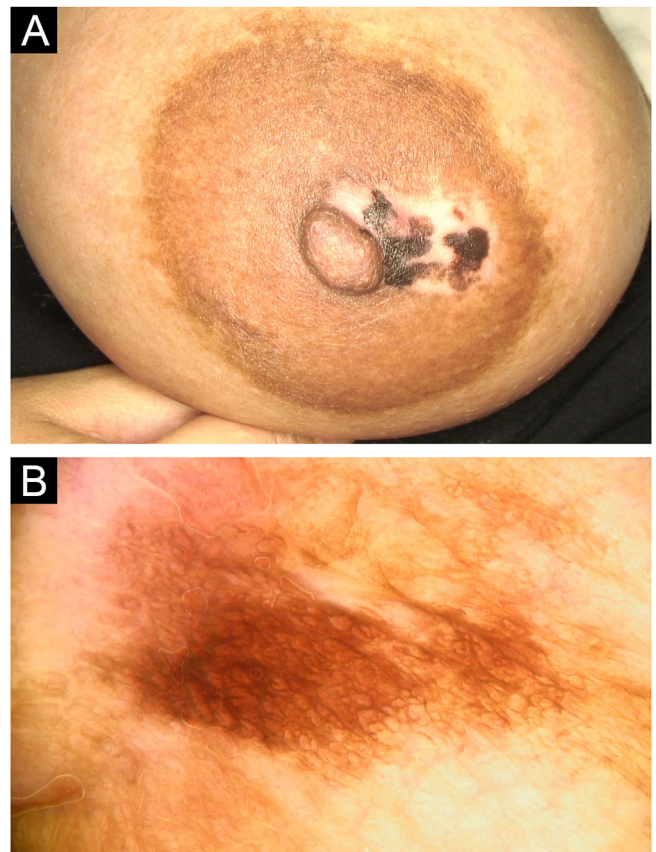


Fig. 3 (A) A 3 cm hypopigmented patch interspersed with irregularly pigmented macules on the areola in the second patient. (B) Dermoscopic image showing circular structures forming a ring pattern and a fish scale-like pigmentation variant in the second patient.

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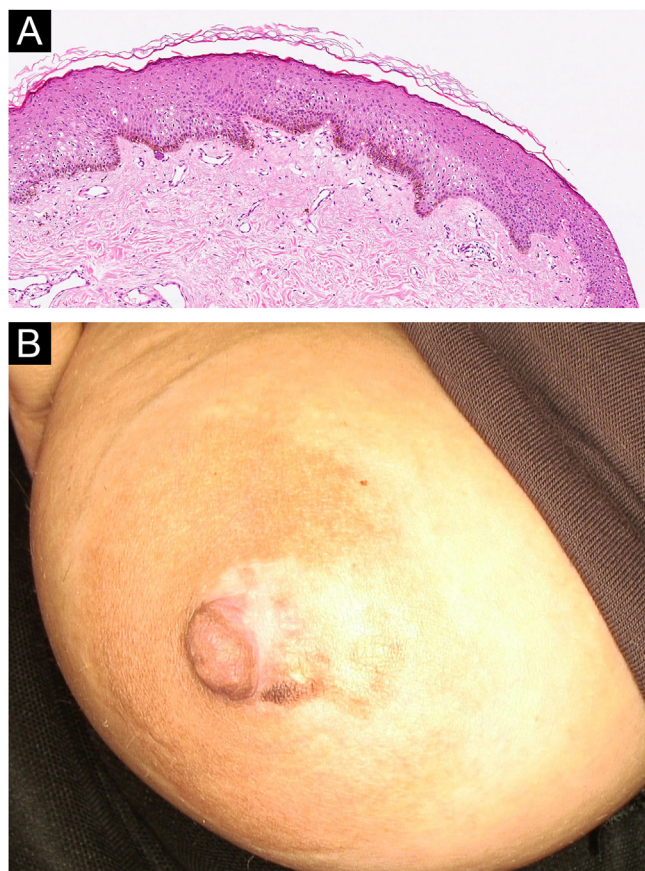


Fig. 4 (A) Histopathological findings of the second patient: irregular acanthosis, elongation of rete ridges, increased basal melanin, dermal edema, melanin incontinence, and perivascular lymphocytic infiltration (Hematoxylin & eosin, $\times 10$). (B) Partial regression of the lesion without treatment after five years in the second patient.

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LETTER – CLINICAL

Pancreatic panniculitis following endoscopic retrograde cholangiopancreatography (ERCP): a case report[☆]

Dear Editor,

Pancreatic panniculitis is a rare cutaneous manifestation that occurs in 0.3–3% of patients with pancreatic disease. It is postulated that damage to the pancreas causes hematogenous release of digestive enzymes, which increases the permeability of the microcirculation within the lymphatic vessels and leads to fat saponification with necrosis of the subcutaneous tissue. The most common underlying etiology is acute pancreatitis (88% of cases), while pancreatic neoplasms account for approximately 12%.^{1–4}

This case report describes a case of pancreatic panniculitis that occurred after a cholangiography examination.

A 76-year-old caucasian woman with hypertension was admitted to a referral hospital for gastroenterology care due to abdominal pain, loss of appetite, nausea, vomiting, and jaundice for three days. Laboratory tests on admission showed anemia (hemoglobin 10.2 g/dL), leukocytosis with neutrophilia (11,930 mm³), eosinophilia (450 mm³), elevated transaminases (AST 85 μ /L [normal 14–36 μ /L], ALT 331 μ /L [normal < 35 μ /L]), alkaline phosphatase (180 μ /L, normal 36–126 μ /L), gamma-GT (285 μ /L, normal 12–43 μ /L), total bilirubin (7.10 mg/dL, normal 0.2–1.3 mg/dL), and direct bilirubin (3.5 mg/dL, normal 0–0.3 mg/dL), with no change in amylase or lipase.

An abdominal CT scan was performed, which identified dilation of the intra- and extrahepatic bile ducts, with obstruction in the distal portion of the common bile duct at the level of the duodenal papilla. Subsequently, endoscopic retrograde cholangiopancreatography (ERCP) was performed, combined with sphincterotomy and insertion of a plastic biliary stent. Since no stones were identified in the common bile duct, papillitis, pancreatic head tumor, or dis-

tal cholangiocarcinoma were hypothesized as the cause of the obstruction.

Five days after the ERCP, the dermatology team was contacted due to the appearance, post-procedure, of nodular, painful, erythematous lesions located on the upper and lower limbs (Figs. 1 and 2), which had worsened significantly over the previous 24 hours. A deep skin biopsy revealed spontaneous drainage of yellowish-brown material from the site. The secretion was sent for culture, which was negative. New laboratory tests revealed elevated amylase (123 μ /L, [normal 30–110 μ /L]) and lipase (618 μ /L, [normal 36–126 μ /L]). Histopathological examination revealed acute suppurative panniculitis with lymphocyte and neutrophil infiltration, steatonecrosis with foci of incipient calcification, and ghost cells (Fig. 3).

Clinical, laboratory, and histopathological findings indicated the diagnosis of pancreatic panniculitis. The treating team was advised regarding the skin condition, which should be managed symptomatically until the underlying disease is resolved, with complete spontaneous resolution within 45 days. The patient has been followed for two years with a probable diagnosis of distal cholangiocarcinoma. She has been asymptomatic since the biliary stent implantation, and surgical treatment is contraindicated due to her advanced age and comorbidities.

The characteristic lesions of pancreatic panniculitis are erythematous and painful nodules, which appear suddenly, located primarily on the lower limbs but also on the buttocks, trunk, and upper limbs. The nodules may fluctuate, ulcerate, and drain a yellow-brown oily secretion. In 40% of cases, skin lesions may precede abdominal symptoms.^{1,4,5}

Among the differential diagnoses, it is worth mentioning: erythema nodosum, nodular vasculitis, alpha-1 antitrypsin deficiency, lupus panniculitis, subcutaneous T-cell panniculitis-like lymphoma, Bazin's indurated erythema, and other infectious panniculitis.^{1–3}

Histopathological examination is classically marked by focal subcutaneous steatonecrosis and the presence of pathognomonic ghost cells (anucleated necrotic adipocytes with thick, obscure walls, containing fine, basophilic granular intracytoplasmic material).^{1,2,4,5}

Treatment is supportive, with resolution observed after treatment of the underlying pancreatic process. Analgesic medications such as nonsteroidal anti-inflammatory drugs,



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

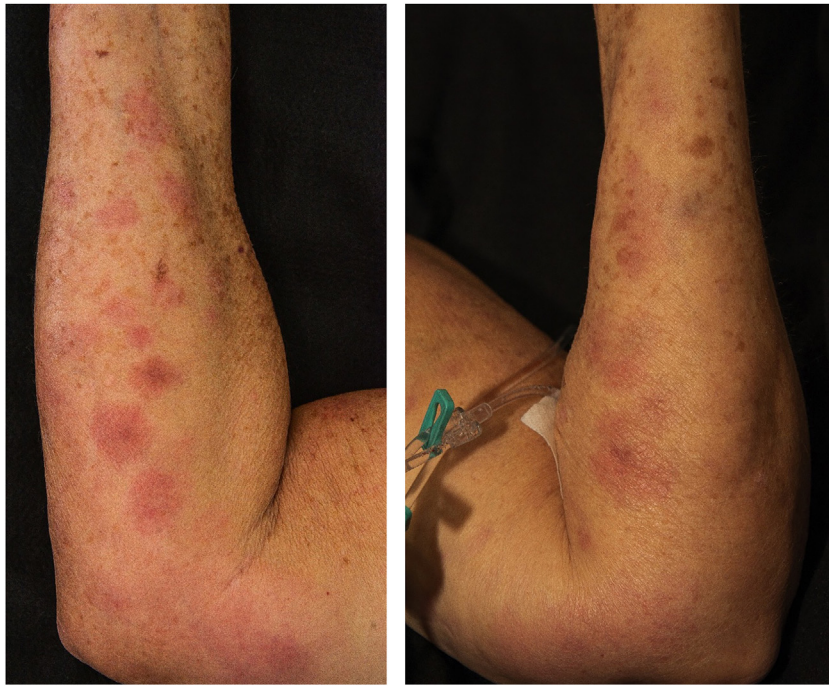


Fig. 1 Erythematous and painful nodules affecting the entire length of the upper limbs.

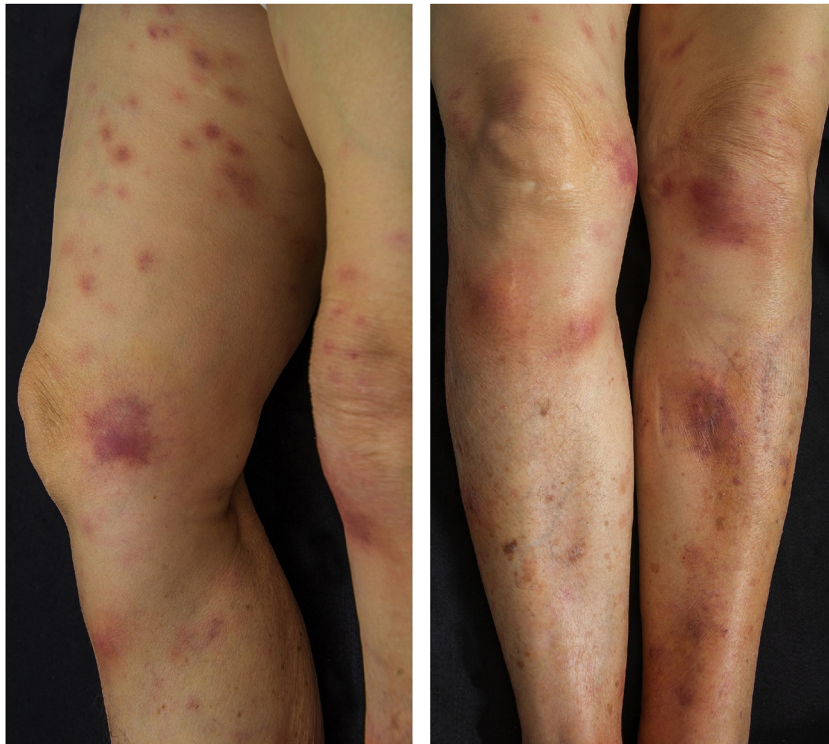


Fig. 2 Erythematous and painful nodules affecting the entire length of the lower limbs.

corticosteroids, and immunosuppressants are frequently used but are often ineffective.^{1,2,4}

Acute pancreatitis after ERCP is a complication that occurs in up to 3%–10% of cases, depending on patient risk factors and the complexity of the procedure. It is characterized by acute inflammation of the pancreas associated with mechanical manipulation of the pancreatic duct, con-

trast injection, or edema caused by local trauma.⁶ The onset of pancreatic panniculitis after ERCP is uncommon but may precede abdominal symptoms.^{7–10}

In conclusion, this report describes a case of pancreatic panniculitis as a complication of ERCP, without prior pancreatic disease. Dermatologists should be alert to the diagnosis of this complication after biliary tract procedures.

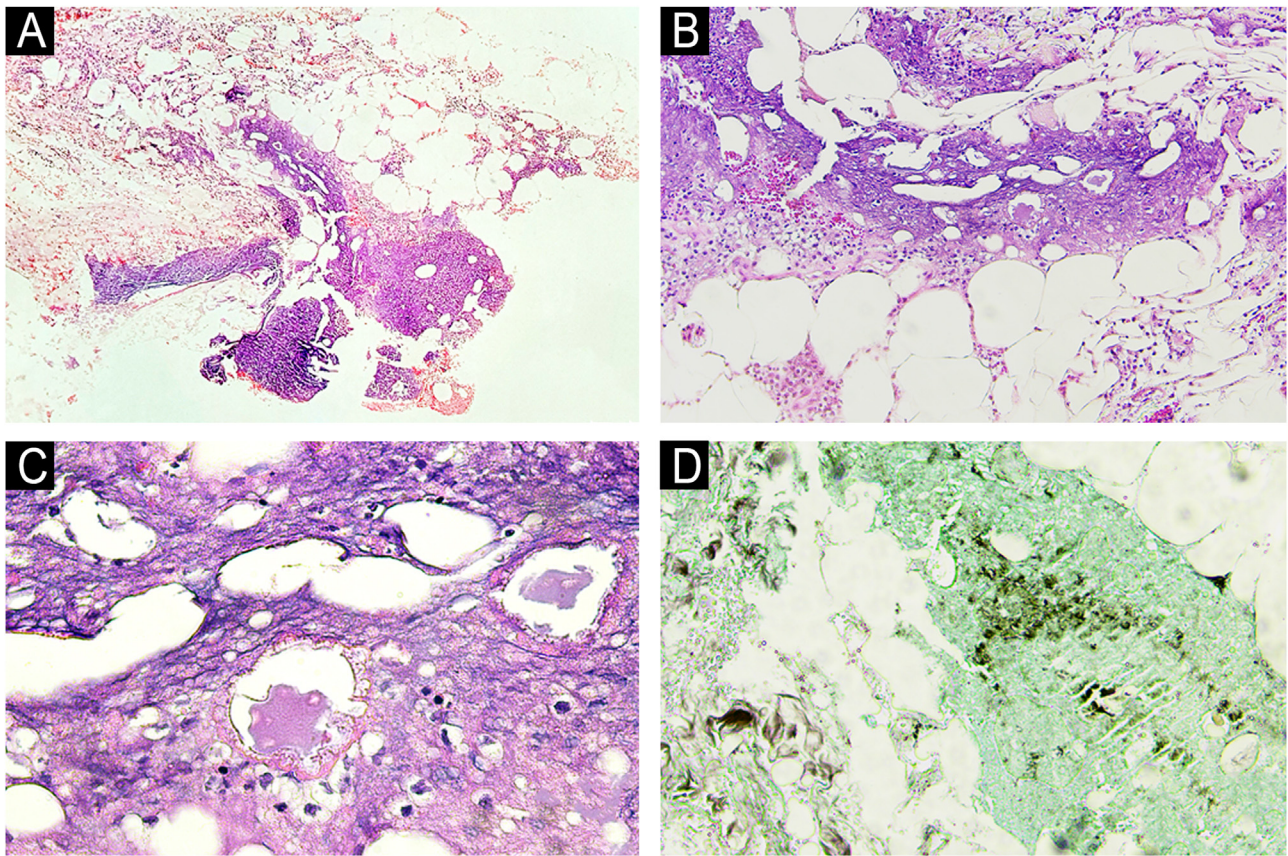


Fig. 3 Histopathological examination of pancreatic panniculitis. (A) Acute suppurative panniculitis with lobular predominance (Hematoxylin & eosin, $\times 100$). (B) Lymphocyte and neutrophil inflammatory infiltrate (Hematoxylin & eosin, $\times 200$). (C) Steatonecrosis with "ghost cells" (Hematoxylin & eosin, $\times 400$). (D) Foci of calcification amid steatonecrosis (von Kossa, $\times 400$).

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Conflicts of interest

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Editor

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LETTER – CLINICAL

Segmental dyskeratosis congenita – A diagnostic challenge[☆]



Dear Editor,

Dyskeratosis congenita (DC) is a telomeropathy with a classic triad: dystrophic nails, oral leukoplakia, and reticular cutaneous pigmentation.^{1–3} It occurs primarily in males and can be autosomal recessive or dominant, or an X-linked recessive disorder. A mutation in the *DKC1* (Diskerin 1) gene on the X chromosome was initially discovered, resulting in reduced telomerase activity and consequent telomere shortening, marking the first link between telomeres and disease in humans.¹

Mutations in the *ACD*, *CTC1*, *NAF1*, *NHP2*, *NOP10*, *PARN*, *POT1*, *RTEL1*, *STN1*, *TERC*, *TERT*, *TINF2*, *WRAP53*, and *ZCHC8* genes have also been described,² increasing the complexity of the disease. The *TINF2* (12.5%), *RTEL1* (14.5% – AD and 7.5% – AR), *TERT* (23.5%), and *DKC1* (16% in both gender and 22% in males) genes are the most commonly affected.¹

A 40-year-old Caucasian female patient with palmoplantar and nail alterations, as well as asymptomatic patches on the trunk, which had begun at the age of four, was examined.

On examination, the entire right sole, left heel, and focally on the right palm, revealed hyperkeratosis with lamellar desquamation (Fig. 1A–B). Nail involvement was heterogeneous: micronychchia was observed on the right from the second to the fourth toes (Fig. 1C), where the plantar region was most affected. Anonychia also appeared on the right second and fourth fingers. The left hand showed a decrease in nail plate width of the third finger, pterygium of the second, and canalicular dystrophy of the fourth finger (Fig. 2).

The patient also had irregular, reticulated hyperchromic patches, bordering the midline on the abdomen (Fig. 3A). Segmental pigmentary alterations with hyper- and hypochromia were also observed on the dorsum of the right hand (Fig. 3B). The oral mucosa showed no abnormalities.

Laboratory tests were unremarkable; mycological examination of the soles was negative. Anatomopathological analysis of the hyperkeratotic lesion on the right palm showed significant rectification of the epidermis with ortho-hyperkeratosis. Fibrosis and proliferation of small vessels were observed in the dermis (Fig. 4A). The hyperpigmentation on the abdomen revealed vacuolar degeneration foci of basal cells with mild pigment incontinence (Fig. 4B). Fontana-Masson staining of the hyperpigmented area demonstrated irregular distribution of melanin in the epidermis and dermal melanin (Fig. 4C).

Her only son had bilateral palmoplantar hyperkeratosis, micronychchia, and leukoplakia on the tongue. He underwent a bone marrow transplant due to bone marrow aplasia at the age of four, causing significant thrombocytopenia. DNA sequencing revealed a mutation in the *TINF2* gene – p.Arg282His (c.845 G>A), described in autosomal dominant cases.

Telomeres consist of identical repeats of amino acids, which have a protective effect on chromosomes and shorten throughout life. Mutations in the proteins involved in this process lead to premature cell aging.^{1,2}

Dyskeratosis congenita is a rare multisystem telomeropathy.^{3,4} It has characteristic mucocutaneous manifestations: reticulated hyperpigmentation of the skin, dystrophic nails, both present in the patient's case, and leukokeratosis in the mucous membranes,^{3,4} identified only in the patient's son.

This patient's segmental clinical presentation is likely due to mosaicism, a later mutation, called a postzygotic mutation, resulting in two cell populations, either carrying the mutation or not, with the clinical repercussions of changes following embryonic lines, seen here in the nail involvement and pigmentary alteration. This phenomenon also occurs in the gonads, where two populations of cells are present, known as gonadal mosaicism. Fertilization of an egg carrying the mutation leads to a more severe condition, as seen in the patient's son, with all of his nails affected, leukoplakia, and bone marrow aplasia, interestingly without pigmentation changes.

The nails are most commonly affected and may disappear or be absent at birth, leading to a tapered appearance of the fingers. The variety of changes seen in this patient makes diagnosis difficult. Anonychia, onychoschizia, longitudinal striae or fractures, trachyonychia, koilonychia,

[☆] Study conducted at the Dermatology Service, Santa Casa de Porto Alegre, Porto Alegre, RS, Brazil.

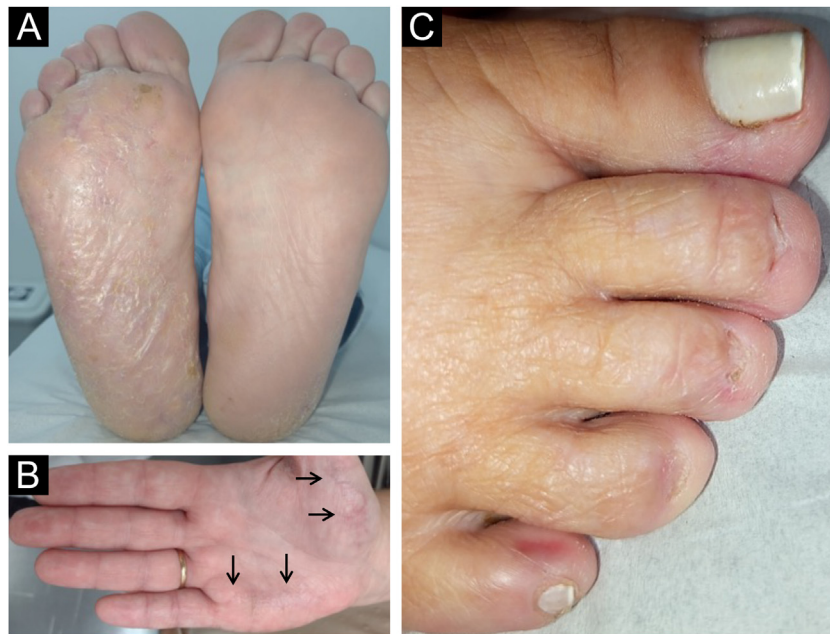


Fig. 1 (A) Diffuse hyperkeratosis on the right sole. (B) Focal hyperkeratosis on the right palm (arrows). (C) Micronychia of the second to fourth right toes.

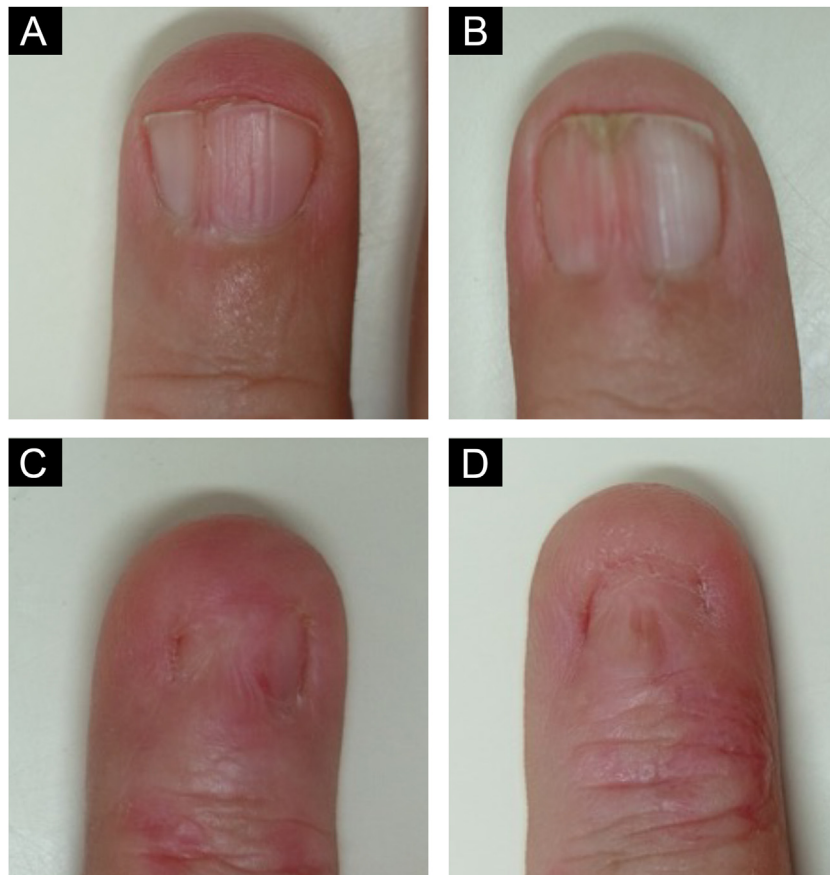


Fig. 2 Variability of nail involvement (A) Vertical ridges. (B) Mild pterygium. (C) Severe pterygium. (D) Anonychia. The skin of the distal phalanges of the most affected nails (C–D) shows mild erythema and desquamation.

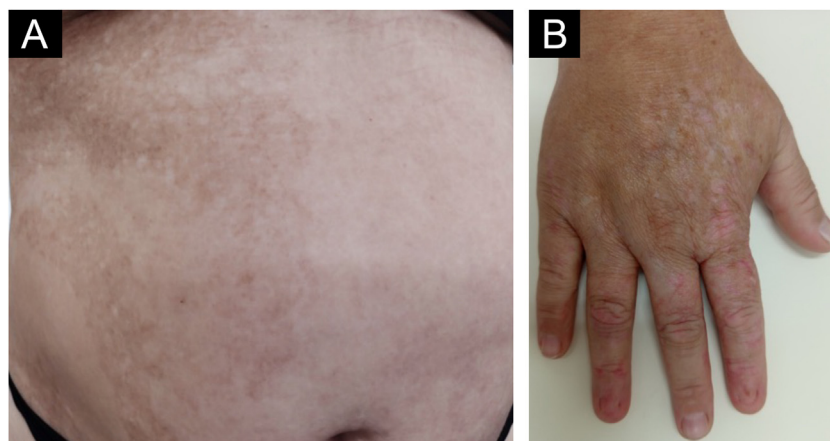


Fig. 3 (A) Segmental hyperpigmented macules on the right abdomen. (B) Segmental hypo- and hyperpigmentation located on the dorsum of the right hand.

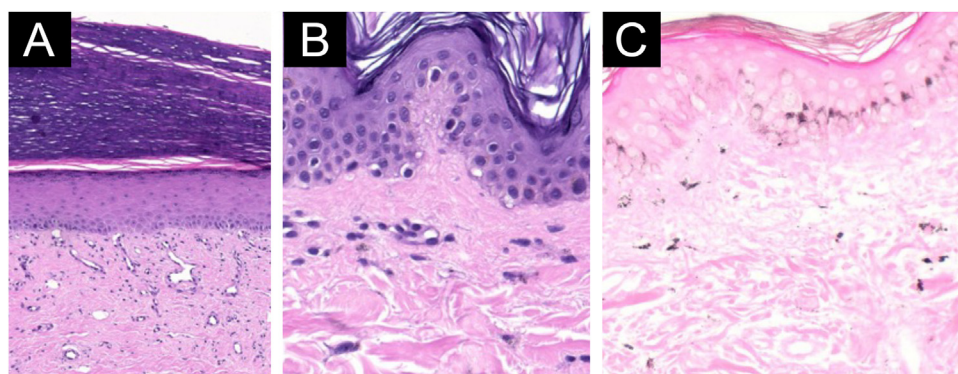


Fig. 4 Light microscopy showing nonspecific findings. (A) Hyperkeratotic lesion on the right palm with significant rectification of the epidermis with orthohyperkeratosis; fibrosis and proliferation of small vessels are observed in the dermis (Hematoxylin & eosin $\times 200$). (B) Hyperpigmentation on the abdomen with vacuolar degeneration foci of basal cells with mild pigmentary incontinence (Hematoxylin & eosin $\times 400$). (C) Fontana-Masson staining demonstrating irregular distribution of melanin in the epidermis and pigmentary incontinence ($\times 200$).

pterygium, leukodinia, and melanonychia have already been described.^{1,2}

The mutation found has been previously described,⁴⁻⁶ affecting not telomerase, but a complex called the telosome, which protects telomeres and regulates telomerase,⁷ leading to premature telomere shortening.^{5,6}

In a cohort of 175 patients with DC,⁵ *TINF2* gene involvement was demonstrated in 33 (18.8%, slightly higher than other reports)¹ of whom; 32 had aplastic anemia. As control, they used 244 patients with bone marrow failure, and three individuals had a mutation in this gene, exemplifying the complexity of the issue.⁵ Mutations in *TINF2* can lead to retinopathy, also called Revesz syndrome.⁸

Men are more affected than women,¹ which highlights the importance of the X-linked recessive inheritance pattern. Women with X-linked DC tend to have milder phenotypes and less severe clinical presentations. This is due to the phenomenon of lyonization,⁷ a process that inactivates one of the two X chromosomes in female cells, generating reduced transcriptional activity. In these cases, symptoms always appear at an older age.⁷

Delayed diagnosis of DC is due to the broad spectrum of clinical presentations, the lack of specific laboratory tests, and the absence of conclusive histopathology,^{3,4} as seen in the present case. Dermatologists should be alert, as the disease can present with serious hematological complications and malignancies, such as leukemia, squamous cell carcinoma from leukokeratosis, and non-Hodgkin's lymphoma.

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LETTER - CLINICAL

Sodium thiosulphate for recalcitrant dystrophic calcinosis cutis – An effective but tricky treatment option[☆]



Dear Editor,

Calcinosis cutis (CC) is the deposition of insoluble calcium salts in the skin and subcutaneous tissue.¹ Dystrophic CC is the most common subtype. Caused by local injury, it is frequently associated with connective tissue diseases. Although rare, dystrophic CC affects 18%–49% of systemic sclerosis (SSc) patients.² CC has a high morbidity due to pain, functional impairment, ulceration, and secondary infections, leading to disability.³ Lacking large-scale controlled trials, dystrophic CC remains without standard therapy. Intralesional sodium thiosulfate (STS) was proposed as a therapeutic option based on case reports and small case series.

A 50-year-old woman with limited SSc, evolving over 19-years, referred stiffness, pain and ulceration on the first four digital pulps of each hand for one year. She underwent surgical excision of calcium deposits of the 2nd and 3rd fingers bilaterally and started diltiazem 90 mg/day. For two years, there was symptomatic progression. Skin involvement also included sclerodactyly and malar cutaneous telangiectasia. In addition, her SSc was complicated by oesophageal dysmotility, partially controlled with proton pump inhibitors, and severe Raynaud phenomenon (RF), under bosentan. No evidence of pulmonary arterial hypertension or other systemic involvement. Laboratory tests were positive for Antinuclear antibodies (ANA) and anticentromere antibodies (ACA). Physical examination revealed painful, stiff, skin-coloured papules, 4–10 mm, distributed on the pulp of the 1st, 2nd and 4th right fingers and the 1st left finger, compatible with CC (Fig. 1), as confirmed by hand radiography (Fig. 2). Intralesional STS treatment was proposed due to significant morbidity, progression under diltiazem and the involved site. The procedure was performed using an aseptic technique and under digital nerve block, with a 250 mg/mL solution.



Figure 1 Skin-coloured papules, distributed on the pulp of fingers of both hands.



Figure 2 Hands simple radiography (oblique view) before treatment with intralesional sodium thiosulfate.

[☆] Study conducted at the Dermatology and Venereology Department, Unidade Local de Saúde de Coimbra, Coimbra, Portugal.



Figure 3 Hands simple radiography (oblique view) after 25 sessions of treatment with intraleisional sodium thiosulfate.

Depending on the size of the lesion and pulp distensibility, 0.1–1 mL of STS solution was injected into the base of the calcifications. Initially, at a 6 to 8-week interval, and after improvement, every 3-months. 25 sessions were performed in 5-years, with continuous symptomatic improvement and better functional status. Hand radiography confirmed a sustained reduction in calcification size (Fig. 3). During the first 2-years, episodes of ulceration and spontaneous drainage of liquified calcium deposits were reported, both self-limited. Additionally, 2 local infections were treated with oral antibiotics. There were no systemic adverse events or analytical abnormalities. However, 2 weeks after the last administration, the patient developed necrosis on the pulp of the 1st right and 2nd left fingers. Treatment with bosentan was suspended 3-months earlier due to long-term control of RF. Oedema from STS infiltration may have triggered a more pronounced RF episode, leading to pulp necrosis. The patient underwent treatment with iloprost 0.4 ng/Kg/min for 3-days and resumed bosentan, with complete healing. Currently, she is asymptomatic, with residual calcifications in hand radiography.

In dystrophic CC, chronic cellular damage and hypoxia can trigger ectopic calcification with normal serum calcium levels.⁴ CC usually presents as firm, painful plaques or nodules, associated with functional impairment.³ Lesions can ulcerate, fistulize and become infected. In patients with SSc, extensor surfaces, palms and soles are commonly involved.⁴ Pharmacological therapy is the first-line, mainly high-dose calcium-channel inhibitors, bisphosphonates, colchicine and minocycline.⁵ Surgery is reserved for small symptomatic lesions as primary treatment or an adjunct to drug therapy.⁶ Successful treatment with intravenous, topical and intraleisional STS has been reported in a small number of patients. STS is a chelating agent that increases calcium solubility up to 100.000 times, in addition to anti-inflammatory, vasodilative and anti-oxidative effects.⁷ Intravenous administration has adverse events, such as headaches, vomiting, hypotension, hypernatremia and metabolic acidosis, limiting its use in systemic diseases.⁸ Topical STS is not associated with systemic adverse events but is slow, requires strict compliance and may inadequately penetrate the skin, being recommended on small lesions.^{1,7}

Intraleisional STS provides local delivery to deep lesions without systemic adverse effects. The concentration of 250 mg/mL is the most frequently described.⁴ The volume (0.1–1 mL) and the interval between administrations (weekly to 3-months) vary according to lesions' size, patient tolerance and clinical evolution.^{1,4,7} Intraleisional STS has a rapid onset and complete remission is described in 50%–100% of patients.⁴ Transient local pain and secondary infections are the most frequently reported adverse events.⁸ Additionally, it may be advantageous in SSc patients with thickened skin.⁸

In conclusion, intraleisional STS seems a promising option in recalcitrant, severe CC. The safety profile reinforces its applicability, but patient selection is mandatory due to a long treatment course. In addition, RF treatment is essential, as the vascular compression due to the intraleisional administration may predispose to digital ischemic necrosis. Randomized controlled trials are needed to improve the optimal dosage, administration technique, and minimize the risk of pulp necrosis.

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LETTER - CLINICAL

Subacute skin lesions in systemic lupus erythematosus: an impressive and well-tolerated response to anifrolumab[☆]



Dear Editor,

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease with a wide spectrum of clinical manifestations.¹ Muco-cutaneous lesions are common in SLE, affecting up to 80% of patients. Cutaneous lesions can cause significant morbidity and potentially lead to irreversible damage. When exposed to exogenous noxae (such as ultraviolet light), SLE patients' skin presents enhanced susceptibility to cell damage. SLE skin has interferon (IFN) hyperresponsiveness to inflammatory stimuli, serving as a

key site of autoantigen sensitisation, triggering systemic inflammation.²

The heterogeneity of clinical presentation of SLE contributes to its therapeutic challenge.³ This report presents an impressive and successful treatment outcome for cutaneous manifestations of SLE.

We describe the case of a 37-year-old woman with a one-year history of extensive erythematous annular lesions on the upper thorax, back, extensor surfaces of arms and forearms, gluteal region, and posterior upper thigh (Fig. 1) and non-scarring alopecia. The Cutaneous Lupus Erythematosus Disease Area and Severity Index activity (CLASI-A) score was 25, no damage (dyspigmentation or scarring) was observed. She also complained about inflammatory polyarthralgias, xerophthalmia and xerostomia. She had no relevant prior personal or family history. Laboratory tests revealed positivity for anti-SSA and anti-nuclear antibodies (titer of 1/1000; speckled pattern), with normal blood

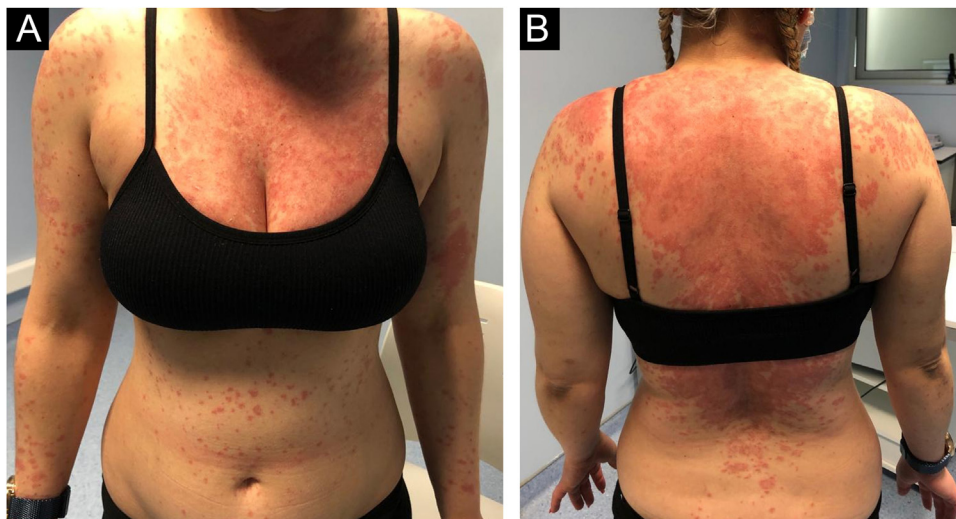


Figure 1 (A–B) Subacute cutaneous lupus showing annular erythematous plaques coalescing into polycyclic plaques with raised borders and scaling before treatment.

[☆] Study conducted at the São João Local Health Unit, Hospital Center of São João, Porto, Portugal.

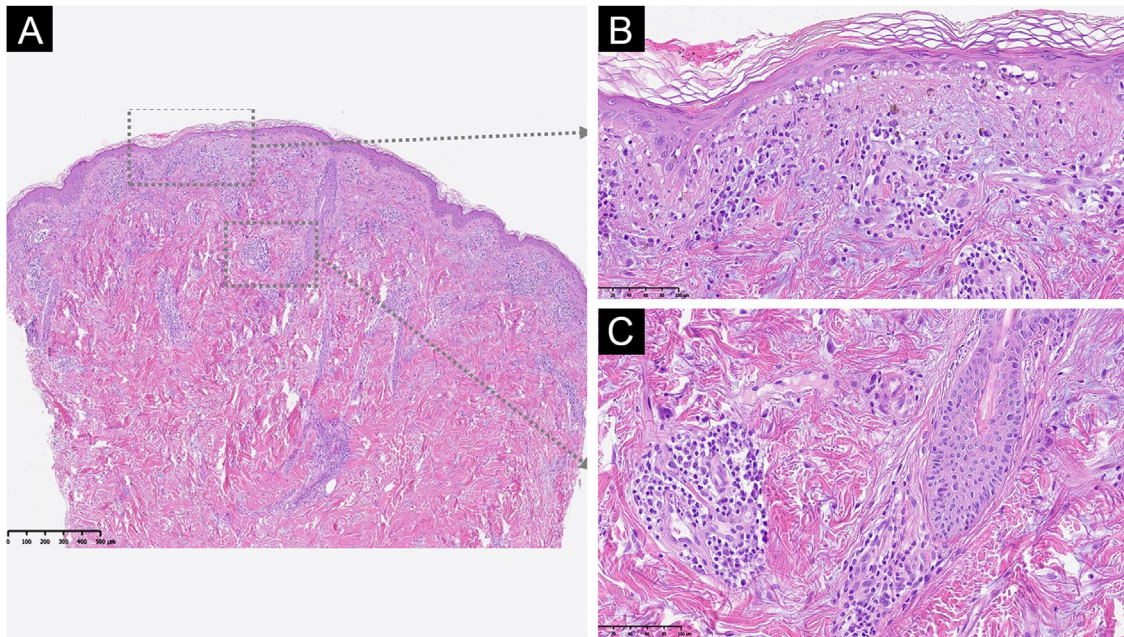


Figure 2 Morphological features consistent with the clinical diagnosis of subacute cutaneous lupus erythematosus subtype. Skin biopsy (Hemaxitolyn & eosin stain) showed epidermal thinning (A, $\times 40$), areas of interface dermatitis with basal layer vacuolization (B, $\times 100$), dermal mucin, pigment incontinence and perivascular lymphocytic infiltrate (C, $\times 100$).



Figure 3 (A–B) Improvement after two infusions of anifrolumab with total resolution of the lesions.

cell count, complement levels, and kidney function. Skin biopsy revealed histopathological findings (Fig. 2), as well as IgM deposition along the dermal epidermal junction on direct immunofluorescence, supporting the clinical diagnosis of subacute cutaneous lupus erythematosus. Schirmer's test was normal, and the salivary gland biopsy didn't reveal histopathological changes.

A diagnosis of SLE was established based on the 2019 EULAR/ACR Classification Criteria for Systemic Lupus Erythematosus, and hydroxychloroquine was initiated. However, only improvement of the articular involvement was observed. For that reason, oral prednisolone up to 40 mg/day, topical betamethasone, and azathioprine up to 1.5 mg/kg/day were introduced, without response. Aza-

thioprine was discontinued due to severe lymphopenia. Mycophenolate mofetil 1500 mg/day was tried, but lymphopenia was once again observed. The iatrogenic effect was confirmed systematically with normalization of white cell count after drug withdrawal.

Given the patient's significant disease activity despite multimodal therapy, anifrolumab 300 mg infusion was started every 4-weeks. One month later, the patient showed a dramatic improvement of the skin lesions (Fig. 3) and the non-scarring alopecia with a CLASI-A score drop to 7. The dose of prednisolone was progressively tapered to 5 mg/day in three months. No adverse effects have been noted during biologic therapy.

Activation of the type I IFN pathway is recognized as playing a critical role in the pathogenesis of SLE, promoting dendritic cell formation, activation of T-cells, and autoantibodies production by B-cells.^{1,4,5} Anifrolumab, a fully human monoclonal antibody that selectively binds to IFN receptor subunit 1, inhibits signaling by all type I interferons.^{3,5,6} This blockade may reverse immune dysregulation and prevent further tissue damage in SLE.⁴

Anifrolumab was recently approved for the treatment of moderate-severe SLE in addition to the standard care for patients without renal or CNS involvement.^{4,5,7} The main three anifrolumab trials (MUSE,⁵ TULIP-1⁸ and TULIP-2³) evaluated cutaneous manifestation response using the CLASI score. All trials showed a rapid significant reduction in CLASI activity with anifrolumab. Sustained oral prednisolone tapering until dosage ≤ 7.5 mg/day was also achieved.^{3,5,7,8} Another important observation was the rapid skin response, which can impact daily life, since the most commonly involved areas are exposed and visible.^{2,6}

This case highlights the value of anifrolumab in the treatment of cutaneous lupus after the failure of multiple therapies, due to ineffectiveness or adverse effects.

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LETTER - CLINICAL

Unilateral palpebral lupus miliaris disseminatus faciei successfully treated with lymecycline[☆]



Dear Editor,

A 26-year-old male patient with no previous relevant medical history presented with small reddish and yellowish papules on the right upper eyelid, which had evolved over 2 months. These lesions were asymptomatic. On physical examination multiple micro-papules, 1 to 2 mm in diameter, grouped on an erythematous base and confluent on the right upper eyelid. Dermoscopy showed rounded, polylobulated lesions which spared follicular openings, with an orange-reddish background and short telangiectatic vascular structures surrounding the follicular openings (Fig. 1).

Initially, the patient was treated with topical fusidic acid under the suspicion of folliculitis of the eyelid. However, after 2-weeks without improvement, a punch biopsy of a

papular lesion was performed. Histological findings revealed orthokeratosis with preserved epidermal structure. In the dermis, an area of necrosis surrounded by granulomas composed of numerous epithelioid histiocytes, a few giant cells, and lymphocytes was found, consistent with the diagnosis of lupus miliaris disseminatus faciei (LMDf) (Fig. 2).

Based on clinical and histopathological findings, a diagnosis of LMDf was established. Treatment with oral lymecycline 300 mg/day and topical metronidazole 0.75% twice a day for 2-months was prescribed. At the end of treatment, complete regression of the lesions was observed, which has been maintained after 16 months of follow-up.

Lupus miliaris disseminatus faciei or acne agminata is a chronic inflammatory granulomatous disease affecting adolescents and young adults, with a male predominance.¹ Clinically, it manifests as multiple erythematous-yellowish or brown papules, 1–3 mm in diameter, involving the central face and eyelids, especially the lower eyelids, although they are rarely the only site of involvement. Additionally, this condition is usually bilateral, unlike our case, where

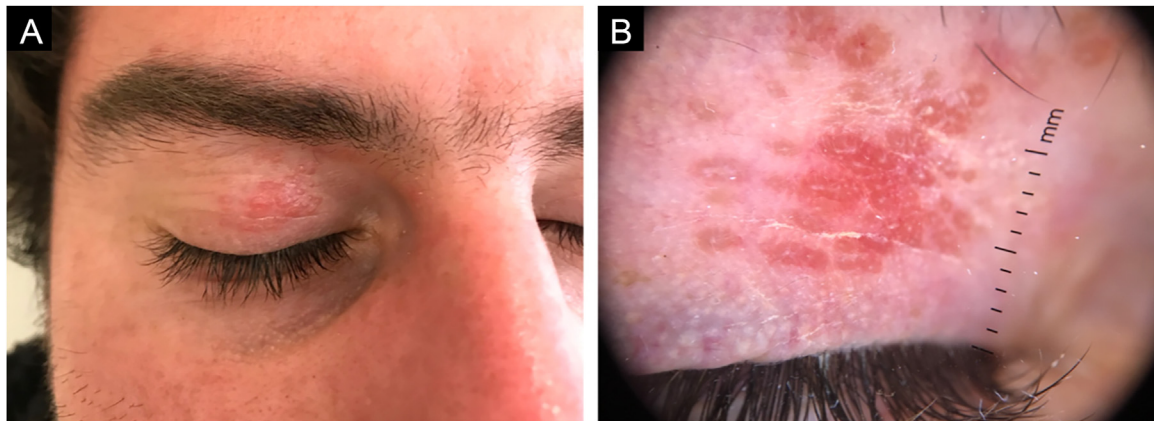


Fig. 1 (A) Multiple micropapules, 1 to 2 mm in diameter, grouped on an erythematous base and confluent on the right upper eyelid. (B) Dermoscopy shows polylobulated lesions with a rounded appearance, sparing follicular openings, on an orange-reddish background, and short telangiectatic vascular structures surrounding follicular openings.

[☆] Study conducted at the Clínica Alemana de Santiago, Vitacura, Santiago, Chile.

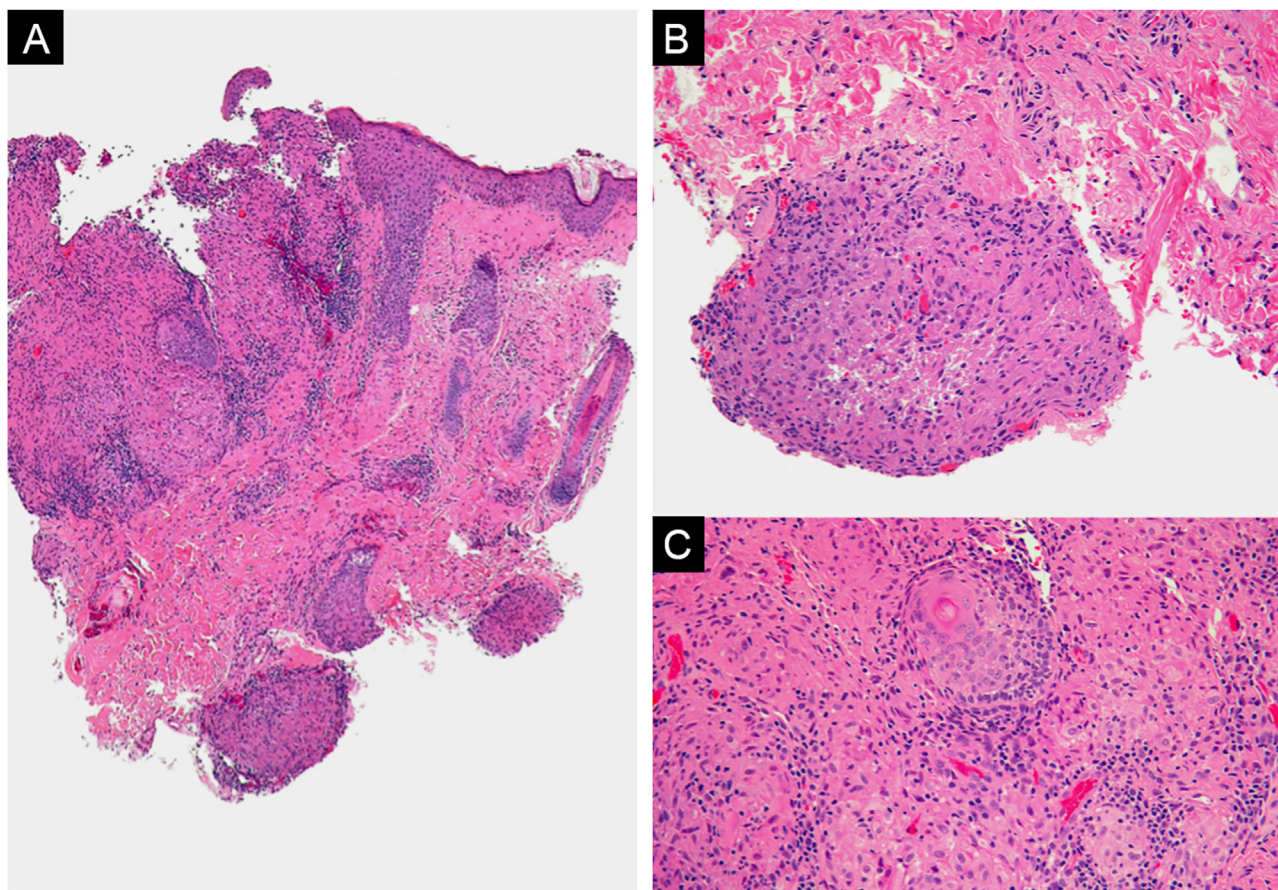


Fig. 2 (A) Multinodular dermal inflammatory infiltrate (Hemaxitolyn & eosin, $\times 40$). (B) The infiltrate consists of lymphocytes, plasma cells, and histiocytes forming epithelioid granulomas (Hemaxitolyn & eosin, $\times 200$). (C) Some granulomas show central necrosis (Hemaxitolyn & eosin, $\times 200$).

the involvement was unilateral and on the upper eyelid. Typically, the lesions resolve spontaneously after 1 to 2 years, leaving small punctate scars on the skin.¹

On diascopy, the papules often have an “apple jelly” appearance.² Dermoscopy displayed the presence of central targetoid follicular plugs with white striae on a brownish-orange background. The keratotic follicular plugs seen in dermoscopy develop as a result of lateral pressure on the hair follicles.³

In the past, LMDF was considered a variant of lupus vulgaris or a tuberculoma, due to histopathological features showing epithelioid cell granulomas with central caseous necrosis. However, in these patients, methods to demonstrate the presence of tuberculous mycobacteria are consistently negative.¹ Some authors have considered LMDF synonymous with granulomatous rosacea due to similarities in histopathological characteristics. However, both conditions have clinical and histopathological differences and respond to different treatments.⁴ Currently, it is believed that the condition occurs secondary to the rupture of the hair follicle, releasing antigens – primarily from *Cutibacterium* acnes – into the dermis, triggering a foreign body reaction via cellular immunity. This theory is based on pathological observation showing granulomas forming around ruptured pilosebaceous follicles.⁵

Definitive diagnosis requires histopathology, which typically shows perifollicular epithelioid granulomas, neutrophilic abscesses, and caseous necrosis in 13%–48% of cases.⁵

The differential diagnosis of LMDF includes granulomatous rosacea (GR), lupus vulgaris, papular sarcoidosis, the papular form of granuloma annulare, and chalazion.

The most important differential diagnosis is granulomatous rosacea.⁴ Both conditions show epithelioid granulomas centered on pilosebaceous units in histopathological studies; however, the granulomas of GR are smaller and lack central necrosis. Clinically, GR can be distinguished by presenting flushing, erythema, and centropal telangiectasias, unlike LMDF, which only presents papules.⁴

Since the etiology and pathogenesis remain unclear, there are no standard treatment recommendations. However, lesions resolve spontaneously, although they leave small, depressed scars. Case series have reported a wide range of treatments aimed at faster lesion resolution and scar prevention.⁶ These include dapsone, doxycycline, minocycline, isotretinoin, clofazimine, isoniazid, intraleisional triamcinolone, oral corticosteroids, 1450 nm diode laser, and, more recently, apremilast.⁶

In 2020, Kaushik et al. reported the use of apremilast 30 mg every 12 hours in a series of 3 patients who were

refractory to other treatments such as doxycycline and isotretinoin. In this series, the 3 patients showed rapid improvement within 4 weeks without adverse effects.⁶

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LETTER - CLINICAL

VEXAS syndrome: cutaneous manifestations and *UBA1* gene variants in the diagnosis of a rare autoinflammatory syndrome – Case report[☆]

Dear Editor,

VEXAS syndrome (VS) is a rare, recently described autoinflammatory disease that primarily affects men over 50 years of age and is caused by somatic mutations in the *UBA1* gene, located on the X chromosome.^{1,2} The clinical presentation includes constitutional symptoms (fever, night sweats, fatigue, weight loss) and hematological, musculoskeletal, cardiopulmonary, and cutaneous manifestations (Fig. 1).²⁻⁶

Skin involvement occurs in 80%–100% of cases and is characterized by erythematous and/or violaceous papules and plaques, sometimes edematous, predominantly on the back, upper limbs, neck, and face. Erythematous to purpuric papules and plaques are mainly observed on the lower limbs.⁷ The cutaneous condition is often initially diagnosed as Sweet's syndrome or vasculitis based on the histopathological findings of neutrophilic dermatosis and leukocytoclastic vasculitis, respectively.¹ Although there are no established diagnostic criteria for VS, bone marrow evaluation is essential to identify cytoplasmic vacuoles in myeloid and erythroid precursors. However, for a definitive diagnosis, genetic confirmation of mutations in the *UBA1* gene is necessary.⁸

Treatment is still uncertain, with glucocorticoids being the most useful medications.⁸ The prognosis is poor, with a 5-year mortality rate of 30%–40%.⁷ However, bone marrow transplantation and gene-editing therapies appear promising, according to recent studies.⁹ The objective of this case report was to highlight the cutaneous manifestations in VS and to reinforce the importance of genetic testing in patient prognosis and in understanding VS.

A 64-year-old man presented to the emergency room due to weight loss of 16 kg in the previous six months, blood in the stool for five months, anemia for four months, a his-

tory of fatigue for one month, and fever above 38 °C for three days. He also reported the appearance of asymptomatic skin lesions for one week. Physical examination revealed erythematous-violaceous plaques on the trunk, back, upper limbs, palms, soles, and face, and violaceous macules and papules on the lower limbs, which did not disappear with digital pressure (Fig. 2A- and B). Laboratory tests revealed elevated serum C-reactive protein (CRP) of 152 mg/L, macrocytic anemia with a hemoglobin of 6.2 g/dL and a mean corpuscular volume of 116.5 fL, neutrophilia of 14,400 μ L, 23% of which were rods (3,319 μ L), and thrombocytopenia of 53,000 μ L.

Biopsies were performed of skin lesions on the trunk, consistent with Sweet's syndrome, and on the left lower limb, consistent with leukocytoclastic vasculitis (Fig. 3). Direct immunofluorescence of the lesions on the lower limb showed no immune deposits.

For initial management, prednisone was prescribed at a dose of 1 mg/kg/day, with significant improvement of the lesions 48 hours after starting corticosteroid therapy. Antibiotic therapy was also administered for fever associated with leukocytosis with a left shift in the leukogram, and erythropoietin was administered for anemia.

The bone marrow biopsy revealed findings suggestive of myelodysplastic syndrome, and a bone marrow biopsy revealed hypercellularity with myelodysplastic/myeloproliferative abnormalities associated with megakaryocytosis and grade 1 myelofibrosis. Based on these findings, VS was hypothesized. Genetic sequencing of the patient's bone marrow specimens revealed the presence of the c.1741 + 15G>A mutation in the *UBA1* gene (Fig. 4).

Skin changes, present in most patients with VS, are usually the first manifestation of the syndrome, reinforcing the essential role of the dermatologist in early identification of the disease. In a case of Sweet's syndrome associated with vasculitis in the lower limbs and constitutional symptoms, in addition to the involvement of other systems, especially hematological ones, in men over 50 years of age, VS should be considered as a differential diagnosis.

Early and timely recognition of suspected cases leads to assertiveness in ordering genetic testing. The identification of new pathogenic somatic variants in the *UBA1* gene allows targeted genetic evaluation, making it faster and more



[☆] Study conducted at the Hospital Universitário Polydoro Ernani de São Thiago, Florianópolis, SC, Brazil.

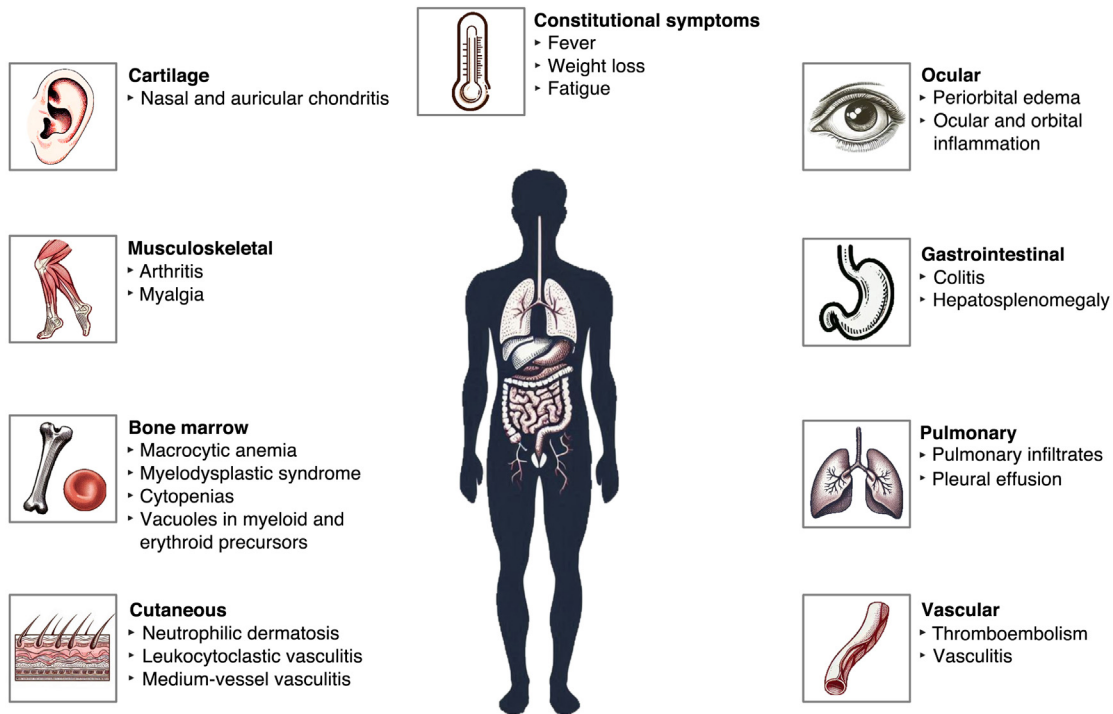


Fig. 1 Clinical manifestations of VEXAS syndrome. Source: The authors, 2025. Created with Microsoft Designer 2025.

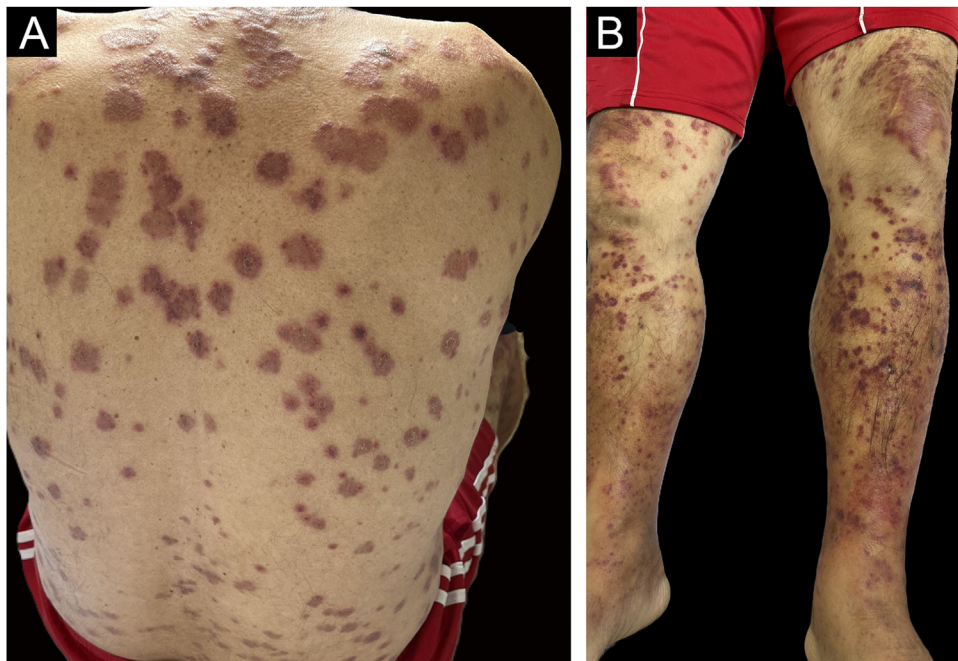


Fig. 2 Cutaneous manifestations. (A) Erythematous-violaceous papules and plaques, with edematous edges, some with a tendency to coalesce, on the back. (B) Palpable purpura on the lower limbs.

effective. There are possibly still numerous undescribed pathogenic variants related to VS. Genetic sequencing of this patient identified a variant of uncertain significance, as it is not among those already described to date (Fig. 4).¹⁰ Therefore, it is presumed that this is yet another unrecognized VS-related variant.

Raising awareness of VS among dermatologists is essential to facilitate early diagnosis. New pathogenic variants in the *UBA1* gene identified in VS should be documented for a better understanding of the disease and more efficient genetic evaluation, aiming to mitigate the high morbidity and mortality.

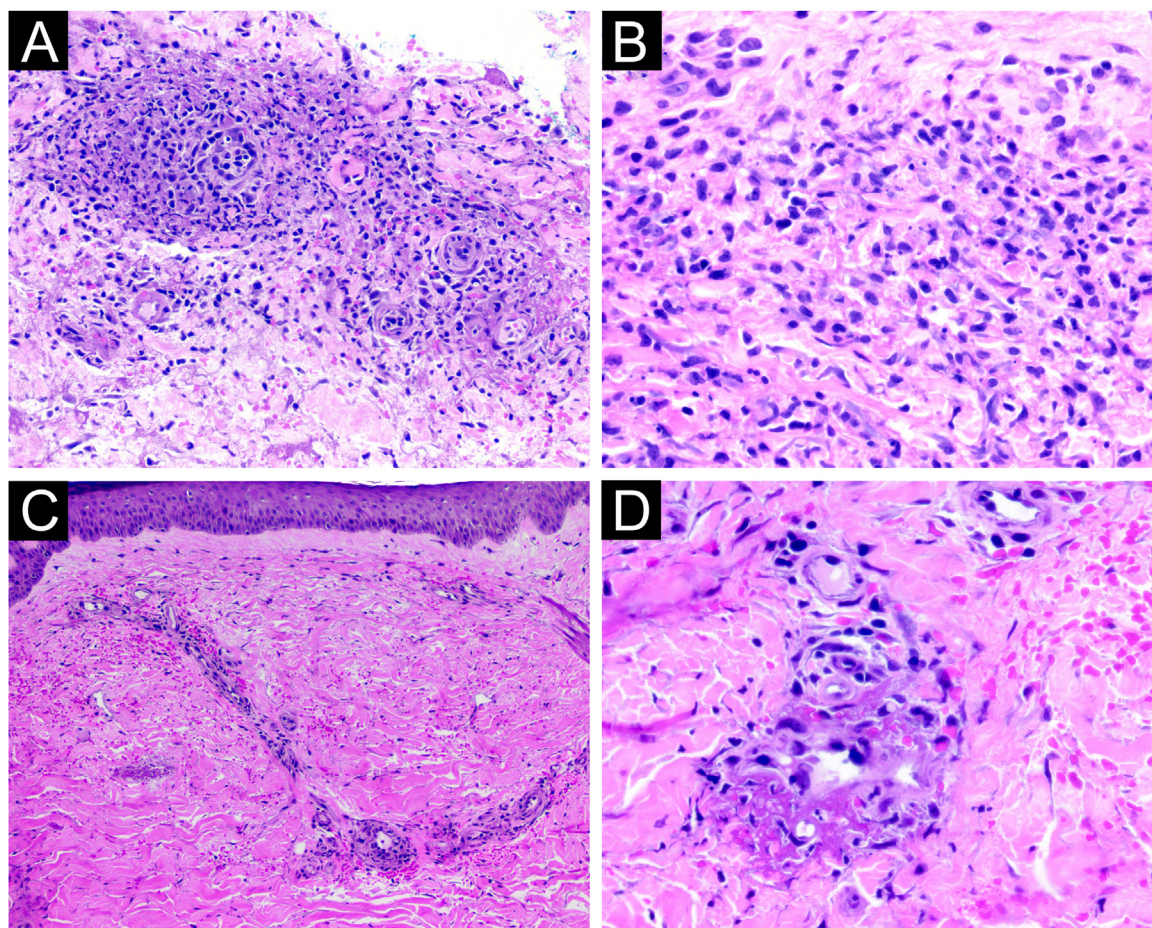


Fig. 3 Histopathological findings. Biopsy of a lesion on the trunk showed mono- and polymorphonuclear infiltrate, with particulate neutrophils and extravasated red blood cells, without signs of vasculitis (A, Hematoxylin & eosin, $\times 200$; B, Hematoxylin & eosin, $\times 400$). Biopsy of a lesion on the lower limb showed extravasated red blood cells, mixed perivascular inflammatory infiltrate with leukocytoclasia, and the presence of fibrin thrombi in the capillary wall (C, Hematoxylin & eosin, $\times 100$; D, Hematoxylin & eosin, $\times 400$).

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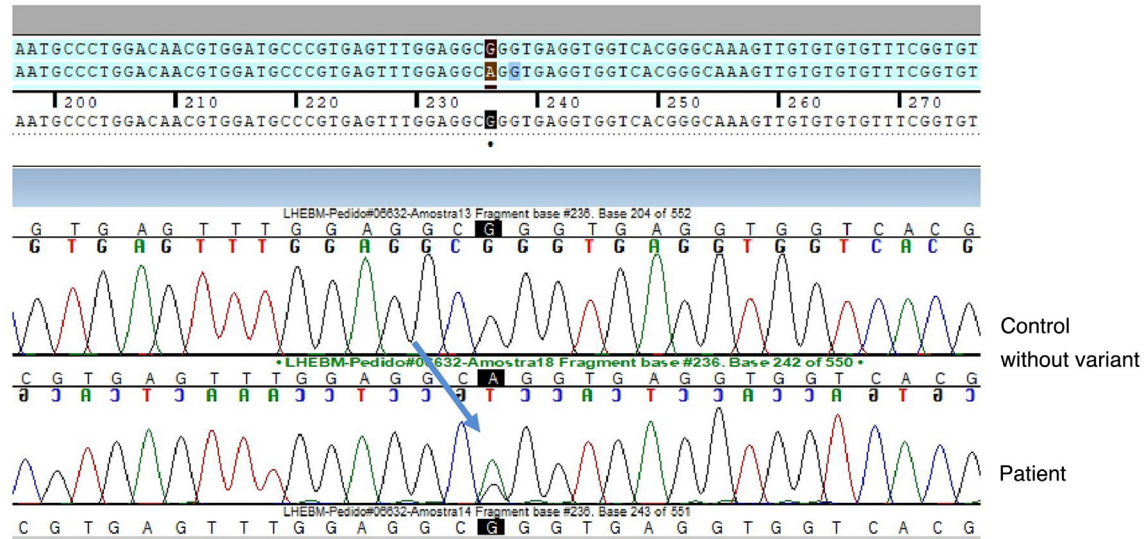
Amanda Amaro Pereira: Data collection, or analysis and interpretation of data; intellectual participation in the propaedeutic and/or therapeutic conduct of the studied cases.

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Sequencing results of exons 3, 14, 15 and 16 of the UBA1 gene (NG_009161)

Illustrative example of UBA1 gene sequencing



There was a substitution of nitrogenous base G for A in the intronic region between exons 15 and 16

Fig. 4 Genetic testing of the *UBA1* gene with DNA sequencing using the Sanger method of exons 3, 14, 15 and 16. Mutation identified between exons 15 and 16, with the nitrogenous base G being replaced by A.

Availability of research data

Not applicable.

Conflicts of interest

None declared.

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LETTER - DERMATOPATHOLOGY

Acrometastasis in renal cell carcinoma: a case report and literature review[☆]



Dear Editor,

Acrometastasis is an exceptionally rare manifestation of bone metastasis, involving the distal regions of the extremities, such as the hands and feet, and accounting for only about 0.1% of all skeletal metastases.¹ Despite the relatively high incidence of bone metastases in advanced stages of solid malignancies, the occurrence of metastases in acral locations remains uncommon. Its diverse and often non-specific presentation may mimic infections, inflammatory disorders, or traumatic injuries, leading to misdiagnosis or delayed recognition. In some cases, patients may initially present to dermatology or orthopedic clinics with localized symptoms, prompting further investigation and revealing an underlying malignancy. The rarity and diagnostic challenges associated with acrometastasis underscore the importance of maintaining clinical suspicion in patients with unusual acral symptoms, particularly when there is a known history of cancer. Early identification, although unlikely to significantly alter the overall poor prognosis, can inform appropriate palliative or therapeutic strategies.

A 51-year-old male patient presented to our dermatology outpatient clinic with a 3–4 month history of swelling, erythema, and pain localized to the distal phalanx of the right thumb. The patient had a known history of renal cell carcinoma (RCC) and was under active oncological surveillance.

Dermatological examination revealed a firm, purplish-red swelling encompassing the distal phalanx, accompanied by erosion of the nail folds, thickening of the nail plate, discoloration, and irregular nail morphology (Fig. 1A). Radiographs revealed marked osteolytic destruction and loss of structural integrity in the distal phalanx (Fig. 1B).

Histopathological evaluation of the lesion revealed neoplastic infiltration characterized by nests and sheets of tumor cells embedded in a desmoplastic stroma. The tumor cells had oval nuclei, a clear eosinophilic cytoplasm, and

prominent nucleoli. Focal areas displayed rhabdoid morphological features (Fig. 2A–C). Immunohistochemical staining revealed strong, diffuse positivity for pan-Cytokeratin (panCK), vimentin, and CD10 and negative staining for Cytokeratin-7 (CK7) and Cytokeratin-20 (CK20). Collectively, these findings confirmed the diagnosis of acrometastasis secondary to RCC. Unfortunately, the patient died of a myocardial infarction before the biopsy results were completed, highlighting the aggressive nature of the disease.

Renal cell carcinoma (RCC) is the most prevalent form of kidney cancer in adults. Skeletal metastases are observed in up to 30% of patients with advanced RCC, significantly compromising quality of life due to debilitating bone pain. Acrometastases, a rare variant of bone metastasis, are frequently associated with a poor prognosis. Acrometastases localized to the hands account for approximately 0.1% of all metastatic cases. Primary malignancies commonly implicated in the development of acrometastases include lung, kidney, breast, and colorectal cancers.^{2,3}

Typical presentations of acrometastasis include erythema, swelling, pain, limited range of motion, and involvement of the nails and adjacent structures. Lesions are most commonly localized to the distal phalanx of the dominant hand, particularly in the third digit.⁴ However, in the case presented here, the lesion was confined to the distal phalanx of the right thumb.

The pathogenesis of acrometastasis remains incompletely understood. Given that the majority of acrometastases are associated with lung cancer, it has been hypothesized that neoplastic cells disseminate primarily through hematogenous routes rather than via the lymphatic system.⁵ Several factors, including increased blood flow, repetitive trauma, bone marrow density, and local cytokine release, have been proposed as potential facilitators of tumor cell colonization at acral sites.^{6–8} Furthermore, enhanced heparanase activity in clear cell renal cell carcinoma (RCC) may promote metastasis by stimulating osteoclastic activity.^{9,10} The upregulation of Receptor Activator of Nuclear factor Kappa-B (RANK) and its Ligand (RANKL) in renal cell carcinomas has been implicated in both enhanced osteoclast-mediated bone resorption and the facilitation of metastatic progression. Notably, RANKL protein has been demonstrated to promote migratory capacity in clear cell renal cell carcinoma cell lines under in vitro conditions.^{11,12}

[☆] Study conducted at the Faculty of Medicine, Selcuk University, Konya, Turkey.

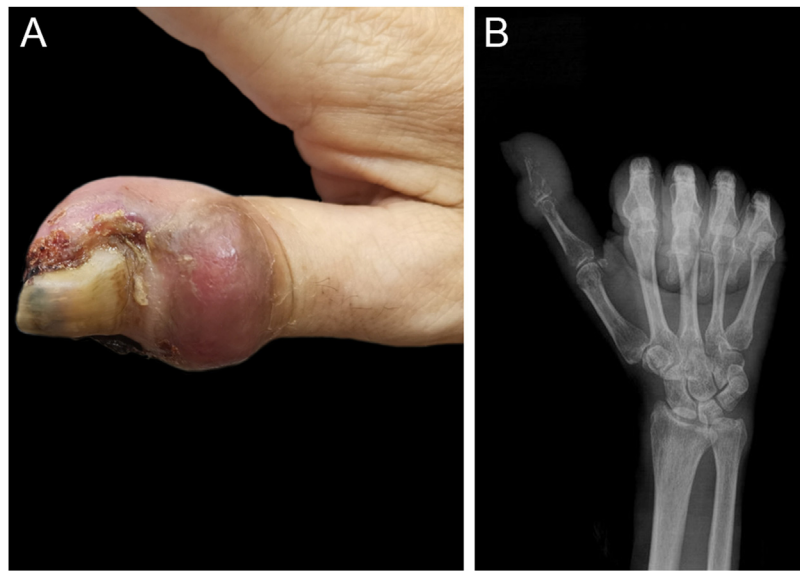


Fig. 1 (A) In the distal phalanx of the right thumb, there was a purplish-red swelling encircling the finger, accompanied by erosions of the nail folds, thickening of the nail plate, discoloration, and morphological irregularities. (B) Radiographic imaging revealed extensive bone destruction and a loss of the anatomical integrity of the distal phalanx.

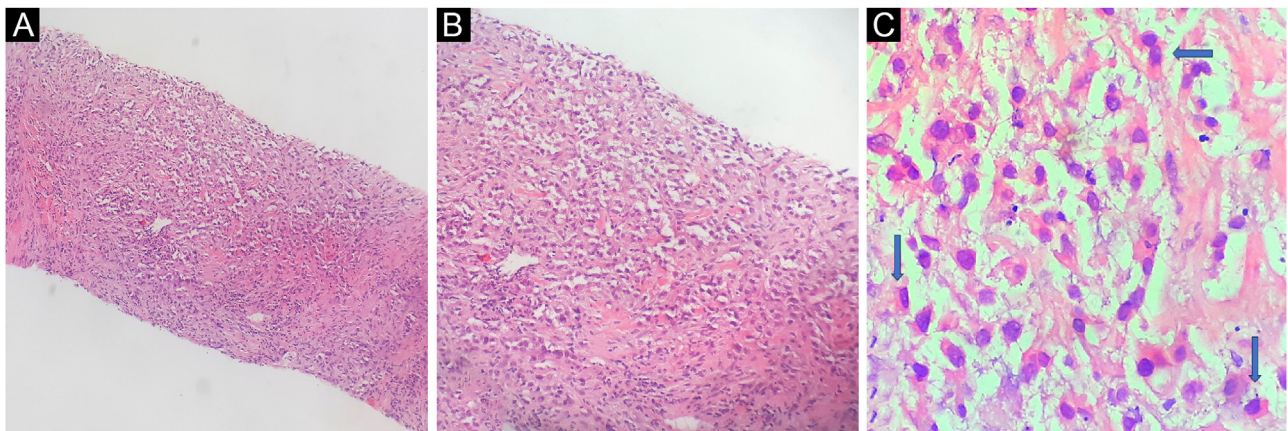


Fig. 2 (A) Tumor nests and layers within desmoplastic stroma (Hematoxylin & eosin, $\times 100$). (B) Tumor cells with oval-round nuclei and clear cytoplasm (Hematoxylin & eosin, $\times 200$). (C) Rhabdoid morphology seen in focal areas (blue arrows) (Hematoxylin & eosin, $\times 400$).

The differential diagnosis of acrometastasis should include chronic paronychia, arthritis, osteomyelitis, trauma, gout, and osseous Paget's disease. Limited follow-up and complex prediagnostic procedures may lead to delayed or incorrect diagnoses, adversely affecting treatment outcomes. Given the poor prognosis of acrometastasis, timely imaging and histopathological evaluation are essential. Histopathology remains key for definitive diagnosis; in our case, the biopsy revealed clear cell carcinoma with rhabdoid morphology, indicating a more aggressive course.¹³

Although acrometastases are uncommon, they should be considered in the differential diagnosis of painful and treatment-resistant digital lesions, especially in individuals with a known history of cancer. Histopathological and immunohistochemical analyses remain the gold standard for establishing a definitive diagnosis. Early identification can

assist in guiding therapeutic strategies; however, the overall prognosis generally remains poor.

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conduct of the studied case; critical review of the literature; final approval of the final version of the manuscript.

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Statement of ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

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LETTER - DERMATOPATHOLOGY

Areolar leiomyoma: clinical and histopathological aspects of two cases[☆]



Dear Editor,

Cutaneous leiomyomas are rare benign smooth muscle tumors. These tumors are most commonly reported in middle-aged women, with an approximate female-to-male sex ratio of 3:1.6. These lesions are differentiated based on the cell of origin and classified as pilar leiomyoma, angioleiomyoma, and dartoic or genital leiomyoma. The objective of this study is to report two cases of areolar leiomyomas and discuss their diagnostic aspects.

Case 1

A 50-year-old woman was sent by a dermatologist to a referral center with a request for a biopsy of a lesion in the left areola. The patient had no known comorbidities and denied associated symptoms such as pain, bleeding, or discharge. Physical examination revealed a rounded, nodular lesion measuring approximately 0.5 cm in diameter, with an irregular surface and brown color, located on the lateral-superior border of the left areola (Fig. 1). Dermoscopy revealed a whitish-yellowish central area and a discreet pigmented network in the periphery. The diagnostic hypothesis of an epidermal cyst or dermatofibroma was raised.

Case 2

A 68-year-old woman presented with a lesion in the left areola without associated symptoms. Physical examination revealed a nodular, hyperchromic lesion located at 10 o'clock in the left areola. The diagnostic hypothesis of epidermal cyst or scar fibrosis was raised.

Histologically, the lesions presented as a proliferation of smooth muscle cells forming intersecting bundles with sparse intervening connective tissue. The cells



Figure 1 Patient in Case 1. Normochromic papule in relation to the mammary areola tissue, measuring approximately 5 mm, with regular contours and well-defined, located on the lateral margin of the areola.

had elongated nuclei and tapered eosinophilic cytoplasm (Figs. 2 and 3). No cytological atypia or mitotic figures were observed. Immunohistochemistry was positive for desmin and smooth muscle actin in both cases (Figs. 4 and 5). It is important to differentiate this from cutaneous leiomyosarcoma, an entity that demonstrates hypercellularity, cellular atypia, and a high mitotic index. The diffuse expression of smooth muscle markers such as desmin and SMA also helps identify leiomyomas and distinguish them from other entities.

Cutaneous leiomyomas are rare benign smooth muscle tumors, with few cases reported since their first description by Virchow in 1854.^{1,2} They have a heterogeneous clinical presentation and are commonly overlooked as a diagnostic hypothesis.³ Cutaneous leiomyomas can be classified into three categories according to the muscle fibers of origin: pilar leiomyomas (originating from the muscle fibers of the arrector pili muscle and the most common subtype), angioleiomyoma (originating from the tunica media of blood vessels, the second most prevalent), and dartoic or genital leiomyoma (originating from the smooth muscles of the scrotum, nipple, areola, or vulva and the rarest presentation). Among genital leiomyomas, those located on the nipples and areolas are even rarer, with little literature available on them.^{4,5}

[☆] Study conducted at the Hospital do Servidor Público Estadual de São Paulo, São Paulo, SP, Brazil.

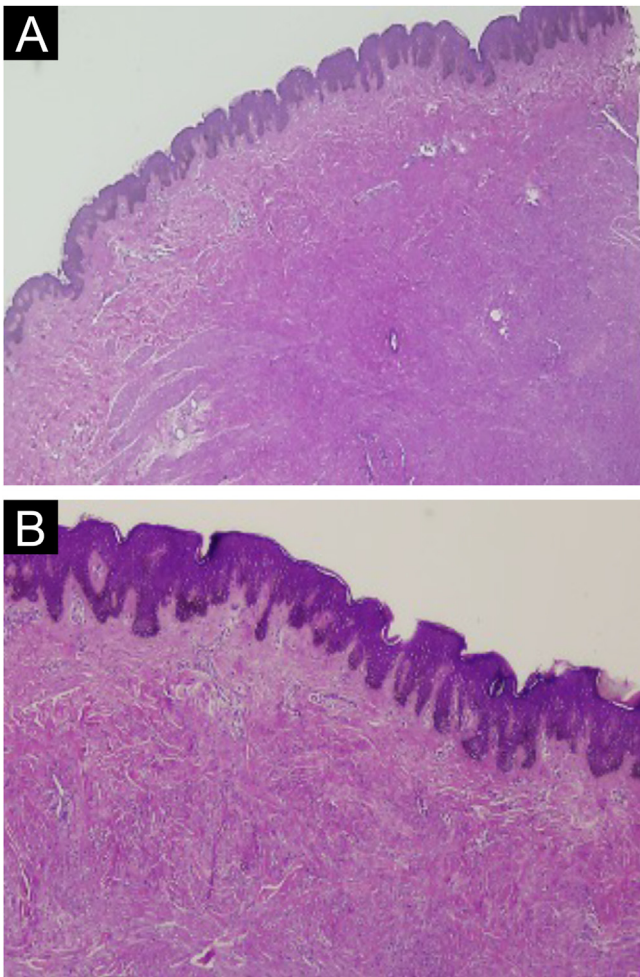


Figure 2 Case 1. (A) Circumscribed dermal proliferation of monotonous smooth muscle cells (Hematoxylin & eosin, $\times 20$). (B) Intertwined bundles of smooth muscle cells with scant intervening connective tissue (Hematoxylin & eosin, $\times 40$).

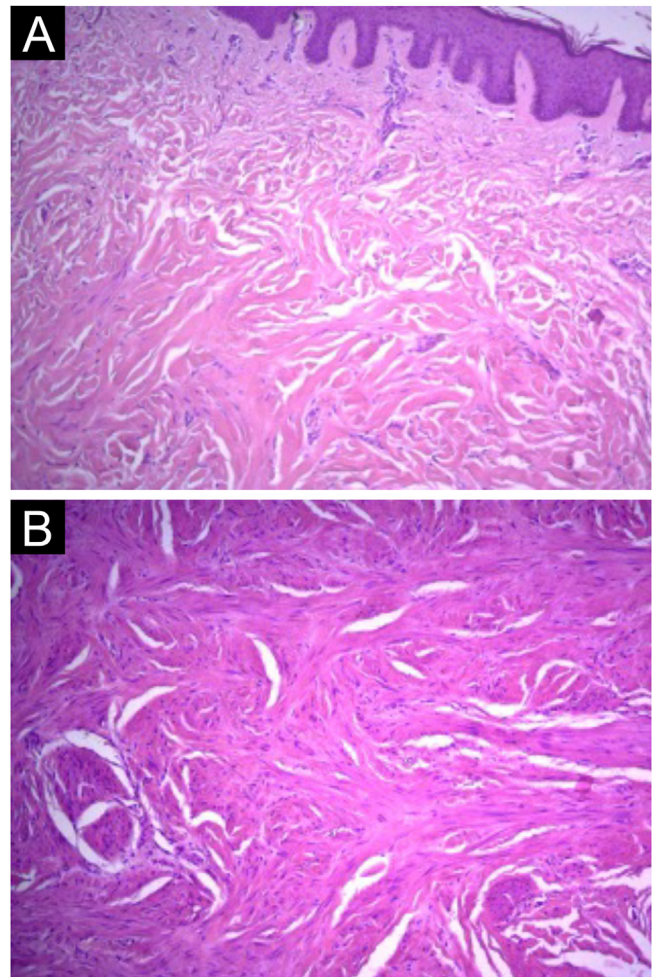


Figure 3 Case 2. (A) Proliferation of smooth muscle cells showing intersecting bundles (Hematoxylin & eosin, $\times 100$). (B) Cells with elongated nuclei, eosinophilic cytoplasm, without significant atypia or mitotic figures (Hematoxylin & eosin, $\times 100$).

Leiomyoma of the nipple is a very rare benign neoplasm, first described by Virchow in 1854.² According to Kaufman et al., the leiomyoma originates in the nipple and parenchyma from the smooth muscle cells surrounding the capillaries in the subcutaneous tissue of the breast.⁶ Diaz-Arias et al. suggested that the origin of these tumors may be (a) teratoid, originating from extensive overgrowth of myomatous elements, (b) embryonic displacement of the smooth muscle of the nipple, (c) angiomatous smooth muscle, (d) multipotent mesenchymal cells, and (e) myoepithelial cells.⁷ Its presentation is heterogeneous, depending on its histological type, and can open up a range of possible differential diagnoses, especially if it is a solitary lesion. Genital leiomyoma most characteristically presents as a single, painless, sporadically pedunculated, papular-nodular lesion, smaller than two centimeters, mainly in the scrotum, penis, and vulva. It can affect the nipple-areolar complex and rarely involves both breasts.^{3,8}

Clinically, cutaneous leiomyomas, especially pilar leiomyomas, generally present as firm papules or nodules, which may be multiple or single, flesh-colored or pink, and range in size from 0.2 mm to 2 cm. They may present with

increased sensitivity and even pain due to muscle contraction and compression of local nerve fibers. If multiple, they may be organized along Blaschko lines^{8,9} and should raise clinical suspicion of Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) syndrome, a rare autosomal dominant hereditary disease caused by a heterozygous germline mutation in the gene encoding Fumarate Hydratase (FH) and characterized by the risk of developing cutaneous pilar leiomyomas, uterine leiomyomas, and papillary renal cell carcinoma type 2.¹⁰

Surgical removal is considered a curative approach for cutaneous leiomyomas. Other forms of treatment include medication options aimed at symptomatic control, such as calcium channel blockers, or destructive methods such as cryotherapy or laser therapy.⁹

Cutaneous leiomyomas are considered rare benign smooth muscle tumors and are classified according to the muscle fibers of origin, with genital leiomyomas being the least common type. This report describes two cases in which their location in the mammary areola makes them even rarer.

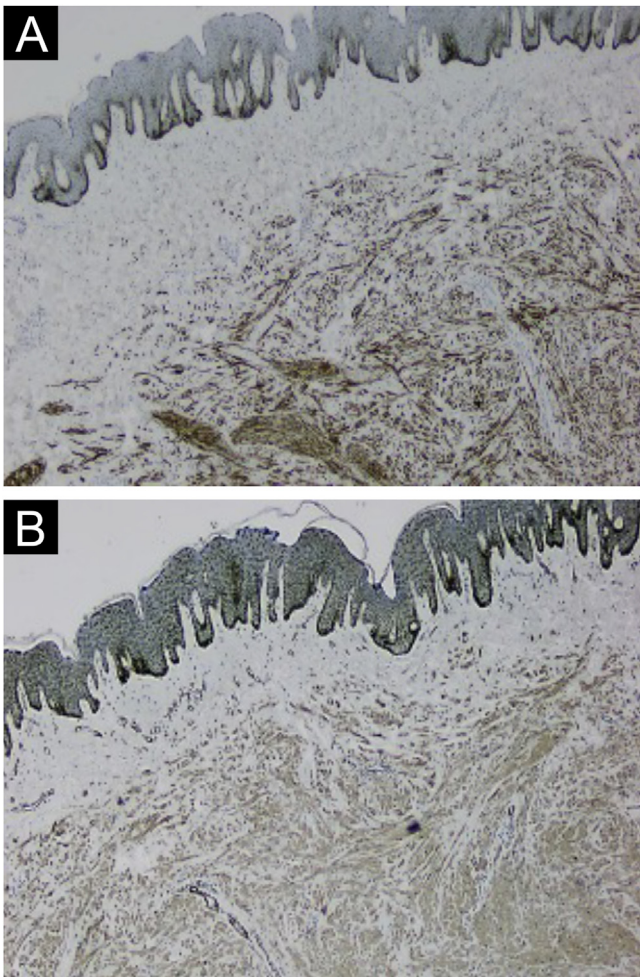


Figure 4 Case 1. (A) Immunohistochemistry with desmin antibody showing positivity in neoplastic cells ($\times 40$). (B) Immunohistochemistry with smooth muscle actin antibody showing positivity in neoplastic cells ($\times 40$).

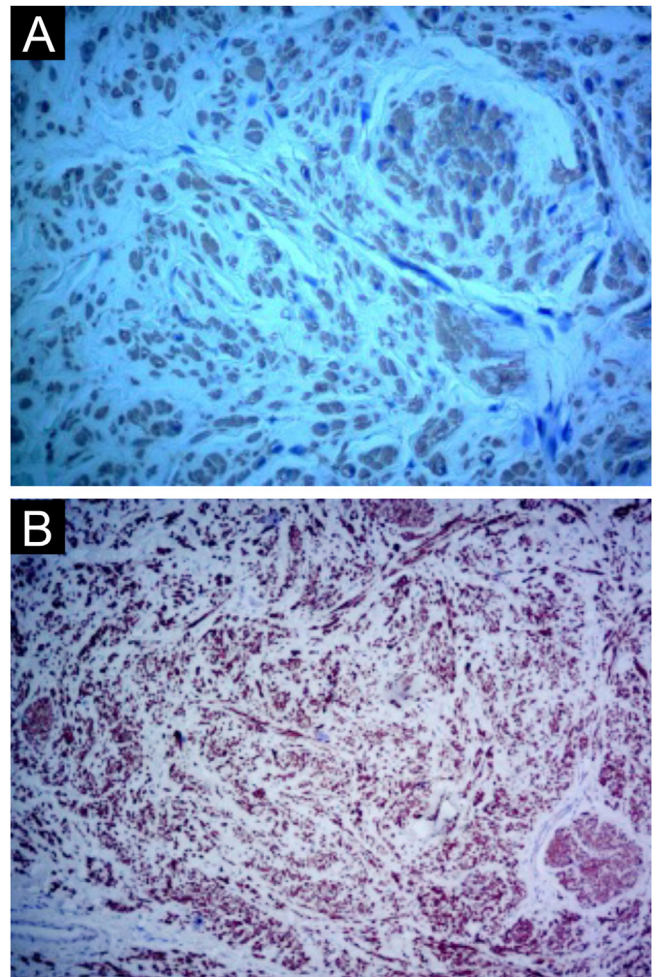


Figure 5 Case 2. (A) Immunohistochemistry with smooth muscle actin antibody, showing positivity in neoplastic cells ($\times 400$). (B) Immunohistochemistry with desmin antibody, showing positivity in neoplastic cells ($\times 400$).

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Research data availability

Not applicable.

Conflicts of interest

None declared.

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LETTER - TROPICAL/INFECTIOUS AND PARASITIC DERMATOLOGY

Cutaneous leishmaniasis due to *Leishmania (L.) mexicana*: first imported case reported in Portugal[☆]



Dear Editor,

Leishmaniasis is a parasitic disease caused by protozoa of the genus *Leishmania*, transmitted through the bite of infected phlebotomine sandflies.^{1–3} Leishmaniasis is endemic in tropical, subtropical, and Mediterranean regions, with its distribution spanning the Old World (Africa, Asia, the Middle East, the Mediterranean Basin) and the New World (Central and South America).³ Leishmaniasis has different clinical presentations, including visceral leishmaniasis (VL), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (ML).^{1,3,4} In Portugal, VL is endemic, with dogs serving as the primary reservoir and CL is considered a rare disease.^{5,6}

CL typically presents in exposed areas (e.g. face, neck, extremities) as painless solitary or multiple papulonodules that may progress to necrosis, ulceration, and scarring.^{1,4}

Leishmania (L.) mexicana is primarily found in Central America, Mexico, and Texas.⁴ This species is associated with small, chronic cutaneous ulcers, with a spontaneous healing rate exceeding 75% within three months.^{1,4}

We report the case of a 32-year-old man with an erythematous nodule on the chin, showing central ulceration covered by yellowish exudate and crusts, with a documented progression over three months (Fig. 1). Six months prior, he had travelled to Mexico (Bacalar jungle) and had been previously treated with antibiotics, without improvement. Initial wound cultures isolated *Klebsiella aerogenes*, prompting treatment with targeted ciprofloxacin for three weeks, with partial improvement. Histopathological examination revealed dermal macrophages containing numerous intracellular *Leishmania* amastigotes (Figs. 2 and 3), further corroborated by a positive skin culture. *L. mexicana* was identified by molecular techniques using Internal Transcribed Spacer 1 - Polymerase Chain Reaction - Restriction



Figure 1 Physical examination revealing a 3 × 3 cm erythematous nodule on the chin, with central ulceration covered by yellowish exudate and crusts.

Fragment Length Polymorphism (ITS1-PCR-RFLP) and Heat Shock Protein 70 (HSP70) sequencing.⁷ The patient was treated with itraconazole (200 mg every 12 hours) for three months, with complete resolution (Fig. 4). To the best of our knowledge, this is the first identification of CL caused by *L. mexicana* in Portugal, representing an imported infection. Imported cases of CL caused by *L. mexicana* complex species have been reported in Europe, though they remain rare.⁸

CL should be suspected in patients with cutaneous non-healing lesions and a history of exposure to endemic areas.^{1,2,4} Differential diagnoses include other infectious conditions (e.g., ecthyma, atypical mycobacterial infections, deep fungal infections), pyoderma gangrenosum, and neoplasms.^{1,4} Accurate diagnosis requires a high index of suspicion and the integration of clinical, histopathological, and molecular findings. Our case highlights the importance of Dermatologists remaining vigilant for imported cases of CL.⁹ The growing number of imported diseases in Europe, such as CL, reflects the impact of globalization, driven by increased international travel and migration. While the likelihood of exotic *Leishmania* species establishing in non-endemic areas is relatively low, due to the absence of their primary reservoir hosts, the potential for local sand fly species to act as competent vectors cannot be disregarded. This raises the possibility that non-native *Leishmania* species could adapt and spread, leading to notable public health concerns.¹⁰

[☆] Study conducted at the Dermatovenereology Service, of Hospital de Egas Moniz of Unidade Local de Saúde de Lisboa Ocidental in Lisbon, Portugal.

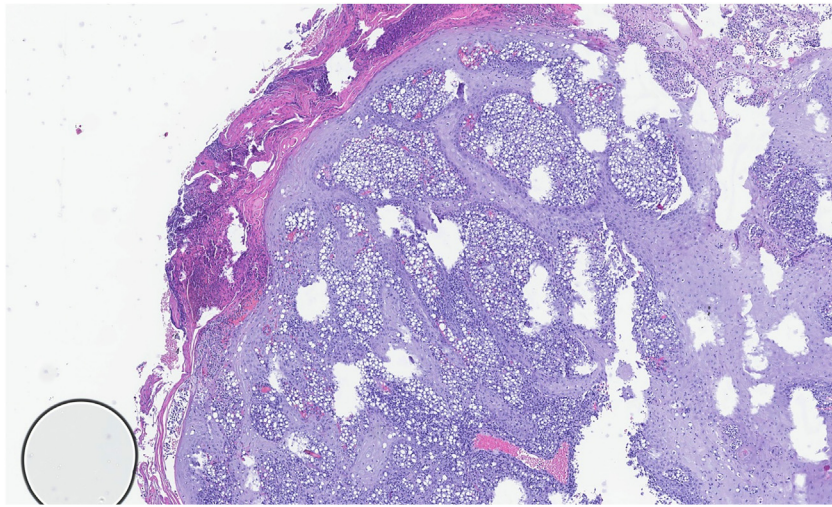


Figure 2 Histopathological examination showing a cutaneous nodule with epidermal hyperplasia and a dense dermal infiltrate extending into the deep dermis and subcutaneous tissue, with areas of granulomatous inflammation (Hematoxylin & eosin, $\times 10$).

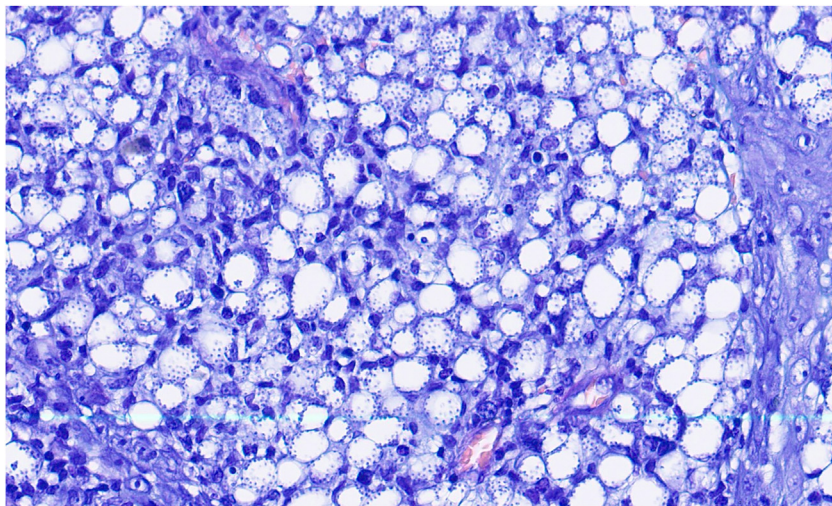


Figure 3 Histopathological examination showing dermal macrophages containing numerous intracellular amastigotes (Giemsa, $\times 1000$).

In cases of complex lesions (e.g. facial lesions), systemic treatment is warranted. First-line systemic therapies include meglumine antimoniate or liposomal amphotericin B.^{1,9} Recent guidelines support oral miltefosine as a convenient, effective alternative. Imidazoles may also be considered for their convenience and security, though prolonged courses and high doses may lead to adverse effects (e.g. hepatotoxicity).⁹ Treatment outcomes are monitored based on clinical resolution, including re-epithelialization, regression of infiltration and erythema, and lesion flattening, with follow-up recommended for up to 12 months post-treatment.¹

Bacterial superinfection, as observed in this case, is an important complication of CL. The presence of *Klebsiella aerogenes* likely contributed to the lesion's size, and exudation, and a delayed diagnosis. While this organism is rarely a

colonizer, its pathogenic role was further supported by the lesion's initial improvement with targeted antibiotic therapy.

This report documents the first identified case of *L. mexicana* in Portugal, representing an imported infection from Mexico. It emphasizes the need for awareness of CL as a differential diagnosis for cutaneous ulcers, particularly in patients with travel histories to endemic regions. Prompt diagnosis and timely treatment are essential to prevent complications. This case further highlights the importance in recognizing the role of bacterial superinfection and highlights itraconazole as an effective treatment option. Continued surveillance and awareness are essential to manage the growing incidence of imported diseases in dermatological practice.



Figure 4 Physical examination reveals only post-inflammatory hyperpigmentation.

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Research data availability

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LETTER - THERAPY

Effectiveness and safety of tralokinumab in a patient with severe atopic dermatitis and hepatitis B virus[☆]

Dear Editor,

Atopic dermatitis (AD) is a chronic, inflammatory, and pruritic dermatological condition affecting millions of individuals worldwide.¹ The treatment landscape for moderate-to-severe AD has significantly evolved in recent years with the advent of new biologic therapies, including tralokinumab. Tralokinumab is a monoclonal IgG4 antibody approved for the treatment of moderate-to-severe AD in adults and adolescents. It specifically binds to Interleukin-13 (IL-13), inhibiting its interaction with its receptors.^{2–4} Despite its efficacy, the emerging nature of these immunomodulatory therapies raises questions about their safety and effectiveness in populations with chronic infections, such as Hepatitis B Virus (HBV), as these patients are often excluded from clinical trials because of the risk of reactivation. While isolated case reports suggest that dupilumab may be safe in patients with chronic HBV, there are no specific data regarding tralokinumab.⁵ Here, we present the first documented case of a patient with moderate-to-severe AD and chronic HBV infection treated with tralokinumab.

A 77-year-old woman with a 30-year history of untreated chronic HBV infection presented to our dermatology department with intensely pruritic erythematous lesions over the past 3-years. The patient, originally from the Philippines, had a history of allergic rhinitis and flexural eczema during childhood. Since then, her eczema had remained reasonably well controlled, with occasional flares of pruritic lesions that she managed with topical corticosteroids prescribed by her general practitioner. Based on the diagnostic criteria of Hanifin and Rajka,⁶ she was diagnosed with AD. She had previously received up to 48 sessions of narrow-band UVB phototherapy (cumulative dose: 43.567 mJ/cm²)

and short-term courses of high-dose corticosteroids during disease flares, with partial response.

On physical examination, erythematous-brown plaques with a scaly surface were observed predominantly on the flanks and lateral aspects of the upper and lower extremities (Fig. 1A). The eczema area and severity index (EASI) was 31, and the body surface area affected was 21%. A skin biopsy was performed, revealing irregular acanthosis with spongiosis and occasional eosinophils. Direct immunofluorescence (DIF) of healthy skin was negative.

Initial laboratory evaluation revealed evidence of minimally replicative chronic HBV infection, with positive HBsAg, anti-HBc, and anti-HBe antibodies, but negative HBeAg and anti-HBs. The viral load was 1112 IU/mL. Serum lactate dehydrogenase (LDH) was elevated at 377 IU/L (reference range [RR] 135–214 IU/L), and total IgE was >5000 KU/L (RR 0–100), while other laboratory parameters, including liver enzymes, and anti-BP180, anti-BP230, anti-DG1, and anti-DG3 antibodies, were either negative or within normal limits. Peripheral blood immunophenotyping showed no abnormal cell populations. Tests for other hepatotropic viruses were negative, and abdominal ultrasonography ruled out hepatic lesions.

Given the lack of response to initial therapeutic approaches and the clinical progression of the disease, treatment intensification was deemed necessary. After consulting with the hepatology team, entecavir 0.5 mg/day was started to manage viral replication, and the use of immunosuppressive treatments such as cyclosporine was discouraged. Subsequently, tralokinumab therapy was started at a dose of 300 mg every two weeks.

Over the following months, the patient experienced significant clinical improvement, with a marked reduction in pruritus and lesions, leading to an EASI score of 3 by the sixth month of treatment (Fig. 1B). The therapy was well tolerated, with no adverse effects reported. Liver function remained stable, and HBV viral load decreased to <10 IU/mL during this period.

This is the first documented case of tralokinumab's safety in a patient with active chronic HBV infection and moderate-to-severe AD. Previous reports have focused on dupilumab in similar contexts. Karen Ly and Mary Patricia Smith described two patients with AD and chronic HBV infection treated with concomitant dupilumab and entecavir.⁷ In one case, HBV viral load was already undetectable at



[☆] Study conducted at the Department of Dermatology, Hospital Universitario de La Princesa, Madrid, Spain.

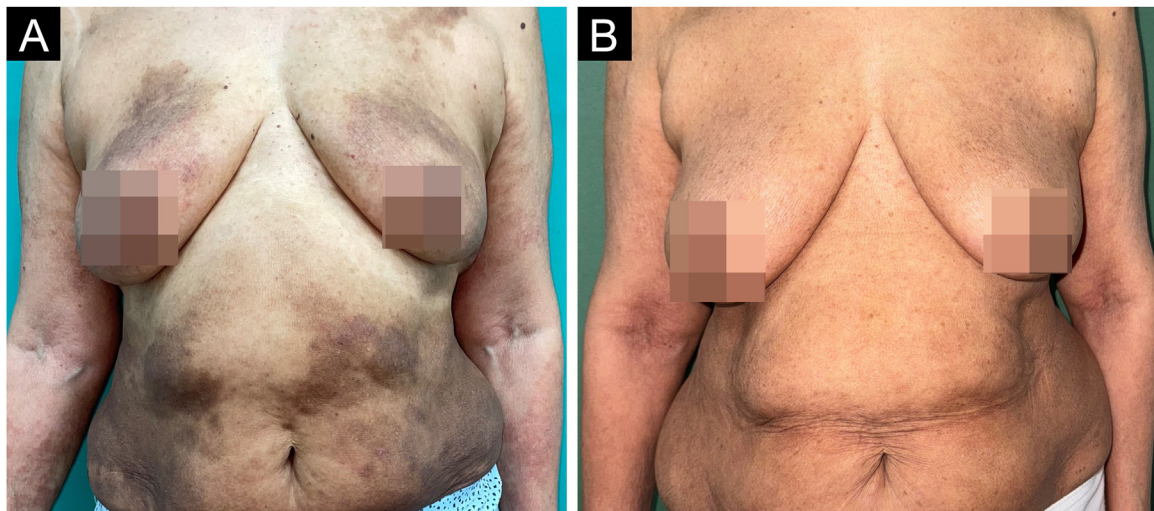


Fig. 1 (A) Baseline clinical presentation prior to initiating tralokinumab. Erythematous-brown plaques in a phototype IV patient, symmetrically distributed primarily over the flanks, chest, and anterior thighs. (B) Clinical presentation after six months of tralokinumab. Attenuation of the lesions with blurring of the well-defined borders.

the start of dupilumab treatment, while in the other, the viral load decreased from 19,120 IU/mL to undetectable before starting therapy. Matsutani and Imai conducted an observational study involving five patients with positive anti-HBc antibodies and no prior HBV vaccination who received dupilumab. Among these, only one patient exhibited transiently detectable HBV DNA at week-76 ($<1.30 \log \text{ IU/mL}$), which resolved spontaneously.⁸ However, all patients were HBsAg-negative at the initiation of treatment, and none had active or acute HBV infections.

Our case provides unique insights, as it involves a patient with untreated, active chronic HBV infection. The combination of entecavir and tralokinumab demonstrated safety, with no evidence of HBV exacerbation during treatment.

This case highlights the potential safety of tralokinumab in patients with active chronic HBV infection and AD. Although further studies are needed to validate these findings, this report underscores the importance of individualized approaches when managing patients with concurrent chronic infections and inflammatory skin diseases.

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Mario Aparicio-Domínguez: Review; validation.

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LETTER - THERAPY

Linear psoriasis unresponsive to multiple biological therapies (anti-TNF, anti-IL-12/23, and anti-IL-23): a case report[☆]



Dear Editor,

Linear psoriasis (LP) is an exceptionally rare subtype of psoriasis that follows Blaschko's lines. Based on its coexistence with non-segmental plaques of psoriasis vulgaris (PV), LP is classified as either the superimposed type (when it coexists with PV) or the isolated type (when it is the sole manifestation).¹

We present the case of a 20-year-old Caucasian woman diagnosed with extensive psoriasis vulgaris at the age of 11, affecting all body areas. Initial treatments included topical methylprednisolone and narrowband UVB phototherapy with minimal improvement. At the age of 16, she started ustekinumab (Fig. 1), achieving near-complete remission, except for a persistent linear plaque on the posterior leg. The linear lesion showed a marked response to daily application of a fixed-dose combination of calcipotriol (50 µg/g) and betamethasone dipropionate (0.5 mg/g) for four weeks, resulting in near-complete resolution. However, when the regimen was changed to a maintenance schedule of twice-weekly application, the lesion recurred, although with reduced extent and severity.

The treatment was discontinued for one year as the patient moved to another country and became pregnant. Upon her return, treatment with certolizumab was initiated, resulting in general clearance with persistence of the linear plaque. Postpartum exacerbation led to a switch to risankizumab, which cleared all lesions except the linear posterior leg plaque (Fig. 2). The clinical progression and characteristics of her lesions led to a diagnosis of linear psoriasis, unmasked by biological treatments.

Few cases of linear psoriasis have been reported in the literature, with superimposed LP type being more common than isolated LP type. The primary differential diagnosis for the isolated type is inflammatory linear verrucous epidermal



Fig. 1 Patient with extensive plaque psoriasis prior to the initiation of biologic therapy with ustekinumab.

nervus (ILVEN), which typically presents earlier with highly pruritic lesions that are refractory to treatment, unlike the generally asymptomatic lesions of LP.^{2,3} Differentiating these conditions can be challenging due to their clinical and histological similarities. The presence of psoriasis in other regions can be pivotal in diagnosing LP.³ In cases of diagnostic uncertainty, a skin biopsy is recommended to distinguish linear psoriasis from ILVEN. Histopathologically, ILVEN is cha-

[☆] Study conducted at the Sagrat Cor University Hospital, Quirónsalud Hospital Group, Barcelona, Spain.

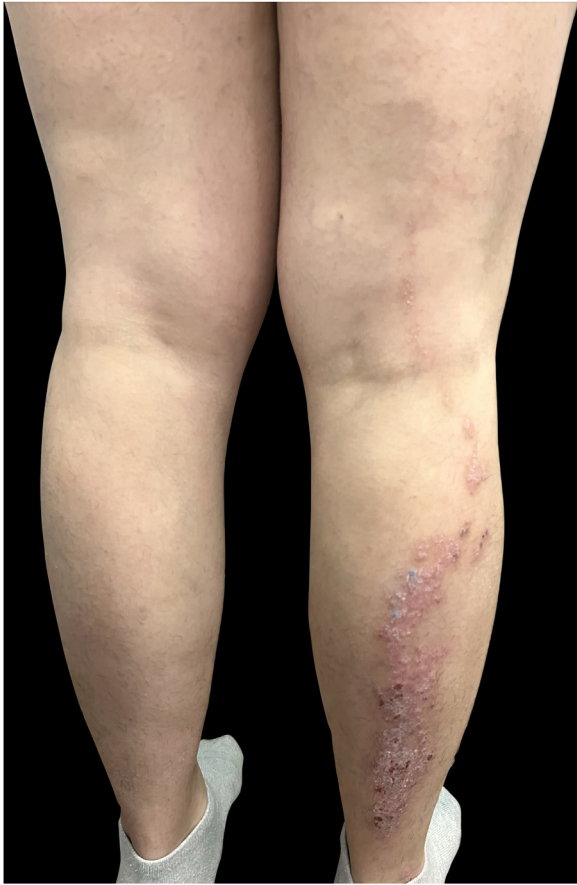


Fig. 2 Patient receiving treatment with risankizumab, demonstrating persistence of a linear plaque following Blaschko's lines.

racterized by an alternating pattern of orthokeratosis and parakeratosis, often associated with granular layer changes, papillomatosis, and a chronic lymphomonocytic infiltrate. In contrast, linear psoriasis typically shows uniform psoriasiform hyperplasia, neutrophilic aggregates, and Munro microabscesses. Immunohistochemical markers can further aid in the distinction: ILVEN usually demonstrates low Ki-67 expression, normal keratin 10 levels, and absence of involucrin, whereas linear psoriasis is associated with high Ki-67 expression, reduced keratin 10, and presence of involucrin.⁴

With approximately 50 reported cases, the pathogenesis of LP remains poorly understood. However, genetic mosaicism – specifically, postzygotic mutations occurring during embryogenesis leading to loss of heterozygosity (LOH) – is suspected to play a key role. LOH may also account for the severity and chronicity of linear psoriatic lesions, as well as their resistance to antipsoriatic treatments.^{3–5} Postzygotic genetic alterations result in clones of keratinocytes predisposed to develop psoriatic lesions distributed along Blaschko's lines. It is specifically proposed that somatic recombination is an underlying mechanism, potentially explaining the segmental distribution and treatment resistance often observed in these lesions.⁶

This case underscores the distinctive clinical challenge posed by LP, particularly when superimposed on PV. To date,

only ten cases of LP treated with biological therapies have been documented, all of which involved LP superimposed on PV and were managed with anti-TNF agents or ustekinumab. Notably, LP exhibited refractoriness to anti-TNF therapy, whereas two of the three reported cases responded to Ustekinumab.⁴ To our knowledge, there is no available literature regarding the efficacy of alternative targeted therapies, such as anti-IL-23 or anti-IL-17 agents, in the management of LP.

We present the first reported case of superimposed LP demonstrating resistance to three distinct biological targets: anti-TNF, anti-IL-12/23, and anti-IL-23. The persistence of linear plaques despite advanced biological therapies suggests an intrinsic resistance, potentially associated with genetic mosaicism and loss of heterozygosity (LOH).

Resistance to ustekinumab – the most effective therapy reported to date – may suggest a potential cross-resistance to IL-23 inhibition. Nevertheless, based on our case and the existing literature, we believe that biological therapy may not be the most suitable treatment for this type of lesion. Further research is needed to elucidate the molecular mechanisms of LP and develop more effective treatments.

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LETTER – THERAPY

Low-level laser therapy for the treatment of oral manifestations in a patient with toxic epidermal necrolysis: a case report[☆]

Dear Editor,

Toxic epidermal necrolysis (TEN) is an acute, potentially life-threatening mucocutaneous condition characterized by epidermal necrosis and detachment in response to primarily pharmacological triggers.^{1–3}

Although more than 90% of patients with TEN present with oral mucosa involvement, evidence-based treatment protocols for these manifestations are still lacking, given the low incidence of this disease.¹

We report the case of an adult patient with TEN, in which we used low-level laser therapy (LLLT) for his refractory-to-treatment oral manifestations.

A 38-year-old man with a history of bariatric surgery and depression, receiving chronic treatment with aripiprazole, escitalopram, esomeprazole and multivitamins; and starting modafinil, trazodone and acetazolamide within the past month, was referred to our department with a 5-day history of asthenia, unmeasured fever, conjunctivitis, anorexia and dysphagia. Generalized skin lesions subsequently appeared.

Upon admission, he was febrile (39°C), tachycardic (110 bpm), and tachypneic, requiring orotracheal intubation for mechanical ventilation.

Physical examination revealed a generalized vesiculobulbous rash involving more than 60% of the body surface area, along with skin denudation on the back and genitals, and hemorrhagic cheilitis. Nikolsky's sign was positive.

A skin biopsy was performed, and histopathology revealed total epidermal necrosis, with a mild superficial perivascular lymphocyte infiltrate and negative direct immunofluorescence.

Additional laboratory tests ruled out infectious and autoimmune diseases.



TEN (SCORTEN scale: 3-points) was diagnosed, and multidisciplinary management was established, including withdrawal of non-essential drugs and cutaneous-systemic support measures. Causality assessment tools did not allow us to determine the culprit drug, given the patient's polypharmacy and similar treatment initiation period.

Pulse methylprednisolone (500 mg/day for 3-days, with subsequent tapering) and intravenous immunoglobulin (2 g/kg over 3-days) were initiated. Serial skin and blood cultures were also performed, with early initiation of antibiotic therapy planned in case of superinfection.

Due to persistent clinical activity, a single dose of Etanercept 50 mg subcutaneously was prescribed on the fifth day of hospitalization.

The patient subsequently presented a favorable clinical cutaneous response, but with persistent hemorrhagic cheilitis and oral ulcers (Fig. 1). Therefore, on the eleventh day of hospitalization, PCR tests for Herpes Simplex Virus I/II and *Mycoplasma pneumoniae* on the oral mucosa were repeated, which were negative, and it was decided to initiate LLLT.

Using the *Laser Duo* device (InGaAlP, MMOptics), daily LLLT sessions were performed, with wavelengths of 660 nm and 808 nm, and a fluence of 6 J/cm² per application point, including lips, jugal mucosa, hard palate, and tongue (Fig. 2).

A total of 6 sessions were completed, which were subsequently discontinued due to the favorable clinical response (Fig. 3A–C), assessed as pain reduction and resolution of the hemorrhagic cheilitis.

The patient was finally discharged on his 26th day of hospitalization, with no complications resulting from LLLT up to the current 6-month follow-up.

LLLT is a noninvasive light therapy that does not involve thermal or ablative phenomena and, as its name suggests, consists of the administration of low-density energy.⁴

Its mechanism of action is based on photobiomodulation, a process in which the interaction of photons with mitochondrial cytochromes and porphyrins produces a temporary release of nitric oxide, stimulating the synthesis of adenosine triphosphate and promoting the formation of reactive oxygen species, resulting in cell activation.^{4,5} Successively, various intracellular pathways that modulate the synthesis of proteins and nucleic acids are triggered; the levels of cytokines and inflammatory mediators are regulated; and cell differentiation and proliferation are promoted.^{5,6}

[☆] Study conducted at the Clínica Universidad de los Andes, Las Condes, Santiago, Chile.



Figure 1 Hemorrhagic cheilitis and tongue ulcers, prior to the initiation of low-level laser therapy.

Several studies have linked LLLT with analgesic, anti-inflammatory, and restorative properties,^{4,5} which have promoted its use in various conditions, including those with mucosal involvement, such as oral lichen planus, mucous membrane pemphigoid, recurrent aphthous stomatitis, and mucositis secondary to chemotherapy, among others.^{5,7-9}

To our knowledge, there are only 3 previous reports of its use in cases of serious adverse drug reactions, including TEN (all in pediatric patients), with favorable clinical outcomes, as in the case of our patient.¹⁻³

As a limitation of the case presented, it is not possible to rule out a potential late benefit of systemic therapies



Figure 2 Application of low-level laser therapy. With the *Duo Laser* device (InGaAlP, MMOptics), daily sessions were carried out, with wavelengths of 660 nm and 808 nm, and a fluence of 6 J/cm² per application point, including lips, jugal mucosa, hard palate and tongue.

in our patient's oral manifestations, which may have been complementary or overlapping with the action of LLLT. Furthermore, guidelines on the optimal parameters for the use of LLLT are still lacking.



Figure 3 (A–C) Clinical response of the oral mucosa. (A) 48 hours from the start of Low-Level Laser Therapy (LLLT). (B) 72 hours from the start of LLLT. (C) 1-week after hospital discharge (23-days from the first LLLT session).

In conclusion, LLLT may represent a valid therapy for refractory oral manifestations in patients with adverse drug reactions like TEN, given its analgesic, anti-inflammatory, and restorative properties. Nonetheless, randomized trials to support these findings are warranted.

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Research data availability

Does not apply.

Conflicts of interest

None declared.

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LETTER - THERAPY

Upadacitinib treatment of refractory livedoid vasculopathy: a case report and literature review[☆]



Dear Editor,

Livedoid vasculopathy (LV) is a rare, chronic, recurrent vascular disease that manifests as erythema, purpuric macules, painful ulcers, livedo reticularis, atrophic porcelain-white scars of the lower extremities, typically in ankles and feet. Although the pathophysiological process is not yet fully elucidated, thrombosis of the dermal vessels appears to be a key event.¹ The conventional therapies consist of anticoagulants, antiplatelets, corticosteroids, immunosuppressive agents, thrombolytics,² etc. However, patients commonly encounter disease relapse. Upadacitinib, a relatively new JAK1 inhibitor, has never been reported to be used in treating LV in the retrieved literature. Herein, we report a case of refractory LV resistant to conventional therapy which exhibited great efficacy following treatment with Upadacitinib.

A 30-year-old female presented with over 5-year history of painful, ulcerative lesions of the feet and ankles. Physical examination showed multiple purpura maculae, painful ulcerations with small, dilated blood vessels, as well as sporadic porcelain-white scars (Fig. 1). Laboratory investigations were found with positive anti-cardiolipin antibody, and helped us rule out other LV-associated systemic disorders. A skin biopsy revealed ulceration formation, vascular dilation, swollen vessel walls with fibrinoid necrosis, erythrocyte exosmosis, as well as infiltration of perivascular lymphocytes and neutrophils (Fig. 2). The examination findings and clinical manifestations were strongly consistent with the diagnosis of LV. Although the patient was previously prescribed rivaroxaban, aspirin, mycophenolate mophenolate, and oral corticosteroids (prednisone 30 mg once daily), she was still confronted with disease relapse. We initiated Upadacitinib at a daily dose of 15 mg orally, along with topical ointment, hirudoid (mucopolysaccharide polysulfate cream). The patient manifested significant improvement in erythema and pain within 10-days, and achieved nearly complete resolution of ulceration and remained only post-inflammatory hyperpigmentation within 6-weeks (Fig. 3). No

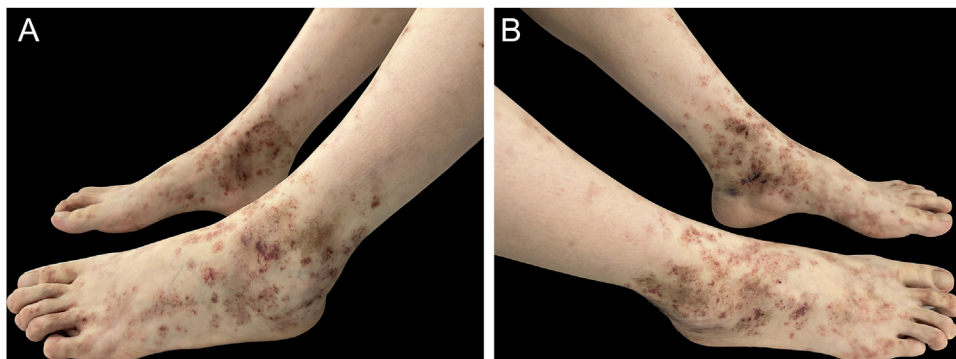


Fig. 1 Physical examination showed multiple purpura macula, painful ulcerations with small dilated blood vessels as well as sporadic porcelain-white scars.

[☆] Study conducted at the Department of Dermatology, Zhongshan Second People's Hospital, Zhongshan City, Guangdong Province, China.

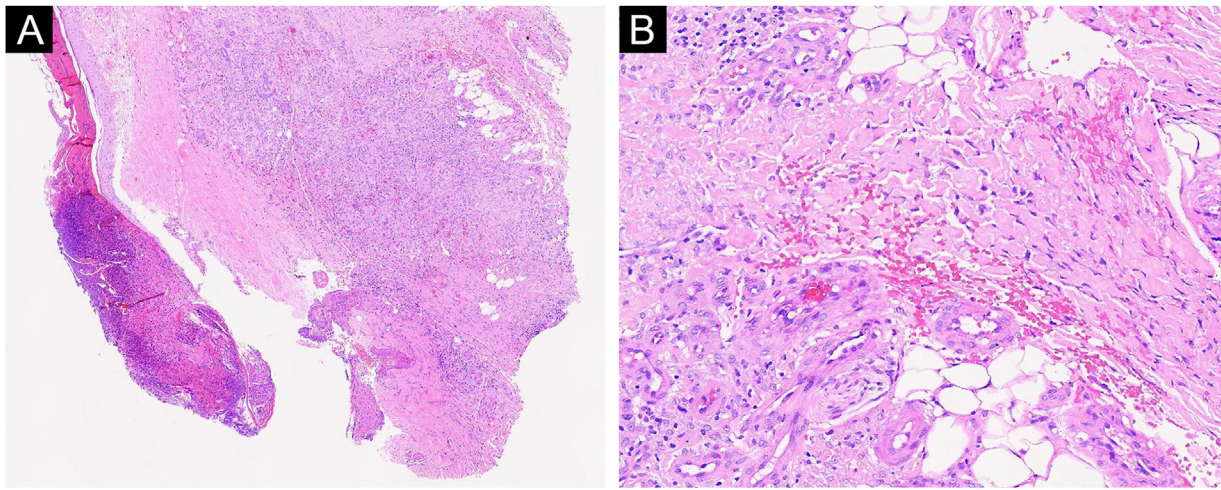


Fig. 2 Pathological and immunohistochemical specimens. (A) Low-power view showed ulceration formation, increased vascular proliferation and dilation (Hematoxylin & eosin, $\times 50$). (B) The infiltration of perivascular lymphocytes and swollen vessel walls with fibrinoid necrosis, erythrocyte exsmosis (original magnification: $\times 400$).

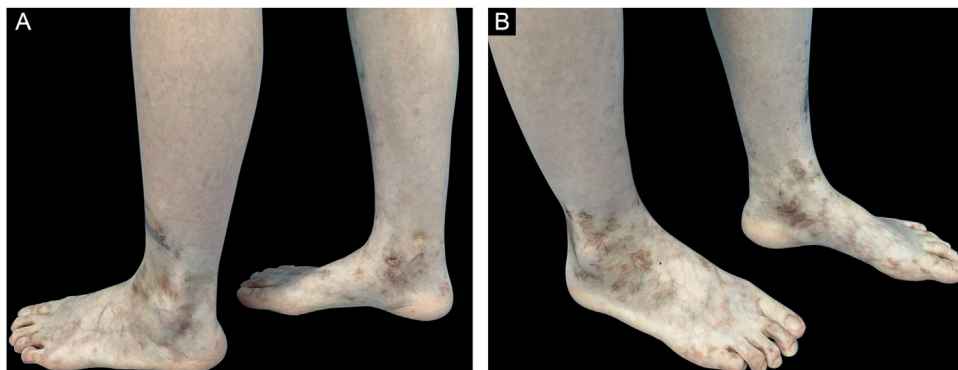


Fig. 3 After 6-weeks of treatment with Upadacitinib, the patient manifested significant improvement in erythema and pain, achieved nearly complete resolution of ulceration and remained only hyperpigmentation.

adverse events were observed during the 20-week follow-up. For clinical assessment, the expected time for Upadacitinib maintenance is 6-months, so as to reduce the recurrence of the patient.

The Janus Kinase (JAK) and Signal Transduction Transcription Activator (STAT) signal transduction pathways interplay with a wide range of immunocytes and over 50 cytokines. It was reported JAK-STAT pathways have enhanced activity in vascular endothelial cells;³ moreover, JAK signaling could significantly affect inflammation, coagulation, and thrombosis formation.⁴ The overactivation of JAK/STAT pathways induces immune imbalance and vascular damage.

LV is a thrombo-occlusive vascular disorder, which on histopathology manifests as hyaline thrombosis, fibrin deposits in vessel walls, along with perivascular focal lymphocyte infiltration. As described previously, it is still difficult to treat and prone to relapse. Existing experience suggests that steroids were suggested to be effective even as a monotherapy, and the traditional anti-inflammatory drugs could successfully improve the clinical outcomes. Concurrently, employing colchicine and prednisolone as monotherapy could exhibit higher efficacy than using pentoxifylline and aspirin alone in LV patients, indicating an

indispensable role of inflammation in LV pathogenesis.⁵ Given its pathophysiology, JAK inhibitors should theoretically play an important role in preventing the flares and recurrence of LV.

Previous small-scale retrospective studies and case reports have shown considerable efficacy when utilizing JAK inhibitors in LV treatment,^{5,6} as summarized in Table 1. Han et al. observed 8 patients who received 2 mg/day of baricitinib for treating refractory LV, and found that all enrolled patients experienced a significant regression with a mean remission time of 7.75-weeks. Similarly, in the case series of Song et al., 3 patients with LV were prescribed 2 mg/day of baricitinib. One patient obtained darkening and reduced erythema by month-6, and the other two obtained complete ulcer healing, respectively, by month-1 and month-2. Regarding other JAK inhibitors, Chen et al. reported the rapid improvement in a 31-year-old female developing LV after using abrocitinib 100mg once daily. In addition, Jia et al. administered tofacitinib 5mg twice per day on a 17-year-old male with refractory LV, the ulcers were completely healed within a month with no recurrence during the 56-week follow-up. The aforementioned clinical prac-

Table 1 Overview of JAK inhibitors as a novel treatment for livedoid vasculopathy.

Study	No.	Sex	Age	Duration of Disease	Previous Treatment	Treatment	Outcome	Adverse event	Follow-up time
Han et al.	8	5F/3M	8~36	7~120 months	Diverse therapies (Aspirin, corticosteroid; thalidomide; tripterygium glycosides; rivaroxaban; enoxaparin; compound glycyrrhizin; Chinese traditional anti-inflammatory drugs)	Baricitinib 2 mg/day	All experienced significant regression; remission times ranging from 3- to 13-weeks, with a mean remission time of 7.75 ± 3.45 weeks	None	11–28 weeks
Chen et al.	1	1F	31	2-years	NR	Abrocitinib 100 mg/day	Complete remission was achieved after 6-weeks, with only post-inflammatory hyperpigmentation remaining	None	12-weeks
Song et al.	3	1F/2M	8–26	6~72 months	Diverse therapies (Prednisone, rivaroxaban, thalidomide, aspirin)	Baricitinib 2 mg/day	Patient 1: reduced erythema by month-6; Patient 2/3: Complete healing of ulcer by month 1/2	None	
Jia et al.	1	1M	17	3-years	Colchicine, thalidomide, dipyridamole, rivaroxaban and aspirin	Tofacitinib 5 mg twice daily	Complete healing of ulcer by month-1	None	56-weeks

JAK, Janus Kinase; M, Male; F, Female; NR, Not Report.

tice suggests that JAK inhibitors are promising therapeutic options to treat LV. Upadacitinib is an oral, small-molecule JAK1 inhibitor that has been approved for multiple inflammatory diseases in dermatology. There are no reports to date for its application on LV. In our case, using 15 mg/day of Upadacitinib, the patient achieved great improvement within 10-days and the ulceration completely healed within 6-weeks.

To our knowledge, this is the first report in which Upadacitinib was utilized to treat LV. Further studies should be conducted to confirm its efficacy and long-term safety.

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