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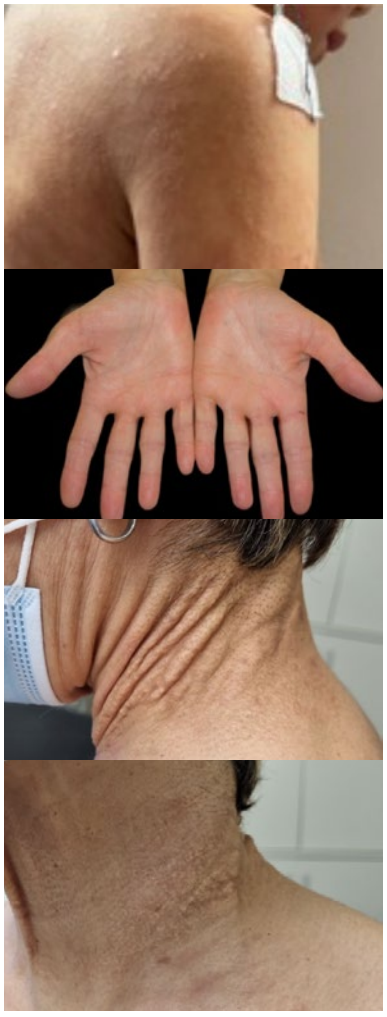

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EDITORIAL

Relationships between the industry and dermatologists: a vision without conflicts of interest

Relaciones entre la industria y los dermatólogos: una visión sin conflictos de intereses

*Rosario Aguero[1,2], Pablo Uribe[2,3], José L. López-Estebaranz[4], and Cristian Navarrete-Dechent[2,3]**

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In dermatology practice, as in other medical specialties, exposure to potential conflicts of interest (COI) is commonplace. COI refers to situations in which professional judgment aimed at prioritizing patient well-being may be compromised by secondary personal benefits, whether financial or of another nature[1]. Healthcare workers may be influenced by the industry through gifts, fees, and travel expenses, among other perks. Academics may also benefit from publishing scientific articles related to certain products or devices, with others of advantages (e.g., recognition and career advancement).

Collaboration between dermatologists and the pharmaceutical and medical device industries has been a constant source of significant advances, enabling the development of new drugs, devices, and therapies that have transformed the diagnosis and treatment of many dermatological diseases. However, it is essential to properly recognize and manage COI to make sure that clinical decisions are based on the best available evidence and not on possible external benefits.

In clinical practice, COI may significantly influence treatment prescriptions and recommendations. Regarding the influence of the industry on scientific publications, it has been shown that studies sponsored by pharmaceutical companies are more likely to report favorable results for their products, a trend that warrants special attention in dermatology due to its rapidly evolving technological and therapeutic landscape[2]. On the other hand, these studies tend to have more rigorous methodologies and larger participant numbers, which could be seen as an advantage[2]. In the realm of medical devices (e.g., lasers, dermatoscopes, or other diagnostic devices), results without clear clinical relevance may also be published. It is, also, crucial to declare COI when publishing scientific works, especially in the case of clinical practice guidelines and therapeutic recommendations, where expert opinion plays a significant role. Their validity and transparency are fundamental[3].

Transparency and education in managing COI are essential at all levels, from medical schools and residencies to workplaces. Although COI was recognized several decades ago, since the early 21st century, there has been a movement toward greater openness in physician-industry relationships, driven by regulatory changes and increased ethical awareness. However, much remains to be done, especially in regions where regulations are not at the same level as in developed countries. Since most literature and ethical guidelines come from Europe and the United States, we believe that it is important to discuss and adapt these guidelines to the Latin American context, where regulations are generally less stringent or non-existent.

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International examples show how COI can be effectively managed in dermatology. The American Academy of Dermatology has established a guide titled Professional and Ethical Standards for Dermatologists[4]. Table 1 illustrates the recommendations from this guide on COI management. In addition, the legislation known as the Sunshine Act allows for public transparency. Through a website (https://openpaymentsdata.cms.gov/), it is possible to view the amounts and types of compensation that any healthcare worker has received from the industry throughout their career. This system allows patients to be informed of possible influences that could affect their health-care providers. Similarly, the Spanish Academy of Dermatology and Venereology has implemented the Ethical and Good Governance Code, which provides clear guidelines for COI management[5]. This code not only sets the expected conduct standards for dermatologists in relation to the industry but also promotes medical practice that prioritizes patient interests over any secondary benefits. In Chile, for instance, a group called "Doctors Without Brand" (https://medicossinmarca.cl/) has emerged, promoting a critical and COI-free perspective among doctors from all specialties.

In addition to encouraging transparency, it is crucial for dermatologists to receive ongoing education on ethical principles and how they apply in practical situations, striving to maintain high professional integrity. This includes the complete and transparent disclosure of any financial or personal physicians or researchers they may have with external entities. Complete disclosure policies not only clarify these links but also strengthen public trust in medicine.

In conclusion, while COI is an inevitable reality in modern medicine, it should not overshadow the great benefits that can arise from collaborations between clinicians and the industry. We must foster an environment where integrity, transparency, and ethics are the norm, not the exception. By doing so, we uphold the ethics of our profession and improve the care we provide to our patients. This is an ongoing task that requires commitment, vigilance, and, above all, unwavering dedication to our ethical principles.

Table 1. Recommendations from the American Academy of Dermatology for managing conflicts of interest[4]

Section	Recommendation
Conflicts of interest in clinical practice	Dermatologists should resolve conflicts of interest in the patient's best interest, seeking reasonable alternatives to guarantee the most appropriate care. If unresolved, the patient should be informed of the conflict.
Financial or ownership interest	If the dermatologist has a financial or ownership interest in durable goods, such as medical supply providers, imaging centers, surgery, or other health-care facilities, they must disclose this to the patient. Furthermore, the dermatologist is required to be informed about all relevant legislation in these cases.
Industry compensation	The dermatologist should ideally inform the patient of any compensation received from the industry that could create any conflicts of interest. It is considered unethical to receive compensation from the industry for using a specific device or drug.
Clinical research and disclosure of conflicts of interest	Dermatologists who are authors of scientific articles must disclose any financial interest related to the drug, equipment, or procedure in question.
Sale of drugs and devices	Although dermatologists have the right to dispense drugs, devices, and other patient care-related items, they should not financially exploit the patient or dispense products without beneficial effects. The patient must have the option to accept or seek items outside the dermatologist's office.

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ORIGINAL ARTICLE

Cardiff Acne Disability Index: cultural and linguistic validation in Uruguayan Spanish

Cardiff Acne Disability Index: validación cultural y lingüística al español de Uruguay

Nelson Turra, Cecilia Durán, Gabriela Otero, Cecilia Izuibejeres, Camila Otero, and Caroline Agorio*

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Abstract

Background: *The Cardiff Acne Disability Index (CADI) is a specific tool for measuring the impact on the quality of life of patients with acne, and has been translated and validated into multiple languages.* **Objective:** *We present the definitive Uruguayan Spanish version of the CADI questionnaire and its validation process.* **Material and methods:** *The translation from its original version in English was carried out following international recommendations, including translation by several professionals, a back-translation into English, and a subsequent comprehensibility test carried out on individuals with acne. Then an observational, prospective, and multicenter validation study was conducted, including 54 individuals with acne who completed the questionnaire twice within a 14-day interval.* **Results:** *The cross-cultural translation and adaptation process identified, and resolved compatibility difficulties. Similarly, its clarity and understandability were demonstrated. The questionnaire showed good internal consistency, with a Cronbach's alpha coefficient of 0.81, and good test-retest reliability, with a Pearson coefficient of 0.86, and an intraclass correlation coefficient of 0.84.* **Conclusions:** *The CADI, a valuable tool for assessing the impact of acne on our patients, is available to be used in Uruguay.*

Keywords: *Acne. Quality of life. Disability scale. Validation. Cardiff acne disability index.*

Resumen

Antecedentes: *El Cardiff Acne Disability Index (CADI) es una herramienta específica para la medición del impacto en la calidad de vida de los pacientes con acné, que ha sido traducido y validado a diversos idiomas.* **Objetivo:** *Presentar la versión definitiva en español de Uruguay del cuestionario CADI y su proceso de validación.* **Material y métodos:** *La traducción de su versión original en inglés se realizó siguiendo recomendaciones internacionales, incluyendo la traducción por varios profe- sionales, una retrotraducción al inglés y un posterior testeo de comprensibilidad llevado a cabo en individuos con acné. Luego se realizó un estudio de validación de tipo observacional, prospectivo y multicéntrico, incluyendo 54 individuos con acné que completaron el cuestionario en dos oportunidades separadas por un intervalo de 14 días.* **Resultados:** *El proceso de traducción y adaptación transcultural identificó y resolvió las dificultades de compatibilidad. Igualmente, se demostraron su claridad y comprensibilidad. El cuestionario mostró buena consistencia interna, con un coeficiente alfa de Cronbach de 0.81 y buena fiabilidad test-retest, con un coeficiente de Pearson de 0.86 y un coeficiente de correlación intraclase de 0.84.* **Conclusiones:** *El CADI, una herramienta valiosa para evaluar el impacto del acné en la vida de los pacientes, está dispo- nible para ser usado en Uruguay.*

Palabras clave: *Acné. Calidad de vida. Escala de discapacidad. Validación. Cardiff acne disability index.*

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Introduction

The concept of health-related quality of life (HRQoL) is a multidimensional and subjective construct, determined by the effects of illness, its treatment, and a series of individual aspects. In 1995, the World Health Organization detailed its essential aspects: "HRQoL is subjective, multidimensional, includes both positive and negative feelings, which can change over time. In this regard, this construct is multidimensional and includes physical, psychological, and social aspects[1]."

The evaluation and measurement of HRQoL gain relevance in the context of chronic or recurrent medical conditions, allowing consideration of the patient's perception of their problem and adding functional criteria-physical, social, and emotional-to the medical evaluation[2]. In this way, the measurement of HRQoL allows the physician to evaluate the impact of treatment, compare therapeutic results, and conduct a cost-benefit evaluation. There are different types of tools that can be used to measure HRQoL, which can be classified as follows:

- Generic scales: these are used to evaluate all patients, regardless of their disease, and thus allow for comparison between individuals with different diseases as well as between healthy individuals and those who are ill[3,4].
- Specific scales: these allow for the evaluation of different aspects of health, well-being, or quality of life in relation to a particular pathology, making them more sensitive than generic tools[4,5].

Acne is a very common skin condition among young people, with reported prevalence rates of up to 96% during adolescence[6,7]. Regarding its clinical presentation, various acne severity scales have been described, with a notable proposal from the European Dermatology Forum in 2016, which categorizes acne into four grades: grade 1, comedonal acne; grade 2, mild-to-moderate papulopustular acne; grade 3, severe papulopustular or moderate nodular acne; and grade 4, severe nodular acne[8].

On the other hand, the association between acne and HRQoL impairment has been described[6,9,10] and specific tools have been developed for its evaluation[8], such as the Cardiff Acne Disability Index (CADI), a 5-question questionnaire with four possible responses, scoring between 0 and 3 (minimum questionnaire score of 0 points and maximum of 15 points). The CADI questionnaire allows for grading the severity of HRQoL impairment due to acne, with 0 points indicating no impairment; 1-5 points, mild impairment; 6-10 points, moderate impairment; and 11-15 points, severe impairment[11,12].

Regarding the content of the questions, each one aims to evaluate different aspects related to HRQoL impairment associated with acne: questions 1 and 2 address the psychosocial consequences of acne; question 3 focuses on evaluating the psychosocial consequences in patients with acne on the chest or back; question 4 investigates the psychological consequences of acne; and question 5 seeks to understand the patients' subjective self-perception of the severity of their condition.

The CADI questionnaire has been translated and validated into various languages[13-20] is widely used in HRQoL studies in patients with acne[21-23], demonstrating its importance and high value as a diagnostic support tool. However, before this study, only the Spanish version from the United States was available, which, due to cultural and linguistic idiosyncrasies, could not be universally extrapolated and used by all Spanish-speaking countries without undergoing a rigorous process of transcultural adaptation, validation, and institutional accreditation by Cardiff University, which holds the copyright of the questionnaire. For this reason and considering the absence of a Uruguayan version of the CADI questionnaire, the objective was set to validate it for Spanish speakers in Uruguay.

Methods

The process of transcultural adaptation and validation of the questionnaire consisted of several successive stages that maximized quality control, which are described below.

Transcultural and linguistic adaptation

The process of adapting the CADI questionnaire to its Uruguayan Spanish version was conducted following international guidelines and recommendations[24-26]. The objective of this stage was to make sure that each question and response reflected what was truly intended to be expressed, seeking conceptual rather than literal similarity, to guarantee that the words and phrases used reflected the specific cultural and linguistic aspects of each country.

Initially, the original English questionnaire was independently translated into Spanish by 2 certified translators (versions #1 and #2). Subsequently, both versions were reconciled with the help of a third translator (version #3). A back-translation into English was then performed, and discrepancies were discussed with the coordinator (version #4). Afterward, the research team

including dermatologists, a medical psychologist, and a pediatrician-all bilingual in Spanish and English-conducted a critical evaluation and reconciliation with the validated Spanish version of the CADI questionnaire from the United States provided by Cardiff University (version #5) (Fig. 1). In the second stage, its clarity and comprehensibility were assessed through a structured interview applied to a group of young people with acne.

Validation study and statistical analysis

We conducted a multicenter, observational, prospective, and analytical study including 54 individuals with acne of different ages and both genders, who had not been included in previous evaluations and who came from Hospital de Clínicas de Montevideo Dr. Manuel Quintela, Centro Auxiliar de Las Piedras Dr. Francisco Espínola, and a secondary school in Montevideo. All participants were examined and categorized according to the severity of their acne, using the classification proposed by the European Dermatology Forum in 2016. They were then administered the 5th version of the CADI questionnaire for Uruguay on two successive occasions, separated strictly by a 14-day interval. This methodology was chosen based on another study of transcultural and linguistic adaptation of the same questionnaire into French[17]. The justification for the 14-day period between the two evaluations was that this time frame would be short sufficient to prevent changes in the individual's health status and long enough to prevent them from remembering their previous responses.

Statistical analysis was performed with the support of STATA software version 12.0. For internal consistency analysis, responses from the first application were considered and analyzed using Cronbach's alpha coefficient, with a target value of ≥ 0.7. Test-retest correlation analysis was performed with the overall results of both applications, using Pearson's coefficient and the intraclass correlation coefficient, with target values of ≥ 0.8. To rule out potential discrepancies between the 2 applications, the paired samples t-test was used.

Accreditation of the questionnaire

Once the questionnaire was validated, it was notarized before a public notary of the Oriental Republic of Uruguay. Finally, the results and the final version of the questionnaire were reported to Cardiff University for approval and acceptance.

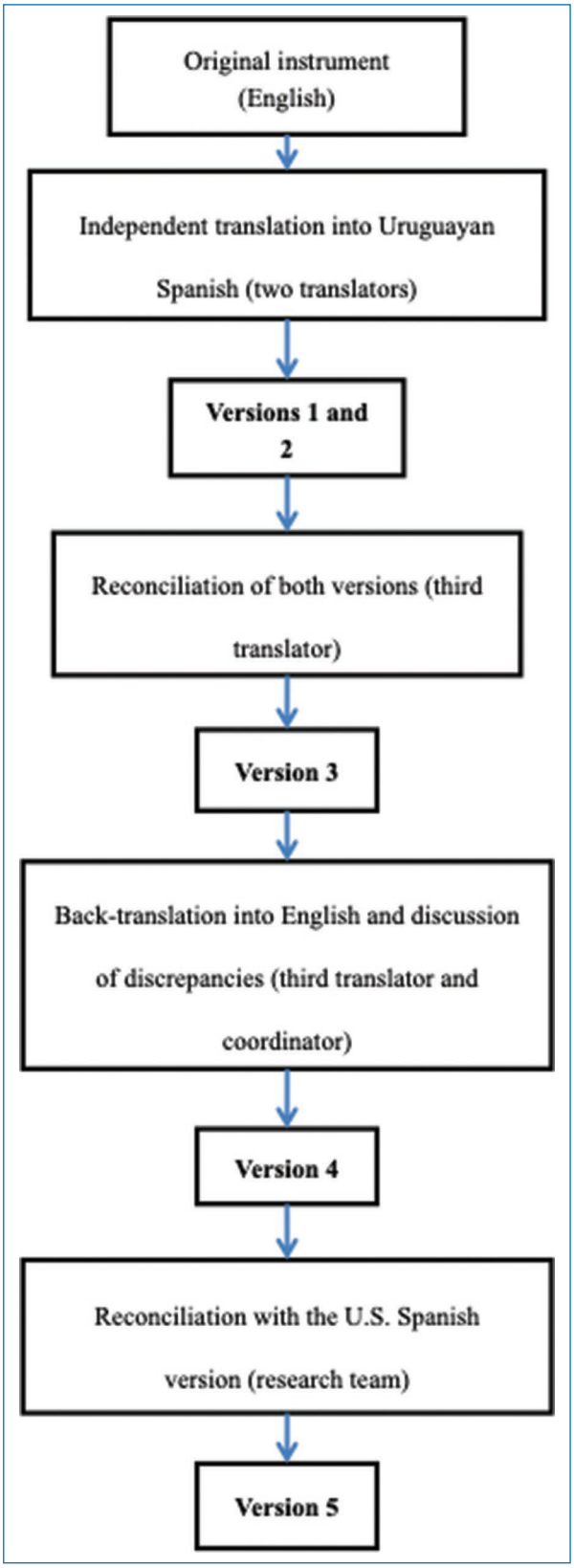

Figure 1. Summary of the translation process of the Cardiff Acne Disability Index from its original in English to Uruguayan Spanish.

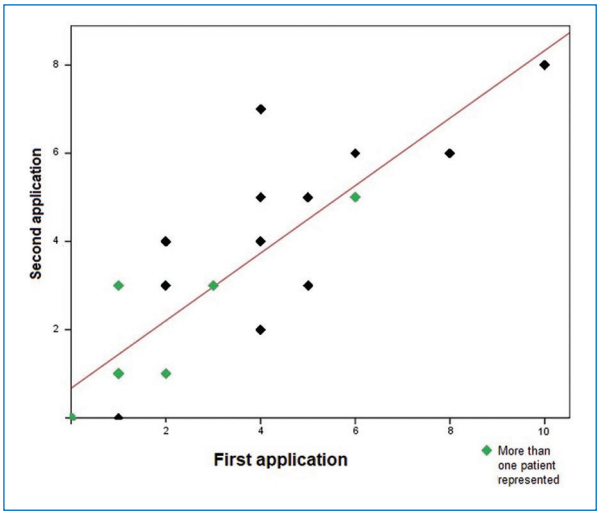

Figure 2. Correlation analysis of both applications of the Cardiff Acne Disability Index for Uruguay. A strong correlation between both applications of the questionnaire is evident (the green dots represent more than one participant).

Ethical and legal considerations

The study was developed and executed in full compliance with international recommendations on clinical research (Declaration of Helsinki of the World Medical Association). Informed consent was obtained from the participants and their legal guardians, the institutional approval of the participating school was obtained, and approval was secured from the ethics committees of the School of Medicine of the University of the Republic, the Hospital de Clínicas, and Centro Auxiliar de Las Piedras. In addition, authorization and licensing were requested from Cardiff University, which granted our group the rights to conduct the transcultural adaptation and subsequent validation of the CADI questionnaire into Uruguayan Spanish.

Results

The translation process successfully identified and resolved the cultural and linguistic compatibility challenges described across the different reconciled versions. The comprehensibility test conducted on 10 acne patients was satisfactory, demonstrating the clarity of the questionnaire. The validation study included 54 individuals with acne. Thirty-six of them completed the questionnaire twice, while 18 could not be contacted for the second application or responded outside the strictly stipulated time frame.

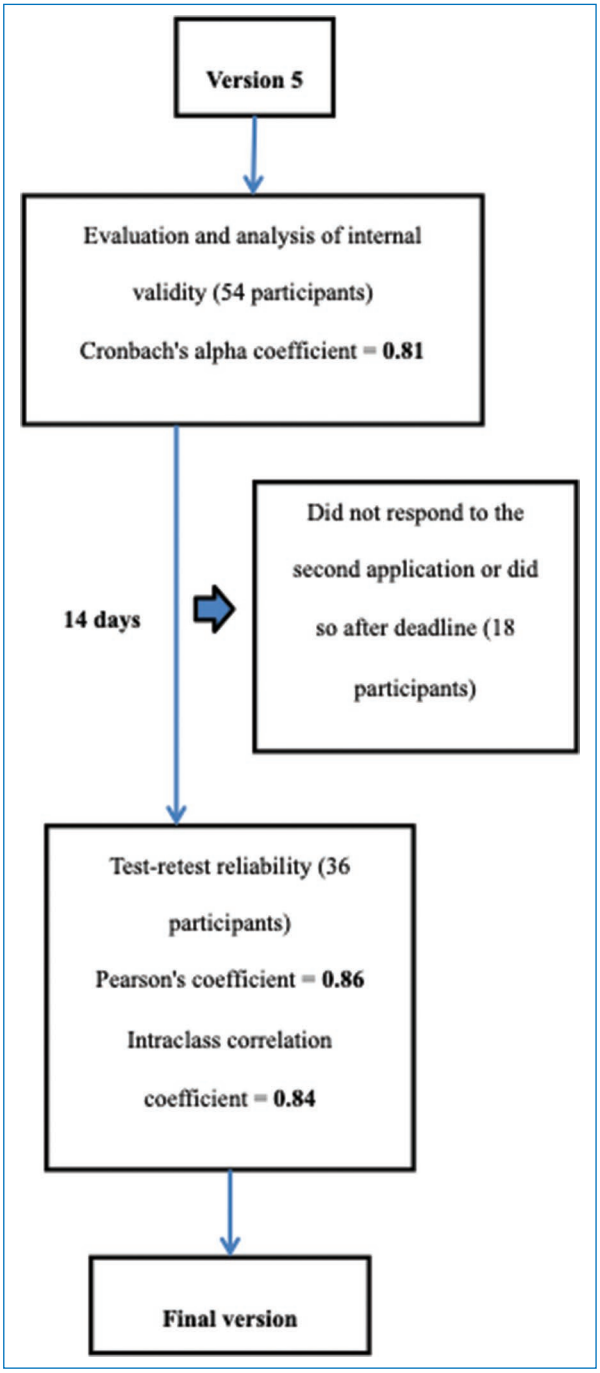

Figure 3. Summary of the validation process of the Cardiff Acne Disability Index for Uruguay. Good internal consistency and high test-retest reliability are demonstrated.

A total of 63% of the participants (34) were men, and 37% (20) were women. Ages ranged from 12 up to 34 years (mean, 16 years; median, 15 years). A total of 85% (46) declared living in Montevideo, while 15% (8) resided in other departments of the country. Regarding acne severity, 24% (13) had grade 1 acne; 48% (26) had grade 2; 22% (12) had grade 3; and 6% (3) had grade 4.

1. Como consecuencia de tener acné, ¿has estado agresivo, frustrado o avergonzado durante el último mes?	☐ (a) De hecho, muchísimo ☐ (b) Mucho ☐ (c) Un poco ☐ (d) No, para nada
2. ¿Creés que el acné que tuviste el mes pasado interfirió con tu vida social diaria, con eventos sociales o con tu relación con personas del sexo opuesto?	☐ (a) Muchísimo; afectó todas mis actividades ☐ (b) Moderadamente; en la mayoría de las actividades ☐ (c) A veces o solo en algunas actividades ☐ (d) No, para nada
3. Durante el último mes, ¿dejaste de cambiarte de ropa o ponerte el traje de baño en lugares públicos, debido al acné?	☐ (a) Todo el tiempo ☐ (b) La mayor parte del tiempo ☐ (c) A veces ☐ (d) No, para nada
4. ¿Cómo te hizo sentir el aspecto de tu piel durante el último mes?	☐ (a) Muy deprimido y triste ☐ (b) Generalmente preocupado ☐ (c) A veces preocupado ☐ (d) No me molestó
5. Indicá qué tan mal creés que está tu acné ahora:	☐ (a) Nunca estuvo peor ☐ (b) Es un problema importante ☐ (c) Es un problema menor ☐ (d) No es un problema

Figure 4. Final Uruguayan version of the Cardiff Acne Disability Index questionnaire. *© Cardiff Acne Disability Index. R.J. Motley, A.Y. Finlay, 1992.*

The internal consistency analysis of the questionnaire showed a Cronbach's alpha coefficient of 0.8, while the correlation analysis of the overall test-retest scores showed a Pearson's coefficient of 0.86 (Fig. 2) and an intraclass correlation coefficient of 0.84.

No statistically significant differences were identified among the total scores obtained after applying the CADI questionnaire for Uruguay twice, as confirmed by the paired samples t-test (t = 0; p = 1). Fig. 3 illustrates the validation process, and Fig. 4 the final version of the CADI questionnaire for Uruguay, which was recognized and accepted by Cardiff University. The Uruguayan Spanish version of the CADI questionnaire resulting from this study is now available for download from the university's official site at https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/cardiff-acne-disability-index.

Discussion

It is a fact that chronic skin diseases, such as acne, have a significant impact on the patients' HRQoL, who often perceive their skin condition differently than their physicians[27]. The use of instruments to measure HRQoL helps shift the focus from being physician-centered to being more patient-centered[16].

The decision was made to perform the cross-cultural adaptation and validation of the CADI questionnaire, considering the lack of specific HRQoL scales for acne patients in Uruguay, while highlighting its wide international dissemination and easy application in clinical practice[11]. To guarantee the successful development of the project, the cross-cultural adaptation and validation process followed the guidelines specified by international recommendations[24-26], which resulted in the CADI questionnaire for Uruguay undergoing a rigorous quality control process.

Regarding the translation and cross-cultural adaptation process of the questionnaire, we prioritized a conceptual rather than a literal approach, ensuring the use of words and phrases that reflect Uruguayan culture. During the validation process, individuals of different ages, socioeconomic strata, and departments of residence in Uruguay participated, with the aim of ensuring that the final version had broad representativeness and good external validity.

In terms of the internal consistency analysis of the CADI questionnaire for Uruguay, we note that previous validations have reported similar or lower Cronbach's alpha coefficients, with results such as 0.72 for the Hindi version[16], 0.74 for the Serbian version[13], 0.73 for the Brazilian Portuguese version[15], 0.76 for the Chinese version[19], 0.79 for the Persian version[18], and 0.87 for the French version[17]. In addition, a high correlation was found between the overall scores of both questionnaire applications, which allowed us to confirm its good test-retest reliability.

Finally, we believe it is important to note that this version of the CADI questionnaire is only applicable to the Uruguayan population and should not be used with

individuals from other Spanish-speaking countries, as it may lack comprehensibility and validity for those subjects. Therefore, we hope that the results of our work will serve as motivation for other research groups to carry out the validation process of the CADI questionnaire in their respective countries, so they can incorporate this valuable tool into their daily clinical practice.

Conclusions

The results of this study show that the Uruguayan version of the CADI questionnaire is valid, reliable, and clear. In addition, it is a practical tool of great utility for the evaluation of patients with acne, adding relevant information to medical records by considering patients' perceptions of their condition. The CADI questionnaire, highly useful for assessing the impact of acne on patients' lives, is now available in Uruguay.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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REVIEW ARTICLE

Straightening: "hair, an aspect of human individuality"

Alisados: «el cabello, un aspecto de la individualidad humana»

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Abstract

Hair is an important element of human individuality. The pursuit of more manageable hair has driven the development of straightening procedures, which can be physical or chemical and temporary or permanent depending on their duration. Straightening affects only the visible part of the hair, without altering its natural growth, so it must be performed periodically to maintain the desired effect. The increasing popularity of hair straightening, even among young people, has raised medical concerns. The esthetic and physical impact of hair products is often overlooked despite their wide availability in the market. This study focuses on the morphology, chemical composition, and molecular structure of hair, as well as the risks and adverse effects associated with straightening products and techniques, both locally and systemically.

Keywords: *Hair cosmetics. Hair. Hair straightening. Scalp.*

Resumen

El cabello es un aspecto importante de la individualidad humana. La búsqueda de un cabello más manejable ha impulsado el desarrollo de procedimientos de alisado, que pueden ser físicos o químicos y temporales o permanentes según su duración. Los alisados afectan solo la parte visible del cabello, sin alterar su crecimiento natural, por lo que deben realizarse periódicamente para mantener el efecto deseado. El aumento en la popularidad del alisado capilar, incluso entre los jóvenes, ha suscitado preocupaciones médicas. A menudo se pasa por alto el impacto estético y físico de los productos capilares, a pesar de su amplia disponibilidad en el mercado. Este estudio se centra en la morfología, composición química y estructura molecular del cabello, así como en los riesgos y efectos adversos asociados con los productos y técnicas de alisado, tanto a nivel local como sistémico.

Palabras clave: *Cosméticos capilares. Alisados. Cuero cabelludo. Cabello.*

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Introduction

Hair represents a valuable aspect of human individuality[1], and the quest for more manageable and versatile hair has driven the exploration of chemical transformations, such as straightening. This process, aimed at turning curly hair into a smoother texture, has a long history that dates back to ancient Egypt. Paintings and papyri from that era reveal that women used various creams to straighten and add shine to their hair[2]. By the late 19th century, hot combs invented in France were used to temporarily straighten hair[2,3].

In the mid-1900s, Sarah Breedlove, later known as C.J. Walker, an African American woman, created pomade made of petroleum-based oils and vegetable resins that revolutionized the styling of ethnic Afro hair. She invented the pressing and curling style, using Vaseline-based pomade and a metal comb where hair fibers were straightened at temperatures ranging from 150 up to 250 °C[1-3].

Hair is highly malleable and can be modified in length, color, and shape with a variety of products[4]. Straightening processes can be physical or chemical, temporary or permanent[1,4]. The first chemical straighteners emerged in the 1940s; they were mixtures of sodium or potassium hydroxide with starch but were irritating[2,4]. By the late 1950s, professional chemical straightening products with sodium hydroxide were introduced, becoming popular for their ability to manipulate wet hair and create various styles[2,4].

By 1965, a permanent home straightener based on sulfites was available. However, these products had drawbacks, such as hair weakening and scalp irritation[2,4]. In 1978, a relaxer cream with calcium hydroxide and guanidine carbonate was patented. Avlon Industries introduced a straightening system in 1985 tailored to different hair types and scalps[2-4].

By 2006, between 70% and 80% of African-American women in the United States were using chemical straightening products[2-4]. The preference for straight hair now extends beyond beauty standards, becoming a matter of practicality and hygiene[1-4]. However, these products only affect the hair shaft, so new growth remains unchanged, requiring recurrent straightening[2-4].

The increasing popularity of hair straightening among younger people has become a medical concern[3-5]. Although dermatologists are familiar with scalp conditions, the esthetics and physical effects of hair products are often overlooked. While hair products are widely available, medical information about them is limited[1-5]. Therefore, this review aims to address this knowledge gap, exploring the morphology, chemical composition, and molecular structure of hair, as well as evaluating the risks and adverse effects, both local and systemic, associated with hair straightening products and techniques.

Hair fiber structure

Hair is a keratinized structure, formed from the invagination of the epidermis into the dermis, from which small sac-like structures called hair follicles originate. Thus, it can be divided into two main parts: the follicle and the hair shaft or hair fiber, which extends from its root or bulb, passes through the various layers of the epidermis, surpasses the stratum corneum, and continues as a cylindrical filament. Anatomically, the hair fiber consists of three layers[5,6].

Cuticle

The outermost layer of the hair is a protective covering formed by overlapping scales, similar to a roof, that surround the central core of the fiber. Its primary function is to protect the hair cortex from external environmental damage. It is mainly composed of keratin, lipids, and keratin-associated proteins (KAP). In addition, the cuticle is coated on the outside by a thin membrane over the surface of the scale cells called the epicuticle, which contains 18-methyl eicosanoic acid (18-MEA) bound to sulfur-rich proteins[4-7]. The 18-MEA is responsible for the hair's hydrophobicity, which is crucial for its easy management, integrity, and protection[4-7]. Each cuticle cell consists of three protein layers: the A-layer, a tough layer with high cystine content; the exocuticle or beta-layer, also rich in cystine; and the endocuticle, with low cystine content. Cystine, one of the most important amino acids, contains two cysteine amino acids from different portions of the peptide chains connected by two sulfur atoms, forming a strong bond called a disulfide bridge[4-7].

The cell membrane complex (CMC) consists of the intercellular junction of cell membranes from two cuticle cells, two cortical cells, and cuticle-cortex cells joined by the beta layer, considered the most important intercellular cement of the CMC. Both the endocuticle and the CMC are very vulnerable to chemical treatments such as bleaching and hair straightening[4-7].

The number of scales in the cuticle varies depending on the type of hair, ranging from six to eight scales thick in Asians, slightly fewer in Caucasians, and even fewer in African hair. A thinner cuticle layer makes African hair more prone to breakage[4-7].

Cortex

The cortex comprises the bulk of the hair shaft, accounting for approximately 90% of its structure[5-7]. It is composed of elongated fusiform cells, joined by a complex cellular matrix (CMC), and contains melanin granules. In addition, the cortex consists of macrofibrils made up of keratin intermediate filaments arranged parallel to the hair fiber axis, which are embedded in an amorphous matrix composed of KAP[4-7].

The macrofibrils in the cortex adopt a helical arrangement, while the intermediate filaments contain subunits called protofilaments. Each protofilament houses short sections of alpha-helical proteins, forming polypeptide chains. The alpha-helix is held together by chemical forces such as ionic, hydrogen, van der Waals forces, and disulfide bonds. This helical structure gives hair its elasticity and strength[4-7]. The hair straightening process involves breaking these chemical bonds to stretch and modify its shape[4-7].

Medulla

The medulla is an inconsistent structure surrounded by the cortex that contains keratin and lipids. It is usually found in gray hairs, thick hairs, and beards. It can be continuous or discontinuous and is more prevalent in Caucasians than in Asians and Africans. If present, it typically constitutes a small percentage of the hair mass. It contains mitochondrial DNA. Its function is unknown, but it is believed to contribute minimally to the mechanical properties of human hair fibers[4,8,9].

The appearance of hair largely depends on the health of the cuticle. The intact and closed cuticle acts as a protective shield against harmful environmental elements. When the cuticle scales are open (raised), substances can be deposited in its structure. The physicochemical transformation of the cuticle scales changes the appearance of the hair, leading to changes in its smoothness, color, and even texture. Therefore, from a cosmetic perspective, the cuticle is the most important component of the hair fiber; however, the cortex plays a crucial role in affecting hair color and mechanical properties[10].

Keratin, intermolecular bonds, stability, and strength hair fibers

Keratin is a fibrous and sulfurized protein characteristic of the skin, hair, and nails. Like all proteins, it is made up of long chains of amino acids linked together. The main component of keratin is cysteine, which contains sulfur in the form of thiol (HS-group) in its composition. Depending on the proportion of this amino acid, keratin can be harder or softer. Both the cuticle and the cortex are made of hard keratin, as they contain a high proportion of sulfur-rich amino acids, while the medulla and the outer root sheath are made of soft keratin, with a lower proportion of sulfur. Being a fibrous protein, the amino acid chains are not isolated but are grouped together to form bundles[5-10].

The three chains of alpha-keratin bind together to form protofilaments, a union that is maintained by three types of bonds: disulfide, hydrogen, and salt bonds. The amino acid chains that makeup keratin have a helical arrangement known as alpha-helix or alpha-keratin. This structure is kept stable by the electrostatic attraction between hydrogen and oxygen atoms belonging to two amino acids in the same keratin chain (intrachain). These are called hydrogen bonds, which are weak bonds that are easily broken by agents such as water, heat, and mechanical stretching[5-10].

When this happens, the structure of alpha-keratin changes to beta-keratin, a more elongated structure. This change in chemical structure can be observed when hair is wet, showing that its length increases[5-10]. Disulfide bonds are the strongest bonds and are formed between two cysteine molecules from different chains. These bonds are primarily responsible for the cohesion of the keratin fiber. The susceptibility of these bonds to oxidation or reduction is key in most chemical hair modifications[5-10].

What determines the curliness of hair fibers?

Curly hair presents a curvilinear configuration and twists in different directions, making it weak, difficult to manage, and prone to breakage. In addition, its flat structure hinders light reflection and tends to be dry, resulting in increased moisture absorption from the environment and, consequently, increased volume[1,11].

The terms “European hair” and “Caucasian hair” are used to describe wavy to straight hair, while “East Asian hair” refers to straight hair, and “African hair” is associated with curly, afro, or very curly hair. The curvature of hair has been studied from various perspectives. Anthropologically, it is suggested that curly hair might be an evolutionary and adaptive mechanism related to regulating scalp temperature and protecting against UV rays. This theory is based on curly hair’s ability to stand away from the skin, thus providing protection and cooling[12].

From a medical standpoint, the shape of the hair fiber is determined by the morphogenesis of the hair follicle, where proliferation and differentiation mechanisms drive the formation of curly hair and establish the support structures needed to maintain its curvature[12]. Several genes, such as the VDR gene, are associated with hair curvature and may contribute to its shape. However, more research is needed to fully understand the genetics behind this characteristic[12]. Several hypotheses have been proposed to explain hair curvature, including the influence of straightening and perming treatments on disulfide bonds. Although these bonds are related to curvature formation, their main role seems to be to provide support to the hair fiber[11-13].

While there has been progress in understanding the biology of the hair follicle in recent decades, many unanswered questions remain about the underlying causes of hair curvature. Further research is needed to fully understand this process at the molecular and cellular level[13].

Physical and thermal straightening agents

Hot comb

The hot comb was invented by the Frenchman François Marcel Grateau as a tool for women with curly and thick hair to achieve a smooth and fine appearance traditionally modeled by historical Egyptian women. The Parisian is credited with revolutionizing hairstyling with this invention and introduced hot curling irons to France in 1872[13,14]. It is believed that Elroy J. Duncan invented and manufactured the first hot comb in the US thanks to entrepreneur Madame C.J. Walker, who popularized it by combining the hot comb with pressed oil. It is a temporary straightening method, as it produces the hydrolysis of keratin, changing the weak hydrogen bonds. The initial technique involved applying a base of petroleum jelly to the hair, followed by straightening with a heated metal hairstyling device. Over time, the hot comb fell out of use due to the implementation of new technologies[1,13,14].

Hair dryer and flat iron

This technique combines mechanical and thermal straightening, offering temporary solutions that last until the next wash. The hair needs to be damp for hydrogen bonds to break and temporarily open the helical structure of the strand, resulting in relaxation[1,15]. The combined use of the dryer and flat iron dehydrates the hair, keeping it straight. High temperatures can denature the proteins in the hair fiber; generally, hair dryers are more damaging than natural air drying. However, a study showed that using a hair dryer with continuous movement at a minimum distance of 15 cm from the hair could be less damaging than natural drying[14,15].

Chemical straightening agents

Hair fibers can be transformed through progressive or permanent chemical straightening. Typically, progressive straightening methods use alkaline substances, while permanent straightening uses acidic substances[1,5,16].

Acidic straighteners

In the early 2000s, a technique known worldwide as Brazilian keratin was introduced, offering relaxation and electrostatic reduction of the hair, making it more manageable and enhancing its color and shine. Its main component is formaldehyde, an organic chemical also known as methanal, formalin, formic aldehyde, oxymethylene, methyl aldehyde, and oxomethane. Formaldehyde is widely used for its chemical properties and functions as a preservative in various everyday products, with concentrations ranging from 0.2% up to 5% as a nail hardener[5,16]. Although banned by global health agencies, high levels of formaldehyde are popularly used in hair straightening procedures. Formaldehyde binds to the keratin molecule at the sites of broken hydrogen and water bonds, promoting molecular cross-linking, smoothing cuticles, and controlling the curvature of hair fibers[1,5,16].

Formaldehyde releasers are chemical compounds that, at high temperatures, release formaldehyde as one of their final products, such as methanediol, timonacic acid, and glyoxylic acid, which are not yet authorized by global health organizations. These releasers are activated by heat, typically from a flat iron, causing dehydration of the molecule and eventual formation of formaldehyde, glyoxylic acid, and glyoxylic cysteine. The flat iron is applied at a temperature of 230°C between 15 and 20 times on the same hair strand, causing protein loss and hair degradation. Unlike hydroxides and thiols, it can be applied to previously straightened or dyed hair[1,5,16].

Glutaraldehyde is a saturated dialdehyde that has gained wide acceptance as a high-level disinfectant. Commercially, it is obtained as an acidic pH solution at 2%, 25%, or 50%, so its properties change depending

on its concentration. It has been used as a straightener since the ban on formaldehyde. It is a relatively common preservative in cosmetics and can be used in concentrations of up to 0.2%[5,16].

Cosmetic companies have attempted to develop products with new active ingredients not based on formaldehyde or other types of preservatives. In 2011, carbocysteine was developed, a dibasic amino acid that reduces hair volume by up to 90%, hydrates it, and adds shine. It involves sealing the cuticle of the strands, reconstructing the hair fiber, reducing frizz, and aiding growth, but if done gradually, it gives the effect of straightening. Thus, stylists use this product in processes such as "thermal sealing" and "deep hydration." However, for the product to work, a process of reordering cystine bonds is essential, which can be achieved using a flat iron (high temperatures) or glyoxylic acid[5,16].

Alkaline or relaxing straighteners

Straightening agents for hair are potent alkalis, such as metal hydroxides, including ammonium hydroxide, sodium hydroxide, lithium hydroxide, or guanidine hydroxide. These chemical substances are used to break the chemical bonds in the protein chains of the hair fiber, allowing for restructuring of the chains to achieve hair straightening[1,2,16].

There are several types of relaxers:

- Bleach-based relaxers: These are used to straighten extremely curly hair and use sodium hydroxide or, alternatively, potassium hydroxide as the base relaxant. This type of relaxer works by breaking disulfide bonds in the cortex, causing softening and swelling of the fibers. Although it is gentler on the scalp, it leaves calcium mineral residues on the hair shaft, making the hair drier, more brittle, and less shiny[1,2,16].
- Non-bleach relaxers: These use guanidine hydroxide to break the bonds between the protein chains of keratin through lanthionization. In this process, one-third of amino acids react to cystine and are replaced by lanthionine, an analog of cystine containing a single sulfur atom, which contributes to making the hair softer. The high pH and conversion of cystine to lanthionine weaken the hair shaft. In this case, the effect is less aggressive on the hair and scalp[1,2,16].

The alkaline pH of hydroxides causes swelling in the hair shaft, opens its cuticle, and allows the product to penetrate the cortex associated with the straightening. After drying the hair, an acidic pH agent is applied to neutralize the process, reshaping the hair into the desired new structure. This process must be repeated every 4–8 weeks[1,2,16].

- Thiol relaxers: This group includes ammonium thioglycolate, aminomethylpropanol thioglycolate, and ethanolamine thioglycolate. The most widely used relaxant is ammonium thioglycolate, which has a pH between 9 and 9.3 and breaks the sulfur bonds in cystine amino acids, along with softening the hair fibers. Its main application is for straightening straight, curly, and wavy hair. In this case, it is necessary to wash the hair before applying the relaxant, and the process is completed with neutralization using an oxidizing agent, usually hydrogen peroxide. It is important to note that for the relaxers described, the product application is done on dry hair[1,2,16]. When the same techniques do not involve the use of thermal tools, it is referred to as relaxation[1,16].

Adverse effects of chemicals

Systemic adverse effects

In 2009, the International Agency for Research on Cancer categorized formaldehyde, also known as formol, as a human carcinogen[17-19]. In response to this classification, the U.S. Food and Drug Administration (FDA) has taken steps to address concerns about its use in hair products. Although a complete ban has not yet been implemented, the FDA has proposed stricter regulations to control the presence of formaldehyde in these products[17-19].

As an alternative to formaldehyde, glutaraldehyde has been used as a straightening agent. Although glutaraldehyde mutagenicity is similar to that of formaldehyde, it is 6-8 times more powerful in producing cross-links in DNA and about 10 times more intense, potentially causing damage to nasal mucosa tissues upon inhalation. Due to the health hazards posed by formaldehyde-based straighteners, especially when subjected to high temperatures, this component is classified as a human carcinogen due to its malignant effects on the respiratory and hematologic systems[16-20].

A study found that children exposed prenatally to formaldehyde in the third trimester had a higher likelihood of developing Wilms' tumor. In addition, there is an identified link between pregnancy and maternal exposure to hair dyes and straighteners with the development of leukemia at early ages[15,16-20].

Furthermore, recent research states that women who use hair straighteners or relaxers have an increased

risk of developing uterine cancer. However, these results were obtained from a specific population, and no definitive product causation has been identified. Approximately, 60% of the participants who used these straightening products were African American women and information about the brands or ingredients of the products used was not collected. This suggests that the results are preliminary and further studies are needed to validate them[18-21].

Several studies have characterized exposure to formaldehyde among workers and clients during keratin straightening treatments. These studies have shown that products, even those labeled as "formaldehyde-free," have the potential to produce formaldehyde concentrations exceeding current occupational exposure limits. In addition, other studies have found that the use of thermal tools, such as hair straighteners and hair dyes, may increase the risk of breast and ovarian cancer[19-21].

Regarding alkaline straighteners, there has been a notable decrease in cystine compared to virgin hair, especially with bleach-free relaxers. The use of other hair techniques along with straightening increases vulnerability to damage. Moreover, combining hair straightening with hair implants has been associated with areas of permanent alopecia. Combining straightening with hair dye resulted in greater protein loss, with the combination with sodium hydroxide being the most aggressive. The combination of straightening with ammonium thioglycolate, bleaching, and flat ironing resulted in hair with irregular contours, shedding, cuticle deformation, and potential cortical damage. Although different ethnicities seem to have different susceptibilities to straightening, using conditioning agents may help minimize structural damage. Despite the side effects, many women choose to straighten their hair[19-21].

Local adverse effects

The most common local adverse effect of chemical straighteners is the loss of the hydrophobic fatty acid layer of the cuticle, which includes 18-methyl eicosanoic acid. This loss impedes water passage into hair fibers and alters its physical properties, resulting in decreased hair shine and increased susceptibility to static electricity and frizz induced by humidity. Another local adverse effect is the breakage and rearrangement of disulfide bonds. Thermal treatments can decompose tryptophan residues into quinurenine-like oxidation products, causing a yellowish appearance in white hair and darkening in bleached hair. Although the hair may appear more manageable after thermal straightening with the addition of lipid products, the reality is that after shampooing and removing the lipids, the hair dries out, exposing it to heat damage[16-21].

Acidic chemicals, such as formaldehyde, can increase the distance and opening of cuticle scales, as well as cause irregularities in their edges, fissures, and severe lifting of the cuticle with exposure to the cortex, which damages the hair fiber. Although formaldehyde may improve the macroscopic appearance of the hair by giving it shine, at a microscopic level, cuticle irregularities, reduced breakage resistance, color change, and trichoptilosis have been reported. In the scalp, cases of flaking, pain, atrophy, and contact eczema can occur. In addition, reports in medical literature may underestimate these effects, as users often consider them normal. Burns and severe cases of contact eczema with secondary infection have been reported. Long-term consequences of acute inflammation may be related to scarring alopecias. Furthermore, irreversible alopecia has been described, and hair straightening has been associated with centrifugal scarring alopecia and a higher risk of traction alopecia, especially when associated with braids. Proximal generalized trichorrhexis nodosa has also been linked with hair straightening[16-22].

Conclusions

Hair is a component of human external appearance, and its importance transcends beauty concepts in all cultures worldwide. Straightening products are chemicals used to change hair curling patterns. Maintaining natural hair is often more labor-intensive than relaxed or straightened hair, and in the absence of optimal hair care, it causes significant damage to the hair fiber. However, the literature reports alterations in the hair shaft, scalp, and even systemic repercussions secondary to the chemical products used for hair straightening or relaxing. Health professionals, especially dermatologists, should be aware of the specifics of different straightening techniques and the potential health risks they carry to guide patients in safeguarding their safety. Stylists and their clients should be informed about the risks and benefits of these chemical treatments.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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REVIEW ARTICLE

Neutrophil extracellular traps and dermatology

Trampas extracelulares de neutrófilos y dermatología

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Abstract

Neutrophils constitute the first line of defense of the organism, acting as sentinels toward sources of infection or inflammation. Their known microbicidal mechanisms are degranulation, phagocytosis, generation of reactive oxygen species, and cytokine secretion. In 2004, the formation of neutrophil extracellular traps (NETs) was described. These are composed of DNA and granules with potent cytotoxic and inflammatory properties, capable of immobilizing and eliminating different microorganisms. These positive effects of pathogen control are counteracted by their pro-inflammatory and deleterious behavior in various diseases. Aberrant formation or elimination of traps has been associated with the externalization of modified self-antigens in peripheral blood and tissues; thus, they have been implicated in the pathogenesis of autoimmune and autoinflammatory diseases. In dermatology, they have been described as cutaneous lupus erythematosus, psoriasis, neutrophilic dermatoses, and some severe adverse drug reactions. Advances in the understanding of this newly described role of neutrophils through NET generation will allow the development of new specific therapeutic strategies.

Keywords: *Neutrophils. Neutrophil extracellular traps. Neutrophil extracellular traps. ETosis. Autoimmunity. Anti-neutrophil extracellular traps therapies.*

Resumen

Los neutrófilos constituyen la primera línea de defensa del organismo, son las células centinela ante los focos de infección o inflamación. Los mecanismos microbicidas conocidos son: desgranulación, fagocitosis, generación de especies reactivas de oxígeno y secreción de citocinas. En el año 2004 se describió la formación de trampas extracelulares de neutrófilos (NETs, por su acrónimo en inglés). Estas están compuestas por ADN y gránulos con potentes propiedades citotóxicas e inflamatorias, capaces de inmovilizar y eliminar diferentes microorganismos. Estos efectos positivos sobre el control de patógenos se ven contrarrestados por su comportamiento proinflamatorio y deletéreo en diversas enfermedades. La formación o eliminación aberrante de trampas se ha asociado a la externalización de autoantígenos modificados en la sangre periférica y en los tejidos, por lo que se han implicado en la patogénesis de enfermedades autoinmunes y autoinflamatorias. En dermatología se han descrito en patologías como lupus eritematoso cutáneo, psoriasis, dermatosis neutrofílicas y algunas reacciones adversas graves a fármacos. Los avances en el conocimiento de este nuevo mecanismo de acción de los neutrófilos mediante la generación de NETs permitirán el desarrollo de nuevas estrategias terapéuticas específicas.

Palabras clave: *Neutrófilos. Trampas extracelulares de neutrófilos. NETs. ETosis. Autoinmunidad. Terapias anti-NET.*

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Introduction

Neutrophil extracellular traps (NETs) are the result of the extracellular release of nuclear chromatin associated with various cytotoxic granular proteins. They serve as a defense mechanism against microorganisms in the extracellular environment. While NETs offer antimicrobial protection, excessive formation or improper clearance can pose a problem, as their nuclear and/or cytoplasmic components can induce sterile inflammation and autoimmune responses, leading to various skin diseases.

Neutrophils

Neutrophils, or polymorphonuclear leukocytes (PMNs), are the body's first line of defense and make up about 50% up to 70% of circulating leukocytes. They have a multilobed nucleus of compact chromatin and a cytoplasm enriched with granules and secretory vesicles containing abundant lytic enzymes and antimicrobial peptides that can capture and eliminate pathogens[1,2]. They function at tissue level, maintaining a balance between production in the bone marrow and clearance by macrophages through phagocytosis[3].

Neutrophils arise through granulopoiesis from a hematopoietic stem cell that differentiates into multipotent progenitor cells and eventually into granulocytic-monocytic progenitors (GMPs). Under the control of granulocyte colony-stimulating factor (G-CSF), GMPs act on myeloblasts, which undergo various stages of maturation – promyelocyte, myelocyte, metamyelocyte, and band cell – culminating in the mature neutrophil[1,4,5] (Fig. 1). In the absence of inflammation, these mature neutrophils are stored in the bone marrow, spleen, liver, lungs, and other tissues. Their half-life in peripheral blood is about 6-8 h, but they can survive up to 5.4 days[1,5]. Moreover, during granulopoiesis, granules are formed sequentially, and based on their protein content, they can categorized into primary (azurophilic), secondary (specific), tertiary (gelatinase), and secretory vesicles, with ficolin-1 granules found only in mature neutrophils[4,6] (Table 1).

Neutrophil heterogeneity

Neutrophil populations are heterogeneous, displaying multiple phenotypes and functional states, particularly in chronic inflammation, autoimmunity, and cancer. Through centrifugation of a blood sample, leukocytes are separated based on their density gradient. PMNs that settle on erythrocytes are normal-density neutrophils (NDNs) – separated from peripheral blood mononuclear cells (PBMCs) – float in the upper layer at the interface between plasma and Ficoll-Paque (a cell separation medium)[6,7]. PBMCs include low-density neutrophils (LDNs), a heterogeneous population of immature and mature neutrophils. The immature subset may result from increased granulopoiesis in acute inflammation, while the mature subset may arise from activated NDNs or aberrant neutrophil precursors[7,8,9] (Fig. 2A).

These LDNs exhibit a pro-inflammatory phenotype, characterized by increased synthesis of cytokines, type 1 interferon (IFN-1), tumor necrosis factor-alpha (TNF-α), mitochondrial reactive oxygen species (ROS), greater capacity to form NETs with externalized modified nucleic acids, and greater potential to damage the vasculature. This contributes to the pathogenesis of several immune-mediated inflammatory diseases, such as systemic lupus erythematosus (SLE) or psoriasis, with a direct relationship between LDN quantity and disease severity[7,9,10] (Fig. 2B).

Leukocyte adhesion and migration cascade

When pathogens enter a wound or during an inflammatory process, macrophages release cytokines, and chemokines (TNF-α and interleukin 1 [IL-1]), sending chemical signals to neutrophils, stimulating, and activating the leukocyte adhesion cascade. Local endothelial cells increase their permeability and express adhesion receptors (E-selectins and P-selectins), thus allowing the recruitment of circulating neutrophils. Subsequently, firm adhesion integrins, such as intercellular adhesion molecules 1 and 2, and integrins are activated, enabling the neutrophil to enter between endothelial cells, extravasate, and through matrix metalloproteinase 9 (MMP-9), cross the basement membrane, and enter subendothelial tissues – diapedesis – migrating to the infection site[1,4]. Although functional implications remain unclear, some neutrophils can migrate away from inflammation sites through reverse transendothelial migration, contributing to the resolution of inflammation. However, they have a greater capacity to produce ROS and may travel to other organs, promoting tissue damage[1,10] (Fig. 1, lower inset).

Once in the tissues, neutrophils perform various functions, such as releasing granular contents sequentially (degranulation) or fusing with phagosomes; assembling the nicotinamide adenine dinucleotide phosphate oxidase

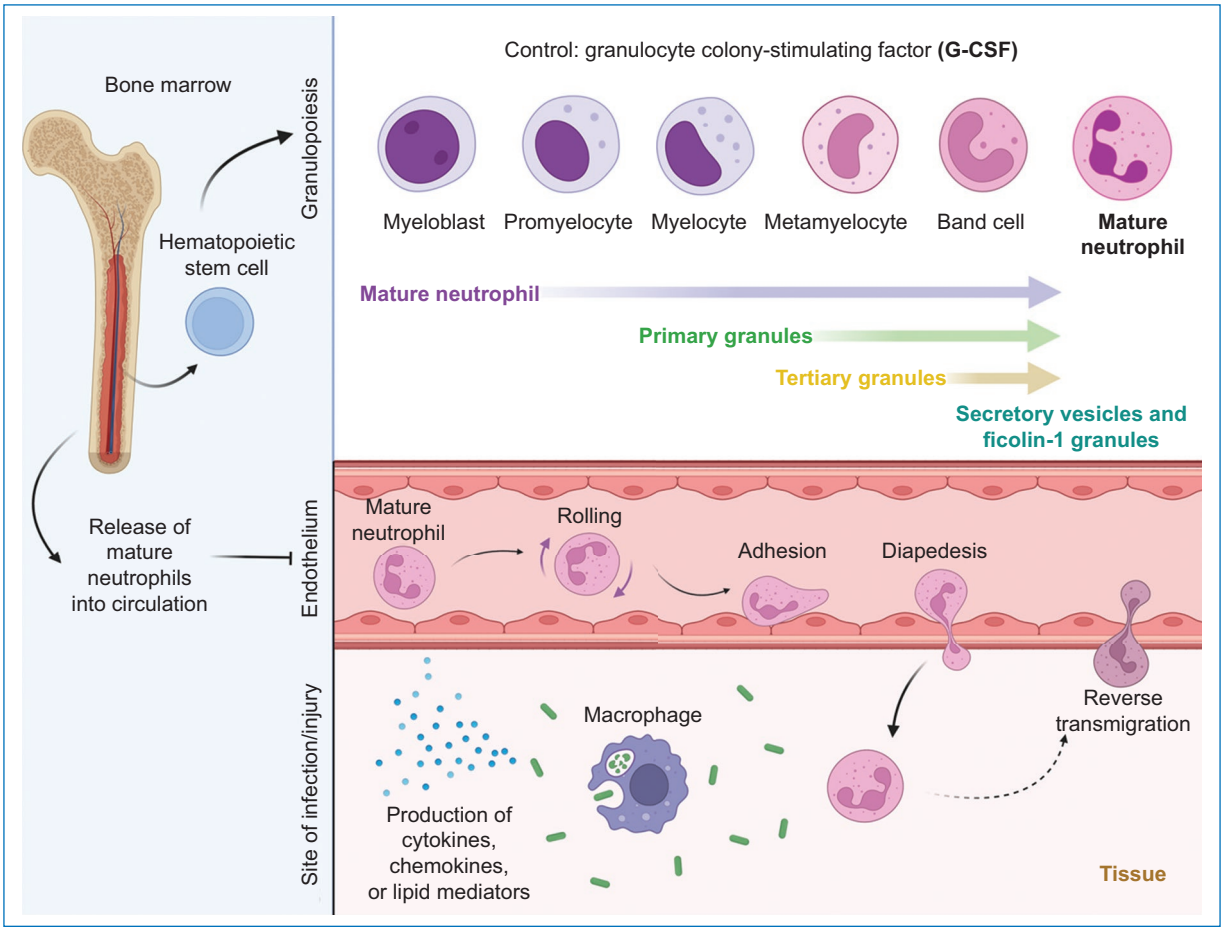

Figure 1. Granulopoiesis process and leukocyte adhesion and migration cascade. After the progressive differentiation of neutrophils and sequential formation of granules that grant them their effector functions, mature polymorphonuclear leukocytes exit the bone marrow into circulation, where they activate and migrate in response to any detected chemotactic agents, through various steps, to the site of infection or injury. They can also return to circulation through reverse transmigration *(created with BioRender.com).*

Table 1. Neutrophil granules and functions

Type of granule	Contained proteins	Functions
Primary, azurophilic, or peroxidase-positive	Myeloperoxidase, neutrophil elastase, cathepsin G, proteinase 3, lysozymes, neutrophil serine protease 4, α-defensins, azurocidin	Antimicrobial activity Involved in NETosis Extracellular matrix degradation
Secondary or specific	Collagenase, lactoferrin, LL-37 (cathelicidin), β2-microglobulin, haptoglobin, pentraxin-3, SLPI, flavocytochrome b, cytochrome b558 (membrane-bound component of NADPH oxidase)	Migration, antimicrobial activity Lactoferrin, the key role in NETosis
Tertiary or gelatinase	Matrix metalloproteinase (gelatinase), arginase 1, ficolin 1, Mac-1 surface receptors, lipocalin	Exocytosis Extracellular matrix remodeling, tissue migration
Secretory vesicles	Alkaline phosphatase, actin	Neutrophil recruitment (early stages of inflammatory response)
Ficolin 1	Actin and vanin-2	Migration and adhesion

NADPH: nicotinamide adenine dinucleotide phosphate; NET: neutrophil extracellular traps; SLPI: secretory leukocyte protease inhibitor.
Adapted from McKenna et al., 2021[6].

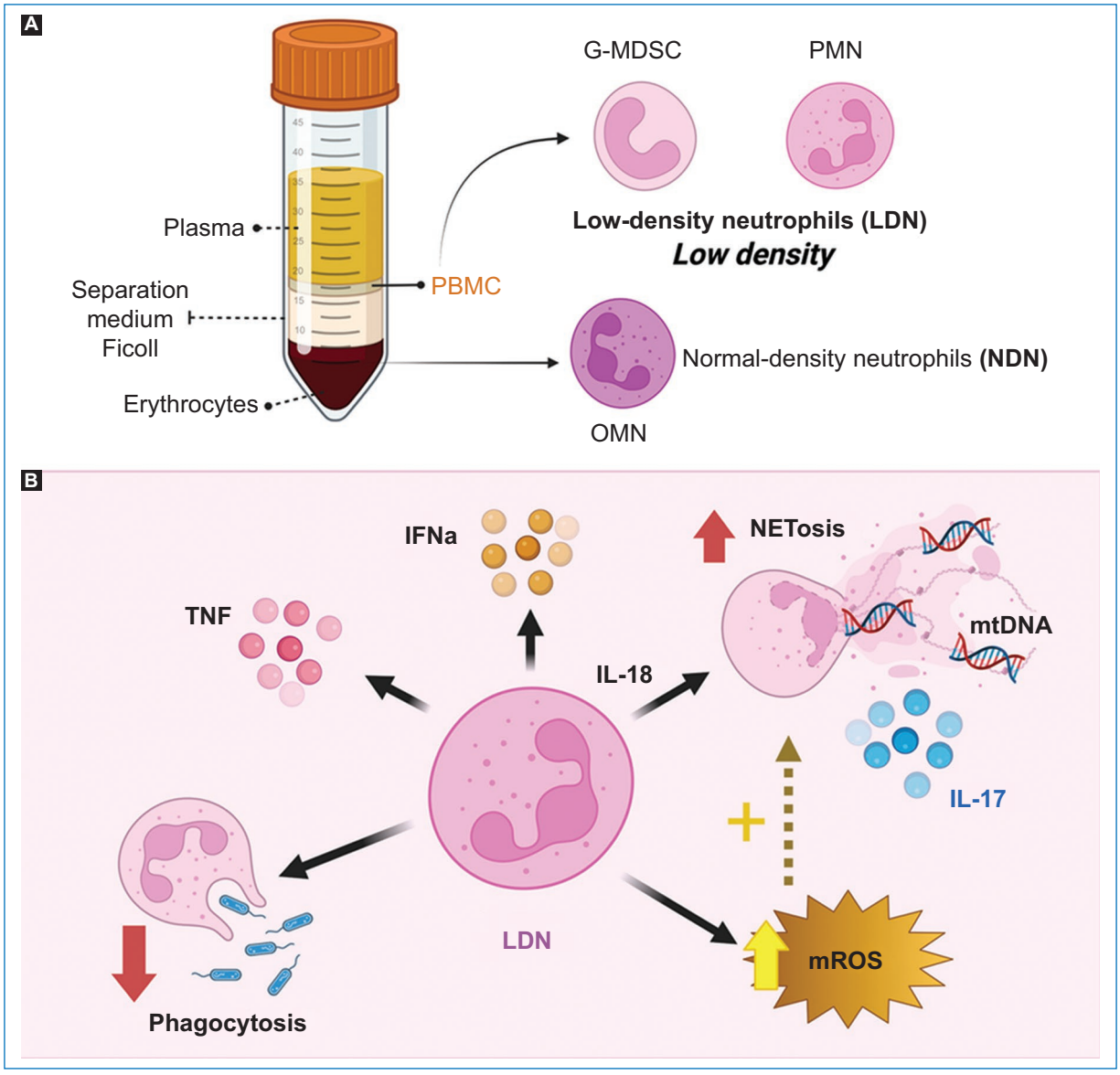

Figure 2. Neutrophil heterogeneity. **A**: after centrifugation, leukocytes are separated by density gradient. The least dense cells, peripheral blood mononuclear cells, including LDNs, separate at the top, comprising granulocytic myeloid-derived suppressor cells (G-MDSCs) and PMNs with immunosuppressive properties. **B**: properties of LDNs *(created with BioRender.com)*. mtDNA: mitochondrial DNA; IL: interleukin; IFN-α: interferon-alpha; TNF: tumor necrosis factor.

(NOX) enzyme complex; and producing large quantities of ROS, which are highly toxic to many microorganisms. They also release pro-inflammatory cytokines (TNF-α and IL-1β) and chemokines (IL-8) to recruit other immune cells and enhance the immune response. Neutrophils can also engulf microorganisms in a phagocytic vacuole (phagolysosome) to destroy them. Recently, neutrophils have been described as releasing NETs into the extracellular space when the microorganism is too large to be ingested[1,4-6].

NETs

This mechanism involves the deployment and release of modified chromatin decorated with granular, nuclear, and cytoplasmic proteins[11,12] (Fig. 3A). In 1958, Hirsch first described the bactericidal capacity of histones (the main protein component of chromatin) but could not explain how this intranuclear protein could contact microorganisms[13]. In 1975, Anker et al. described the ability of leukocytes to spontaneously and repeatedly

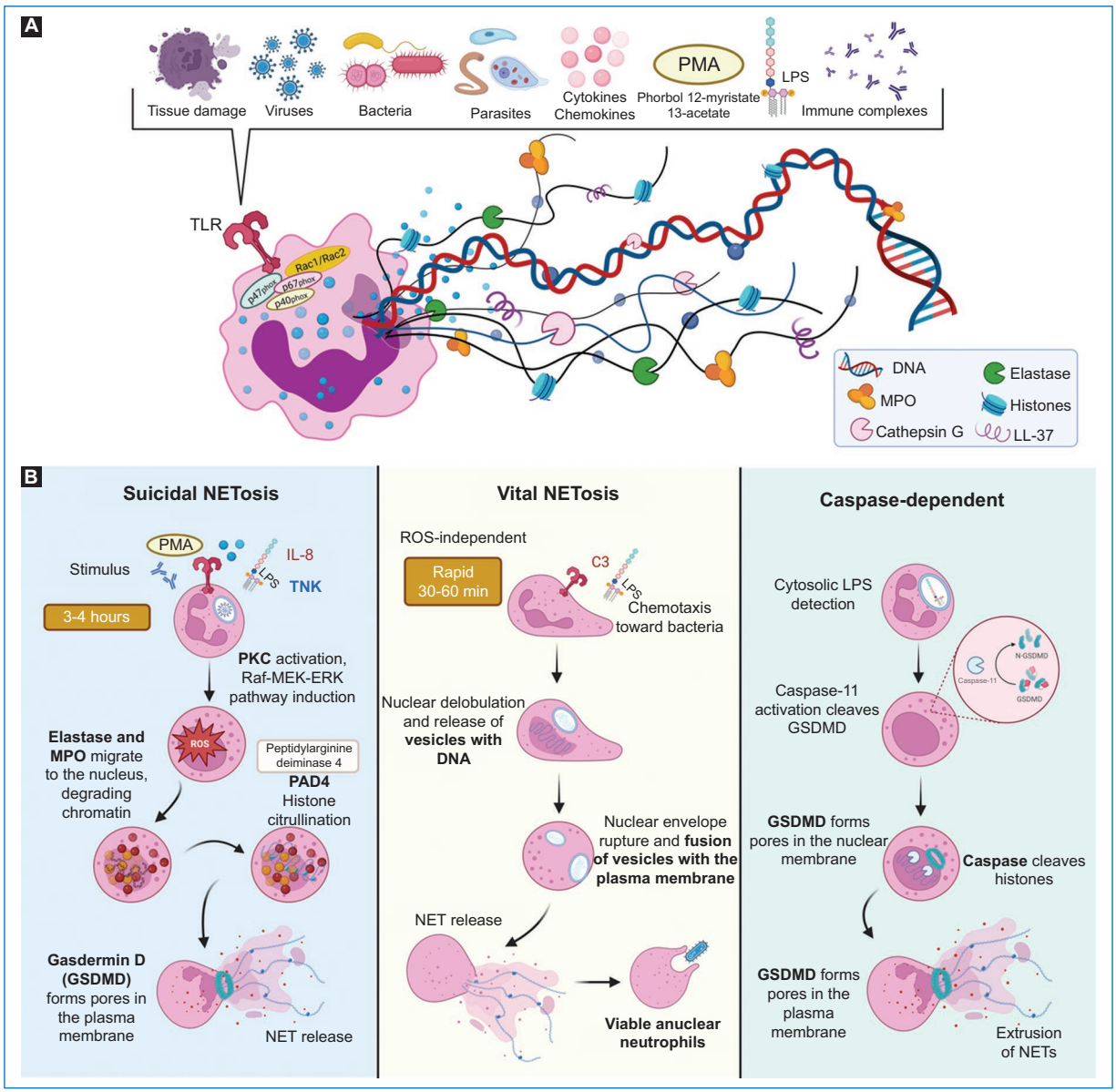

Figure 3. NETs and mechanisms of formation. **A**: different stimuli for NET formation. **B**: probable mechanisms of NET formation *(created with BioRender.com)*. NET: neutrophil extracellular traps; PM: plasma membrane; PAD4: peptidyl arginine deiminase-4; PKC: protein kinase C; PMA: phorbol 12-myristate 13-acetate.

release DNA *in vitro*, maintaining new DNA synthesis without decreasing cell viability[14].

For decades, it was believed that neutrophils mainly died by apoptosis, necrosis and necroptosis. However in 1996, Takei et al. observed by electron microscopy that neutrophils treated with a potent activator (phorbol 12-myristate 13-acetate; PMA) showed morphological atypical changes of apoptosis or necrosis, describing the sequence of events involved in the formation of NETs. These cells died by chromatin decondensation, nuclear membrane dissolution, and chromatin release coated with granular proteins[15]. These findings were confirmed by Brinkmann et al., in 2004, who formally introduced the term "neutrophil extracellular traps" after demonstrating, through electron and confocal microscopy, the extrusion of fibrous structures containing DNA from activated neutrophils, coated with proteins synthesized in granules and histones with bactericidal and sequestration capabilities[16].

Initially, the NET release was associated with neutrophil death, so the process was termed NETosis. However, chromatin release has also been identified in

other immune cells (eosinophils, basophils, mast cells, lymphocytes, monocytes, macrophages, and DCs), so this process is now known as ETosis[12,17].

Formation mechanism

NETs form after cell activation through recognition of various stimuli, including microbial products, such as lipopolysaccharides (LPS), fungal elements, and non-infectious triggers such as immune complexes (ICs), monosodium urate crystals, and nitric oxide (NO)[5,18] (Fig. 3A). Although not fully understood, three probable mechanisms of NET formation have been described, as explained below.

Suicidal NETosis

This is the classic and most extensively characterized form, lasting 3-4 h and ending in cell death. This mechanism is stimulated by PMA, N-formylmethionyl-leucyl-phenylalanine, LPS, TNF-α, IL-8 (CXCL8), and NO, which activates protein kinase C. This, in turn, phosphorylates RAF kinase, activating the RAF-MEK-ERK pathway and phosphorylating the NOX complex, leading to ROS production, which eventually promotes the activation and translocation of serine proteases, such as myeloperoxidase (MPO) and neutrophil elastase (NE), from granules to the cytoplasm, diffusing passively through nuclear pores[11,17-19] (Fig. 3B).

Chromatin decondensation occurs through histone degradation by NE activity, enhanced by MPO and histone citrullination by calcium-dependent peptidyl arginine deaminase 4 (PAD4), which weakens histone-chromatin connections, leading to chromatin degradation. After nuclear and granular membrane destruction, involving the pore-forming protein gasdermin D (GSDMD), electrostatic binding of granular contents to decondensed chromatin occurs. Then, at approximately 220 min, pores form in the cytoplasmic membrane by GSDMD, through which the DNA trap bound to proteins with antimicrobial activity is released into the extracellular space[12,17,18] (Fig. 3B).

Vital NETosis

It is a dynamic process that occurs within 30-60 min in response to infections by Gram-positive and Gram-negative bacteria, with stimulation of toll-like receptor 2 (TLR-2) or complement 3 (C3) to prevent bacterial dissemination. It keeps the neutrophil membrane intact and maintains its phagocytosis and chemotaxis functions. It is independent of ROS production, with vesicles being released from the nuclear envelope into the extracellular space, where they lyse and form NETs. Through a ROS-dependent pathway, viable neutrophils release NETs composed of mitochondrial DNA in response to granulocyte-macrophage colony-stimulating factor, LPS, and C5a[12,17,19] (Fig. 3B).

Caspase-dependent NETosis

This mechanism begins with the activation of caspase 11 by the stimulation of cytosolic LPS and Gram-negative bacteria leading to the cleavage of GSDMD, resulting in the formation of a pore in the nuclear membrane, allowing caspase 11 to enter and cleave histones, relaxing the chromatin, which is then released from the cell through a pore in the plasma membrane generated by GSDMD[17] (Fig. 3B).

Beneficial effects of NETs

NETs act as bactericidal agents against Gram-negative (aerobic: *Shigella spp., Pseudomonas aeruginosa, Escherichia coli, Salmonella enteritidis, Salmonella typhimurium, and Klebsiella pneumoniae*) and Gram-positive bacteria (aerobic: *Staphylococcus albus* and *Staphylococcus aureus*; anaerobic: *Propionibacterium spp.*), as well as some fungi (*Candida spp.* or *Aspergillus spp.*). These organisms induce NETosis through recognition of β-glucan on hyphae by extracellular matrix components or activation of NOX[18]. In dermatophytosis caused by *Trichophyton rubrum*, NETs form through ROS production[20]. During parasitic infections with *Plasmodium falciparum* and *Toxoplasma gondii*, NETs form through the MEK-signal-regulated kinase (ERK) pathway, limiting the parasites' dissemination. Against *Leishmania spp.*, histones restrict replication, alongside other NET-associated compounds (NE, MPO, and collagenase)[18,21].

During inflammation resolution and tissue repair, NETs stimulate wound healing and regulate angiogenesis, potentially affecting skin homeostasis[10,22].

Deleterious effects of NETs

NETs may contribute to the pathogenesis of diseases such as diabetes, acute respiratory distress syndrome, and heart diseases. In viral infections (influenza, HIV, severe acute respiratory syndrome coronavirus 2, and respiratory syncytial virus), excessive neutrophil recruitment activates TLR-4, TLR-7, and TLR-8, releasing

ROS and larger NETs that enhance cellular and alveolar apoptosis, worsening the disease[18]. The presence of tumor-associated neutrophils has been reported too, contributing to cancer dissemination by promoting mitochondrial functions in malignant cells, which, in turn, release IL-8 and G-CSF, inducing further NETosis. Finally, NET formation in circulation promotes coagulation, vascular occlusion, and thrombosis[5,17,18,21,23].

NETs and autoimmunity

Clearing cellular debris and NETs after an infection is of paramount important. Degradation of NETs starts with the involvement of deoxyribonuclease (DNase) I, and the remnants are endocytosed and lysed by macrophages, which release pro-resolving lipid mediators to limit acute inflammation and restore tissue homeostasis[12,23]. However, improper NET formation (aberrant NETosis), due to defects in DNase enzymes or inadequate macrophage clearance, can lead to chronic inflammation, tissue damage, and organ failure[17,22].

The content of NETs represents a source of alarmins and modified autoantigens, which, when exposed in an inflammatory microenvironment, are recognized by the immune system, triggering an autoimmune response in predisposed individuals[17,24].

NETs can prime T-cells to respond more effectively to antigens, triggering the production of antibodies by memory B-cells. They also stimulate plasmacytoid dendritic cells (pDCs) to produce high levels of IFN-1 through TLR stimulation, which prepares neutrophils for an intensified response to ICs. In addition, they activate resident tissue fibroblasts, attracting antigen-presenting cells and specific T-cell activation, resulting in a positive feedback loop[5,10].

NETs and skin diseases

SLE

In SLE, there is the production of autoantibodies against nuclear antigens and dysregulation of IFN-1 signaling, which is associated with skin involvement and the infiltration of neutrophils and NETs in the skin[10,25]. Neutrophils of lupus patients exhibit multiple phenotypic and functional abnormalities, particularly LDNs, which are more pro-inflammatory, with an increased capacity for NET formation dependent on mROS production, triggered by ribonucleoprotein immune complexes (RNP ICs). The increased synthesis of mROS promotes the oxidation of genomic and mitochondrial nucleic acids that are externalized in the NETs, which, along with apoptotic keratinocytes, activate endosomal TLRs in pDCs, leading to the upregulation of IFN-1 synthesis and subsequent interferogenic response in target cells. LDNs also increase NET formation in cutaneous lupus erythematosus lesions[7,9] in response to ultraviolet B (UVB) radiation and interaction with local skin components; they also contain MMP-9, which damages the endothelium and promotes vascular injury. In addition, NETs can modulate the function of other immune and resident tissue cells, such as fibroblasts, perpetuating vasculopathy and tissue damage[7,10,26].

Exposure to UVB radiation promotes increased neutrophil infiltration in the skin, which can travel to the kidneys through reverse transmigration and exacerbate systemic disease[10,26]. Changes to NET clearance by serum endonucleases, associated with the presence of DNase 1 inhibitors, have been reported increasing the half-life of modified nucleic acids and causing greater immune dysregulation[10,27] (Fig. 4).

Psoriasis

At present, it is suggested that the pathogenesis of the disease involves dysregulation of the innate and adaptive immune response, with interactions between neutrophils, keratinocytes, macrophages, and DCs, playing key pathogenic roles[28-30]. In the early stages, circulating neutrophils are attracted to subcorneal areas by the action of chemoattractants (CXCL16, leukotriene B4, and CXCR2 ligands) produced by activated keratinocytes and immune cells[10] (Fig. 5A).

Through NETs, NE protease induces keratinocyte proliferation, cathepsin G can contribute to local inflammation by activating IL-36, while proteinase 3 can cleave inactive pro-forms of the alarmin LL-37 (cathelicidin) produced by keratinocytes, acting as an autoantigen. Other effects on immune dysregulation, keratinocyte proliferation, and angiogenesis are due to increased ROS production by LDNs and NETs, as well as their involvement in the exaggerated secretion of IL-17 and inflammatory mediators, increasing neutrophil count, which has the potential to promote vascular damage[7,10,28].

The presence of NETs both systemically and in affected skin correlates with disease activity and represents a potent source of autoantigens. NETs synergistically activate TLR-4 and IL-36 receptor (IL-36R) in keratinocytes to secrete the neutrophil chemoattractant lipocalin 2 (LCN2), which regulates neutrophil chemotaxis and NET formation, fostering a vicious cycle of inflammatory responses[10,18,28]. LL-37 binds to NET nucleic acids (DNA or

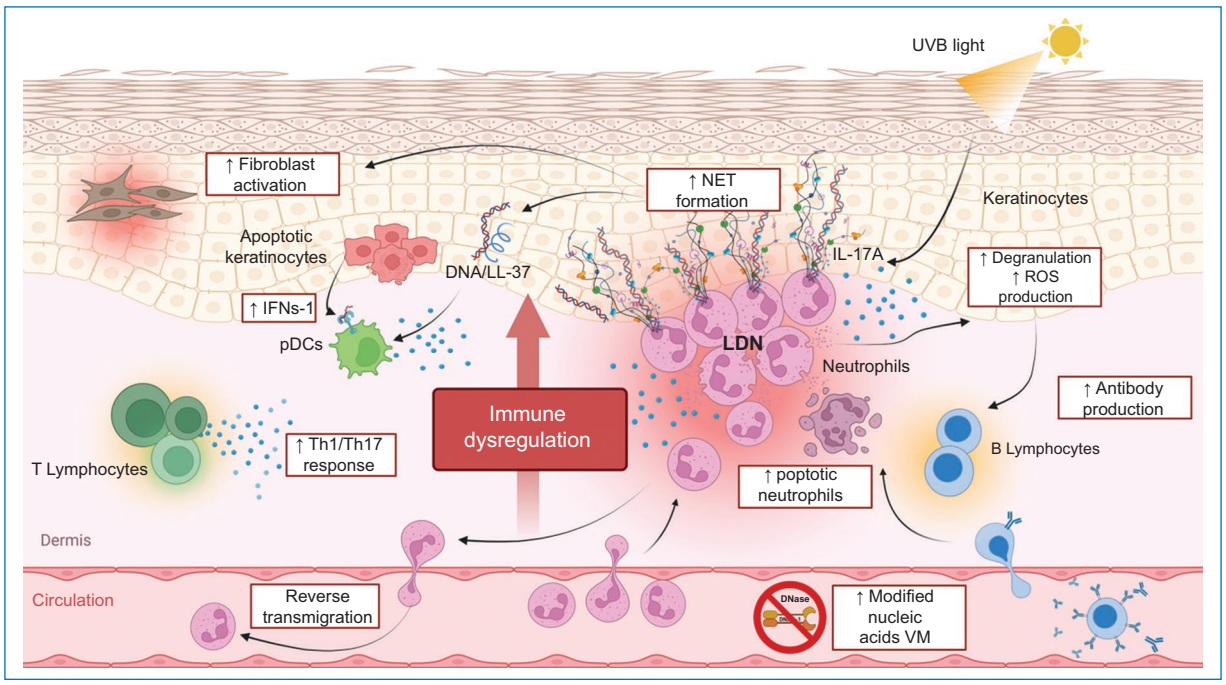

Figure 4. NETs in cutaneous lupus erythematosus. Low-density neutrophils are predisposed to form NETs in lesioned skin, which can be exacerbated by ultraviolet B exposure and interaction with skin components. Along with damaged keratinocytes, NETs provide an additional source of modified nucleic acids that may promote activation of endosomal toll-like receptors in plasmacytoid dendritic cells and upregulation of interferon 1 synthesis. They activate resident fibroblasts, perpetuating tissue damage. Some neutrophils can migrate to the kidney through reverse transmigration, exacerbating systemic disease *(adapted from Nakabo et al., 2022[10]; created with BioRender.com)*. Th: helper T cell; HL: half-life; NET: Neutrophil extracellular traps; TLR-4: toll-like receptor 4.

RNA) and is overexpressed both in the blood and psoriatic skin (Fig. 5B). pDCs recognize DNA/LL-37 or NE complexes and the secretory leukocyte protease inhibitor (SLPI), inducing IFN-1 production. Meanwhile, RNA/LL-37 complexes are recognized by conventional dendritic cells (cDCs), perpetuating inflammation through greater TNF-α and IL-6 production. LL-37 also enhances IL-8 secretion by activating mitogen-activated protein kinase p38 and extracellular ERK, inducing the release of human β-defensin 2. The overexpression of this peptide is associated with low susceptibility to skin infections and anti-apoptotic effects on keratinocytes, increasing cell proliferation[28-30].

Neutrophilic dermatoses

In neutrophilic dermatoses (ND), neutrophilic infiltrates predominate, with aberrant NET formation promotING inflammation in affected skin[10,31,32]. Pathogenesis involves interactions between genetic factors (e.g., *IL36RN*, *CARD14*, and *PSTPIP1*), immunological and epigenetic factors (mental stress, metabolic states, smoking), and environmental triggers that increase pro-inflammatory cytokines (IL-1, IL-36, IL-17, and TNF), chemokines, and other effector molecules inducing neutrophil chemotaxis and transmigration to affected skin. Activated neutrophils in lesional skin release more inflammatory mediators through degranulation, secretory vesicles, and NETs, where they activate resident and immune cells, such as keratinocytes, pDCs, and macrophages. Proteases activate IL-1/IL-36 cytokines in skin lesions, and along with excessive ROS production, they damage the vascular endothelial barrier, promoting fibrinogen oxidation, explaining the vasculitis and prothrombotic state in ND[11,32,33].

Recently, it was found that G-CSF, the main regulator of neutrophil biology, is strongly activated in hidradenitis suppurativa lesions and enhances neutrophil responses with NET formation, both systemically and in lesional ski[10,32], especially in dermal tunnels, where pro-inflammatory mediators increase transepithelial neutrophil traffic and NET formation, recruiting B-cells and DCs that contribute to auto-amplified inflammation and the continuous discharge of debris observed in severe disease[11,34].

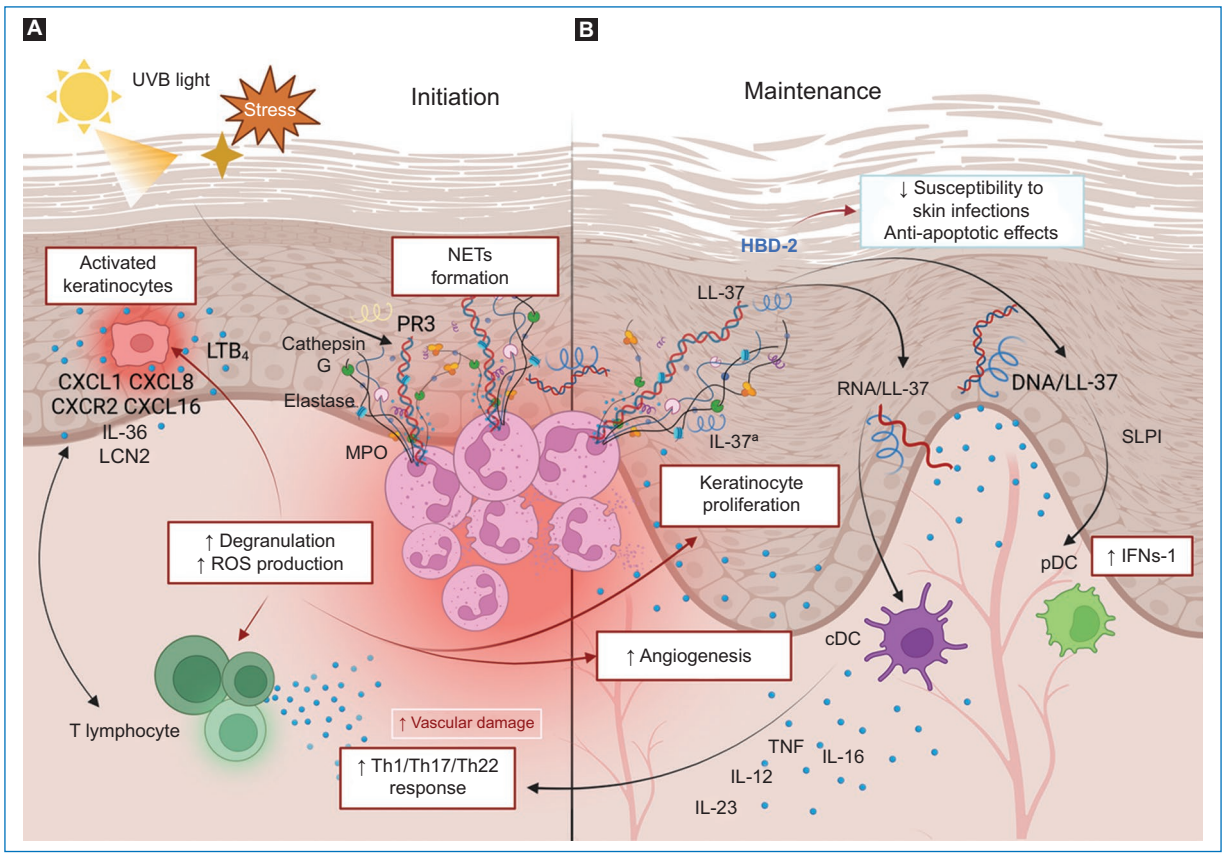

Figure 5. NETs in psoriasis. **A**: circulating neutrophils are attracted to subcorneal areas by different chemotactic agents produced by activated keratinocytes and various immune cells. Enhanced ROS production by neutrophils contributes to immune dysregulation, keratinocyte proliferation, and angiogenesis. NETs synergistically activate TLR-4 and IL-36R in keratinocytes to secrete the neutrophil chemoattractant LCN2, potentiating a vicious cycle of inflammatory responses. **B**: they also induce IFN-1 production by pDCs, which recognize the DNA/LL-37 complex *(created with BioRender.com)*. pDC: plasmacytoid dendritic cells; HBD-2: human β-defensin 2; IFN-1: interferon 1; IL: interleukin; IL-36R: interleukin 36 receptor; LCN2: lipocalin 2; LTB4: leukotriene B4; NET: neutrophil extracellular traps; PR3: proteinase 3; ROS: reactive oxygen species; SLPI: secretory leukocyte protease inhibitor; TLR-4: toll-like receptor 4.

Stevens-Johnson syndrome and toxic epidermal necrolysis

In these severe, potentially life-threatening adverse drug reactions, cytotoxic CD8+ T-cells and associated effector molecules, such as soluble FasL, perforin/granzyme B, granulysin, and IL-15, are involved. Recently, the presence of NETotic neutrophils has been elucidated both in the epidermis and dermis of damaged skin[35]. LCN-2 derived from drug-specific CD8+ T-cells triggers NET formation, which, in turn, releases LCN-2, amplifying trap formation in a paracrine feedback loop. Furthermore, NET-derived LL-37 induces the expression of formyl peptide receptor 1 (FPR1) on keratinocyte surfaces, promoting their necroptosis (mediated by annexin A1), releasing more LL-37, further inducing FPR1 in adjacent keratinocytes, potentially intensifying the LL-37/FPR1-annexin A1 axis during disease progression[11,35] (Fig. 6).

Serum levels of NET-associated dsDNA, LL-37, and the MPO-DNA complex are exclusively elevated in patients with Stevens–Johnson syndrome and toxic epidermal necrolysis, and in these cases, NET formation is much higher than in other above-mentioned skin diseases[11,35].

Therapeutic strategies

Evidence that NETs/ETs can trigger proinflammatory conditions is extensive; however, there are currently no specific therapies targeting the formation of these traps. Several therapeutic strategies have been suggested,

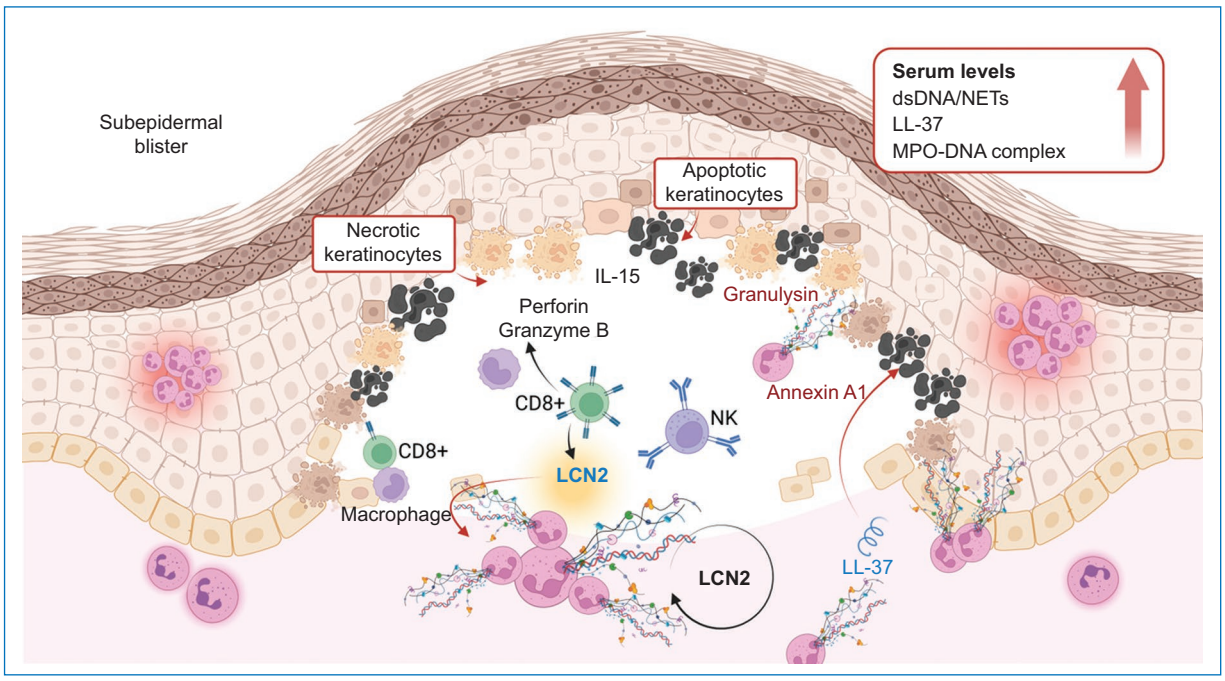

Figure 6. NETs in Stevens–Johnson syndrome and toxic epidermal necrolysis. LCN2 production by drug-specific CD8+ T lymphocytes stimulates NET production. NET-derived LL-37 mediates annexin A1 production, promoting further keratinocyte necroptosis *(created with BioRender.com)*. LCN2: lipocalin 2; LL-37: cathelicidin; MPO: myeloperoxidase; NET: neutrophil extracellular traps.

including the depletion or reduction of neutrophil numbers, blocking chemotaxis, activation, or toxic mediators derived from neutrophils and/or the formation of NETs.

Some pharmacological compounds, known and used in different diseases, have been proposed for their indirect effects on NETs, such as hydroxychloroquine, methotrexate, prednisolone, biologics, such as rituximab, belimumab, or tocilizumab, as well as some antimicrobials. However, these are not very specific and may affect important neutrophil functions[24].

Therapies targeting NET formation or neutralizing the released molecules could be useful in autoimmune conditions, especially if other neutrophil functions are preserved[10]. DNase I is the most widely used enzyme to disrupt NETs both *in vivo* and *in vitro* (well-tolerated in patients with cystic fibrosis), suggesting it could be used in other diseases, though it has a short half-life and is rapidly inactivated[17].

Clinical trials are currently underway to determine the safety and efficacy profile of PAD4 inhibitors (Cl-amidine, BB-chloro-amidine) due to their critical role in histone citrullination, which have proven effective in *in vitro* human cell models; however, inhibiting PAD4 remains concerning due to its involvement in gene regulation and cellular differentiation[10,17,24]. Neutrophil elastase inhibition, with Alvelestat® (AZD9668) and Sivelestat®, has shown efficacy in inactivating the toxic effects of NETs *in vitro* and *in vivo* murine studies; though promising, its role in systemic autoimmune disorders remains to be determined[10,17,23]. Neutralizing ROS and NET formation in SLE could be the target of drugs, such as N-acetylcysteine (NAC), mROS Inhibitors, and antioxidants such as Vitamins C and D24.

Therapeutic strategies targeting neutrophils are still in the pipeline or in preclinical phases and could be tested in the future, potentially becoming useful tools for this group of diseases[10,24].

Conclusion

NETs consist of modified chromatin release, decorated with granular, nuclear, and cytoplasmic proteins. They can be induced by a wide range of both physiological (microorganisms and their components) and pharmacological stimuli. While the mechanisms of formation are not fully understood, three types have been proposed so far: suicidal NETosis (classic), with cell death; vital NETosis, where cells retain not only their viability but also all natural effector functions; and caspase-dependent NETosis in association with GSDMD.

Although NETs have beneficial antimicrobial, antifungal, antiparasitic effects, and even help resolve inflammation and tissue repair, excessive production, with inadequate clearance by macrophages and defects in degradation by DNase I, leads to chronic inflammation, tissue damage, and organ failure.

Once exposed to the immune system, NETs are a source of autoantigens, leading to autoimmune and autoinflammatory diseases that affect the skin, such as SLE, psoriasis, neutrophilic dermatoses (NDs), and severe cutaneous adverse drug reactions.

Although NETs research is relatively new, recent and significant progress has advanced the understanding of neutrophils and their homeostatic and pathogenic functions, representing possible therapeutic targets in autoimmune skin diseases, which is expected to lead to paradigm shifts in treatment, improving patient outcomes.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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CASE REPORT

Gianotti-Crosti syndrome, about a case report

Síndrome de Gianotti-Crosti, a propósito de un reporte de caso

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Abstract

An unusual case of Gianotti-Crosti syndrome is presented in a recognized hospital in the city of Medellín, Colombia. This article aims to demonstrate how arduous the diagnosis of this pathological and the variants it may have. A systematic search was carried out in databases such as PubMed and ScienceDirect, with a period of 20 years, which included original articles, topic reviews, and reports of unusual cases of Gianotti-Crosti. All articles used are duly referenced and before the report, informed consent was obtained from the parents, who accepted the dissemination. An association of coinfection with other viral diseases was found, so it should be considered among the differential diagnoses of exanthematous diseases, especially in the pediatric population. Gianotti-Crosti syndrome, also known as papular acrodermatitis of infants, is of unknown incidence due to underdiagnosis. It begins with prodromes and subsequently the appearance of a monomorphic papular or papulovesicular exanthema with a benign and self-limited course without sequelae. There is no curative treatment; the objective is to minimize the symptoms and improve the patient's comfort.

Keywords: *Acrodermatitides. Gianotti-Crosti syndrome. Infantile papular acrodermatitis*

Resumen

Se presenta un caso inusual de síndrome de Gianotti-Crosti en un hospital reconocido de la ciudad de Medellín, en Colombia. Se pretende demostrar cómo y cuán arduo puede ser el diagnóstico de esta patología y las variantes que puede tener. Se realizó una búsqueda sistemática en bases de datos, tales como PubMed y ScienceDirect, de un periodo de 20 años, en la que se incluyeron artículos originales, revisiones de tema y reporte de casos inusuales de Gianotti-Crosti. Todos los artículos están debidamente referenciados y previo al reporte se diligenció el consentimiento informado a los padres, quienes aceptaron la difusión. Se encontró asociación de coinfección con otras enfermedades virales, por lo que se debe considerar entre los diagnósticos diferenciales de enfermedades exantemáticas, sobre todo en la población pediátrica. El síndrome de Gianotti-Crosti, también conocido como acrodermatitis papular del infante, es de incidencia desconocida por subdiagnóstico. Inicia con pródromos y posteriormente aparece un exantema papular o papulovesicular monomorfo de curso benigno y autolimitado sin secuelas. No existe un tratamiento curativo; el objetivo es minimizar la sintomatología y mejorar el confort del paciente.

Palabras clave: *Acrodermatitis. Síndrome de Gianotti-Crosti. Acrodermatitis papular infantil.*

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Introduction

The Gianotti-Crosti syndrome, also known as infantile papular acrodermatitis, was first described in 1953 as a previously unknown acrodermatitis in children. In 1955, Fernando Gianotti described several children with maculopapular rashes, lymphadenopathies, and acral lesions. Subsequently, in 1957, along with Agostino Crosti, they identified a total of 8 additional cases and published *Dermatosi infantile eruttiva acroesposta di probabile origine virosica*. Since Crosti was the head of the department, he was listed as the first author; hence, the name Gianotti-Crosti syndrome[1] was coined.

The exact incidence of this syndrome is unknown, as it is an underdiagnosed, rarely reported disease, overlapping with other nonspecific viral exanthems. It mainly affects infants between 2 and 6 years old and adolescents up to approximately 15 years old, with no sex predilection, prevailing in the summer and spring seasons[2,3], and is of a benign and self-limiting course[4]. Below, a case of Gianotti-Crosti syndrome in an infant is described, with the purpose of illustrating the clinical aspects and the challenges that can arise in diagnosing and managing this condition.

Case report

A 4-year-old boy, with a personal history of asthma and a first-degree family history of atopy, came to the Dermatology service service with a 1-month history of prodromal symptoms and the appearance of multiple erythematous plaques and very pruritic papules, initially located in the pretibial region and the back of the feet, which later generalized, affecting 90% of the total body surface area. The lesions were symmetrically located on the cheeks, trunk, and extensor regions of the limbs; one of them, located on the chest, showed a Koebner phenomenon (Fig. 1). Paraclinical tests were requested, including complete blood count, C-reactive protein (CRP), ferritin, liver profile, renal function, infectious profile with serology for syphilis, human immunodeficiency virus (HIV), M and G immunoglobulins for cytomegalovirus (CMV) and Epstein-Barr virus (EBV), and antibodies for hepatitis and monkeypox, which were within normal ranges, except for a slight elevation of lactate dehydrogenase (402 U/L). The skin was biopsized too.

In the outpatient setting, he was treated with ivermectin, steroids, and antihistamines for suspected scabies and atopic dermatitis, without improvement. In the in-hospital setting, given the extent, superinfection, and suspicion of a possible Kaposi varicelliform eruption, treatment with clindamycin, acyclovir, and systemic steroid was initiated.

Skin biopsies showed foci of hyperkeratosis, parakeratosis, acanthosis, and formation of spongiotic vesicles. In the dermis, a perivascular inflammatory infiltrate was observed both in the superficial and deep layers of the skin, as well as a deep perivascular lymphocytic infiltrate, without vasculitis. The histopathological finding was consistent with Gianotti-Crosti syndrome (Fig. 2).

Finally, after 10 days of in-hospital management, the patient showed a complete resolution of the skin lesions (Fig. 3) and was discharged with tapered oral steroids, antihistamines, and emollients. At the follow-up, he experienced a recurrence 6 weeks later, followed by complete improvement thereafter.

Discussion

Gianotti-Crosti syndrome is an underdiagnosed condition with unknown etiology. It is associated with infections by Hepatitis B virus, Epstein-Barr virus, cytomegalovirus, herpesvirus 6, influenza, and parainfluenza, among others[5-7]. This supports a relationship between the presence of viral infections and the development of the disease. Vaccination has become another frequent cause, especially within the first 20 days after vaccination, posing a higher risk if the person has a viral infection at the time of vaccination, due to a delay in the local immune response[3,8-10].

While viral infections are considered the most important factor in the development of Gianotti-Crosti syndrome, immunostimulation, and immunomodulation also play a significant role, which is why they sometimes have elevated IgE concentrations[11,12] which is another reason why children with atopic dermatitis are more predisposed to it[3,13].

Around 30% of patients present with prodromal symptoms, such as respiratory or GI infections, a week before the development of the skin rash[14-16]. The classic finding is the appearance of monomorphic pink to reddish-brown, itchy, confluent papules or papulovesicles, 1-5 mm in diameter, distributed symmetrically on the cheeks, the extensor regions of the limbs, and the buttocks. These lesions tend to be chronic, with a mean duration of about 4 weeks. A total of 35% of patients present with lymphadenopathies in the cervical, axillary, or inguinal region. Hepatic involvement is uncommon and mainly coexists with a viral infection; alterations in liver function tests or splenomegaly are rare, and if present, they usually take time to resolve[13,17,18].

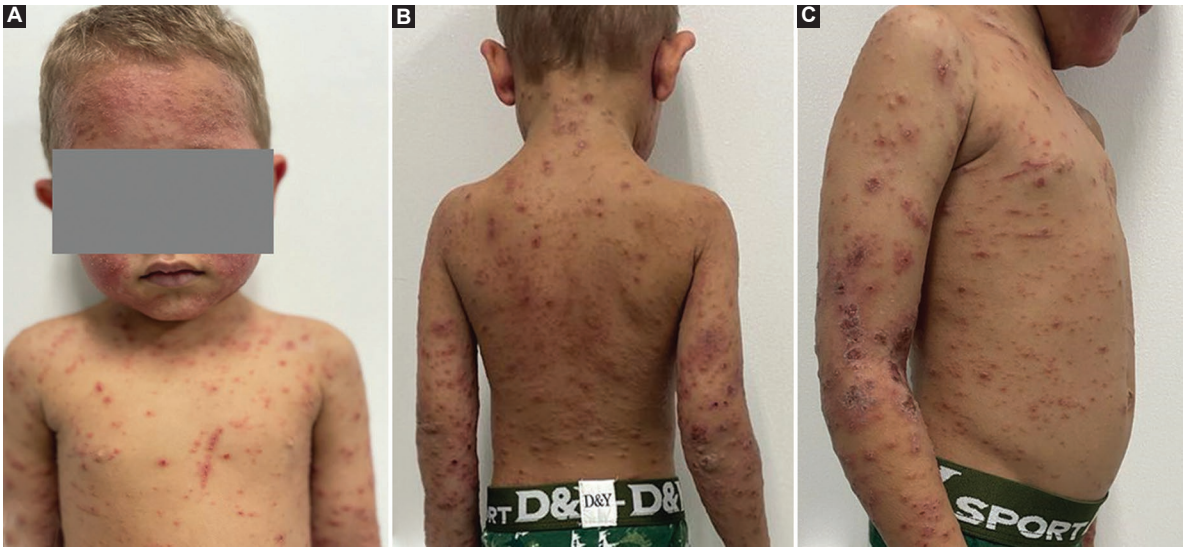

Figure 1. A: multiple erythematous papules converging to form larger plaques, located on the frontal region and the cheeks. Note the patient's facial edema and the linear lesion on the chest (Koebner phenomenon). **B** and **C:** multiple erythematous papules and plaques, some with bloody crust and others with serous crust, involving the trunk and upper limbs.

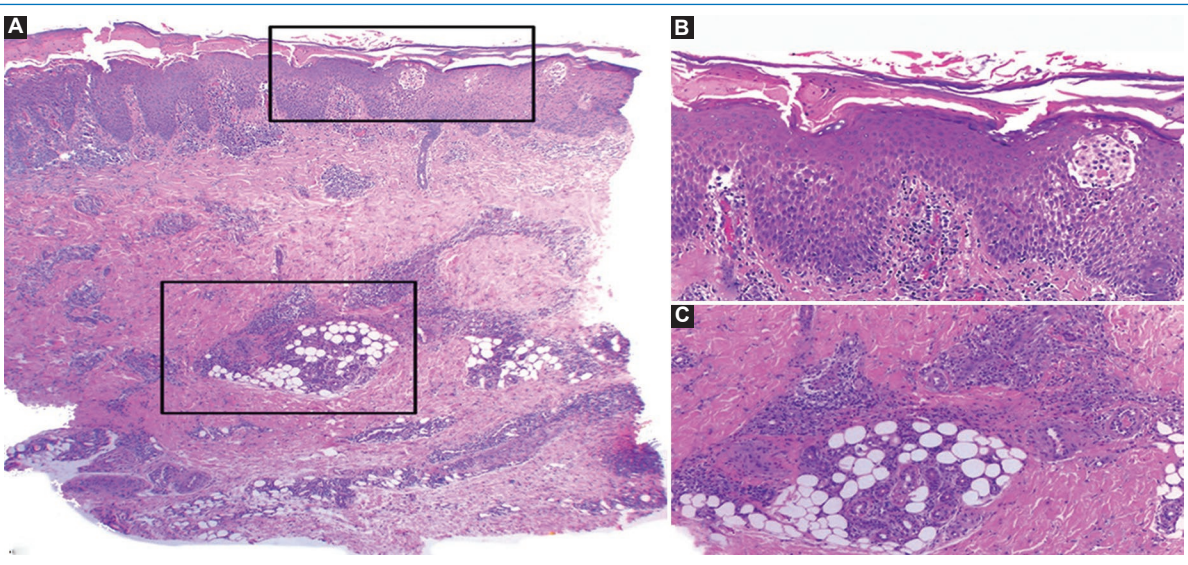

Figure 2. A: H&E 4×. In the panoramic view, skin is represented up to the subcutaneous tissue, epidermis with acanthosis, spongiosis, and pseudovesicles. In the dermis, the presence of superficial and deep perivascular inflammatory aggregates, involving up to the subcutaneous tissue. **B:** H&E 10×. The epidermis in greater detail shows hyperkeratosis with foci of parakeratosis, serous material in the stratum corneum, and a prominent granular layer. **C:** H&E 10×. Greater detail of the superficial and deep perivascular lymphocytic infiltrate without damage to the vessel wall.

The diagnosis is clinical, but in challenging cases, a skin biopsy can be useful, especially when signs are atypical or there is chronicity in the lesions despite treatment, as in the case of our patient, who after a 4-week course of the disease, and despite the treatment administered, had a recurrence 6 weeks later.

Skin biopsy offers key findings that guide the diagnosis, although they can be nonspecific, such as focal

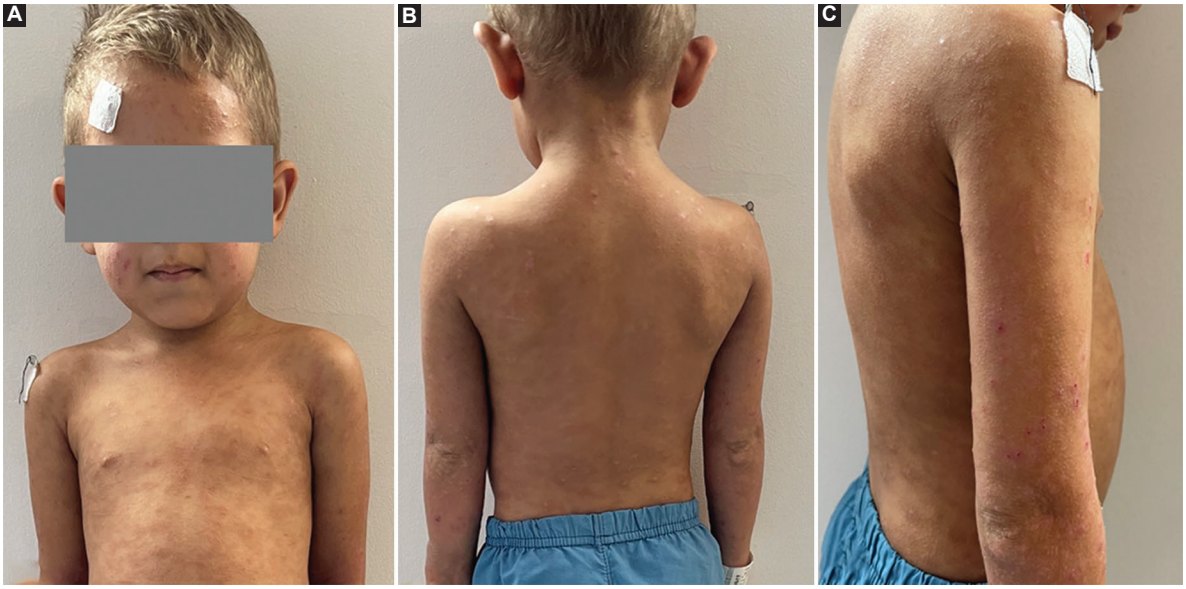

Figure 3. A: some erythematous and other normochromic papules, located on the skin of the frontal region and the cheeks. Note the resolution of facial edema. **B:** multiple macules with irregular, poorly-demarcated, hypopigmented borders, located on the trunk and upper limbs. **C:** some excoriated erythematous papules on the upper limbs.

spongiosis, papillary dermis edema with extravasation of erythrocytes, mild acanthosis, hyperkeratosis, parakeratosis with intense perivascular infiltration with lymphocytes and histiocytes in the upper dermis, and dilated dermal capillaries[17,19]. In Gianotti-Crosti syndrome, two main histological patterns have been described: non-vesicular and vesicular. The latter occurs more frequently, with spongiotic vesicles in the epidermis, along with epidermal changes such as acanthosis and spongiosis, as identified in the present case. In the dermis, a perivascular inflammatory infiltrate is observed both in the superficial and deep layers of the skin[1]. It seems obvious that sometimes, the findings can range from imperceptible to very noticeable; however, they are not diagnostic on their own.

Although more common in childhood, cases in adults have also been reported. Ting et al.[4] reported the cases of a 37-year-old Asian woman, previously healthy, who presented with prodromal symptoms and subsequently developed a pruritic papular rash on the limbs, with normal blood chemistry and a negative infectious profile, biopsy with nonspecific findings but suggestive of Gianotti-Crosti syndrome, treated with systemic steroids and showing complete resolution within 3 weeks, and the case of another 21-year-old Caucasian woman with Gianotti-Crosti syndrome, who received topical clobetasol as treatment and showed complete resolution within 4 weeks.

Although the Gianotti-Crosti syndrome is a short-duration disease, cases of chronic Gianotti-Crosti syndrome have been reported in the literature. Chin and Liy-Wong[20] reported the case of a 3-year-old patient with a 20-month history of Gianotti-Crosti syndrome, in whom the only relevant history was prior hand-foot-mouth disease. This, more than an active infection, reflects a post-infectious inflammatory process, a condition that resembles the clinical picture of our patient, which was prolonged until the resolution of the lesions.

Treatment is primarily symptomatic, as there is no specific management. Emollients, topical antipruritics, systemic antihistamines, and medium-potency topical steroids for 7-14 days are used, and only in severe cases systemic steroids are used[1].

Despite the benign and self-limiting nature of Gianotti--Crosti syndrome, the prolonged course and extent of skin involvement can sometimes be puzzling. However, it is important to remind parents and patients that the sequelae are minimal or non-existent.

This case highlights the importance of always considering this diagnosis in patients presenting with extensive and long-lasting rashes, in whom other viral etiologies have been ruled out[1,13]. Family physicians, pediatricians, and dermatologists should consider Gianotti-Crosti syndrome within the differential diagnoses of viral exanthems that are common in pediatric patients.

Conclusions

Gianotti-Crosti syndrome is a condition that should always be suspected in the pediatric population, but it can also occur in adults. It should be considered in association with other viral infections and in generalized maculopapular exanthems. Although the cutaneous signs can sometimes be disproportionate, it is benign and self-limiting without sequelae. The goal is always to ensure comfort and relieve the patient's symptoms.

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The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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CASE REPORT

Pseudoxanthoma elasticum, beyond the skin

Pseudoxantoma elástico, más allá de la piel

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Abstract

Pseudoxanthoma elasticum, also known as Grönblad–Strandberg syndrome, is a rare disease, with autosomal recessive inheritance, which is characterized by the pathological mineralization of the elastic fibers of the connective tissue, mainly affecting the dermis, blood vessels, and Bruch's membrane at ocular level. The disease is caused by pathogenic variants of the ABCC6 gene, which causes extracellular accumulation and deposition of calcium and other minerals in elastic tissue. We present a case diagnosed in adulthood, highlighting the importance of early diagnosis, prevention of complications, and current therapeutic approaches.

Keywords: *Pseudoxanthoma elasticum. Grönblad–Strandberg syndrome. Angioid streaks. Genodermatosis.*

Resumen

El pseudoxantoma elástico, también conocido como síndrome de Grönblad-Strandberg, es una enfermedad rara, de herencia autosómica recesiva, que se caracteriza por la mineralización patológica de las fibras elásticas del tejido conjuntivo, con afección principalmente de la dermis, los vasos sanguíneos y la membrana de Bruch en el ojo. La enfermedad es causada por variantes patogénicas del gen ABCC6, que provocan la acumulación extracelular y el depósito de calcio y de otros minerales en el tejido elástico. Presentamos un caso diagnosticado en la adultez, destacando la importancia de su diagnóstico precoz, la prevención de las complicaciones y los enfoques terapéuticos actuales.

Palabras clave: *Pseudoxantoma elástico. Síndrome de Grönblad-Strandberg. Estrías angioides. Genodermatosis.*

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Introduction

Pseudoxanthoma elasticum is a rare disease characterized by the pathological mineralization of the connective tissue elastic fibers, primarily affecting the skin, eyes, and cardiovascular system. It is inherited in an autosomal recessive manner with complete penetrance, and the affected gene is ABCC6, which encodes a transmembrane protein responsible for transporting certain anions. The genetic defect is located on chromosome 16p13.1. In the skin, it manifests as yellowish papules that merge to form plaques, giving a cobblestone appearance. Diagnosis is usually achieved in adulthood, in the 2nd or 3rd decades of life. We present the case of a patient diagnosed with pseudoxanthoma elasticum in adulthood.

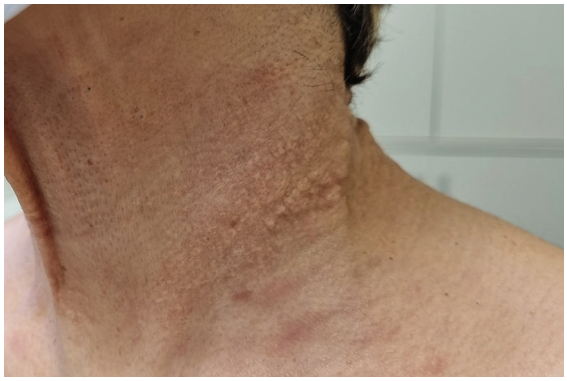

Figure 1. Millimetric skin-colored papules with a cobblestone appearance in the cervical region.

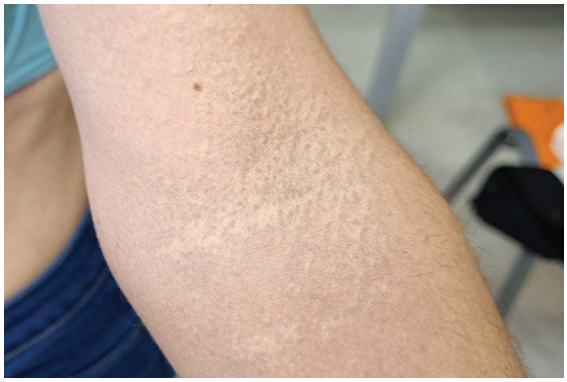

Figure 2. Millimetric papules in the antecubital fossa.

Case report

A 48-year-old woman presented with a personal history of kidney stones, irritable bowel syndrome, and a 3-year history of decreased visual acuity in her right eye before the consultation. Her gynecological and obstetric history includes 4 uneventful pregnancies (3 vaginal deliveries and 1 C-section). The patient consulted the dermatology department for small brown-yellowish papules that coalesced to form large plaques, giving a cobblestone appearance, located on the neck, axillae, antecubital fold, and periumbilical region (Figs. 1 and 2), along with redundant skin on the lateral neck and axillae (Fig. 3). In addition, hyperpigmented, brownish macules were observed in the central thoracic and abdominal regions. All lesions were pruritic, with a 1-year history, without mucosal involvement. Suspecting pseudoxanthoma elasticum, cutis laxa, and mid-dermal elastolysis, a skin biopsy of 2 lesions – 1 cervical and 1 abdominal – was performed. Histopathological examination of the lesions revealed irregularly basophilic altered fibers in the mid-dermis with focal deposits of granular calcific material between the fibers (Fig. 4). Orcein staining showed fragmented elastic fibers forming purple clumps (Fig. 5), consistent with pseudoxanthoma elasticum. The ophthalmological history was looked into, as well as an eye examination from November 2020 was requested. Fundoscopy of both eyes revealed the presence of deep grayish bands consistent with angioid streaks. In the right eye, an elevated lesion in the macular area was observed, along with a whitish subretinal lesion consistent with fibrosis. This was interpreted as a scarring sequela of a neovascular membrane, responsible for the decreased visual acuity (Fig. 6). The patient was referred for cardiovascular, gastroenterological assessment, and family genetic counseling for multidisciplinary management. The cardiovascular examination included an ECG, exercise stress test, and Doppler echocardiography, all of which showed normal parameters and no signs of heart disease. Abdominal ultrasound, fecal occult blood test, and upper and lower GI endoscopy also turned out normal. No family member had skin lesions; a sister of the patient had a history of hypertension. Although the patient was advised to seek genetic counseling, she has not yet done so.

Discussion

Pseudoxanthoma elasticum is a genetic disease characterized by fragmentation and calcification of elastic fibers, leading to dermatological, ophthalmological, and cardiovascular defects[1]. It was first described in 1896

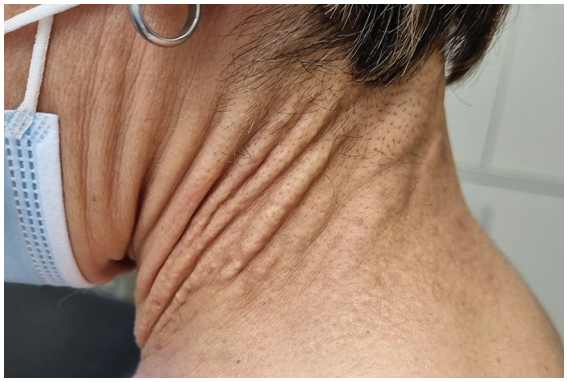

Figure 3. Redundant and lax skin on the lateral cervical area.

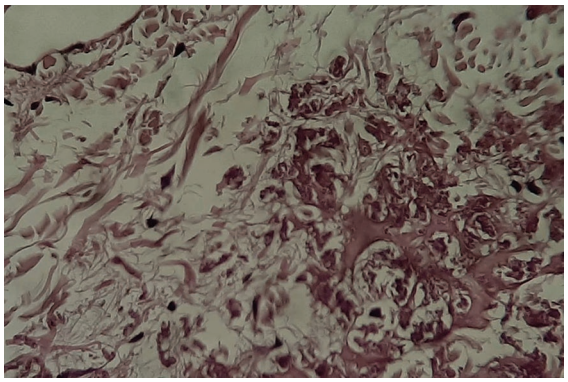

Figure 5. Orcein technique (10×). Fragmented elastic fibers forming clumps are observed.

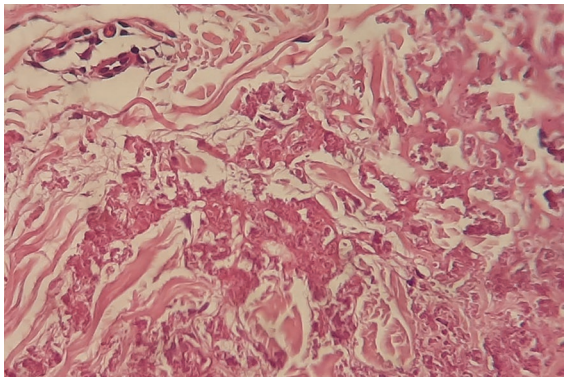

Figure 4. Hematoxylin-eosin stain (10×). In the dermis, clumps of fragmented fibers with a slightly eosinophilic granular appearance are observed.

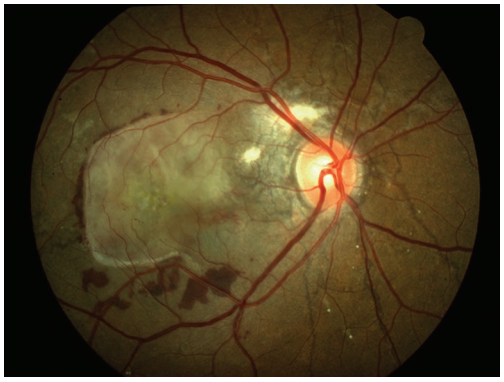

Figure 6. Right fundus. In the nasal peripapillary region, irregular grayish bands corresponding to angioid streaks are observed.

by the French dermatologist Ferdinand–Jean Darier, and its name refers to the characteristic yellowish tone and particular skin laxity[2]. The prevalence of pseudoxanthoma elasticum is estimated at 1 in 25,000-100,000 people. Pseudoxanthoma elasticum is an autosomal recessive inherited disease in which a loss-of-function mutation is detected in the ABCC6 gene. This gene encodes an ATP-binding transporter. Its absence results in decreased ATP secretion by hepatocytes, with the corresponding decrease in plasma concentrations of inorganic pyrophosphate, an inhibitor of mineralization, and thus ectopic calcification especially in soft tissues, as well as a significant reduction in serum fetuin-A concentration, an important anti-mineralization protein[3,4].

Regarding clinical signs, cutaneous findings are usually the first signs and consist of small yellowish or skin-colored papules that progressively merge to form large asymptomatic plaques. They primarily affect areas of skin folds (neck, axillae, and groin). The skin becomes loose, wrinkled, and redundant. These changes are usually observed in childhood and adolescence and progress slowly and unpredictably into adulthood, with pseudoxanthoma elasticum being most widely diagnosed in adulthood. Changes in the oral and genital mucosa and semi-mucosa have also been reported[5]. The characteristic ocular sign described include "peau d'orange," angioid streaks, choroidal neovascularization, hemorrhages, and scar formation. "Peau d'orange" is the first ocular alteration and consists of small dark spots that give a mottled appearance to the periphery of the temporal area of the retina. Although angioid streaks are a common finding, they are not pathognomonic, as they can be present in other diseases, such as sickle cell anemia, thalassemia, and

Ehlers–Danlos syndrome. They are generally asymptomatic and correspond to discontinuities in the calcified elastic layer of Bruch's membrane. As the disease progresses, calcification of Bruch's membrane can trigger choroidal neovascularization in the posterior pole of the retina, leading to hemorrhage, scarring, loss of central vision, and blindness, as it happened in our patient[2]. Cardiovascular signs are due to degeneration of the vessels tunica media and can result in GI hemorrhage, acute myocardial infarction, or cerebral infarction, among others[6,7].

There is no international consensus on the clinical and genetic diagnosis of pseudoxanthoma elasticum. In 2010, Plomp et al.[8] conducted a review and proposed an update to the classification previously made by Pope et al.[6], thus defining major and minor diagnostic criteria based on clinical and histopathological signs (Table 1). For a definitive diagnosis, 2 or more major criteria are required (Table 2)[2,6,8]. Our patient meets 3 major criteria supporting the diagnosis of pseudoxanthoma elasticum. Histopathology of the skin lesions is essential for definitive diagnosis. The characteristic alterations are deformed and fragmented elastic fibers in the reticular, mid, and deep dermis. In advanced cases, calcium deposits are visible in systematically stained sections as purple clumps. Sometimes, elastin (Verhoeff-van Gieson) and calcium (von Kossa) stains are necessary to visualize the characteristic changes of elastic fibers[9,10]. Regarding genetic diagnosis, although the study of the genes involved is not strictly necessary, the involvement of the ABCC6 gene confirms the diagnosis; it is useful for determining whether asymptomatic family members of the affected patient are carriers of this disease[6,11]. In the case presented here, although genetic counseling was indicated, the patient has not attended the genetic counseling session. Recently, mutations in the ENPP1 (ectonucleotide pyrophosphatase 1) and GGCX (gamma-glutamyl carboxylase) genes have been involved in pseudoxanthoma elasticum. The former is involved in pyrophosphate metabolism – which is the basis of ectopic mineralization in pseudoxanthoma elasticum – and the latter is involved in encoding essential antioxidant enzymes[12].

There are numerous differential diagnoses, such as actinic elastosis, mid-dermal elastolysis, fibrous white papulosis of the neck, cutis laxa, anetoderma, and connective nevi, among others[6,13].

At present, there is no specific treatment. Management focuses on prevention and symptomatic treatment of its complications. Annual dermatological and biannual ophthalmological control is required. Contact sports, activities with a high risk of trauma, or increased cranial pressure should be avoided[3,6]. Esthetic surgery for excess skin – considering possible scarring complications – and the use of fractional Co_2 laser for improving skin texture have been described[4,14]. The current approach for treating cardiovascular and systemic signs is based on reducing cardiovascular risk factors[2]. Several studies suggested that the mineral composition of the diet, particularly magnesium supplementation, could prevent mineral deposition in connective tissue[3,9]. Regarding prognosis, pseudoxanthoma elasticum causes significant morbidity mainly due to decreased visual capacity and skin changes. Massive upper GI bleeding, ischemic heart disease, peripheral

Table 1. Updated diagnostic criteria according to Plomp et al.[8]

Major criteria	
Cutaneous	I. Yellowish papules or plaques on the lateral neck or in flexural folds; or II. Biopsy of affected skin showing an increased number of morphologically altered fibers, with fragmentation, clumping, or calcification of elastic fibers.
Ophthalmological	I. "Peau d'orange" appearance in the retina; or II. ≥ 1 angioid streaks, with a minimum length of the optic disc diameter. If in doubt, perform fluorescein angiography (FA) as a confirmatory method.
Genetic	I. Pathogenic mutation in both alleles of the ABCC6 gene; or II. First-degree relative with definitive diagnostic criteria for pseudoxanthoma elasticum independently.
Minor criteria	
Ophthalmological	I. 1 angioid streak < 1 optic disc diameter in length; or II. ≥ 1 comet lesion in the retina; or III. ≥ 1wing lesions in the retina.
Genetic	I. Pathogenic mutation in one allele of the ABCC6 gene.

Table 2. Updated categorization of pseudoxanthoma elasticum according to Plomp et al.[8]

Definitive	≥ 2 major criteria from different categories.
Probable	2 major ophthalmological criteria; or 2 major cutaneous criteria; or 1 major criterion + ≥ 1 minor criteria from a different category than the major criterion.
Possible	1 major criterion, excluding other causes of pseudoxanthoma.

vascular disease, and cerebrovascular disease are causes of death[6,15].

We presented a case of pseudoxanthoma elasticum whose diagnosis was made through a detailed dermatological examination. We highlight the role of the dermatologist and the importance of the skin as the first organ to show systemic diseases.

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Ethical disclosures

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CASE REPORT

Rapid response of hand eczema with psoriasis overlap to upadacitinib

Rápida respuesta de eccema de manos y psoriasis superpuesta a upadacitinib

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Abstract

Palmoplantar psoriasis is a clinical form of psoriasis that can represent a diagnostic challenge due to its clinical and histological similarity to hand eczema. The concomitant presentation of both pathologies is uncommon and has a limited response to common treatments. The four isoforms of Janus kinases (JAK) are crucial intracellular mediators associated with cytokine receptors. Upadacitinib has been approved for several diseases, including psoriatic arthritis and atopic dermatitis, and has demonstrated efficacy in psoriasis vulgaris as a secondary endpoint in patients with psoriatic arthritis. We present a case of overlapping psoriasis/chronic hand eczema that, after several therapeutic failures, obtained an excellent clinical response to upadacitinib.

Keywords: *Upadacitinib. Psoriasis. Janus kinases.*

Resumen

La psoriasis palmoplantar es una forma clínica de psoriasis que puede representar un reto diagnóstico por su similitud clínica e histológica con el eccema de manos. La presentación de ambas afecciones de forma concomitante es infrecuente y cuenta con una limitada respuesta a los tratamientos habituales. Las cuatro isoformas de Janus cinasas (JAK) son mediadores intracelulares asociados a receptores de citocinas. El upadacitinib ha sido aprobado para varias enfermedades, incluyendo la artritis psoriásica y la dermatitis atópica, y ha demostrado eficacia en la psoriasis vulgar como objetivo secundario en pacientes con artritis psoriásica. Presentamos un caso de superposición de psoriasis y eccema crónico de manos que tras varios fracasos terapéuticos tuvo una respuesta clínica excelente al upadacitinib.

Palabras clave: *Upadacitinib. Psoriasis. Janus cinasas.*

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Introduction

Psoriasis and eczema are two inflammatory skin diseases that, despite being common in the general population, rarely coexist in the same individual[1]. Palmoplantar skin involvement due to these conditions often has a significant impact on quality of life due to its frequent association with local symptoms such as itching or painful fissures, functional limitations, and marked effects on self-esteem[2]. Simultaneous lesions of psoriasis and eczema in this location are usually a therapeutic challenge, leading to frequent relapses and a tendency toward chronicity[3]. We present a case of overlapping psoriasis and chronic hand eczema that, after several therapeutic failures, achieved an excellent clinical response to upadacitinib.

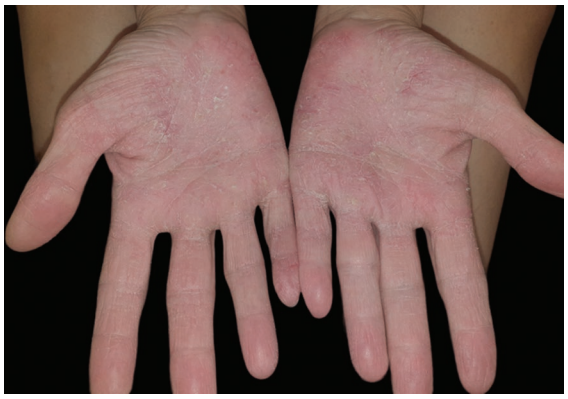

Figure 1. Palmar side of both hands before starting upadacitinib. Notable scaling on an erythematous background and skin fissures.

Case report

A 58-year-old woman presented with a past medical history of hypertension and predominantly palmoplantar psoriasis since her youth, with erythematous scaly plaque lesions without pustules (Fig. 1), occasionally located on her limbs. Although she did not exhibit associated arthritis, her skin condition limited her activities of daily living, with a Dermatology Life Quality Index (DLQI) score of 19 and significant itching of 8/10 on the numerical scale. She received numerous therapeutic lines with unsatisfactory results: Potent topical corticosteroids and phototherapy (ineffective), methotrexate (gastrointestinal intolerance), and acitretin (cutaneous intolerance). After starting apremilast, she initially responded well, but efficacy was lost after nearly 3 years of treatment, which was consistent with an exacerbation of palmar-dominant itching and lesions on her elbows. On her hands, she exhibited erythematous scaly plaques with a few vesicles on the lateral sides of the fingers, resembling dyshidrosis (Fig. 2). Due to refractoriness to conventional therapies and contraindication of cyclosporine due to the patient's hypertension, adalimumab was initiated, resulting in remission of the elbow lesions but overt worsening of the palms, with exacerbation of the eczematous component. Although a short course of oral corticosteroids was prescribed for control, relapse occurred upon discontinuation. Histopathological examination of the hand skin revealed findings of overlapping chronic eczema and psoriasis (Fig. 3): acanthosis with regular epidermal hyperplasia, suprapapillary atrophy, and regions of orthokeratosis with underlying hypergranulosis, alternating with regions of parakeratosis and absence of the granular layer. Although secukinumab was subsequently prescribed at the conventional dose for psoriasis, initially leading to improvement, therapeutic control was not achieved after 6 months of treatment. Patch tests were performed with no clinically relevant results. Since the predominant clinical-pathological findings were consistent with overlapping hand psoriasis and eczema, upadacitinib was initiated at a dose of 15 mg/day, resulting in a very rapid clinical response, with complete remission of itching within 48 h and of lesions 15 days after being put on upadacitinib (Fig. 4). At the 6-month follow-up, the patient remains asymptomatic, with a DLQI of 0 and no lesions. To date, the patient has not experienced any adverse effects and will continue to be monitored for potential relapses.

Discussion

Psoriasis and eczema are diseases that, although they can share indistinguishable clinical and histological findings, are described by their own pathophysiology involving different elements and inflammatory cascades for each[3]. Psoriasis is characterized by the prominence of T-helper (Th) 1/Th17 cells and high expression of filaggrins, while eczema is characterized by Th2/Th22 cells and low expression of filaggrins with secondary colonization by *Staphylococcus aureus*.

These etiopathogenic differences partly explain why biological therapies for one disease can exacerbate or trigger the other, suggesting that suppression of Th1/Th17 cytokines can divert inflammatory pathways and trigger Th2-mediated diseases, and *vice versa*[1]. We believe that the exacerbation of eczema observed

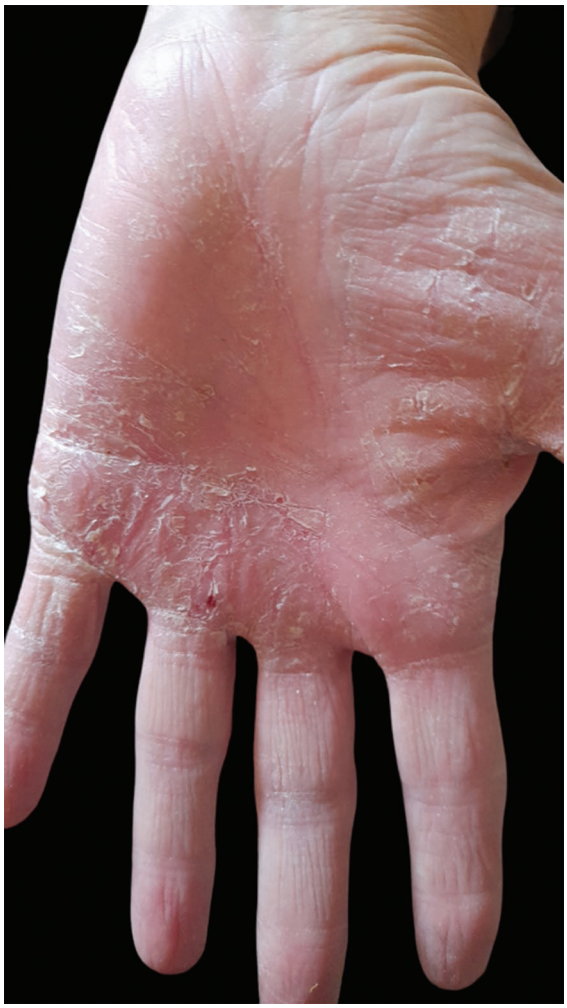

Figure 2. Palmar region in greater detail. Areas where the skin involvement predominantly manifests as fissures, scaling, and erythema.

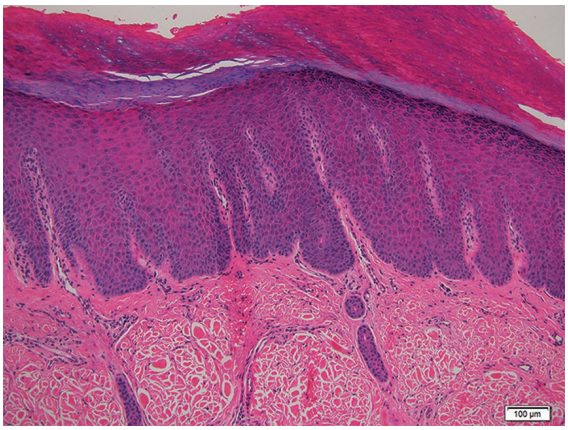

Figure 3. Hematoxylin-eosin stain. Overlapping histological findings of psoriasis and chronic hand eczema. The right half of the image shows orthokeratosis with underlying hypergranulosis (eczema), whereas the left half shows parakeratosis with the absence of the granular layer (psoriasis).

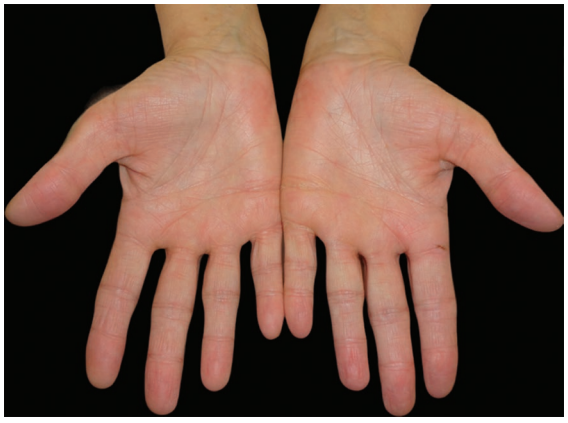

Figure 4. Response to upadacitinib. Significant improvement with complete resolution of lesions 15 days after starting upadacitinib.

in our patient after initiating adalimumab for psoriasis is due to this reaction, which, rather than being paradoxical, is to be expected.

This is clinically interesting because, although rare, these diseases can coexist in the same individual[1,3]. Finally, regarding treatment, since they respond to different cytokines, the simultaneous presentation of both diseases offers a limited therapeutic range[3].

Janus kinase (JAK) inhibitors provide a therapeutic option with a distinct mechanism of action which, unlike biological drugs, has a combined effect on multiple pro-inflammatory cytokines through its action on JAK enzymes[4].

Upadacitinib is a JAK 1 inhibitor with indications for rheumatoid arthritis, psoriatic arthritis, axial/ankylosing spondyloarthritis, atopic dermatitis, and ulcerative colitis. Although it is not currently approved for psoriasis, it has demonstrated efficacy on the skin in patients with psoriatic arthritis. In the SELECT-PSA 1 study, the number of patients achieving a response in the psoriasis area and severity index 75/90/100 was similar or greater with upadacitinib than with adalimumab after 56 and 104 weeks on therapy[5].

Gargiulo et al.[3] describe a series of four patients who clinically presented with overlapping psoriasis and atopic dermatitis. All of them, like our patient, had multiple

previous therapeutic failures, palmoplantar involvement, and excellent clinical responses of both conditions after starting upadacitinib.

Due to the above-mentioned opposite pathogenesis for psoriasis and eczema, these cases may require therapeutic approaches that cover broad inflammatory pathways, leading to various limitations: conventional drugs (corticosteroids, cyclosporine, and methotrexate) are not recommended long-term due to their safety profile, and cytokine-targeted drug options would only be effective if combined biologic agents for psoriasis and atopic dermatitis were used, which would be a financially difficult burden to bear[3]. In this regard, JAK inhibitors stand out as a therapeutic option without these limitations, having demonstrated a long-term safety profile similar to that of biologic drugs, but with a broad anti-inflammatory spectrum that allows their use in monotherapy[4].

Conclusion

Although the information currently available on upadacitinib in patients with cutaneous psoriasis is limited, the response to this drug observed in the patient we have presented suggests it as a potentially safe, convenient, and effective therapeutic option. Therefore, we believe it is justified to expand studies in this regard and to identify subgroups of patients who could particularly benefit from its use, such as those with associated psoriatic arthritis, palmoplantar skin involvement, or concomitant eczematous components.

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