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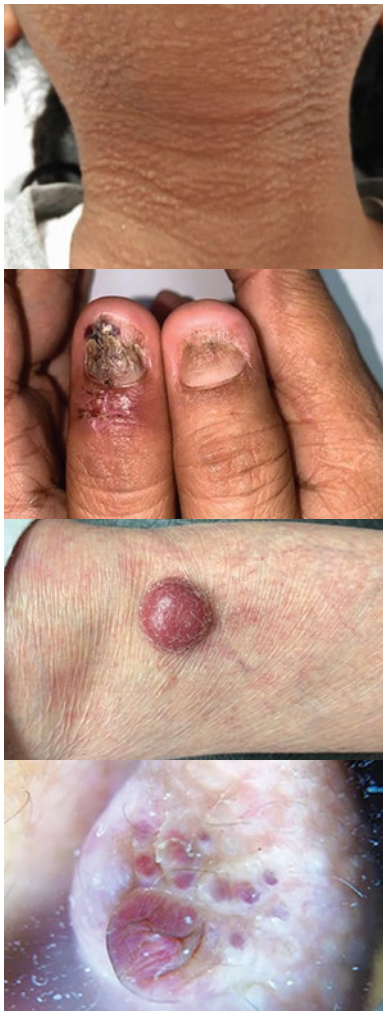

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CLINICAL CASE

Self-healing juvenile cutaneous mucinosis: a rare form of mucinosis

Mucinosis cutánea juvenil autorresolutiva: una forma rara de mucinosis

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Abstract

Self-healing juvenile cutaneous mucinosis (SJCM) is a rare primary dermal mucinosis. It presents with a sudden eruption of papules and nodules following flu-like symptoms. We hereby report a case of a 12-year-old girl, presenting with a typical eruption coupled with periorbital edema and joint nodules. SJCM diagnosis was based on a combination of clinical and characteristic histological findings. In our patient, the condition spontaneously resolved within 4 weeks and has remained asymptomatic throughout the 3-year follow-up period.

Keywords: *Mucinosis. Self-healing juvenile cutaneous mucinosis. Pediatric dermatology.*

Resumen

La mucinosis cutánea juvenil autorresolutiva (SJCM, por sus siglas en inglés) es una mucinosis dérmica primaria rara. Se manifiesta con una erupción repentina de pápulas y nódulos que suele estar precedida por sintomatología pseudogripal. Aquí se reporta el caso de una niña de 12 años, que presentaba una erupción cutánea típica junto con edema periorbital y nódulos articulares. El diagnóstico de SJCM se basó en una combinación de hallazgos clínicos e histológicos característicos. En nuestra paciente, la clínica se resolvió espontáneamente en cuatro semanas y ha permanecido asintomática durante el período de seguimiento de 3 años.

Palabras clave: *Mucinosis. Mucinosis cutánea juvenil autorresolutiva. Dermatología pediátrica.*

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Introduction

Self-healing juvenile cutaneous mucinosis (SJCM) is a rare primary dermal mucinosis with only approximately 30 reported cases[1-3]. It presents with a sudden eruption of indurated papules and nodules, often preceded by fever or flu-like symptoms. SJCM typically resolves spontaneously after weeks, months, or even years[2]. Here, we report a case of SJCM with a prolonged clinical follow-up.

Case report

An otherwise healthy 12-year-old girl presented with a pruritic rash on her neck and face, which was preceded by odynophagia, cough, and arthralgias. Twelve days later, she consulted due to the persistence of symptoms despite treatment with antihistamines and corticosteroids. Physical examination revealed multiple confluent skin-colored papules on the face, neck and back, and periorbital edema. Infiltrated nodules in the joints of the hands and knees (Fig. 1) and joint edema in knees, left elbow, and wrist were also noticed. Blood tests revealed a neutrophil count of 10,663/mm^3 (range, 1,800-8,000/mm^3) and an erythrocyte sedimentation rate of 14 mm (range, 5-10 mm). Proteinogram and thyroid function tests were normal. Viral serologies against Epstein-Barr virus, cytomegalovirus, HIV, and parvovirus-B19 were negative, as was the autoimmunity profile (rheumatoid factor, citrullinated peptide, HLA-B27, antinuclear, anti-Ro, and anti-La antibodies). Normal flora was isolated in the pharyngeal swab. A skin biopsy performed on a knee nodule revealed a fibroblastic proliferation associated with the deposit of a basophilic material that separated the collagen fibers, primarily located in the superficial dermis, and that stained with Alcian blue (Fig. 2). Based on the clinicopathological findings, SJCM was diagnosed. The patient presented spontaneous healing of all skin lesions and joint edema in 4 weeks (Fig. 3) and remains asymptomatic after 3 years of follow-up.

Discussion

SJCM is a rare primary dermal mucinosis that has been reported in all pediatric age groups, with a slight male predominance[2]. It presents with a papular and nodular eruption around the head, trunk, and interphalangeal joints, associated with periorbital edema and joint symptoms, and typically resolves spontaneously. Papules are composed of large deposits of mucin in the superficial dermis and are associated with fibroblastic proliferation. Nodules exhibit a similar pattern but with more pronounced fibroblastic proliferation.[3] The differential diagnosis includes other dermal mucinoses, rheumatoid arthritis, lupus tumidus, and juvenile dermatomyositis[3-5]. The etiology of SJCM is unknown, but the presence of nodules in periarticular areas suggests that mucin deposition could develop in response to joint inflammation, occasionally after certain infections (including rotavirus and human herpesvirus 6)[5].

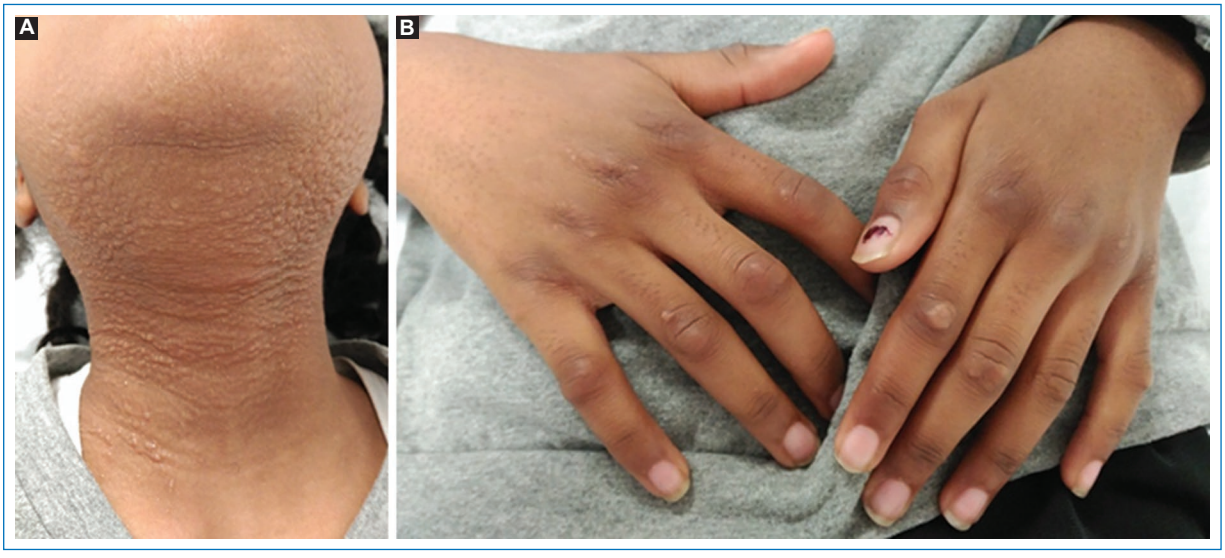

Figure 1. Clinical presentation of self-healing juvenile cutaneous mucinosis. **A**: multiple confluent skin-colored papules on the anterior neck, associated with edema. **B**: several nodules over the metacarpophalangeal and proximal interphalangeal joints in both hands.

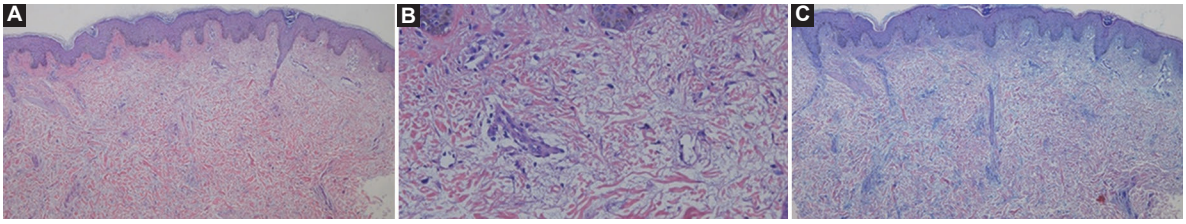

Figure 2. Histology of self-healing juvenile cutaneous mucinosis. Preserved epidermis is observed. Fibroblastic proliferation, especially in the superficial dermis, is associated with an increase in the separation of collagen bundles (**A**: H&E, ×40. **B**: H&E, ×200), due to the deposition of a basophilic material that corresponds to mucin (**C**: Alcian blue, ×40).

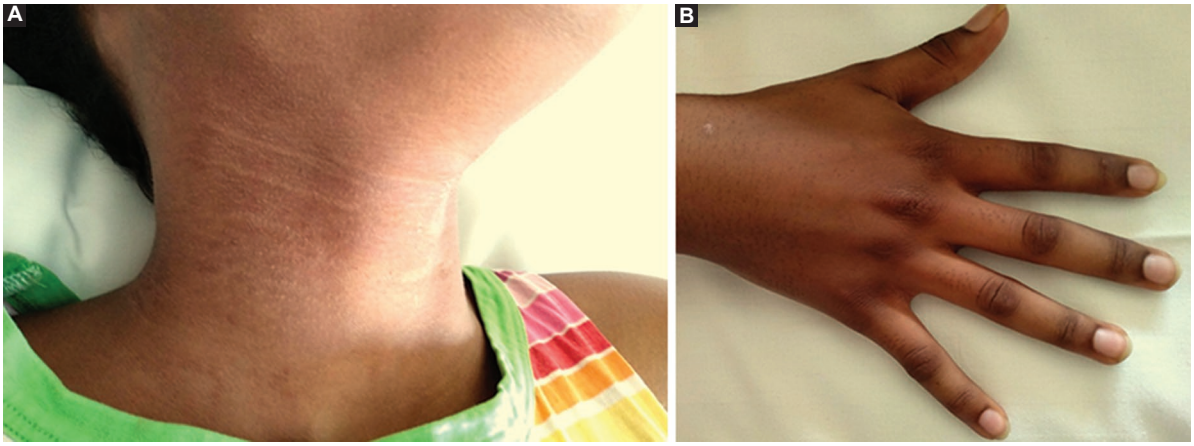

Figure 3. Resolution of self-healing juvenile cutaneous mucinosis. **A** and **B**: complete and spontaneous resolution of the skin eruption after 4 weeks.

Cutaneous lesions usually resolve without treatment, although the time frame ranges from 1 month to 2.5 years[2]. Non-steroidal anti-inflammatory drugs, corticosteroids, immunoglobulins, and isotretinoin have been used with little success in refractory cases[2,3]. Atypical presentations include adult-onset forms, recurrent forms, cases with onset in the context of neoplasms (nephroblastoma)[6], or familial aggregation[7]. Two cases with transition into an autoinflammatory rheumatologic disease and into fibroblastic rheumatism have been described.

This case report highlights the key features of SJCM, including flu-like symptoms, a painful eruption of papules and nodules in characteristic areas, indurated periorbital edema, joint involvement, compatible histological findings, and spontaneous resolution. This patient is one of the exceptional cases of SJCM reported to have undergone prolonged follow-up.

Conclusion

SJCM is characterized by the sudden eruption of papules and nodules, typically accompanied by edema and joint involvement. Histopathological findings of mucin deposition and fibroblastic proliferation, along with spontaneous resolution, are hallmarks of the disease. Follow-up is crucial due to potential associations with other rheumatological conditions.

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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 considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Morgado-Carrasco D, Fustà-Novell X, Bosch-Amate X, Giavedoni P. Mucinosis cutáneas. Piel. 2019;34:282-93.
2. Bishnoi A, Jindal AK, Anjani G, Patra PK, Chatterjee D, Vinay K, et al. Self-healing juvenile cutaneous mucinosis, a sclerodermoid disorder simulating juvenile dermatomyositis: a case-based review. Rheumatol Int. 2020;40:1911-20.
3. Luchsinger I, Coulombe J, Rongioletti F, Haspeslagh M, Dompmartin A, Melki I, et al. Self-healing juvenile cutaneous mucinosis: clinical and histopathologic findings of 9 patients: the relevance of long-term follow-up. J Am Acad Dermatol. 2018;78:1164-70.
4. Pucevich MV, Latour DL, Bale GF, King LE Jr. Self-healing juvenile cutaneous mucinosis. J Am Acad Dermatol. 1984;11:327-32.
5. Aydingöz IE, Candan I, Dervent B. Self-healing juvenile cutaneous mucinosis. Dermatology. 1999;199:57-9.
6. Wadee S, Roode H, Schulz EJ. Self-healing juvenile cutaneous mucinosis in a patient with nephroblastoma. Clin Exp Dermatol. 1994;19:90-3.
7. González-Enseñat MA, Vicente MA, Castellá N, Vila J, Arimany J. Self-healing infantile familial cutaneous mucinosis. Pediatr Dermatol. 1997;14:460-2.

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CLINICAL CASE

SARS-CoV-2 vaccine-associated fixed drug eruption

Eritema fijo asociado a la vacuna contra el SARS-CoV-2

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Abstract

In 2019, the pandemic caused by severe acute respiratory syndrome coronavirus 2 led the world to a desperate search for immunization. Since the mass vaccination, various adverse reactions have been reported, mostly cutaneous. Many of the reported cutaneous events are secondary to ribonucleic acid messenger (RNAm) vaccines. Fixed drug eruption is a Type IV hypersensitivity reaction characterized by the recurrence of lesions at identical sites with each exposure to the causative agent, most of which are drug-induced. We report the first Latin American case of fixed-drug eruption due to Pfizer RNAm vaccine.

Keywords: *Severe acute respiratory syndrome coronavirus 2. Vaccine. Maculopapular drug eruptions.*

Resumen

En 2019, la pandemia generada por el coronavirus 2 del síndrome respiratorio agudo grave (SARS-CoV-2) llevó al mundo a la desesperada búsqueda de la inmunización. A partir de la vacunación masiva se han notificado diversas reacciones adversas, en su mayoría cutáneas. Muchos de los eventos cutáneos manifestados son secundarios a las vacunas basadas en ácido ribonucleico mensajero (ARNm). El eritema fijo pigmentario es una reacción de hipersensibilidad de tipo IV caracterizada por la recurrencia de lesiones en sitios idénticos con cada exposición al agente causante, la mayoría producidas por fármacos. Comunicamos el primer caso latinoamericano de eritema fijo secundario a la vacuna de ARNm de Pfizer.

Palabras clave: *SARS-CoV-2. Vacuna. Erupciones maculopapulares por fármacos.*

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Introduction

Since December 2020, large vaccination campaigns have been conducted in Europe, initially using messenger ribonucleic acid (mRNA) vaccines Comirnaty (Pfizer/BioNTech; BNT162b2) and Moderna (Moderna; mRNA-1273), and later also the viral vector-based vaccine Vaxzevira (AstraZeneca; AZD1222), all of which were approved by the European Medicines Agency. In addition, the Janssen COVID-19 vaccine (Johnson and Johnson; Ad26.COV2.S) was also approved for use in Europe. There are other vaccines against COVID-19, such as Convidecia (CanSino Biologics), Sputnik V (Gamaleya Research Institute), and CoronaVac (Sinovac), which were approved by, at least, one country. With the development of vaccines designed to prevent COVID-19, various adverse effects on the skin have emerged, most of which are due to mRNA vaccines[1]. Among the described manifestations is fixed drug erythema, a dermatosis generally associated with drug administration[2]. However, it has been shown that this hypersensitivity reaction can be triggered by other substances, such as vaccines, oral contraceptives, and even quinine found in tonic water[3]. Despite being a frequent toxicodermia, its association with COVID-19 vaccination is very rare, and there are currently some case reports.

Case report

A 16-year-old male, with no relevant past medical history, presented in July 2022 with a 2-week history of multiple asymptomatic erythematoviolaceous macules of different sizes located on the trunk and extremities (Fig. 1). He denied the use of drugs, illegal substances, or supplements; he also denied fever or other associated symptoms. With a presumptive diagnosis of fixed erythema, the patient underwent a histological study of a lesion, which reported a skin section covered by epidermis with hyperkeratosis, acanthosis, and numerous dyskeratotic keratinocytes. At higher magnification, an inflammatory infiltrate was evident in a perivascular arrangement in the papillary and superficial reticular dermis. There was vacuolar degeneration of the basal layer and numerous dyskeratotic keratinocytes. More specifically, the inflammatory infiltrate was predominantly composed of lymphocytes, with isolated eosinophils, arranged at the perivascular level. Congested vessels were lined by endothelial cells (Figs. 2 and 3).

The patient did not return for follow-up, but in January 2023, he visited again with a 2-day history of lesions with similar morphological and topographical characteristics to those seen during the previous consultation. A comparison was made with photographic files to confirm this (Figs. 1 and 4). During the directed questioning, the patient reported that both episodes were preceded by the administration of the first and second doses of the Pfizer vaccine.

Additional examinations reported normal laboratory routines and negative serologies for viruses.

In the context of a dermatosis characterized by the recurrence of lesions in identical sites after the administration of the Pfizer vaccine, and with histopathology consistent with a toxicodermia while excluding other

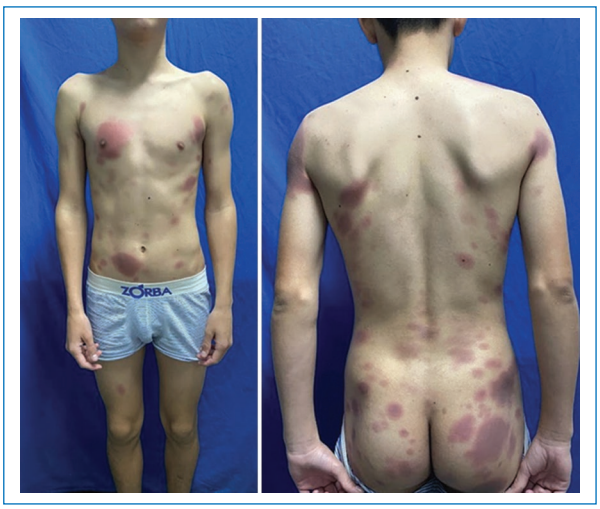

Figure 1. First consultation. Erythematoviolaceous macules on the anterior trunk and upper and lower limbs. Similar lesions on the back and thighs.

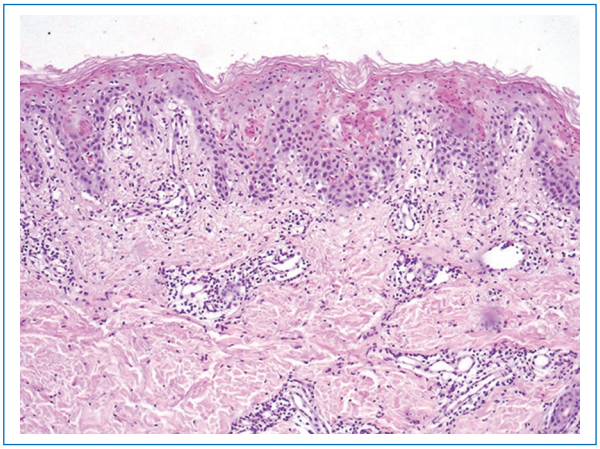

Figure 2. Overview of the skin biopsy with hematoxylin-eosin.

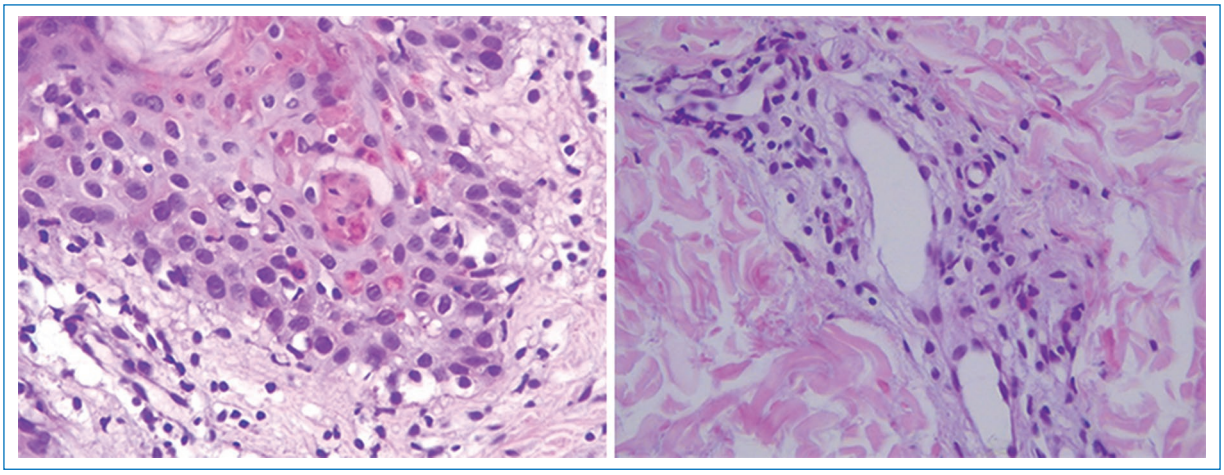

Figure 3. Infiltrate of lymphocytes and eosinophils predominantly perivascular, with dyskeratotic keratinocytes.

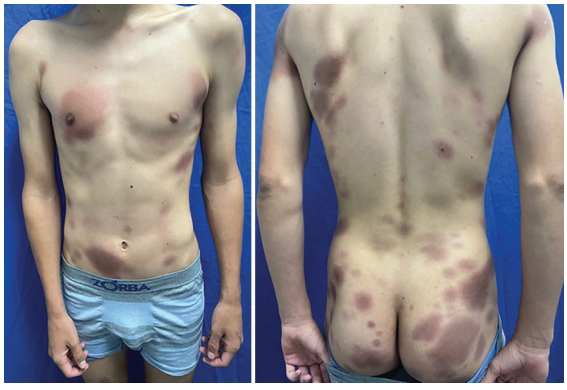

Figure 4. Second consultation. Erythematoviolaceous macules are observed in the same anatomical locations as in the first consultation.

causal agents, the clinical picture is interpreted as fixed erythema due to the Pfizer mRNA vaccine.

Me prednisolone was prescribed, 20 mg for 5 days, with improvement of the lesions and residual hyperpigmentation. The patient was advised to avoid mRNA-type COVID-19 vaccines, and he decided not to complete the recommended vaccination schedule in Argentina consisting of four doses.

Discussion

With the emergence of COVID-19, numerous signs in various organs have been reported. Although it is known that the primary infection is respiratory, various skin signs caused by this virus have been reported in recent years, and their recognition is particularly relevant for diagnostic suspicion in oligosymptomatic respiratory patients[4]. As the pandemic progressed, different types of vaccines emerged with the aim of halting the pandemic and the most devastating effects caused by the infection.

Among the types of vaccines for SARS-CoV-2 most widespread in the population are mRNA vaccines, which have proven to be very effective in preventing COVID-19; however, various skin reactions have been observed following their administration.

BioNTech-Pfizer and mRNA-Moderna are mRNA vaccines targeting the spike protein of SARS-CoV-2. Their synthetic mRNA encodes a protein identical to the spike glycoprotein of SARS-CoV-2, allowing the production of an immunogenic spike glycoprotein that subsequently triggers adaptive immune responses from T and B cells. This SARS-CoV-2 glycoprotein binds to the endothelial cells of the intradermal capillaries after vaccination, producing the symptoms[4].

Manifestations can be local reactions at the injection site, urticaria, morbilliform papulovesicular rash, pityriasis, and vasculitis-like rash. In very few cases, fixed eruption has been observed, similar to that produced by drugs[1,5].

Fixed drug erythema is characterized by the appearance of well-demarcated erythematoviolaceous patches or circular plaques that recur in identical sites with each exposure to the causative agent, usually a drug[6]. It can affect individuals of any age, although most cases occur in young adults. The most common locations in females are the extremities, hands, and feet, while in males, it is the genital area[7,8]. It is usually a benign and self-limiting reaction. After the acute phase, residual hyperpigmentation persists at the site of the

Table 1. Cases of fixed drug eruption associated with COVID-19 vaccines

Report	Vaccine	Lesions	Sex, age
Avallone et al.[9]	3 unspecified and 2 Moderna		
Farinazzo et al.[11]	1 Pfizer	Erythematoviolaceous macules	Female, 44 years
Annabi et al.[12]	1 Moderna	Erythematoviolaceous macules	Female, 80 years
Kabir et al.[13]	1 Pfizer	Erythematoviolaceous macules	Female, 50 years
Mintoff et al.[14]	1 Pfizer	Erythematoviolaceous macules	Female, 26 years
Lellig et al.[15]	1 Pfizer	Erythematoviolaceous macules	Female, 54 years
Rekabi et al.[16]	1 Sinopharm	Erythematoviolaceous macules	Female, 38 years
Seol et al.[17]	1 AstraZeneca/unspecified	Erythematoviolaceous macules	Male, 50 years
Choi et al.[18]	1 Pfizer	Blisters	Male, 83 years
Wantavornprasert et al.[19]	1 Oxford-AstraZeneca	Blisters	Male, 74 years
Ben Salem et al.[20]	1 Oxford-AstraZeneca	Blisters	Female, 41 years
Kong et al.[21]	1 Moderna	Blisters	Male, 66 years
Alshammari et al.[22]	1 Pfizer	Blisters	Male, 78 years

initial lesions, which can last several weeks or months. With repeated exposures, more severe lesions may develop, and occasionally forms with coalescent flaccid blisters can occur. Regarding the pathophysiology, the participation of the immune system has been observed, seemingly a type IV hypersensitivity reaction according to Gell and Coombs. Among the various excipients in COVID-19 vaccines, polyethylene glycol in the mRNA vaccines is one of the suspected agents, although the exact biological mechanisms have yet to be elucidated and further studies are needed[9].

It is unknown why lesions tend to appear at the same sites. It is speculated that CD8 + T lymphocytes act as memory cells.

Diagnosis is essentially clinical, based on a detailed interrogation that allows recognition of its clinical presentation and evolutionary characteristics. There are methods that help confirm the diagnosis:

– Patch test: performed by applying the suspected substance to the skin
– Oral provocation test: involving the ingestion of the substance orally (not recommended due to the risk of inducing a severe reaction)
– Skin biopsy[10]: histology shows necrotic and individualized dyskeratotic keratinocytes, with spongiosis and vacuolization of the basal layer of the epidermis. In the dermis, edema and perivascular and interstitial lymphohistiocytic infiltrate appear, with some eosinophils. The presence of pigmentary incontinence is very characteristic, with melanophagic macrophages loaded with melanin in the papillary dermis[6].

More than 100 related drugs have been reported. Among the non-drug causes are the consumption of certain legumes, fruits, additives, and colorants from capsules, as well as exposure to UV radiation[7].

Immediate suspension of the probable causative drug is essential in treatment. In addition, if necessary, symptomatic treatment of the lesions and the use of topical corticosteroids[9].

Fixed drug erythema as an adverse reaction to the COVID-19 vaccine is exceptional. To date, 12 cases have been reported, seven of them from mRNA vaccines (4 with Pfizer and 3 with Moderna), 1 from AstraZeneca, 1 from Sinopharm, and 3 unspecified[9-17]. Furthermore, the blistering variant was reported in five cases[18-22]. The cases were described in Asia, Europe, and North America (Table 1). We report the first Latin American case of fixed drug erythema due to the mRNA COVID-19 vaccine.

We emphasize the importance of the dermatologist's role in reporting new adverse reactions that have been reported with mass vaccination against COVID-19, such as fixed drug erythema, which can simulate other diseases, making its recognition very useful to alert both the patient, preventing more severe reactions, and

the professional, to avoid unnecessary diagnostic tests or treatments.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

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.

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References

1. Qaderi K, Golezar MH, Mardani A, Mallah MA, Moradi B, Kavoussi H, et al. Cutaneous adverse reactions of COVID-19 vaccines: a systematic review. Dermatol Ther. 2022;35:e15391.
2. Avilés Izquierdo JA, Huerta Brogeras M, Suárez Fernández R, Lázaro Ochaíta P. Exantema fijo medicamentoso. Med Integral. 2002;40:251-5.
3. Agustí-Mejias A, Mejías-Boils A, Messeguer F, Alegre De Miquel V. Eritema fijo medicamentoso: claves diagnósticas. Med Fam Semergen. 2011;37:215-8.
4. Magro C, Nuovo G, Mulvey JJ, Laurence J, Harp J, Crowson AN. The skin as a critical window in unveiling the pathophysiologic principles of COVID-19. Clin Dermatol. 2021;39:934-65.
5. McMahon DE, Amerson E, Rosenbach M, Lipoff JB, Moustafa D, Tyagi A, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. J Am Acad Dermatol. 2021;85:46-55.
6. Hermida MD, Consalvo L, Lapadula MM, Della Giovanna P, Cabrera HN. Bullous fixed drug eruption induced by intravaginal metronidazole ovules, with positive topical provocation test findings. Arch Dermatol. 2011;147:250-1.
7. Brahimi N, Routier E, Raison-Peyron N, Tronquoy AF, Pouget-Jasson C, Amarger S, et al. A three-year-analysis of fixed drug eruptions in hospital settings in France. Eur J Dermatol. 2010;20:461-4.
8. Sieira AJ, Costa AJ, Sieira MJ. Exantema fijo medicamentoso causado por amoxicilina. Med Gen Fam. 2015;4:133-5.
9. Avallone G, Quaglino P, Cavallo F, Roccuzzo G, Ribero S, Zalaudek I, et al. SARS-CoV-2 vaccine-related cutaneous manifestations: a systematic review. Int J Dermatol. 2022;61:1187-204.
10. Aguilar-Urbina EW, Plasencia-Meza C, Chávez-Rimarachín M, Aquino-Salverredy R, Velásquez Ojeda A, Bazán Gallo C, et al. Eritema pigmentado fijo ampolloso medicamentoso relacionado con el uso de ivermectina en paciente con neumonía por SARS-Cov-2: reporte de caso. Rev Cuerpo Med Hosp Nac Almanzor Aguinaga Asenjo. 2021;14:394-7.
11. Farinazzo E, Ponis G, Zelin E, Errichetti E, Stinco G, Pinzani C, et al. Cutaneous adverse reactions after m-RNA COVID-19 vaccine: early reports from Northeast Italy. J Eur Acad Dermatol Venereol. 2021;35:e548-51.
12. Annabi E, Dupin N, Sohier P, Garel B, Franck N, Aractingi S, et al. Rare cutaneous adverse effects of COVID-19 vaccines: a case series and review of the literature. J Eur Acad Dermatol Venereol. 2021;35:e847-50.
13. Kabir S, Feit EJ, Heilman ER. Generalized fixed drug eruption following Pfizer-BioNtech COVID-19 vaccination. Clin Case Rep. 2022;10:e6684.
14. Mintoff D, Pisani D, Betts A, Scerri L. SARS-CoV-2 mRNA vaccine-associated fixed drug eruption. J Eur Acad Dermatol Venereol. 2021;35:e560-3.
15. Lellig E, Mouton-Faivre C, Abs D, Bursztejn AC. Fixed drug eruption after Pfizer-BioNTech COVID-19 vaccine: a case report. J Allergy Clin Immunol Pract. 2022;10:1922-3.
16. Rekabi M, Sadati E, Mirzaei J, Pourdowlat G, Akbar Velayati A Honarpisheh P. Fixed drug eruption after the Sinopharm COVID-19 vaccine. JEADV Clin Pract. 2022;1:412-5.
17. Seol JE, Ahn SW, Jang SH, Hong SM, Kim MY, Kim H. A case of recurrent fixed drug eruption following the administration of 2 different coronavirus disease 2019 vaccines verified using intradermal and patch tests. JAAD. 2023;33:23-6.
18. Choi S, Kim SH, Hwang JH, Jang HW, Oh SH, Kim DY, et al. Rapidly progressing generalized bullous fixed drug eruption after the first dose of COVID-19 messenger RNA vaccination. J Dermatol. 2023;50:1190-3.
19. Wantavornprasert K, Noppakun N, Klaewsongkram J, Rerknimitr P. Generalized bullous fixed drug eruption after Oxford-AstraZeneca (ChAdOx1 nCoV-19) vaccination. Clin Exp Dermatol. 2022;47:428-32.
20. Ben Salem C, Khelif A, Sahnoun D, Ghariani N, Sriha B, Denguezli M. Another case of generalized bullous fixed drug eruption following an adenoviral vector-based COVID-19 vaccine (ChAdOx1 nCov-19). J Eur Acad Dermatol Venereol. 2022;36:e516-7.
21. Kong J, Cuevas-Castillo F, Nassar M, Lei CM, Idrees Z, Fix WC, et al. Bullous drug eruption after second dose of mRNA-1273 (Moderna) COVID-19 vaccine: case report. J Infect Public Health. 2021;14:1392-4.
22. Alshammari F, Abuzied Y, Korairi A, Alajlan M, Alzomia M, AlSheef M. Bullous pemphigoid after second dose of mRNA- (Pfizer-BioNTech) Covid-19 vaccine: a case report. Ann Med Surg (Lond). 2022;75:103420.

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CLINICAL CASE

Diagnostic delay in Hermansky-Pudlak syndrome: report of a case

Retraso diagnóstico en el síndrome de Hermansky-Pudlak: reporte de un caso

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Abstract

Hermansky-Pudlak syndrome (HPS) is a heterogeneous group of rare, autosomally recessively inherited disorders that are expressed with oculocutaneous albinism, hemorrhagic diathesis, and systemic manifestations due to the accumulation of lysosomal ceroid material. Its definitive diagnosis is based on clinical characteristics and a decrease in dense platelet granules observed by transmission electron microscopy. Currently, there is no definitive treatment and it is based on multidisciplinary management of its complications. We present the clinical case of a patient with a confirmed diagnosis of HPS, an entity little documented in the literature.

Keywords: *Hermansky-Pudlak syndrome. Oculocutaneous albinism. Bleeding diathesis.*

Resumen

El síndrome de Hermansky-Pudlak es un grupo heterogéneo de trastornos autosómicos recesivos infrecuentes, que se expresan con albinismo oculocutáneo, diátesis hemorrágica y manifestaciones sistémicas por acumulación de material ceroide lisosomal. El diagnóstico se basa en sus características clínicas y en la disminución de gránulos densos de plaquetas observada por microscopia electrónica de transmisión. Actualmente no cuenta con un tratamiento definitivo y se sustenta en el manejo multidisciplinario de sus complicaciones. Presentamos el caso clínico de una paciente con confirmación diagnóstica de síndrome de Hermansky-Pudlak, condición poco documentada en la literatura.

Palabras clave: *Síndrome de Hermansky-Pudlak. Albinismo oculocutáneo. Diátesis hemorrágica.*

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Introduction

The Hermansky-Pudlak syndrome (HPS) is a group of rare, autosomal recessive, sex-unlinked disorders caused by 11 genes implicated in individuals of different ethnic backgrounds[1]. It is clinically expressed with oculocutaneous hypopigmentation, hemorrhagic diathesis, and various systemic signs, such as pulmonary fibrosis, granulomatous colitis, renal failure, cardiomyopathy, skin cancer, and immunodeficiency[2-4]. The cornerstone for its diagnosis is the observation of platelet hypogranulation through transmission electron microscopy (TEM)[5-7]. Molecular tests contribute to its confirmation, are useful for subcategorizing it, and provide prognostic and therapeutic information[6,8,9].

This case report describes a patient who has met the typical criteria for HPS since childhood, with a significant delay in her diagnostic suspicion.

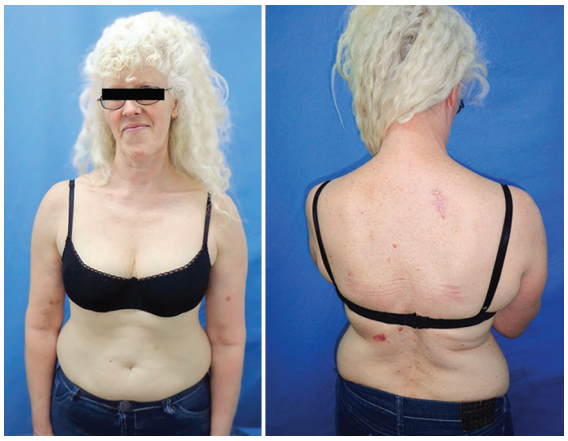

Figure 1. Frontal and dorsal view of the patient with decreased pigmentation of the skin, hair, and eyebrows, signs of photodamage, and surgical scars from the removal of non-melanoma skin cancer.

Case report

A 58-year-old woman with a personal history of human immunodeficiency virus infection, currently on antiretroviral treatment with a good immunological profile, oculocutaneous albinism, and hemorrhagic diathesis that manifested in childhood with episodes of epistaxis, gingival bleeding, spontaneous bruises, and menometrorrhagia in her adolescence, which led to multiple blood transfusions and studies consistent with Glanzmann's thrombasthenia. Her family history included consanguineous parents-first cousins-and oculocutaneous albinism in a maternal great-grandfather. She was referred from the hematology service due to a medical history of multiple skin tumors, with histopathological diagnoses of basal cell carcinomas, undergoing various treatment modalities with resolution.

The physical examination revealed fair skin with signs of photodamage and hypopigmentation of hair, eyebrows, and eyelashes; light-colored eyes with horizontal nystagmus and photophobia (Fig. 1).

With a presumptive diagnosis of HPS, a study of TEM of platelets was requested, which reported a markedly decreased number of dense granules (Fig. 2), thus confirming the diagnosis of HPS in conjunction with the clinical picture and the patient's phenotype.

A multidisciplinary approach was conducted to search for any possible associated systemic complications. The hematological study showed a normal peripheral blood smear platelet count, increased bleeding time, normal prothrombin time, activated partial thromboplastin time, and normal coagulation factors VII and Von Willebrand. Platelet aggregometry showed absent secondary aggregation with adenosine diphosphate and adrenaline, significantly reduced with collagen and arachidonic acid, and normal with ristocetin. Flow cytometry reported a deficiency of membrane glycoproteins IIb/IIIa. Pulmonary function was evaluated with spirometry, and a high-resolution computed tomography of the chest was performed without abnormalities. On ophthalmological examination, she presented decreased visual acuity, horizontal nystagmus, retinal hypopigmentation, and photosensitivity.

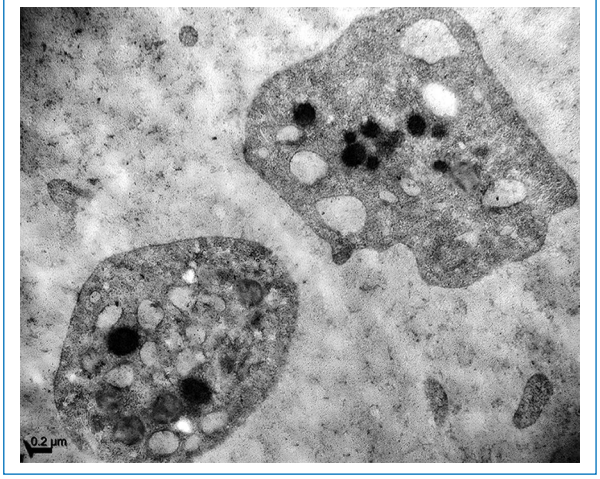

Figure 2. Transmission electron microscopy of platelets. A notable decrease in dense granules is observed.

Table 1. Main clinical signs by systems and screening and follow-up tests

Systems	Clinical signs	Screening and follow-up tests
Integumentary	Hypopigmentation of skin, hair, eyelashes, and eyebrows Photodamage, solar lentigines Actinic keratosis Non-melanoma skin cancer	Annual or more frequent dermatological evaluation for patients with lesions or a history of skin cancer
Hematological	Hemorrhagic diathesis with bruising, epistaxis, gingival bleeding, prolonged bleeding during menstruation or after dental or surgical procedures	Hematological study with platelet count and peripheral blood smear Coagulation times Platelet aggregometry Electron microscopy of platelets
Visual	Nystagmus, photophobia, strabismus, decreased visual acuity, iris transillumination, foveal hypoplasia with retinal and iris hypopigmentation	Annual ophthalmological exam Visual acuity Fundus examination Fundoscopy Iris transillumination
Respiratory	Restrictive pulmonary fibrosis Cough, dyspnea, hypoxia	Pulmonary function tests Spirometry High-resolution chest computed tomography
Immune	Recurrent infections Neutropenia Hemophagocytic lymphohistiocytosis	Evaluate clinical and laboratory signs of immunodeficiency
Urinary	Renal failure	Nephrological evaluation Laboratory with renal function
Cardiovascular	Cardiomyopathy	Cardiological evaluation Electrocardiogram Echocardiogram
Digestive	Granulomatous colitis Abdominal pain, fever, and malabsorption with diarrhea	Gastroenterological evaluation Colonoscopy

She is currently under interdisciplinary follow-up at our institution, with preventive management and monitoring of the various complications of the disease.

From the dermatology department, strict photoprotection guidelines were emphasized, and secondary chemoprevention for non-melanoma skin cancer was initiated with nicotinamide, 500 mg twice daily, with periodic skin evaluation.

Genetic testing is awaited to investigate the subtype of HPS to obtain information on its progression and treatment and confirm or rule out the coexistence of both hereditary platelet disorders, a fact that would be exceptional in the literature.

Discussion

HPS was first described in Czechoslovakia in 1959 by doctors Hermansky and Pudlak[10]. HPS is a group of multisystem hereditary disorders directly linked to the altered biogenesis of organelles associated with lysosomes and the common clinical manifestations of oculocutaneous albinism and abnormal bleeding due to platelet dysfunction[2-4] (Table 1). Its prevalence is low, occurring in 1 in every 500,000 up to 1,000,000 people worldwide, being more frequent in individuals of Puerto Rican descent due to a founder mutation in exon 15 of the HPS gene 1, with a frequency of 1 in every 1800 Puerto Ricans[2-4].

In its pathogeny, a total of 11 subtypes (HPS-1 to HPS-11) have been implicated in humans and 15 in mice[1]. Each subtype is defined by variants in a specific gene that encodes protein components such as adaptor protein-3 (AP-3) and the biogenesis of the organelle-related complexes with lysosomes 1, 2, 3 (BLOC 1-2-3), which directly impact intracellular protein trafficking, essential for the proper functioning of melanosomes, platelet dense granules, and immune cell granules[1-3,5].

The alteration of melanosomes, with partial or total reduction of melanin in melanocytes, manifests with various degrees of hypopigmentation of hair and skin,

along with ocular involvement that causes complications, such as photophobia, strabismus, nystagmus, decreased visual acuity, foveal hypoplasia, and iris transillumination[7,8,11].

Hemorrhagic diathesis is due to defective thrombus formation following impaired exocytosis of dense granules in platelets, resulting from a deficiency of adenosine diphosphate and extracellular disulfide isomerase, with a reduction in fibrin generation and consequent alteration of platelet aggregation[12]. This can manifest from childhood with episodes of epistaxis, ecchymosis, and gingival bleeding, and at older ages with menometrorrhagia, postpartum hemorrhage, or excessive bleeding during surgical or dental procedures[7,12,13].

Pulmonary fibrosis represents the most frequent complication and the leading cause of death between the 4th and 5th decades of life in the HPS subtypes HPS-1, HPS-2, and HPS-4. It shows as fibrotic restrictive lung disease with clinical, histological, and imaging studies similar to those of idiopathic pulmonary fibrosis[7,8]. It is believed to be due to defects in the biogenesis of lamellar bodies, which are found inside type II alveolar cells responsible for surfactant synthesis, and to the activation of immune responses leading to inflammation and fibrosis[2,14]. Patients with subtypes HPS-2 and HPS-10-in addition to pulmonary involvement-have recurrent infections due to an impaired immune response[9]. Recent studies have shown that immunodeficiency is due to mutations in AP-3 that lead to the dysfunction of cytotoxic T cells, dendritic cells, and natural killer cells[13,15].

A subset of patients with HPS-1, HPS-4, and HPS-6 also suffer from granulomatous colitis, a type of inflammatory bowel disease that clinically manifests with abdominal pain, fever, diarrhea, and weight loss, often being indistinguishable from Crohn's disease[7,16].

It is believed that the deposition of a compound called lysosomal ceroid lipofuscinosis, which derives from lipid peroxidation of subcellular membranes of various tissues, would be the cause of the different manifestations of HPS, such as granulomatous colitis, pulmonary fibrosis, cardiomyopathy, and isolated or associated renal failure with lupus nephritis[3,8,17].

Definitive diagnosis is based on identifying the reduction or absence of dense granules in platelets through TEM, along with the clinical picture of oculocutaneous albinism and hemorrhagic diathesis[5-7,9]. Although another hematological study may be performed, its results are not pathognomonic, showing a platelet count with a normal peripheral blood smear and normal coagulation times, along with prolonged bleeding time. Platelet aggregometry is impaired too, with absent or prolonged secondary aggregation due to the lack of dense granules[8,13,17].

Molecular genetic analysis is not essential for diagnosis but helps categorize different subtypes of HPS and provides information regarding prognosis and treatment[5,6,8].

Differential diagnosis should be established with other congenital autosomal recessive conditions related to the dense granule pool syndrome, such as Chédiak-Higashi syndrome (CHS) and Griscelli syndrome (GS). CHS presents with oculocutaneous albinism, bleeding, recurrent respiratory and pyogenic infections, neurological problems, and a childhood tendency to develop hemophagocytic lymphohistiocytosis (HLH). It differs from HPS by showing giant cytoplasmic inclusions in leukocytes in the peripheral blood smear, and upon optical microscopy examination of hair, small pigment granules distributed evenly. GS, in its different subtypes (GS 1, 2, and 3), is clinically similar to CHS and HPS, presenting with partial albinism, silver-gray hair, neurological symptoms, and immune changes with HLH. It is distinguished by the normal presence of dense granules in platelets and the absence of large inclusions in leukocytes[8,9,18].

The most severe complication that patients with CHS, GS, or HPS-2 can suffer from is HLH, an abnormal immune response due to uncontrolled activation of T lymphocytes and macrophages. Clinically, it manifests with fever, lymphadenopathy, hepatosplenomegaly, and laboratory abnormalities such as bicytopenias, increased ferritin, hypofibrinogenemia, and hypertriglyceridemia. HLH is infrequent in HPS-2, unlike in CHS, where it occurs in up to 80% of patients within the first 10 years of life[8].

Our patient has studies consistent with Glanzmann's thrombasthenia, another autosomal recessive hereditary disorder of platelet function due to the absence or reduction of membrane glycoproteins IIb/IIIa, with alteration in platelet adhesion. It manifests with bleeding that can start from birth, most commonly with episodes of recurrent epistaxis and gingival bleeding. It clinically differs from HPS by not exhibiting oculocutaneous albinism and by showing in platelet aggregometry absent or reduced aggregation with all agonists except with ristocetin, with which it is normal, and in flow cytometry shows decreased expression of glycoproteins IIb/IIIa[19].

There is currently no curative treatment for HPS; management is based on a multidisciplinary approach for prevention and early detection of systemic complications[8,9,20]. It is recommended to start pulmonary

evaluations in asymptomatic individuals between 18 and 21 years of age due to the high mortality due to pulmonary fibrosis[7]. For diagnosis, pulmonary function tests, spirometry, and high-resolution computed tomography studies of the chest should be performed[6,14,20], with annual follow-ups unless symptoms of pulmonary fibrosis appear[7,8]. Lung transplantation is the main definitive treatment in these patients[14,20]; however, the approval of new antifibrotic drugs, such as pirfenidone and nintedanib, has proven capable of reducing or delaying the progression of pulmonary fibrosis[7,8,14,20].

Given the tendency to bleeding, prevention, and protection against trauma are imperative. The use of antifibrinolytics, primarily desmopressin, tranexamic acid, aminocaproic acid, and recombinant factor VIIa, is recommended for treating acute bleeding or before surgical or dental procedures. Platelet transfusion is indicated in the case of severe bleeding[7,8,13]. Due to the alteration of platelet aggregation, the use of aspirin or non-steroidal anti-inflammatory drugs is not recommended[4,7,13,20].

Patients with symptoms of granulomatous colitis warrant early evaluation by a gastroenterologist and consideration for colonoscopy[3]. Cases of successful treatment with the monoclonal antibody infliximab have been reported[2,16].

Compared to the general population, HPS is associated with a higher risk of sun damage and skin cancer. As in the case at hand, the most common neoplastic transformation is non-melanoma skin cancer, including basal cell and squamous cell carcinomas[4,8,21]. Although the incidence of melanoma is lower, its typical amelanotic presentation complicates and delays its diagnosis and treatment[22]. Because of this, it is of utmost importance to conduct annual dermatological check-ups based on preventive practices that educate on photoprotection measures, early detection and treatment of precancerous lesions, and the eventual indication for pharmacological chemoprophylaxis for non-melanoma skin cancer to decrease the associated risk and mortality[7,20,23].

Conclusion

The purpose of this report is to raise awareness of a rare and often underdiagnosed disease that presents a medical challenge in its recognition and timely management of comorbidities; thus, it is crucial to always consider its diagnosis and screening in any patient with a history of oculocutaneous albinism and episodes of abnormal bleeding.

We emphasize the crucial role of the dermatologist in its detection and the multidisciplinary approach to its associated complications to provide the necessary preventive and supportive measures that prevent their development or progression, thereby providing a better quality of life for patients affected by this syndrome.

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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 considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Li W, Hao CJ, Hao ZH, Ma J, Wang QC, Yuan YF, et al. New insights into the pathogenesis of Hermansky-Pudlak syndrome. Pigment Cell Melanoma Res. 2022;35:290-302.
2. Bowman SL, Bi-Karchin J, Le L, Marks MS. The road to lysosome-related organelles: insights from Hermansky-Pudlak syndrome and other rare diseases. Traffic. 2019;20:404-35.
3. Wei AH, Li W. Hermansky-Pudlak syndrome: pigmentary and non-pigmentary defects and their pathogenesis. Pigment Cell Melanoma Res. 2013;26:176-92.
4. Ambur AB, Nyckowski TA. Hermansky-Pudlak syndrome. J Osteopath Med. 2022;122:601-2.
5. Huizing M, Malicdan MC, Wang JA, Pri-Chen H, Hess RA, Fischer R, et al. Hermansky-Pudlak syndrome: mutation update. Hum Mutat. 2020;41:543-80.
6. El-Chemaly S, Young LR. Hermansky-Pudlak syndrome. Clin Chest Med. 2016;37:505-11.
7. De Jesús Rojas W, Young LR. Hermansky-Pudlak syndrome. Semin Respir Crit Care Med. 2020;41:238-46.
8. Loredana Asztalos M, Schafernak KT, Gray J, Berry A, Paller AS, Mancini AJ. Hermansky-Pudlak syndrome: report of two patients with updated genetic classification and management recommendations. Pediatr Dermatol. 2017;34:638-46.
9. Takaldani AHS, Javanshir N, Salimi M, Negaresh M. A case of Hermansky-Pudlak with dyspnea. Oxf Med Case Rep. 2023;2023:omad001.
10. Hermansky F, Pudlak P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: report of two cases with histochemical studies. Blood. 1959;14:162-9.

11. Marek-Yagel D, Abudi-Sinreich S, Macarov M, Veber A, Shalva N, Philosoph AM, et al. Oculocutaneous albinism and bleeding diathesis due to a novel deletion in the HPS3 gene. Front Genet. 2022;13: 936064.
12. Sharda A, Kim SH, Jasuja R, Gopal S, Flaumenhaft R, Furie BC, et al. Defective PDI release from platelets and endothelial cells impairs thrombus formation in Hermansky-Pudlak syndrome. Blood. 2015;125: 1633-42.
13. Özdemir N, Celik E, Başlar Z, Celkan T. A rare cause of thrombocyte dysfunction: hermansky-Pudlak syndrome. Turk Pediatri Ars. 2014;49:163-6.
14. Velázquez-Díaz P, Nakajima E, Sorkhdini P, Hernández-Gutiérrez A, Eberle A, Yang D, et al. Hermansky-Pudlak syndrome and lung disease: pathogenesis and therapeutics. Front Pharmacol. 2021;12:644671.
15. Gil-Krzewska A, Murakami Y, Peruzzi G, O'Brien KJ, Merideth MA, Cullinane AR, et al. Natural killer cell activity and dysfunction in Hermansky-Pudlak syndrome. Br J Haematol. 2017;176:118-23.
16. Demirtas CO, Alahdab YO, Kani HT, Atug O, Imeryuz N. Treatment of Hermansky-Pudlak syndrome associated granulomatous colitis with anti-TNF agents: case series and review of literature. Eur J Gastroenterol Hepatol. 2019;31:1597-600.
17. Paredes Aguilera R, López Santiago N, Monsiváis Orozco A, Carrasco Daza D, Salazar-Bailón JL. Síndrome de Hermansky-Pudlak: expresión clínica variable en dos casos clínicos. Bol Med Hosp Infant Mex. 2012;69:300-6.
18. Vizcargüénaga MI. Síndrome de pool de depósito: revisión. Presentación de estudios de laboratorio. Acta Bioquim Clin Latinoam. 2006;40:327-34.
19. García-Chávez J, Hernández-Juárez J, Sánchez-Jara B, García-Lee M, Rodríguez-Castillejos C, Montiel-Cervantes L, et al. Consenso mexicano para el diagnóstico y tratamiento de la trombastenia de Glanzmann. Gac Med Mex. 2022;158:1-17.
20. Seward SL Jr., Gahl WA. Hermansky-Pudlak syndrome: health care throughout life. Pediatrics. 2013;132:153-60.
21. Iwata Y, Kobayashi T, Arima M, Numata S, Yagami A, Okamura K, et al. Case of Japanese Hermansky-Pudlak syndrome patient with deeply invasive squamous cell carcinoma and multiple lesions of actinic keratosis on the face and neck. J Dermatol. 2017;44:219-20.
22. Fan R, Johnston MS, Gowen MF, Damsky W, Odell I, Clune J, et al. Amelanotic melanoma in a patient with Hermansky-Pudlak syndrome. JAAD Case Rep. 2022;27:61-3.
23. Bosch-Amate X, Morgado-Carrasco D, Martínez N. FR - Prevención farmacológica del cáncer cutáneo no-melanoma en pacientes de alto riesgo. Actas Dermosifiliogr. 2020;111:609-10.

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CLINICAL CASE

Primary cutaneous nocardiosis in a pediatric patient

Nocardiosis cutánea primaria en un paciente pediátrico

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Abstract

Primary cutaneous nocardiosis is an opportunistic infection that occurs exceptionally in healthy patients and pediatric age. It is mainly caused by Nocardia brasiliensis and is reported to have a higher incidence in the adult population. We present the case of an immunocompetent pediatric patient secondary to trauma, successfully treated with trimethoprim/sulfamethoxazole. The purpose of presenting this case is to emphasize a rarely reported entity in the pediatric age, which ignorance could lead to erroneous diagnoses and/or treatments.

Keywords: *Nocardia. Nocardia infections. Child.*

Resumen

La nocardiosis cutánea primaria es una infección oportunista excepcional en pacientes sanos y en la edad pediátrica. Es causada principalmente por Nocardia brasiliensis y se reporta con mayor incidencia en población adulta. Presentamos el caso en un paciente pediátrico inmunocompetente secundario a un traumatismo, tratado satisfactoriamente con trimetoprima/sulfametoxazol. El propósito de presentar este caso es enfatizar en una entidad poco reportada en la edad pediátrica, cuyo desconocimiento podría llevar a diagnósticos y/o tratamientos erróneos.

Palabras claves: *Nocardia. Nocardiosis. Pediátrico.*

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Introduction

Primary cutaneous nocardiosis (PCN) is an uncommon opportunistic infection that occurs in only one-third of immunocompetent patients. It is mainly caused by *Nocardia brasiliensis*, a Gram-positive, aerobic, weakly acid-alcohol-fast bacterium. It peaks in incidence between the ages of 30 and 60 years. PCN occurs after direct inoculation, with insect bites and trauma being the main associated factors in reported pediatric cases. As far as we know, a database search in indexed journals, only 28 pediatric cases have been reported, with only one case series being reported[1].

Case report

A 10-year-old male patient, 1 week after sustaining trauma while playing soccer, developed painful lesions on his right foot and was treated with amoxicillin-clavulanic acid, with no improvement. Dermatosis affected the right lower extremity, involving the dorsal aspect of the foot and the medial malleolus, consisting of a few millimetric pustules and three 2 cm × 1.5 cm × 0.3 cm up to 3 cm × 2.5 cm × 0.4 cm gummas with erythematous surface–fluctuant on palpation–with increased local temperature and well-demarcated borders (Fig. 1). Direct examination showed microsiphoned Gram-positive filaments and numerous polymorphonuclear cells, without the presence of grains (Fig. 2). Culture revealed the presence of white-yellowish, chalky colonies with a "popcorn" appearance and a musty odor (Fig. 3). Polymerase chain reaction (PCR) typing identified *N. brasiliensis*. Blood count, lymphocyte subpopulations, immunoglobulins, complement levels, chest X-ray, and right foot X-ray showed no abnormalities. Trimethoprim–sulfamethoxazole (TMP-SMZ) at 10 mg/kg/day was prescribed, for a total of 8 weeks of treatment with favorable response after 7 months of follow-up.

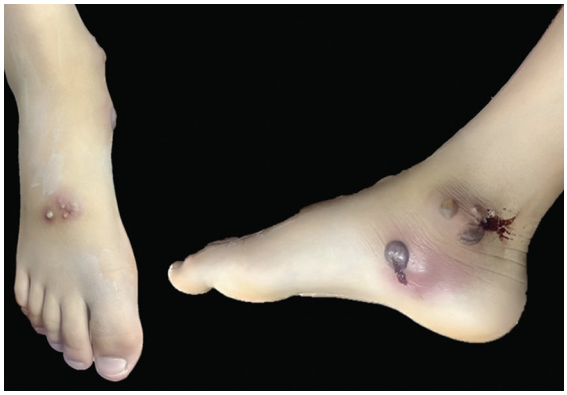

Figure 1. Right foot showing pustules and three gummas due to infection by *Nocardia brasiliensis.*

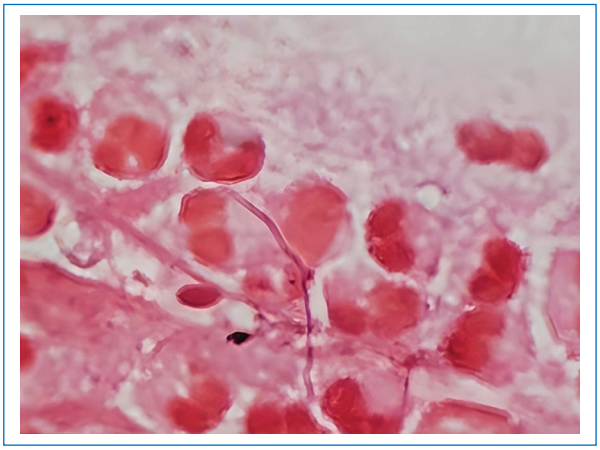

Figure 2. Gram stain: microsiphoned filaments < 1 µm, Gram-positive.

Discussion

Cutaneous infections due to *Nocardia* spp. are divided into actinomycetoma and cutaneous nocardiosis, with the primary form accounting for 1% up to 2% of cases, and *N. brasiliensis* being the main etiological agent. It occurs after traumatic inoculation, with insect bites being the main factor associated with pediatric cases[1,2]. Clinical features are non-specific, ranging from papules, pustules, abscesses, and gummas, with or without lymphangitic tract involvement, appearing and progressing acutely. Diagnosis is established after direct examination, where microsiphoned septate filaments < 1 µm in diameter are observed, which fragment into bacillary and coccoid forms without the presence of grains and may be acid-alcohol-resistant. It can be cultured on blood agar or Sabouraud dextrose agar without antibiotics, where colonies grow between 25°C and 37°C throughout 8-15 days, appearing as white-yellowish, chalky colonies, with an acuminate "popcorn" shape and a "damp soil" odor. However, molecular techniques such as PCR are required, which is considered the reference method for species identification of *Nocardia*[2,3]. To rule out associated immunodeficiency, lymphocyte subpopulations, immunoglobulin profiles, complement levels, and a chest X-ray are necessary, as the lungs are the most common site of dissemination of the cutaneous form[2]. The main differential diagnosis is mycetoma, where grains are observed on direct examination, unlike in PCN,

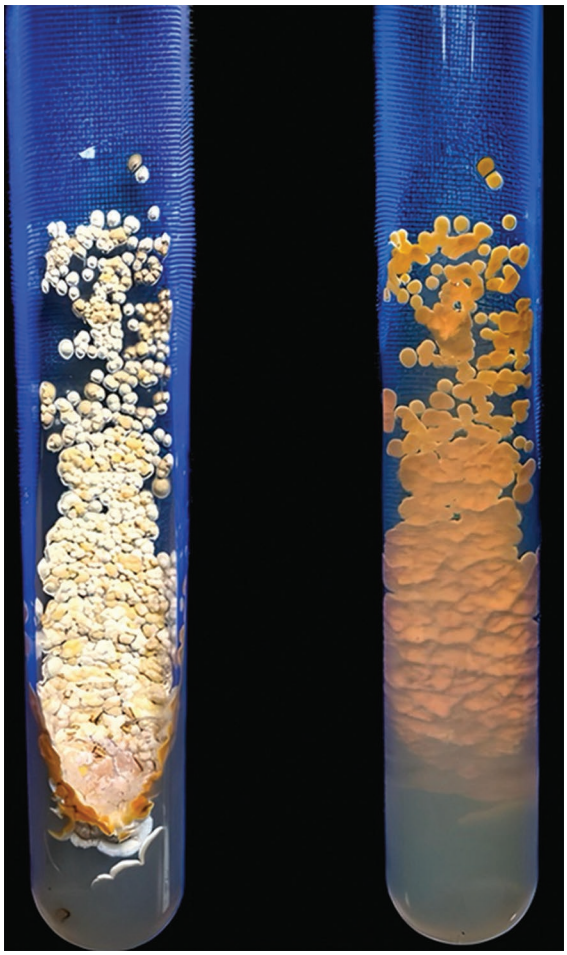

Figure 3. Sabouraud agar culture, white-yellowish acuminate colonies.

where only microsiphoned filaments are seen; other differentials include sporotrichosis, atypical mycobacteriosis, chromoblastomycosis, and soft-tissue infections. Treatment depends on the clinical presentation and the isolated strain. For PCN due to *N. brasiliensis*, TMP-SMZ remains the first-line therapy, with linezolid being considered in cases of dissemination. At present, there is no consensus on the duration of treatment in this age group; however, at least, 6 weeks of treatment are generally recommended[4].

PCN has a good prognosis; however, due to *Nocardia's* ability to inhibit hydrolysis within the phagolysosome, it can remain inside the cells, leading to relapse despite appropriate treatment. In addition, the presence of lymphocytopenia increases the risk of dissemination, requiring close monitoring[1,5].

Conclusion

PCN is a rarely reported condition in pediatric and immunocompetent patients. It should be suspected when there is a history of trauma followed by the appearance of acute lesions that rapidly progress and do not respond to empirical therapy. Isolation in culture and, if possible, PCR-based typing is necessary to diagnose and appropriately treat this rare condition, along with close monitoring due to the potential risk of recurrence or dissemination.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

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Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Fergie JE, Purcell K. Nocardiosis in South Texas children. Pediatr Infect Dis J. 2001;20:711-4.
2. Bonifaz A. Micología Médica Básica. 6th ed. México, DF: McGraw-Hill; 2020.
3. Rouzaud C, Rodriguez-Nava V, Catherinot E, Méchai F, Bergeron E, Farfour E, et al. Clinical assessment of a Nocardia PCR-based assay for diagnosis of nocardiosis. J Clin Microbiol. 2018;56(6).
4. Wang C, Sun Q, Yan J, Liao X, Long S, Zheng M, et al. The species distribution and antimicrobial resistance profiles of *Nocardia* species in China: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2023;17:e0011432.
5. Soueges S, Bouiller K, Botelho-Nevers E, Gagneux-Brunon A, Chirouze C, Rodriguez-Nava V, et al. Prognosis and factors associated with disseminated nocardiosis: a ten-year multicenter study. J Infect. 2022;85:130-6.

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CLINICAL CASE

Postherpetic Wolf's isotopic response

Respuesta isotópica de Wolf posherpética

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Abstract

The Wolf isotopic response is defined as a condition in which a second dermatosis appears in the area of an initial, unrelated, and often resolved skin disorder.There are multiple primary and secondary dermatoses that can be part of it, with herpes zoster being the main trigger. We present the case of a young patient, undergoing the postpartum period, who presented multiple open comedones on a dermatome previously affected by herpes zoster.

Keywords: *Comedon. Herpes zoster. Isotopic response.*

Resumen

Se define como respuesta isotópica de Wolf aquella afección en la que aparece una segunda dermatosis en la zona de un trastorno cutáneo inicial no relacionado y a menudo ya resuelto. Son múltiples las dermatosis primarias y secundarias que pueden formar parte de ella, siendo el herpes zóster el principal gatillante. Exponemos el caso de una paciente, puérpera, que presentó múltiples comedones abiertos sobre un dermatoma previamente afectado por herpes zóster.

Palabras clave: *Comedón. Herpes zóster. Respuesta isotópica.*

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Introduction

Wolf's isotopic phenomenon or response corresponds to the appearance of a second dermatosis in the same location as a previously resolved skin disorder, with which it bears no relation[1-3]. The term "isotopic" (from the Greek iso, meaning same, and topos, meaning place) means in the same site and refers to this sign[2]. It is an uncommon and poorly understood condition, and therefore, likely underdiagnosed[4].

Case report

A 35-year-old female, hypothyroid, treated with levothyroxine, postpartum, exclusively breastfeeding, consulted with a 24-h history of dermatosis that was painful and burning, located on the right hemithorax. Upon physical examination, she presented multiple vesicles with serous content, grouped in clusters, resting on an erythematous base following a dermatomal distribution. With a clinical diagnosis of herpes zoster, treatment was initiated with acyclovir 800 mg orally 5 times a day for 8 days, acyclovir 5% cream 6 times a day for 7 days, and ibuprofen 600 mg every 12 h for 3 days; additionally, protective measures were advised to reduce the risk of contagion to the infant. The patient's progression was favorable, with complete resolution of the lesions, leaving only post-inflammatory hyperpigmentation.

Approximately 1 month later, she consulted again due to the appearance of multiple asymptomatic lesions, clinically consistent with open comedones, located in the same site where she had previously presented herpes zoster. With the dermatoscopy, multiple follicular openings with dark contents were evidenced on residual hyperpigmented macules (Figs. 1 and 2).

Upon suspicion of Wolf's isotopic phenomenon, possible secondary dermatoses such as comedogenic reaction, folliculotropic mycosis fungoides, spiny lichen, and granular parakeratosis were considered. A skin biopsy was performed, and the histopathological study reported multiple dilated follicular ostia with retention of keratinous material consistent with comedones (Fig. 3), leading to the initiation of topical therapy with a combination of adapalene 0.1% and benzoyl peroxide 2.5% gel, once a day, showing complete disappearance of the comedones and a clear improvement of the hyperpigmentation 1 month into therapy.

Discussion

The first cases of Wolf's post-herpetic isotopic response were described by Wyburn-Mason, an English neurologist, who reported a total of 26 cases of malignant tumors in the same site where herpes zoster had previously occurred in 1955. Afterward, in 1985, the Wolf brothers, a dermatologist and a pediatrician, were the first ones to publish a case series of tinea corporis as a secondary dermatosis and attributed the term isoloci response (same locus) to it. In 1995, it was renamed "isotopic response." Finally, in 2002, Italian dermatologist Vincenzo Ruocco proposed including the name Rooni Wolf for her significant contribution, defining it as we know it today[2,5].

The incidence of this disease is unknown; approximately 200 cases are described in the literature[6,7].

We conducted a bibliographic review of the cases reported in the last 10 years, summarized in table 1[8-18]. From the gathered information, we can conclude that herpes zoster is the primary dermatosis reported most

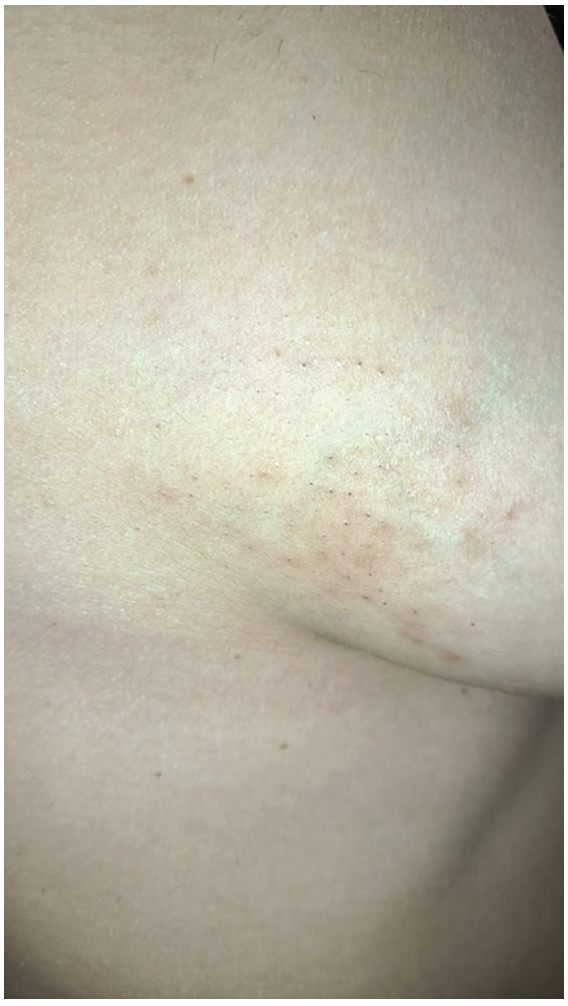

Figure 1. Multiple comedones on areas of residual hyperpigmentation with dermatomal distribution.

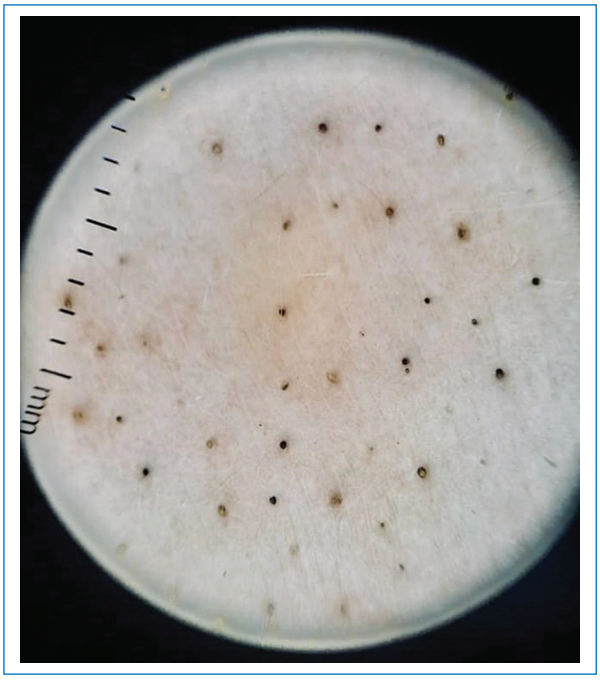

Figure 2. With dermatoscopy: dilated follicular ostia, with keratin plugs, on hyperpigmented areas.

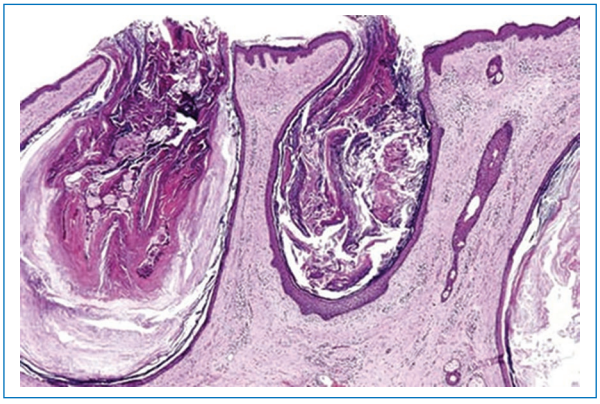

Figure 3. Histopathological study, hematoxylin-eosin stain, 10×: multiple dilated follicular ostia filled with keratinous material around the hair infundibula.

frequently. However, there are also case reports associated with herpes simplex, chickenpox, and local inflammatory processes such as thrombophlebitis, injection sites, and trauma scars[3,6,19]. In contrast, the group of secondary dermatoses is broader and includes lichenoid, granulomatous, tumoral, or infiltrative processes. Regarding sex, there seems to be a higher prevalence among women. In most cases, the time between the resolution of the primary dermatosis and the appearance of the secondary was < 1 year. In addition, a significant percentage of the reported patients had some form of immunosuppression or were on immunosuppressive therapy, which may have predisposed them to develop the viral condition and subsequently the secondary dermatosis[1-3,5-19].

Herpes zoster is caused by a reactivation of the varicella-zoster virus (VZV), being more vulnerable to those individuals who present any form of immunocompromise, although it is increasingly common in immunocompetent patients[20]. While herpes zoster is recognized as the main trigger of Wolf's isotopic response, the exact mechanism through which it would trigger the appearance of the second dermatosis is unknown to this date[3,8]. There are several theories regarding this. On one hand, residual viral particles in the affected tissues could generate persistent inflammatory processes[6]. In addition, a delayed hypersensitivity response to VZV could lead to inflammation, secretion of pro-inflammatory molecules, and local immunosuppression[8]. On the other hand, the viral infection could increase the expression of human leukocyte antigens type II and adhesion molecules in keratinocytes, and consequently, antibodies vs viral particles would cross-react with these molecules, generating persistent inflammation and creating in that dermatome a "predisposed area" for a new dermatosis[21]. Finally, VZV could damage peripheral sensory nerve fibers, type Aδ and C, which would release neuromediators (substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide) and cause both direct tissue damage and alteration of the local immune response[7,22]. While the etiopathogenesis of this disease is a complex one and still under study, most of the proposed hypotheses share common elements, such as the persistent pro-inflammatory state and the involvement of the local neuroimmune system, which would lead to alterations in local vascular and lymphatic structures, perpetuating the above-mentioned mechanisms[7,8,19,21,22]. Moreover, considering that most people do not present Wolf's isotopic response, genetic, environmental, and nutritional factors that may also be involved are considered[6].

Wolf's isotopic response must be differentiated from Koebner's isomorphic phenomenon, which is defined as the appearance of new lesions histopathologically identical to previous skin diseases that appear at the site of a lesion or trauma. While its etiopathogenesis is different from that proposed for Wolf's isotopic response, it is believed that, in some cases, there may be an overlap between the two phenomena[3,23].

On the other hand, memory reaction due to radiation is a phenomenon that also deserves to be differentiated

Table 1. Summary of cases described in the literature[8-18]

Age and no. of cases	Sex and no. of cases	Primary dermatosis and no. of cases	Secondary dermatosis and no. of cases	Interval between both dermatoses and no. of cases	Pathological background and no. of cases
< 20 years: 2 21-40 years: 12 41-60 years: 10 61-80 years: 18 > 81 years: 2	F: 28 M: 16	HZ: 37 HS: 2 Chickenpox: 2 Scar: 1 Injection site: 1 Tinea: 1 (Fungal infection)	Lichen planus dermatitis: 9 Granulomatous dermatitis: 6 Comedones: 4 Eosinophilic dermatitis: 4 Bullous pemphigoid: 3 Psoriasis: 3 Cutaneous leukemia: 2 Vitiligo: 2 Keloid: 2 Prurigo: 2 Follicular lymphoma: 1 Pseudolymphoma: 1 PCBCL: 1 Extrafacial Lever granuloma: 1 PLEVA: 1 BCC: 1 Secondary syphilis: 1	< 1 year: 39 > 1 year: 4 Not reported: 1	Present: 19 Absent: 4 Not reported: 21

CBC: basal cell carcinoma; F: female; HS: herpes simplex; HZ: herpes zoster; PCBCL: primary cutaneous B-cell lymphoma; M: male; PLEVA: pityriasis lichenoides et varioliformis acuta.

from Wolf's isotopic response. It produces an inflammatory reaction in an area previously treated with radiotherapy and is generally triggered by the administration of a drug. Although we find some similarity with Wolf's isotopic response, as both occur in tissues previously exposed to a noxa, the memory reaction due to radiation only develops in an area previously irradiated and, although there are exceptions, the action of a drug, usually a chemotherapeutic agent, is generally required for the inflammatory response to be triggered[24,25].

Regarding treatment, there is no evidence indicating that antivirals prevent the possible appearance of Wolf's isotopic response. The treatment of secondary dermatosis should be individualized in each case[9].

Conclusion

We present a case of a rare dermatosis in routine clinical practice, with few reports in the medical literature. We emphasize the importance of familiarizing oneself with this condition to achieve an accurate diagnosis. Although the interval between primary and secondary dermatoses is not definitively known, we underline the importance of continuous follow-up of patients affected by herpes zoster due to the possibility of Wolf's isotopic response that could facilitate the development of other dermatoses, including neoplasms, which may be potentially serious.

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

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References

1. Downing C, Mendoza N, Sra K, Tyring SK. Virus del herpes humanos. In: Dermatología. 4.ª ed. Barcelona: Elsevier; 2018. p. 1400-24.
2. Barros R, Plaza MG, Verdi MC, Zusaeta MM. Pseudolinfoma post herpes zoster: fenómeno isotópico. Rev Argent Dermatosifilol. 2016;97:39-49.
3. Gurel MS, Savas S, Bilgin F, Erdil D, Leblebici C, Sarikaya E. Zosteriform pemphigoid after zoster: Wolf's isotopic response. Int Wound J. 2016;13:141-2.

4. Reolão BR, Mora DS, Garcia MC, Bonamigo RR. Breast carcinoma metastasis and Wolf's isotopic response. An Bras Dermatol. 2022;97:467-70.
5. Bruzón MP, González YP, Lincheta LF, Pérez AV, de Valle Castro MC. Fenómeno isotópico de Wolf en dos pacientes. Folia Dermatol Cubana. 2020;12(3).
6. Queiroz MT, Almeida JR, Sementilli A, Mattos e Dinato SL, Romiti N. Wolf's isotopic response, presenting as lichen planus. An Bras Dermatol. 2015;90:91-3.
7. Yang Y, Wang T. Wolf's isotopic response of eosinophilic dermatitis after herpes zoster infection: case reports and literature review. Clin Cosmet Investig Dermatol. 2022;15:211-6.
8. Barber D, Robertson L. Granuloma annulare as an isotopic response to herpes zoster. J Cutan Med Surg. 2014;18:413-9.
9. Jaka-Moreno A, López-Pestaña A, López-Núñez M, Ormaechea-Pérez N, Vildosola-Esturo S, Tuneu-Valls A, et al. Wolf's isotopic response: a series of 9 cases. Actas Dermosifiliogr. 2012;103:798-805.
10. Wang T, Zhang M, Zhang Y, Zhang Y, Zhang S, Qu T, et al. Wolf's isotopic response after herpes zoster infection: a study of 24 new cases and literature review. Acta Derm Venereol. 2019;99:953-9.
11. Wollina U, Schönlebe J, Hansel G, Koch A. First case of primary diffuse large B-cell lymphoma of skin as Wolf's postherpetic isotopic response. Dermatol Ther. 2020;33:13714.
12. Melgar E, Henry J, Valois A, Dubois-Lacour MB, Truchetet F, Cribier B, et al. Extra-facial Lever granuloma on a herpes zoster scar: Wolf's isotopic response. Ann Dermatol Venereol. 2018;145:354-8.
13. Mishra E, Patnaik S, Nayak S, Rout AN, Sethukumaran AG, Sahoo RL. Psoriasis as Wolf's isotopic response over BCG scar. Indian J Dermatol Venereol Leprol. 2021;87:712-4.
14. Sinha P, Madakshira MG, Lekshmipriya K, Sharma J. Wolf's isotopic response seen as a rare occurrence of pityriasis lichenoides et varioliformis acuta (PLEVA) lesions over healed lesions of tinea corporis. Indian Dermatol Online J. 2022;13:660-2.
15. Hsu HT, Su HA, Chen YC. Wolf's isotopic response following COVID-19 vaccination. Indian J Dermatol. 2023;68:589.
16. Chun SH, Kim BY, Kim CM, Park JB, Ryu HJ. A case of Wolf's isotopic response presenting as bullous pemphigoid. Ann Dermatol. 2017;29:499-500.
17. Kwak JH, Na CH, Kim MS, Choi H. Superficial basal cell carcinoma at the site of herpes zoster: Wolf's isotopic response or idiopathic? Indian J Dermatol Venereol Leprol. 2023;89(1):1-3.
18. Gayen T, Shome K, Bandyopadhyay D, Roy S, Gharami RC. Secondary syphilid developing over healed lesions of varicella: Wolf's isotopic response? Indian J Dermatol. 2015;60:191-3.
19. Vojvodic A, Tirant M, Nardo VD, Lotti T, Wollina U. Immunocompromised districts of skin: a case series and a literature review. Open Access Maced J Med Sci. 2019;7:2969-75.
20. Ramos Ríos MA, Román AR, Rodríguez YL, Corbo LV. Estrés, infecciones e inmunodeficiencia en una profesional de la salud. Rev Cub Med Int Emerg. 2021;60:1-5.
21. Xu W, Yu C, Le Y, Zhang J. Wolf's isotopic response after herpes zoster infection in chronic lichen sclerosus-like graft versus host disease: case report and literature review. Clin Cosmet Investig Dermatol. 2022;15:2153-7.
22. Panzarelli A. Fenómeno de Köebner versus fenómeno de Wolf: aclarando conceptos. Dermatología Venezolana. 2016;54:19-21.
23. Lee NY, Daniel AS, Dasher DA, Morrell DS. Cutaneous lupus after herpes zoster: isomorphic, isotopic, or both? Pediatr Dermatol. 2013;30:110-3.
24. Jamaluddin MF, Abraham AG, Menon G, Nakatsui T, Roa W. Recurrent radiation recall dermatitis 40 years after radiation therapy for breast cancer. Breast J. 2021;27:543-6.
25. McKay MJ, Foster R. Radiation recall reactions: an oncologic enigma. Crit Rev Oncol Hematol. 2021;168:103527.

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CASES FOR DIAGNOSIS

Characteristics and diagnostic considerations of fibroepithelioma of Pinkus: a debated entity

Características y consideraciones diagnósticas del fibroepitelioma de Pinkus: una entidad debatida

Sara Saldarriaga-Santamaría[1] and Carlos García-Rementería[2]*

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Pinkus fibroepithelioma, a rare variant of basal cell carcinoma, primarily presents in individuals over 50 years of age, with a slight predisposition toward the female sex. Typically located on the trunk and proximal limbs, it shows as a polypoid and pedunculated lesion in shades of pink, light brown, or normochromic[1].

Dermatoscopically, bright white lines, serpentine, punctate, and polymorphic vessels are usually observed. Less frequently, arboriform vessels, ulceration, and milia-like cysts[1-3] are described.

Differential diagnoses include pendulous fibroma, neurofibroma, intradermal nevi, and acrochordons (Table 1)[4-7]. Histologically, basaloid cell strands with a fenestrated pattern and abundant fibrous stroma are key features for diagnosis[1]. Due to its benign behavior, morphology, and molecular features, some authors argue that it could be a type of trichoblastoma[8].

Figure 1A illustrates a 5-year-old lesion, located on the arm of a 30-year-old patient, associated with pruritus and occasional bleeding. The patient reported

Table 1. Main differential diagnoses of Pinkus fibroepithelioma and their clinical features

Differential diagnosis	Clinical features
Pendulous fibroma	Normochromic, pedunculated papules, usually located on the face or neck. Typically arises from plexiform neurofibromas in patients with neurofibromatosis.
Neurofibroma	Normochromic, painless, firm nodules. Typically located on the trunk and limbs. May be solitary or multiple, and in the latter case, associated with neurofibromatosis.
Intradermal nevus	Sessile papules or nodules, normochromic or slightly pigmented. Dermatoscopically, coma vessels are seen, and sometimes brown pigment globules.
Acrochordons	Pedunculated, normochromic papules, are primarily found in intertriginous areas such as the axillae, neck, and groin.

Adapted from Henington and Caroe[4], Farma et al.[5], Kim and Nelson[6], Pandey and Sonthalia[7].

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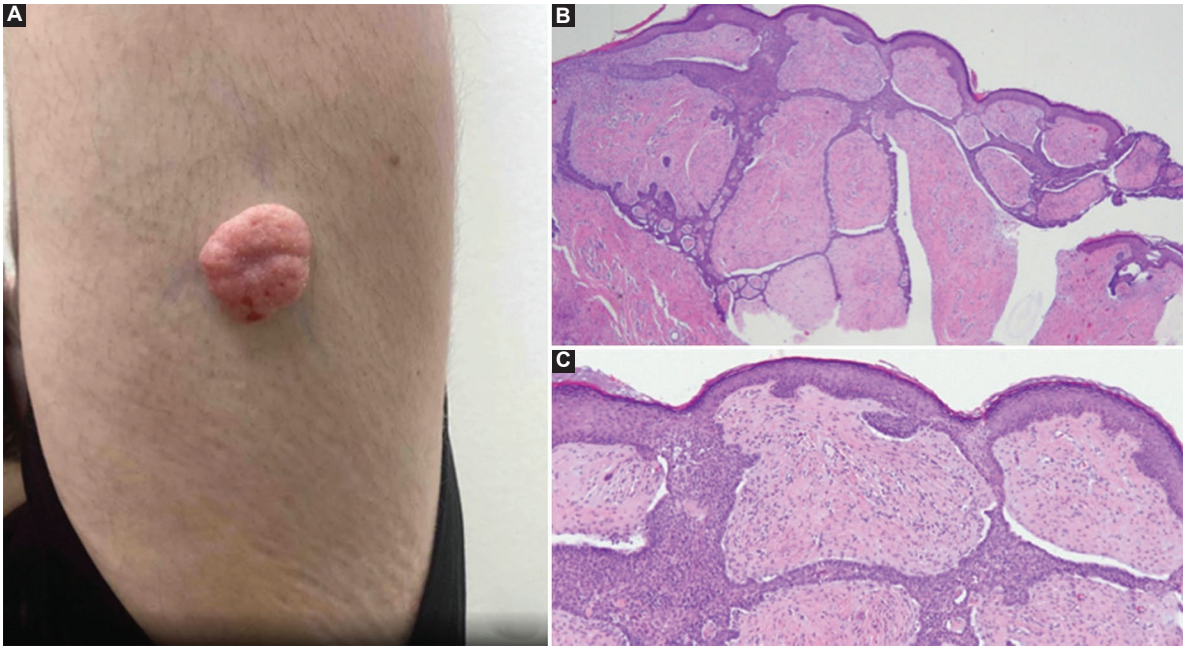

Figure 1. A: pedunculated, erythematous nodule–2 cm × 2.5 cm in diameter–located on the posterior arm of a 30-year-old male. **B** and **C:** sections show skin extending to the reticular dermis, with a malignant epithelial lineage tumor lesion composed of columns of basaloid cells arranged in a reticulated pattern, forming anastomosing cords surrounding islands of fibrous tissue, with stromal retraction and peripheral palisading.

progressive growth within the past year, which led him to seek consultation. A skin biopsy was performed, confirming the diagnosis of Pinkus fibroepithelioma (Figs. 1 B and C).

Ethical considerations

Protection of people and animals. The authors declare that no experiments on humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data; therefore, informed consent was not required. Relevant recommendations were followed.

Statement on the use of artificial intelligence. The authors declare that no generative artificial intelligence tools were used in the writing of this manuscript.

References

1. Nanda JK, Marghoob N, Forero Cuevas DM, Lee KR, Levy M, Reiter O, et al. Clinical and dermoscopic features of Fibroepithelioma of Pinkus: case series with an emphasis on hypopigmented to pink lines intersecting at acute angles. Arch Dermatol Res. 2021;313:633-40.
2. Lupu M, Clatici VG, Barinova E, Voiculescu VM. Fibroepithelioma of pinkus: dermoscopic and reflectance confocal microscopic patterns. Dermatol Ther. 2021;34:e14831.
3. Zalaudek I, Ferrara G, Broganelli P, Moscarella E, Mordente I, Giacomel J, et al. Dermoscopy patterns of fibroepithelioma of pinkus. Arch Dermatol. 2006;142(10):1318-22.
4. Henington VM, Caroe AE. Massive fibroma pendulum: report of a case. AMA Arch Dermatol. 1959;80:580-3.
5. Farma JM, Porpiglia AS, Vo ET. Benign neurogenic tumors. Surg Clin North Am. 2022;102:679-93.
6. Kim JK, Nelson KC. Dermoscopic features of common nevi: a review. G Ital Dermatol E Venereol. 2012;147:141-8.
7. Pandey A, Sonthalia S. Skin Tags. Treasure Island, FL: StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/nbk547724 [Last accessed on 2024 Aug 07].
8. Russell-Goldman E, Lindeman NI, Laga AC, Hanna J. Morphologic, immunohistochemical, and molecular distinction between fibroepithelioma of Pinkus and "fenestrated" basal cell carcinoma. Am J Dermatopathol. 2020;42:513-20.

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CLINICAL CASE

Merkel cell carcinoma, a case report

Carcinoma de células de Merkel, a propósito de un caso

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Abstract

Merkel cell carcinoma (MCC) is a rare and aggressive skin neoplasm due to its high rate of local recurrence and distant metastasis. It affects older patients or those with a certain degree of immunosuppression. It manifests clinically as a rapidly growing tumor, generally in areas exposed to light. We present the case of a patient with MCC located in the left knee who presented a good response to surgical treatment.

Keywords: *Merkel cell carcinoma. Skin cancer. Neuroendocrine carcinoma.*

Resumen

El carcinoma de células de Merkel es una neoplasia cutánea poco frecuente y agresiva por su alta tasa de recurrencia local y de metástasis a distancia. Afecta a pacientes de edad avanzada o con cierto grado de inmunosupresión. Se manifiesta clínicamente como un tumor de crecimiento rápido, generalmente en zonas expuestas a la luz. Presentamos el caso de un paciente con carcinoma de células de Merkel localizado en la rodilla izquierda que presentó buena respuesta al tratamiento quirúrgico.

Palabras clave: *Carcinoma de células de Merkel. Cáncer cutáneo. Carcinoma neuroendocrino.*

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Introduction

Merkel cell carcinoma (MCC) is a rare but aggressive form of skin cancer. It typically presents as a rapidly growing erythematous tumor located in sun-exposed areas, primarily in older individuals with Fitzpatrick skin types I-II and some degree of immunosuppression[1]. We present the case of a patient with MCC located on the left knee.

Case report

This is the case of a 79-year-old male patient with a past medical history of chronic urticaria under evaluation for several years, who consulted our service with a 2-month history of rapidly growing, asymptomatic skin lesion located infrapatellar on his left leg. Upon dermatological physical examination, we identified a tumorous, erythematous, cup-shaped lesion with a smooth surface, well-defined edges, and hard yet elastic consistency, measuring approximately 2 cm in diameter (Fig. 1). The rest of the skin presented marked actinic damage with multiple actinic keratoses on the face and scalp. The presumptive diagnoses were MCC, amelanotic melanoma, angiosarcoma, cutaneous metastasis, basal cell carcinoma, and B-cell cutaneous lymphoma. A Doppler ultrasound was requested, revealing a hypervascularized solid nodular lesion measuring 21 mm × 16 mm × 23 mm in diameter, with invasion into the subcutaneous tissue. The histopathological study of the biopsy of the lesion reported a poorly differentiated small round cell malignant neoplasm (Fig. 2) with lymphovascular invasion. Immunohistochemistry was positive for cytokeratin 20 (CK-20) (paranuclear) (Fig. 3), chromogranin (Fig. 4), and synaptophysin, and negative for CK-7, thyroid transcription factor-1 (TTF-1), and anterior cruciate ligament; 90% of the cells were Ki67 positive. Considering the clinical presentation, histology, and immunohistochemistry, we arrived at the diagnosis of MCC. Detection of polyomavirus in the tumor tissue was not possible due to the lack of availability of this study in our facility.

A full-body positron emission tomography (PET-scan) and high-resolution computed tomography of the chest, abdomen, and pelvis were performed, which ruled out evidence of distant metastasis.

Complete surgical resection of the lesion with 2 cm margins and sentinel lymph node biopsy was performed, and the lymph node was negative for malignancy; thus, the final result was T2 N0 M0. In an interdisciplinary meeting with the dermatology, oncology, surgical

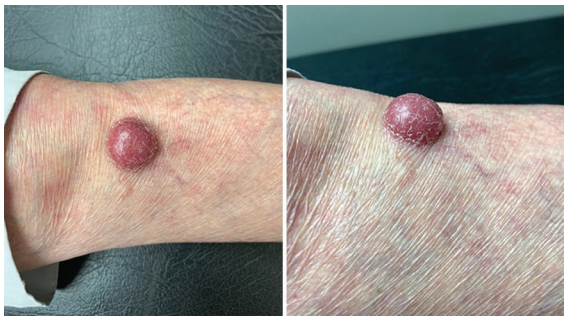

Figure 1. Tumorous erythematous, cup-shaped lesion located infrapatellar on the left.

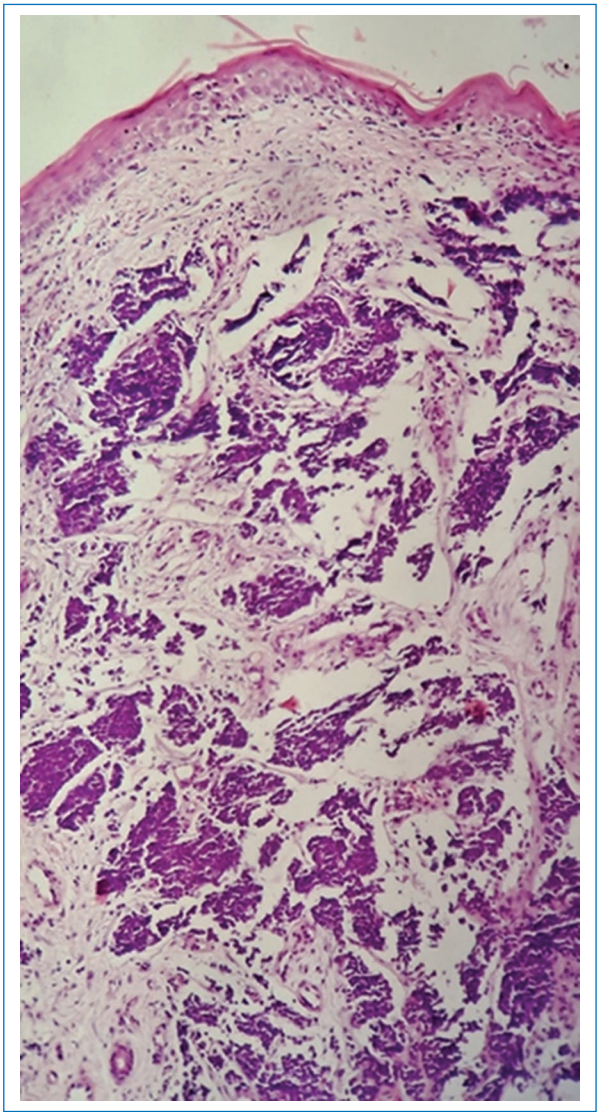

Figure 2. Histopathological study, H/E 4×. In the dermis, expansive and infiltrative tumor proliferation. A mix of sheets, nests, and trabeculae of small neoplastic cells can be seen.

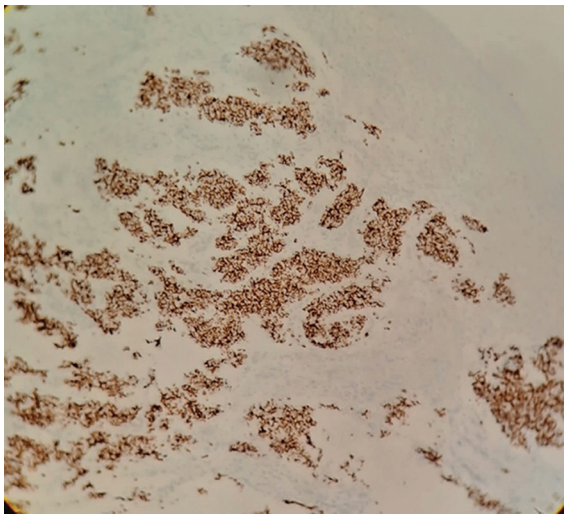

Figure 3. Immunohistochemistry: cytokeratin 20 monoclonal antibody positive, paranuclear staining.

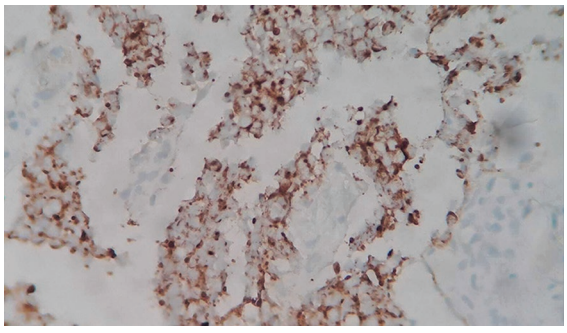

Figure 4. Immunohistochemistry: chromogranin monoclonal antibody positive.

oncology, and radiotherapy departments, radiotherapy of the surgical bed was suggested, but the patient refused. Therefore, clinical follow-up was scheduled every 3 months and radiological follow-up was scheduled every 6 months, with no relapse observed to date, 9 months after diagnosis.

Discussion

MCC is a malignant skin neoplasm composed of highly anaplastic cells that share certain structural characteristics with cells of neuroendocrine origin, which is why it is also called "primary neuroendocrine carcinoma of the skin"[1]. It is an aggressive tumor, first described in 1972 by Toker[2]. Its frequency of occurrence is low, with an incidence rate between 0.1 and 2.5 cases/100,000 people/year, but it is on the rise, with Australia being the country with the most reported cases[3,4]. It primarily affects men, with the average age at diagnosis being 75 years[5,6].

Regarding its etiopathogenesis, the origin of the MCC cell is a subject of debate; some authors relate it to the Merkel cell *per se*, whereas others associate its origin with epidermal stem cells[7]. The main risk factors for its appearance are advanced age, prolonged sun exposure, and immunosuppression (human immunodeficiency virus infection, solid organ transplantation, or hematological neoplasms)[8]. This association between MCC and immunosuppressive states suggests a potential viral origin. Feng et al.[9] described the "MCC-related polyomavirus," a double-stranded DNA virus belonging to the Polyomaviridae family, which was present in 80% of the MCCs studied by these authors. The oncogenic mechanism is completely unknown, but it is known that this virus integrates into the human genome and is capable of coding for an oncoprotein called the "T antigen," which would inhibit the retinoblastoma tumor suppressor protein, evading innate immune response and promoting cell development[6,8]. On the other hand, polyomavirus-negative tumors present mutations in various tumor suppressor genes and are considered associated with IV radiation, as they occur in individuals with a history of prolonged sun exposure[10].

Clinically, it usually appears in areas exposed to sunlight, most frequently on the head and neck, followed by the limbs and trunk, as a painless, solitary, and violaceous-colored tumor[6,11,12]. It exhibits rapid growth and may occasionally ulcerate[13]. Heath et al.[14] described the clinical features of 195 patients, proposing the AEIOU acronym for better lesion identification (Table 1); in our patient, four criteria of this acronym were present. Dermatoscopically, there are no specific signs of MCC, but irregular, arboriform, and linear vessels, as well as bright white areas, can be observed[15].

Differential diagnoses of MCC include basal cell carcinoma, amelanotic melanoma, squamous cell carcinoma, lymphoma, and cutaneous metastasis[14,16].

Histologically, MCC invades and erases the dermal architecture, and the cells are arranged in sheets, nests, or trabeculae, or they present a mixed pattern. These cells are small, with eosinophilic cytoplasm and irregular oval nuclei with finely granular chromatin, described as "salt and pepper." Mitoses are usually abundant[17]. Immunohistochemistry is typically negative for TTF-1 and positive for CK-20 with a characteristic paranuclear staining, as well as neuroendocrine markers such as specific neuronal enolase (also expressed in other neuroendocrine tumors), synaptophysin, and

Table 1. AEIOU acronym*[14]

A	Asymptomatic
E	Rapid expansion
I	Immunosuppression
O	Advanced age (older)
U	UV exposed area

*Three or more criteria: high clinical suspicion.
UV: ultraviolet.

chromogranin (the most specific marker for MCC). Immunohistochemistry is particularly useful in distinguishing MCC from cutaneous metastasis of small-cell lung carcinoma, with the latter being positive for TTF-1 and negative for CK-20[18,19].

Regarding staging, the National Comprehensive Cancer Network (NCCN) recommends performing a full-body PET scan (especially for tumors located in the lower limbs) or HRCT of the chest, abdomen, and pelvis in patients with clinical evidence or high suspicion of local or distant metastasis. It also suggests performing brain MRI in cases of specific symptoms and HRCT of the head and neck in cases of primary tumor localization in that region[20]. Sentinel lymph node study is indicated for staging in patients without evidence of distant metastasis[10].

The NCCN includes the staging of the American Joint Commission on Cancer in its guide, using clinical, radiological, and histopathological examinations to define the tumor, node, and metastasis stage and classify the disease as localized, regional, or disseminated (Table 2)[20].

Once the patient has been staged, the NCCN proposes an algorithm for managing each specific stage. For localized disease, conventional surgical excision with 2 cm lateral margins and up to the fascia in depth is the treatment of choice. Mohs micrographic surgery is an option for areas where healthy tissue needs to be preserved for functional or esthetic reasons[20].

The association with adjuvant radiotherapy of the surgical bed has shown lower recurrence rates. Indications include tumors > 1 cm, head or neck location, and lymphovascular invasion[21]. In our patient, radiotherapy was not performed due to his refusal. Effective monotherapy with radiotherapy has also been described for patients in whom surgical resection is not possible[21]. In the case of a positive sentinel lymph node, lymphadenectomy or radiotherapy of the area is suggested[20]. Although this tumor is chemoresponsive

Table 2. Staging of Merkel cell carcinoma according to the American Joint Commission on Cancer[19]

Clinical (cTNM)			
Stage	**T**	**N**	**M**
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2-T3	N0	M0
IIB	T4	N0	M0
III	T0-T4	N1-N3	M0
IV	T0-T4	Any	M1
Histopathological (pTNM)			
Stage	**T**	**N**	**M**
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2-T3	N0	M0
IIB	T4	N0	M0
IIIA	T1-T4	N1a (sn) or N1a N1b	M0
IIIB	T1-T4	N1b-3	M0
IV	T0-T4	Any	M1

cTNM: clinical tumor, node, metastasis; pTNM: pathological tumor, node, metastasis.

to regimens with doxorubicin, vincristine, and cyclophosphamide, it has high recurrence rates[22]. Immunotherapy with avelumab, nivolumab, and pembrolizumab is the treatment of choice for patients with advanced disease[20,23].

The prognosis of MCC is poor due to the high rate of local recurrence and distant metastasis, which is approximately 40%, higher than that of melanoma. About 90% of metastases occur within the first 3 years of diagnosis[24]. The organs to which it most frequently metastasizes are regional lymph nodes, skin, lungs, bone marrow, and bone, followed by the pancreas, brain, and kidney[20,24]. Predictive factors of poor prognosis include advanced age, tumor size > 2 cm, head or neck location (especially on the lips), associated immunosuppression, and lymphovascular invasion[18,20].

Regarding follow-up, recurrences occur within 24 months in 90% of patients, so clinical examination every 3 months and imaging studies as appropriate to the stage are recommended[20].

We present the case of a patient with MCC localized on the left leg, treated with surgical resection, and

currently under follow-up with no signs of recurrence. We emphasize the importance of early diagnosis, thorough examination, a multidisciplinary approach, and close follow-up in these patients.

Funding

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 Considerations

Protection of humans and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and in compliance with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Ethics Committee of the institution.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from the patients, and have approval from the Ethics Committee. The recommendations of the SAGER guidelines were followed according to the nature of the study.

Statement on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Siqueira SO, Campos do Carmo G, Dos Santos AL, Martins C, De Melo AC. Merkel cell carcinoma: epidemiology, clinical features, diagnosis and treatment of a rare disease. An Bras Dermatol. 2023;98:277-86.
2. Toker C. Trabecular carcinoma of the skin. Arch Dermatol. 1972;105:107-10.
3. Silling S, Kreuter A, Gambichler T, Meyer T, Stockfleth E, Wieland U. Epidemiology of merkel cell polyomavirus infection and Merkel cell carcinoma. Cancers (Basel). 2022;14:6176.
4. Garbutcheon-Singh KB, Curchin DJ, McCormack CJ, Smith SD. Trends in the incidence of merkel cell carcinoma in Victoria, Australia, between 1986 and 2016. Australas J Dermatol. 2020;61:34-8.
5. Mistry K, Levell NJ, Craig P, Steven NM, Venables ZC. Merkel cell carcinoma. Skin Health Dis. 2021;1:e55.
6. Brady M, Spiker AM. Merkel cell carcinoma of the skin. In: StatPearls. Treasure Island, FL: StatPearls; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/nbk482329
7. Xue Y, Thakuria M. Merkel cell carcinoma review. Hematol Oncol Clin North Am. 2019;33:39-52.
8. Yang JF, You J. Merkel cell polyomavirus and associated Merkel cell carcinoma. Tumour Virus Res. 2022;13:200232.
9. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science. 2008;319:1096-100.
10. Rama AS, Neglia V, Abeldaño A. Carcinoma de células de merkel. Dermatol Argent. 2020;26:140-52.
11. National Cancer Institute. Merkel Cell Carcinoma Treatment (PDQ®): Health Professional. Available from: https://www.cancer.gov/types/skin/hp/merkel-cell-treatment-pdq
12. Cullison CR, Zheng DX, Levoska MA, Scott JF, Bordeaux JS. Tumor primary site as a prognostic factor for Merkel cell carcinoma disease-specific death. J Am Acad Dermatol. 2021;85:1259-66.
13. Coggshall K, Tello TL, North JP, Yu SS. Merkel cell carcinoma. An update and review: Pathogenesis, diagnosis, and staging. J Am Acad Dermatol. 2018;78:433-42.
14. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Peñas PF, et al. Clinical 195 patients: the AEIOU features. J Am Acad Dermatol. 2008;58:375-81.
15. Jalilian C, Chamberlain AJ, Haskett M, Rosendahl C, Goh M, Beck H. Clinical and dermoscopic characteristics of Merkel cell carcinoma. Br J Dermatol. 2013;169:294-7.
16. Nyrud MK, Bratland Å, Landrø L, Brevig T, Ryder T, Hermann R, et al. Clinical and dermoscopic characteristics of merkel cell carcinoma. Tidsskr Nor Laegeforen. 2022;142:294-7.
17. Tetzlaff MT, Nagarajan P. Update on merkel cell carcinoma. Head Neck Pathol. 2018;12:31-43.
18. Gauci ML, Aristei C, Becker JC, Blom A, Bataille V, Dreno B, et al. Diagnosis and treatment of Merkel cell carcinoma: European consensus-based interdisciplinary guideline. Eur J Cancer. 2022;171:203-31.
19. Llombart B, Requena C, Cruz J. Actualización en el carcinoma de células de Merkel: epidemiología, etiopatogenia, clínica, diagnóstico y estadificación. Actas Dermosifiliogr. 2017;108:108-19.
20. Schmults CD, Blitzblau R, Aasi SZ, Alam M, Amini A, Bibee K, et al. NCCN Guidelines. Merkel cell carcinoma. Version 1.2023. J Natl Compr Canc Netw. 2023;21:1224-33.
21. Hong AM, Stretch JR, Thompson JF. Treatment of primary Merkel cell carcinoma: radiotherapy can be an effective, less morbid alternative to surgery. Eur J Surg Oncol. 2021;47:483-5.
22. Angeles CV, Sabel MS. Immunotherapy for Merkel cell carcinoma. J Surg Oncol. 2021;12:775-81.
23. Zitvogel L, Kroemer G. Targeting PD-1/PD-1L interactions for cancer immunotherapy. Oncoimmunology. 2012;1:1223-5.
24. McEvoy AM, Lachance K, Hippe DS, Cahill K, Moshiri Y, Lewis CW. Recurrence and mortality risk of Merkel cell carcinoma by cancer stage and time from diagnosis. JAMA Dermatol. 2022;158:382-9.

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CLINICAL CASE

Glomus tumor: presentation of a case from painful nodule on ear helix

Tumor glómico: presentación de un caso de nódulo doloroso en el hélix de la oreja

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Abstract

Glomus tumors are infrequent benign vascular neoplasms that deteriorate patients' quality-of-life due to delays between the onset of symptoms and suspicion of diagnosis, histopathological confirmation, and treatment. These tumoral pathologies rarely present themselves as described in medical textbooks or their usual locations and frequently exhibit atypical symptoms, signs, and anatomical sites, which can confuse the treating physician and can lead to disregarding this dermatosis. A patient with a glomus tumor of the helix in the left ear, with an evolution of > 2 years, is described in this case.

Keywords: *Glomus tumor. Left ear helix. Vascular tumor.*

Resumen

El tumor glómico es un tumor vascular benigno infrecuente que puede deteriorar la calidad de vida de los pacientes debido al retraso entre el inicio de los síntomas, la sospecha diagnóstica, la confirmación histopatológica y el tratamiento quirúrgico. En innumerables ocasiones, las patologías tumorales no se presentan con la clínica ni las localizaciones habituales que describen los libros de medicina; con frecuencia aparecen con síntomas, signos y localizaciones anatómicas atípicos que pueden confundir al médico tratante y no darle la importancia que se merece la dermatosis. Se describe un caso de tumor glómico en el hélix de la oreja izquierda de un paciente con más 2 años de evolución.

Palabras clave: *Tumor glómico. Hélix oreja izquierda. Tumor vascular.*

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Introduction

Glomus tumor was first described by Wood in 1812, and its histological characteristics were reported by Masson in 1924. It is a benign vascular tumor originating in the arteriovenous anastomosis in the reticular dermis and is not very common. An incidence of 1-5% of hand tumors has been reported[1-3], although cases of malignant cutaneous glomus tumors have also been reported, which fortunately are much rarer[4-6]. Glomus tumor has a neuromyoarterial component derived from specialized smooth muscle cells or pericytes in the glomus body–also known as the Sucquet-Hoyer canal–with a thermoregulatory function. Although this tumor is most often solitary, multiple forms have been described in about 10% of cases[7,8], with autosomal dominant inheritance known as glomangiomas or paragangliomas, the latter derived from the APUD cellular system. Glomus tumor is frequently located in distal areas of the extremities, such as fingers, palms, and soles, most commonly under the nail bed. Extradigital presentations are rare, which is why diagnosis is sometimes delayed and can take years after the first consultation.

We present a glomus tumor that appeared as a painful nodule on the helix of the left ear, an unusual anatomical location.

Case report

A 48-year-old male, known to have diabetes without treatment or medical control, with a history of acquired syphilis treated with penicillin and with a serological scar, skin type Fitzpatrick III, reported a 10-year history of a dome-shaped bulge with a spherical pedunculated nodule of a violet color and hard-elastic consistency, solitary, causing pain on palpation (Fig. 1) and when lying on the left side, associated with paroxysmal painful sensations to cold temperatures. An ice cube contact test and puncture with a sharp object were performed, to which the patient reported severe pain, rated 9 on a scale of 1-10.

The incisional biopsy of the lesion confirmed the presence of a glomus tumor with positive immunohistochemical staining for caldesmon and smooth muscle actin.

Discussion

Painful skin tumors are rare versus non-painful ones. For the differential diagnosis of painful tumors, an acronym is used as a guide to differentiate the various types of nodules with the above-mentioned characteristics: eccrine spiradenoma, neurilemmoma, glomus tumor, leiomyoma (angioleiomyoma, piloleiomyoma, and dartos muscle leiomyoma), angiolipoma, neuroma, and dermatofibroma or glomus tumor, leiomyoma, eccrine spiradenoma, neurilemmoma, dermatofibroma, angiolipoma, granular cell tumor, endometriosis, and neuroma[9,10]. In this case, the clinical presentation was a reddish-blue nodule that produced pain on finger pressure and blanched with the same maneuver, suggesting a vascular lesion. The dermoscopy described in the literature mostly corresponds to subungual areas, with a homogeneous white area and disappearance of the lunula. Other descriptions in extradigital areas include homogeneous purpuric lakes surrounded by a whitish area[11], or a multicolored structure pattern with a central purpuric macule surrounded by a whitish area and peripheral brown pigmentation[12], resembling concentric brown rings or telangiectatic macules over a poorly defined blue-gray area[13-15]. In our case, homogeneous red-violet lagoons surrounded by white circular rings were observed (Fig. 2).

This tumor originates in the neuromyoarterial glomus body, a structure involved in thermoregulation, and is found in the fingers, palms, and soles, most frequently in the nail bed. It is categorized into: (1) solitary cutaneous glomangioma, which represents > 90% of the cases, is non-familial, localized, with a fibrous capsule, often painful, and histologically characterized by small endothelial-lined cavities and a high number of glomus cells; (2)

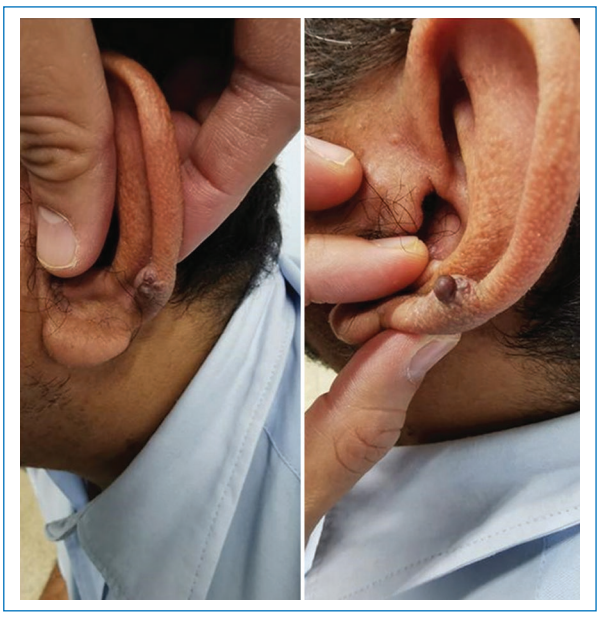

Figure 1. Violet-colored papule over a single skin-colored nodule.

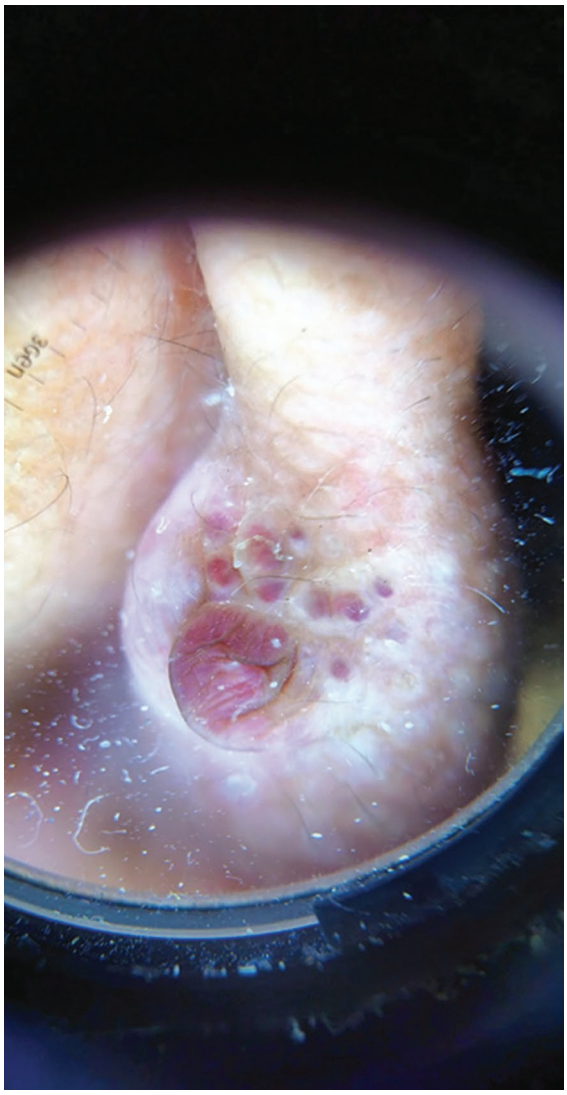

Figure 2. Contact dermoscopy shows homogeneous red-violet lagoons separated and surrounded by circular white rings.

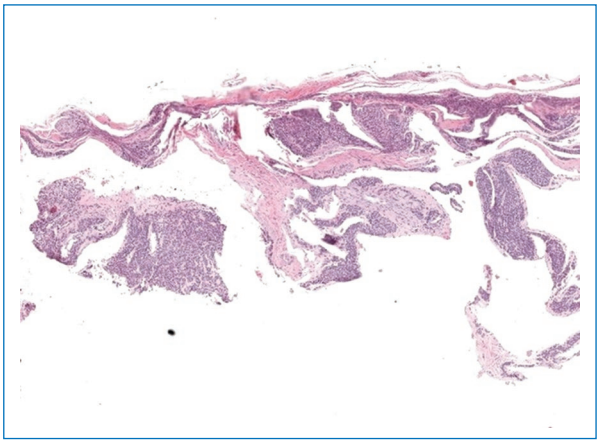

Figure 3. Hematoxylin and eosin stain (×4). Capillary vascular proliferation surrounded by sheets of glomus cells is identified in the dermis.

multiple cutaneous glomangiomas–of autosomal dominant inheritance–which can be localized, segmented, or disseminated, are non-painful, non-encapsulated, and histologically exhibit large, irregular ectatic vessels with few glomus cells; (3) glomangiomyoma is composed proportional amounts of smooth muscle and vascular cells[16].

Glomus tumors are rare, representing approximately 1% up to 5% of all tumors found in the hands, although some authors describe incidence rates < 1%[2,3,17]. In a study conducted at the Mayo Clinic, a 20-year retrospective review found that 61% of cases were extradigital[14]. However, in a study by Kumar et al[2]. from 2014 with patients with neurofibromatosis type 1, 66.7% out of 42 patients had tumors located in the hands, most commonly in subungual areas, whereas 33.3% were located in different areas[2,3,14]. Intraosseous glomangiomas have also been reported[17]. In our case, the appearance of the helix is very rare, with only a few reports in the literature, such as a case reported back in 1931[18]. Clinically, it usually presents as a dermatosis composed of a macule, papule, or nodule of red, violet, or pink color on the skin, or a palpable bump, an increase in curvature or deformity of the nail plate, and sometimes nail dystrophy. In this case, a violet papule was observed on a single, painful skin-colored nodule upon palpation (Fig. 1); the ice-cold water test intensified the pain in the affected area. The Love test consists of applying a pointed object to trigger pain in the lesion area; although this test has a high sensitivity rate, the specificity rate is very low, which in literature is compared to 0%. Hildreth test consists of applying a tourniquet to an extremity to induce ischemia, which reduces or eliminates the pain, with a 91% up to 100% specificity rate and a 77% up to 92% sensitivity rate[9,19]. The cold test involves exposing the tumor to a cold object or substance, which intensifies the pain.

Histopathology reported in the literature shows several components, including glomus cells, blood vessels, and smooth muscle. In solid glomus tumors, nests of uniformly grouped glomus cells are found, without abundant vascularization or smooth muscle tissue. Tumors with significant smooth muscle differentiation are subclassified as glomangiomyomas. Glomangiomas show intradermal nests of monomorphic glomus cells or irregularly formed vascular spaces with nests of polygonal cells with eosinophilic cytoplasm and

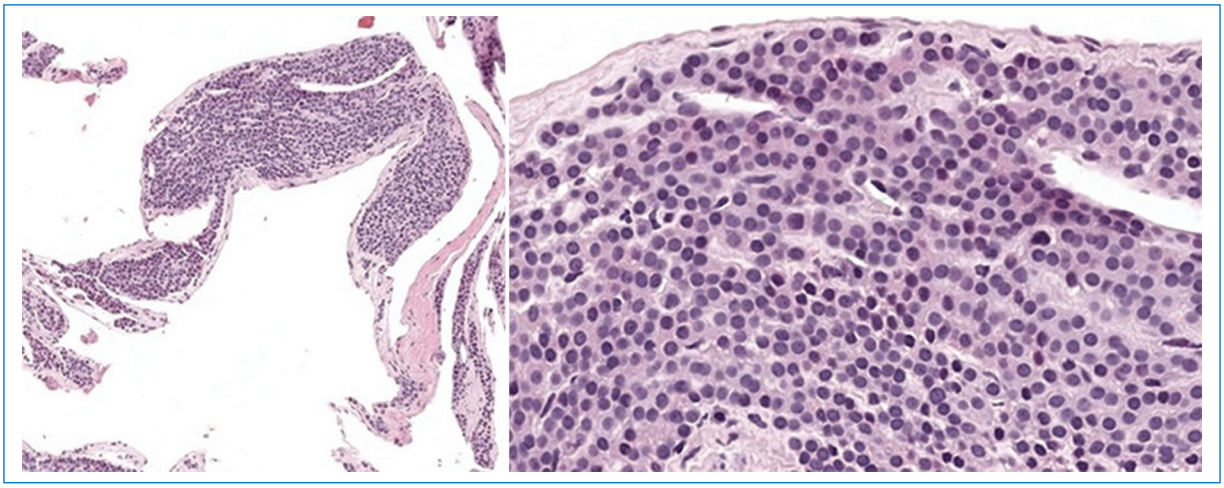

Figure 4. Hematoxylin and eosin stain (×10 and ×40). The vascular spaces are lined by endothelial cells without significant changes. Glomus cells are round with indistinct borders, a round nucleus, and homogeneous chromatin (inconspicuous nucleolus). No mitotic activity is identified.

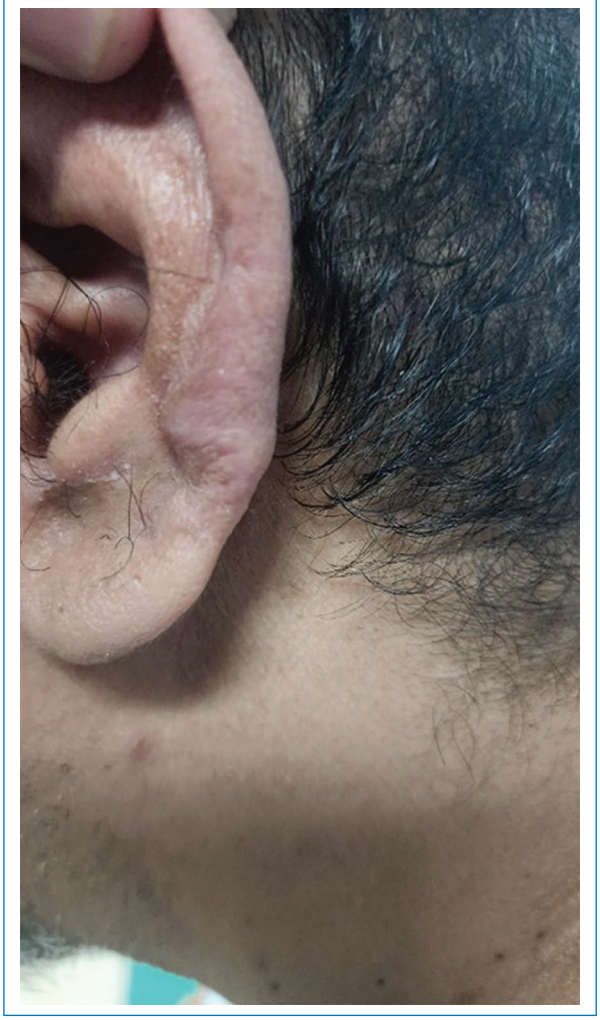

Figure 5. Photo of the left ear after surgical resection of the tumor.

round nuclei[8,11]. In our case, capillary vascular proliferation surrounded by sheets of glomus cells was identified in the dermis layer (Fig. 3), with vascular spaces lined with endothelial cells and rounded glomus cells with a round nucleus, homogeneous chromatin, and inconspicuous nucleoli (Fig. 4). No mitotic activity was documented. These cells showed positivity for smooth muscle-specific actin and H-Caldesmon.

Since this case was a solitary glomus tumor, treatment was complete surgical excision (Fig. 5).

Conclusion

The glomus tumor is a rare benign vascular neoplasm that is mostly located in acral areas, especially subungual regions. Presentation outside of this location is rare, and its appearance on the helix of the left ear makes it a unique case, rarely reported in the literature.

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Conflicts of interest

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Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Pilny J, Švarc A, Vodová H, Kletensky J, Tichá P, Sukop A. Has a glomus tumor always a quick diagnosis? Acta Chir Plast. 2017;59:82-4.
2. Kumar MG, Emnett RJ, Bayliss SJ, Gutmann DH. Glomus tumors in individuals with neurofibromatosis type 1. J Am Acad Dermatol. 2014;71:44-8.
3. Samaniego E, Crespo A, Sanz A. Claves del diagnóstico y tratamiento del tumor glómico subungueal. Actas Dermosifiliogr. 2009;100: 875-82.
4. Kim M, Jung J, Cinn Y, Shim S. A case of atypical glomus tumor: small malignant glomus tumor progressed from symplastic glomus tumor. J Am Acad Dermatol. 2007;56 Suppl 2:AB83.
5. Luzar B, Martin B, Fisher C, Calonje E. Cutaneous malignant glomus tumours: applicability of currently established malignancy criteria for tumours occurring in the skin. Pathology. 2018;50:711-7.
6. Bolado-Gutiérrez P, Ordás-Bayón A, López-Ruiz E, Berjón-García A, Pozo-Kreilinger JJ, Casado-Pérez C. Tumor glómico maligno: a propósito de un caso y revisión de la literatura. Cir Plast Iberolatinoam. 2017;43:187-92.
7. Eber AE, Vasquez T, Perper M, Nouri K, Tosti A. Optical coherence tomography in evaluation of glomus tumor. J Am Acad Dermatol. 2019;81Suppl 1:AB248.
8. Kampshoff JL, Cogbill TH. Unusual skin tumors: merkel cell carcinoma, eccrine carcinoma, glomus tumors, and dermatofibrosarcoma protuberans. Surg Clin North Am. 2009;89:727-38.
9. Ramos-Garibay A, Medina Hernández E. Tumor glómico. Publicación de un caso con topografía poco usual. Rev Cent Dermatol Pascua. 2000;9:160-3.
10. Naversen DN, Trask DM, Watson FH, Burket JM. Painful tumors of the skin: "LEND AN EGG". J Am Acad Dermatol. 1993;28:298-300.
11. Campos García L, Nunes de Sousa Fernandes E, De Paiva Sobreira N, Vasques Bittencourt F. Extradigital glomus tumor: dermoscopic description and histopathological correlation. An Bras Dermatol. 2021;96:765-7.
12. Oliveira A. Dermoscopy in the diagnosis of extradigital glomus tumors. Int J Dermatol. 2016;55:e506-8.
13. Mutsaers ER, Genders R, Van Es N, Kukutsch N. Dermoscopy of glomus tumor: more white than pink. J Am Acad Dermatol. 2016;75:e17-8.
14. Sánchez IM, Ilkovitch D. A case of a glomus tumor presenting as an atypical hyperkeratotic papule of the hypothenar palm. J Am Acad Ddermatol Case Rep. 2018;4:38-40.
15. Allegue F, González-Vilas D, Fachal C, Zulaica A. Mácula telangiectásica como forma de presentación de un tumor glómico solitario. Actas Dermosifiliogr. 2020;111:434-6.
16. Blume-Peytavi U, Adler YD, Geilen CC, Ahmad W, Christiano A, Goerdt S, et al. Multiple familial cutaneous glomangioma: a pedigree of 4 generations and critical analysis of histologic and genetic differences of glomus tumors. J Am Acad Dermatol. 2000;42:633-9.
17. Chuang GS, Branch KD, Cook J. Intraosseous subungual glomus tumor: a cautionary tale. J Am Acad Dermatol. 2012;67:e58-60.
18. Costa AJ. Tumor del Glomus Neuro-mio-arterial del Dedo Índice Izquierdo (tumor Glómico). Bolet Soc Cir Montev. 1932;3:277-92.
19. Findley A, Elston D, Conologue T. Glomus tumor presenting as mobile nodule on the knee. J Am Acad Dermatol. 2011;64(Suppl 1):AB49.

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CLINICAL CASE

Skin lesions caused by human lymphotropic virus 1, a case report

Lesiones en piel por virus linfotrópico humano 1, a propósito de un caso

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Abstract

Infective dermatitis is the pediatric manifestation of infection by human lymphotropic virus type 1 by vertical transmission. The clinic is characterized by exudative, crusty eczema of a chronic and recurrent nature. It presented partial response to antibiotic therapy such as trimethoprim/sulfamethoxazole with recurrences after discontinuing treatment. Dermatologists should become familiar with the characteristic clinical and histological findings, as it could be confused with many common dermatological conditions. The presentation of this clinical case represents a challenge that will allow us to have a better understanding of the pathology and give timely and adequate treatment.

Keywords: *Infective dermatitis. Human lymphotropic virus 1. Pediatrics.*

Resumen

La dermatitis infectiva es la manifestación pediátrica de la infección por virus linfotrópico humano tipo 1 por transmisión vertical. Cuadro caracterizado por eccema exudativo, costroso, de carácter crónico y recurrente. Presenta respuesta parcial a la antibioticoterapia como trimetoprima/sulfametoxazol con recurrencias tras suspender el tratamiento. Los dermatólogos deben familiarizarse con los hallazgos clínicos e histológicos característicos, ya que podría confundirse con muchas afecciones dermatológicas comunes. La presentación de este caso clínico representa un desafío que permitirá tener un mejor entendimiento de la patología, dar un tratamiento oportuno y adecuado.

Palabras clave: *Dermatitis infectiva. Human lymphotropic virus 1. Pediatría.*

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Introduction

Infective dermatitis (ID) is the pediatric manifestation of human T-lymphotropic virus type 1 (HTLV-1) infection transmitted vertically, predominantly in females, resolving in adulthood but potentially presenting as tropical spastic paraparesis and adult T-cell leukemia/lymphoma[1,2]. ID is characterized by chronic, recurrent, and severe exudative crusted eczema that affects the scalp, retroauricular area, folds, and periorificial areas, and may also present with generalized papular rash and clear rhinorrhea[3]. ID is associated with persistent infections by *Staphylococcus aureus* and β-hemolytic *Streptococcus*[3]. Laboratory test results include lymphocytosis, anemia, elevated erythrocyte sedimentation rate, hyperimmunoglobulinemia, and increased CD4+ and CD8+ lymphocyte counts in peripheral blood. Preventive measures include avoiding vertical transmission through elective C-section delivery and reducing breastfeeding to < 6 months[3].

Although the condition shows partial response to antibiotic therapy with trimethoprim/sulfamethoxazole, recurrence occurs upon treatment discontinuation[4].

HTLV-1 infection is an emerging viral disease, with approximately 10 million infected people worldwide; most are asymptomatic, and only about 10% develop the disease with high morbidity and mortality rates. Therefore, dermatologists and dermatopathologists from endemic regions should become familiar with the characteristic clinical and histological findings, as the condition can be mistaken for many common dermatologic disorders, such as atopic dermatitis, seborrheic dermatitis, intertriginous pustulosis, including the differential diagnosis of mycosis fungoides. HTLV-1 has also been associated with other skin conditions such as crusted scabies and xerosis, and it may lead to dermatophytic infections. Therefore, presentation of this clinical case is challenging, enabling us to better understand the condition, provide timely and appropriate treatment, and implement prevention measures to prevent the spread of this condition[5,6].

Case presentation

A 17-year-old male adolescent, the product of a first pregnancy, born through vaginal delivery to non-consanguineous parents who were apparently healthy and from the province of Santo Domingo de los Tsáchilas, with no significant pathological history, presented with no history of transfusions or surgical procedures, denied IV drug use, and had been breastfed for 6 months. He presented with a 2-year history of disseminated and recurrent eczematous lesions along with honey-colored crusts, previously treated multiple times with polyvalent creams (corticosteroid-antifungal-antibiotic) and antihistamines, without satisfactory response, and reported receiving antibiotic therapy with recurrences upon stopping the drug.

Physical examination revealed the presence of erythematous-squamous, exudative dermatosis with honey-colored crusts involving the scalp, forehead, retroauricular folds, external auditory canal, and chest. The plaques had a tendency to converge in a reticulated pattern, primarily affecting the axillary folds, inguinal region, and proximal parts of the limbs (Figs. 1-4).

Supplementary tests showed HTLV-1 reactive serology in peripheral blood by particle chemiluminescence; the mother's serology could not be conducted. Histopathology revealed epidermal acanthosis, hyperplasia with spongiosis, focal hyperkeratosis, and parakeratosis with serous aggregates and inflammatory infiltrate containing neutrophils. Papillary dermis showed edema with dilated vessels, while vessels in the superficial and mid-dermis showed lymphohistiocytic and neutrophilic inflammatory infiltrate. The condition was diagnosed as spongiotic dermatitis consistent with ID (Figs. 5 and 6). The patient was treated with trimethoprim-sulfamethoxazole 160/800 mg daily for a year, loratadine 10 mg daily, betamethasone for pruritic areas, and daily emollients. Follow-up assessments by other services or relevant genetic counseling were not conducted as the patient was lost to follow-up.

Discussion

HTLV-1 is an RNA retrovirus with a 100 nm diameter and tropism for CD4+ T lymphocytes, primarily CD4+, CD25+, and CCR4+ cells. HTLV-1 can also infect CD8+ T lymphocytes, dendritic cells, B lymphocytes, monocytes, and natural killer cells to a lesser extent. Viral replication occurs via reverse transcriptase, and adjacent cells are infected through cell-to-cell contact by forming a "viral synapse." This process is facilitated by a biofilm-like extracellular structure. Notably, HTLV-1 infection is characterized by a low number of free virions, which helps the virus evade detection and attack by the host immune system[7].

Once infection has been established, specific viral proteins are produced, including HTLV-1, leucine transcription factors (HBZ), tax, rex, p12I, p30II, p13II, and $p21^{Rex}$. The tax protein is the most pathogenic, modulating viral gene expression, activating NF-κB signaling pathways, deregulating the cell cycle, disrupting apoptosis, and inducing genomic instability, leading to cell transformation and virus-mediated oncogenesis[8]. Cell proliferation is primarily achieved by initiating viral transcription and replication, promoting cell cycle acceleration, and enhancing

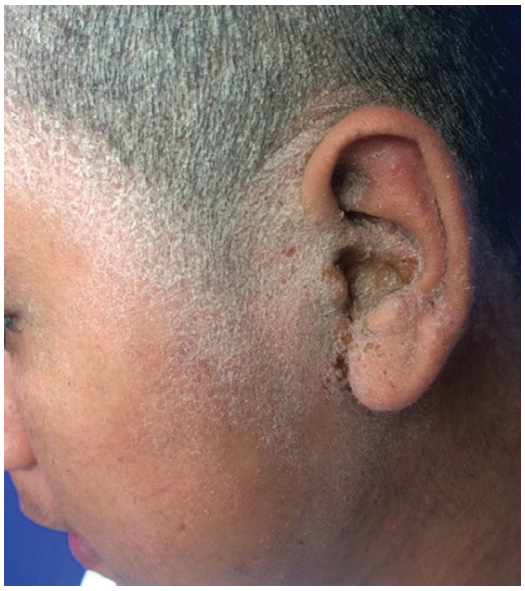

Figure 1. Exudative eczema on the auricle.

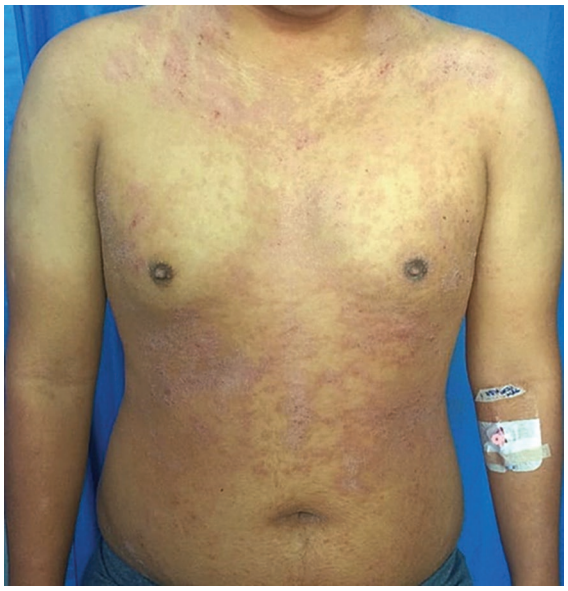

Figure 3. Erythematous-desquamative rash on the chest.

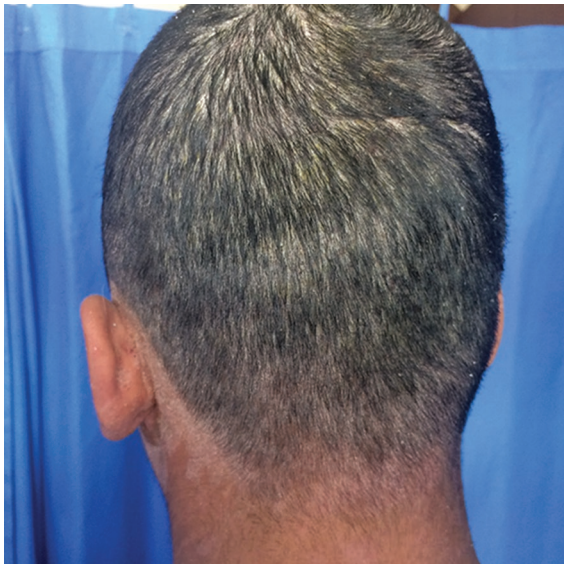

Figure 2. Eczema and scaling on the scalp.

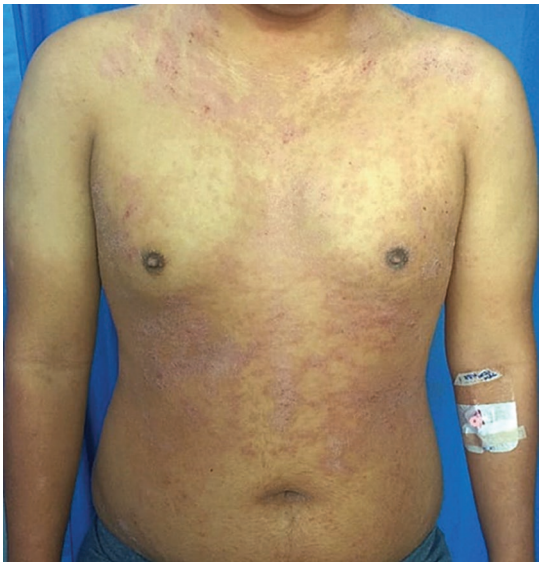

Figure 4. Desquamative rash in the suprapubic region.

interleukin-2 (IL-2) activity and IL-2 receptor production, resulting in the formation of immortal CD4+ and CD8+ T-cell clones. The immune response is of the Th1 type, with increased pro-inflammatory cytokine production that triggers cytotoxic T-cell responses, leading to lysis of infected cells. ID development is associated with increased viral load and the presence of anti-HTLV-1 antibodies.

The main transmission routes include sexual contact, vertical transmission, exposure to contaminated blood products such as blood transfusion or sharing needles[8]. Vertical transmission occurs mainly through breastfeeding in endemic countries, with a risk of up to 30.6% if breastfeeding continues beyond the first 6 months. Studies suggest that the risk of transmission decreases when proviral load (PVL) is < 0.1% and increases significantly when PVL is > 3%[9]. In addition, the risk is higher with prolonged breastfeeding and lower transplacental maternal antibodies.

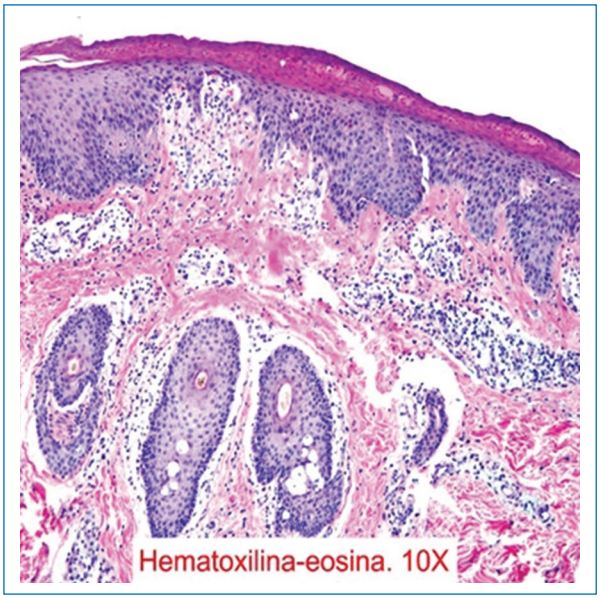

Figure 5. Skin. Epidermis with acanthosis, spongiosis, and parakeratosis with superficial and deep perivascular inflammatory infiltrate.

Table 1. Diagnostic criteria for HTLV-1-related infective dermatitis

Major criteria
Dermatitis in specific areas: scalp, external ear, retroauricular area, eyelid margin, paranasal skin, neck, axillae, inguinal areas.
Chronic watery nasal discharge without other signs of rhinitis and/or peeling of the nostrils.
Chronic recurrent dermatitis with prompt response to appropriate antibiotic therapy, but with recurrence upon treatment discontinuation.
Usual onset in early childhood.
Positive HTLV-1 serology (serology or molecular biology).
Minor criteria
Positive skin or nasal cultures for *Staphylococcus aureus* and/or β-hemolytic *Streptococcus*.
Fine generalized papular rash.
Lymphadenopathy with dermatopathic lymphadenitis.
Anemia.
Elevated erythrocyte sedimentation rate.
Hyperimmunoglobulinemia (IgE and IgD).
Increased CD4 + and CD8 + lymphocytes.

IgE: immunoglobulin E; IgD: immunoglobulin D; HTLV-1: human T-lymphotropic virus type 1.
Modified from La Grenade et al., 1998[19].

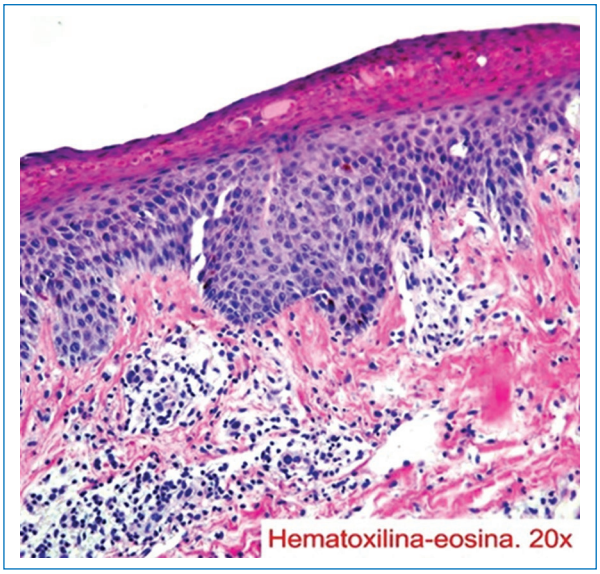

Figure 6. Skin. Epidermis with spongiosis, parakeratosis with serous aggregates, and neutrophils. In the dermis, lymphohistiocytic perivascular inflammatory infiltrate.

HTLV-1 is a cosmopolitan virus with wide global distribution. Endemic areas include Africa, South America, southeast Japan, Trinidad and Tobago, Brazil, Colombia, Peru, Argentina, and Australia[10]. Some literature describes Ecuador as an endemic area; however, no official epidemiological data support this claim[11,12]. Nevertheless, case series report HTLV-1-related neurological complications due to infection in the coastal province of Esmeraldas, where the population predominantly consists of Afro-descendants from lower socioeconomic strata[7].

HTLV-1 laboratory diagnosis is established by detecting anti-HTLV-1 antibodies enzyme-linked immunosorbent assay in blood and cerebrospinal fluid (CSF). If two positive results are obtained, confirmation is established through proviral DNA detection by Western Blot in blood or CSF, allowing differentiation between HTLV-1 and HTLV-213 infections[13]. Polymerase chain reaction in blood, CSF, or other materials (e.g., skin, lymph nodes, etc.) can be useful, especially in cases with indeterminate serology[14-16]. Since HTLV-1 is undetectable in the blood because it rarely leaves the cells, the PVL corresponds to the percentage of peripheral blood mononuclear cells carrying HTLV-1 DNA in their genome, making it the best biological marker for predicting disease risk or progression[17,18].

La Grenade et al. propose diagnostic criteria shown in table 1[19]. Four out of the 5 major criteria are required for diagnosis, with 1, 2, and 5 being mandatory. The patient exhibited 4 of the major criteria (1, 2, 4, and 5).

Treatment for ID is based on prolonged antibiotic therapy targeting *Staphylococcus* and *Streptococcus* until symptoms disappear, typically in adolescence. Good results have been observed with trimethoprim/sulfamethoxazole, although lesions typically recur after discontinuation. Due to the chronic course, alternative antibiotics may be

considered during intercurrent periods, as some patients develop methicillin-resistant *S. aureus* infections[20,21].

In addition, it is worth mentioning that tropical myeloneuropathies such as tropical spastic paraparesis and tropical ataxic neuropathy are endemic chronic conditions recently described in various tropical regions and associated with HTLV-1 serum reactivity[22]. Furthermore, HTLV-1-activated lymphoproliferative diseases may have a poor prognosis due to intrinsic chemoresistance and severe immunosuppression[6,16,22-23]. To date, no effective treatment has been found to improve the prognosis and quality of life of patients, making education on transmission methods, early detection, and long-term follow-up essential for patients with ID diagnosis[24].

Conclusion

We emphasize the importance of recognizing and suspecting this disease. Various dermatologic signs are more common and severe in HTLV-1 seropositive patients. Signs in patients from HTLV-1 endemic areas provide clues for investigating this infection.

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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 considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Bravo F. Infective dermatitis: a purely cutaneous manifestation of HTLV-1 infection. Semin Diagn Pathol. 2020;37:92-7.
2. Gru AA, Plaza JA, Sanches JA, Miyashiro D, Sangüeza OP, Puccio FB, et al. An update on Epstein-Barr virus-and human T-lymphotropic virus type-1-induced cutaneous manifestations. CME Part II. J Am Acad Dermatol. 2023;88:983-98.
3. Di Martino Ortíz B, Riveros R, Medina R, Morel M. Infective dermatitis in an adult patient with HTLV-1. Am J Dermatopathol. 2015;37:944-8.
4. Benencio P, Ducasa N, Arruvito L, Irurzun I, Praino L, Lamberti M, et al. Case report: relevance of an accurate diagnosis and monitoring of infective dermatitis associated with human T-Lymphotropic virus type 1 in childhood. Front Med (Lausanne). 2021;8:758352.
5. Hlela C, Graham N, Bhigjee AI, Taylor GP, Khumalo NP, Mosam A. Human T cell lymphotropic virus type 1- associated infective dermatitis in KwaZulu Natal, South Africa. BMC Dermatol. 2013;13:11.
6. McGill NK, Vyas J, Shimauchi T, Tokura Y, Piguet V. HTLV-1-associated infective dermatitis: updates on the pathogenesis. Exp Dermatol. 2012;21:815-21.
7. Alarcón Guzmán T, Hidalgo SC, Aguirre Navarrete R, Díaz Calderón E, Santibáñez Vásquez R, Navas PC. Manifestaciones neurológicas en infección por HTLV-I. Rev Mex Neuroci. 2007;8:234-40.
8. Ernzen KJ, Panfil AR. Regulation of HTLV-1 transformation. Biosci Rep. 2022;42(3):BSR20211921.
9. Rosadas C, Taylor GP. Mother-to-child HTLV-1 transmission: unmet research needs. Front Microbiol. 2019;10:999.
10. De Castro Viana GM, Da Silva MA, Souza VL, Da Silva Lopes NB, Da Silva DL, Nascimento MD. Interferon beta-1a treatment in htlv-1-associated myelopathy/tropical spastic paraparesis: a case report. Rev Inst Med Trop Sao Paulo. 2014;56:443-5.
11. Imashuku S, Kudo N, Kubo K, Ohshima K. Expansion of natural killer cells in peripheral blood in a Japanese elderly with human T-cell lymphotropic virus type 1-related skin lesions. Case Rep Dermatol Med. 2014;2014:937513.
12. Álvarez C, Gotuzzo E, Vandamme A, Verdonck K. Family aggregation of human T-lymphotropic virus 1-associated diseases: a systematic review. Front Microbiol. 2016;7:1674.
13. Steglich RB, Tonoli RE, Souza PR, Pinto GM, dos Santos Riesgo R. HTLV-1-associated infective dermatitis and probable HTLV-1- associated myelopathy in an adolescent female. An Bras Dermatol. 2015;90:55-8.
14. Einsiedel L, Spelman T, Goeman E, Cassar O, Arundell M, Gessain A. Clinical associations of human T-Lymphotropic virus type 1 infection in an Indigenous Australian population. PLoS Negl Trop Dis. 2014;8:e2643.
15. Okajima RM, De Oliveira AC, Smid J, Casseb J, Sanches JA. High prevalence of skin disorders among HTLV-1 infected individuals independent of clinical status. PLoS Negl Trop Dis. 2013;7:e2546.
16. Itabashi K, Miyazawa T. Mother-to-child transmission of human T-cell leukemia virus type 1: mechanisms and nutritional strategies for prevention. Cancers (Basel). 2021;13:4100.
17. Rivera-Caldón CC, López-Valencia D, Zamora-Bastidas TO, Dueñas-Cuéllar RA, Mora-Obando DL. Infección por el virus linfotrópico humano de células T tipo 1 (HTLV-1) y paraparesia espástica. Avances y diagnóstico 35 años después de su descubrimiento. Iatreia. 2017;30:146-59.
18. Souza LS, Silva TS, de Oliveira MF, Farre L, Bittencourt AL. Clinicopathological aspects and proviral load of adulthood infective dermatitis associated with HTLV-1: comparison between juvenile and adulthood forms. PLoS Negl Trop Dis. 2020;14:e0008241.
19. La Grenade L, Manns A, Fletcher V, Derm D, Carberry C, Hanchard B, et al. Clinical, pathologic, and immunologic features of human T-lymphotrophic virus type I-associated infective dermatitis in children. Arch Dermatol. 1998;134:439-44.
20. Abrams A, Akahata Y, Jacobson S. The prevalence and significance of HTLV-I/II seroindeterminate Western blot patterns. Viruses. 2011;3:1320-31.
21. Tous-Romero F, Pinilla-Martín B, Pérez S. Dermatitis infectiva asociada a HTLV-1: dermatosis a tener en cuenta en pacientes de zonas endémicas. Aten Primaria. 2020;52:785-6.
22. Kendall EA, González E, Espinoza IR, Tipismana M, Verdonck K, Clark D, et al. Early neurologic abnormalities associated with human T-cell lymphotropic virus type 1 infection in a cohort of Peruvian children. J Pediatr. 2009;155:700-6.
23. Cabrera ME, Peña C. Leucemia/linfoma T del adulto HTLV1, un desafío para el clínico. Rev Fac Med Hum. 2020;20:123-30.
24. Rosa BL, Silva TS, Dias MA, Araújo I, Bittencourt AL. Progression of infective dermatitis associated with HTLV-1 to adult T-cell leukemia/lymphoma-case report and literature review. Am J Dermatopathol. 2022;44:368-71.

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CLINICAL CASE

Nail lichen planus: case report with satisfactory response to topical treatment under occlusion

Liquen plano ungueal: reporte de caso con respuesta a tratamiento tópico bajo oclusión

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Abstract

Nail lichen planus (NLP) is an aggressive, disfiguring variant of lichen planus, with suboptimal therapeutic response. We present a case of a 44-year-old female, who presents a 7-month-old history of onycholysis and onychodystrophy. Histopathology reports lichenoid dermatitis, confirming NLP diagnosis. Topical treatment with steroids under occlusion was initiated for 12 weeks, continuing with topical tacrolimus, observing a near-total improvement at 20 weeks. NLP's clinical aggressiveness makes prompt diagnosis and treatment a necessity to minimize damage. Topical treatment under occlusion is a simple and accessible treatment option to be considered.

Keywords: *Nail lichen planus. Topical therapy. Steroids. Tacrolimus. Occlusive treatment.*

Resumen

El liquen plano ungueal (LPU) es una variante agresiva de liquen plano, con respuesta terapéutica subóptima. Presentamos el caso de una mujer de 44 años con onicólisis y onicodistrofia de siete meses de evolución. La histopatología reporta dermatitis liquenoide, confirmando el diagnóstico de LPU. Se maneja con clobetasol bajo oclusión durante doce semanas, continuando con tacrolimús, observando recuperación casi total a las 20 semanas. La agresividad clínica del LPU obliga a un diagnóstico y tratamiento oportuno, minimizando el daño. El tratamiento tópico oclusivo con esteroides e inhibidores de la calcineurina es una opción sencilla y económica, que puede ser considerada.

Palabras clave: *Liquen plano ungueal. Tratamiento tópico. Esteroides. Tacrolimús. Tratamiento oclusivo.*

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Introduction

Lichen planus (LP) is a chronic mucocutaneous disease of unknown etiology with a wide range of clinical variants[1]. The nail variant (Nail lichen planus [NLP]) represents 10% up to 15% of LP cases and corresponds to an aggressive, disfiguring variant with a suboptimal treatment response, with permanent nail matrix damage observed in 4% up to 12% of cases[1,2]. At present, systemic, intramuscular, or intralesional steroids are described as the first-line therapy[2,3]. To a lesser extent, topical steroids under occlusion, with variable response, are also reported[3,4], as well as calcineurin inhibitors[5,6]. Below, a clinical case with a good response to this therapeutic modality is presented.

Case presentation

A 44-year-old woman with a known 10-year history of hypothyroidism on levothyroxine, presented with a 7-month history of dermatosis affecting the fingernails and toenails, with no associated symptoms or history of previous trauma. Physical examination revealed changes in all fingernails and six toenails, with partial absence of the nail plate and keratotic nail bed, as well as onychorrhexis, melanonychia, and onycholysis associated with a few nails (Figs. 1A and B, Fig. 2A). Routine blood tests results turned out within normal parameters.

A longitudinal biopsy of the nail apparatus was taken from the first finger of the left hand (Fig. 1B) for histopathological study, where lichenoid dermatitis with hypergranulosis and a band-like infiltration of lymphocytes and histiocytes was reported, following a band pattern, contacting the basal layer, and affecting the nail bed (Fig. 3A) and, to a lesser extent, the nail matrix (Fig. 3B). Similar changes were reported in the periungual skin, where orthokeratotic hyperkeratosis with ridge flattening and a lymphoid infiltrate contacting the basal layer were observed (Fig. 3C). The diagnosis of NLP was confirmed through clinicopathologic correlation.

The patient refused systemic steroid therapy due to potential side effects, so topical treatment with 0.05% clobetasol propionate ointment was initiated; it was applied to the proximal nail fold and covered with dressings at night. Twelve weeks into therapy more than 50% recovery of the nail plate was observed in the fingernails, with no reported adverse effects (Fig. 1C), prompting the initiation of maintenance therapy with 0.1% tacrolimus ointment. After 20 weeks, almost total recovery of the nail plate was observed in all nails except the toenails of the first digits, where improvement in hyperkeratosis was noted, with a slower response in terms of partial absence of the nail bed and melanonychia (Figs. 1D and 2B). Maintenance therapy continues, and the patient has not experienced any relapses to date, 1 year after treatment initiation.

Discussion

NLP is an aggressive, disfiguring, and recalcitrant variant of LP[1-3]. Histopathological findings correspond to a lichenoid pattern, affecting the nail matrix and the dermis of the nail plate; these include band-like infiltration, hyperkeratosis, hypergranulosis, and acanthosis[2]. Clinical aggressiveness requires early diagnosis and prompt treatment to minimize damage and, therefore, the total disfigurement of the nail, with the subsequent negative impact on quality of life[2,3].

First-line therapy depends on the degree of involvement; if three or less nails are affected, intralesional steroids are preferred by applying triamcinolone directly to the matrix or nail bed, while if > 4 nails are affected, systemic therapy is preferred, either with intramuscular triamcinolone or oral prednisone at 0.5-1 mg/kg[2]. Second-line therapy includes oral retinoids, such as acitretin and alitretinoin, and, if necessary, other agents with immunosuppressive action such as cyclosporine, azathioprine, and mycophenolate mofetil[2,7].

The above-mentioned treatment modalities require close and frequent follow-up, which was challenging during the COVID-19 pandemic[4]. Topical management with steroids under occlusion proved to be a practical therapeutic option during the pandemic, allowing patients to self-apply the drug daily and tolerate it well between follow-up visits[4], although with variable results in the published case reports to date[2-4], especially due to recurrences once the treatment is discontinued. In the case of our patient, this therapeutic option was chosen based on her preference, as she declined systemic steroid therapy due to potential side effects and preferred topical therapy.

In addition to steroids, other treatments include calcipotriol, calcineurin inhibitors, and topical keratolytics, particularly useful in maintenance therapy[4,5]. There have also been reports of a satisfactory response to therapy with topical calcineurin inhibitors, such as tacrolimus, in monotherapy[6,7]. Similarly, topical management has been described with the application of lacquers based on keratinase, 20% urea, and topical retinoids, which are easy to apply and well tolerated, facilitating adherence to treatment in patients with NLP[7]. Recently, the use of oral Janus kinase inhibitors, such as baricitinib[8] and tofacitinib[9] for the management of NLP has been described,

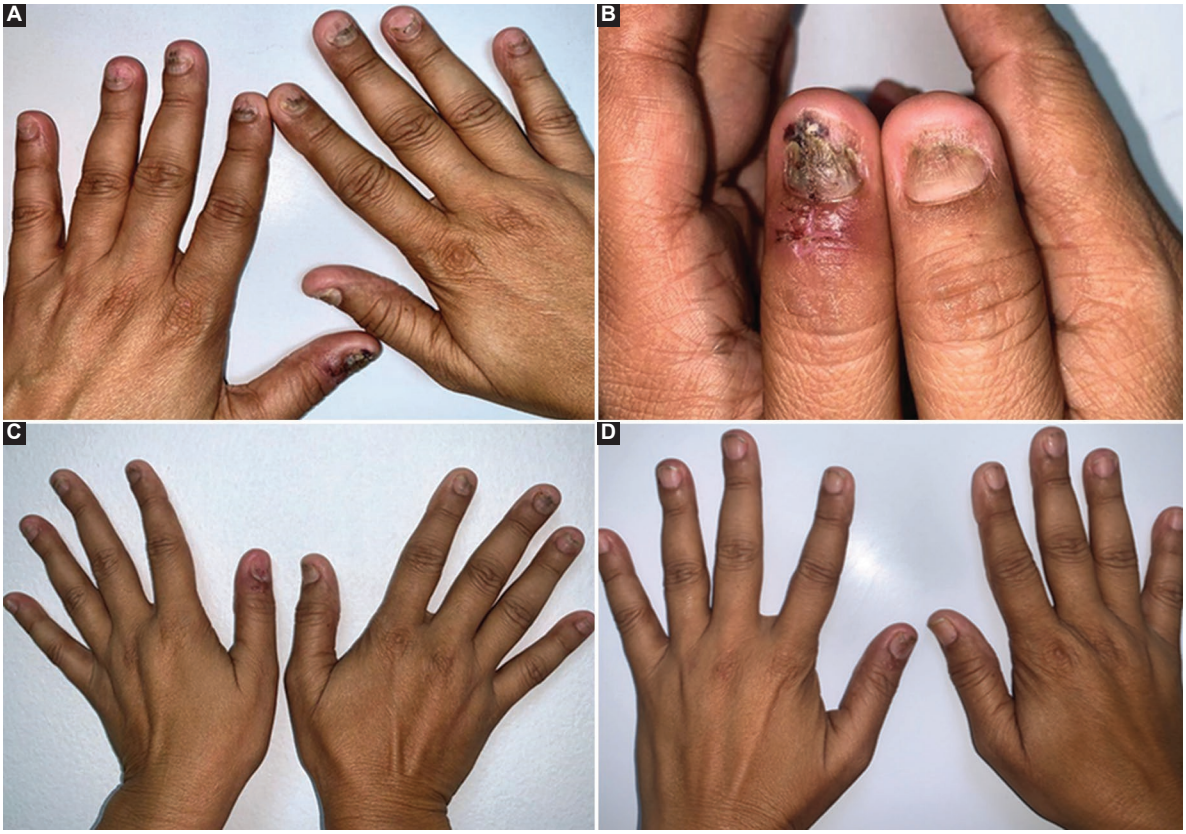

Figure 1. Nail changes and clinical progression in the fingernails of a 44-year-old woman diagnosed with nail lichen planus. **A:** all fingernails are affected, with partial absence of the nail plate, keratotic nail bed, onychorrhexis, melanonychia, and onycholysis associated with some nails. **B:** more detailed nail changes and biopsy site. A biopsy scar is visible on the left-hand first finger nail, distal absence of the nail plate, keratotic nail bed, onychorrhexis, regions of onycholysis, and distal melanonychia. **C:** 12-week follow-up after therapy with 0.05% clobetasol propionate ointment; more than 50% improvement in all nails, with a less keratotic nail bed, onycholysis, and distal melanonychia. **D:** almost total recovery of the nail plate after 20 weeks of therapy, with 0.1% tacrolimus ointment as maintenance therapy. Slight melanonychia and distal onycholysis are observed.

with satisfactory therapeutic responses; these drugs are especially useful in patients with therapeutic failure to other modalities and/or refusal of treatments such as steroids and oral retinoids[8,9]. Despite being a promising option for managing NLP, the accessibility and cost of these small molecules remain a limitation.

In this case, timely diagnosis, early management, and adherence to an accessible, cost-effective, and convenient therapy for the patient resulted in a remarkable clinical improvement.

Conclusion

Topical therapy under occlusion is a relatively simple therapeutic option; feasible in patients with certain nail disease, such as NLP. When choosing the best management for the patient, the number of affected nails, potential adverse effects, and the patient's possibility of adherence to treatment should be considered. Therefore, it is recommended to individualize each patient and provide timely follow-up for optimal management, aiming to minimize the impact on quality of life.

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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.

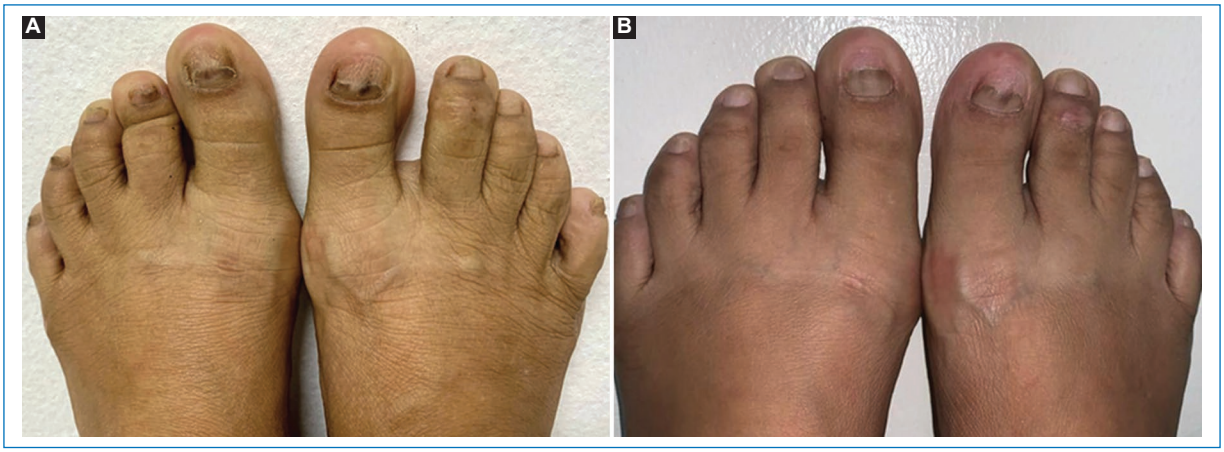

Figure 2. Nail changes and clinical progression of the toenails of a 44-year-old woman diagnosed with nail lichen planus. **A:** 6 toenails are affected, with the almost total absence of the nail plate of the first digits, keratotic nail bed, melanonychia, and onycholysis. **B:** recovery of the nail plate after 20 weeks of therapy; 12 weeks with 0.05% clobetasol propionate ointment, followed by 0.1% tacrolimus ointment as maintenance therapy. Growth of the nail plate with distal melanonychia and less keratotic nail bed on the first digits of both feet. Total recovery is observed in the rest of the affected toenails.

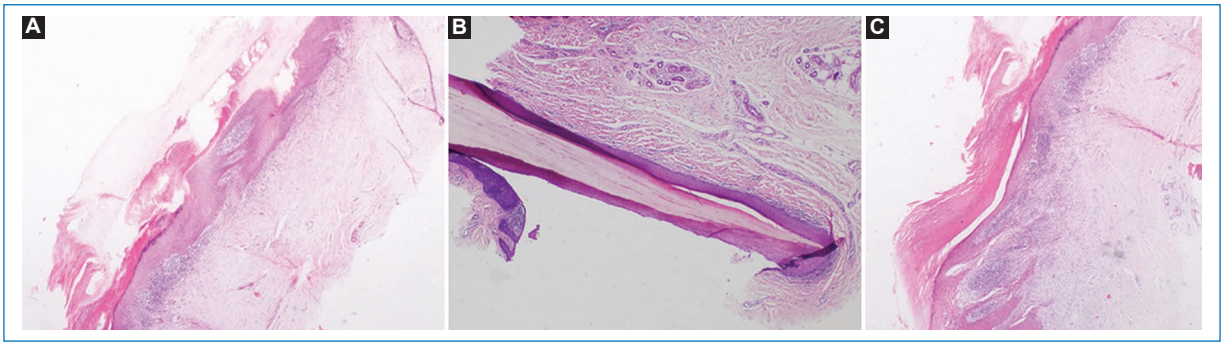

Figure 3. Histopathology of nail annex with lichenoid dermatitis. **A:** nail bed. Presence of lichenoid dermatitis with hypergranulosis and a band-like infiltration of lymphocytes and histiocytes contacting the basal layer. Hematoxylin-eosin ×40. **B:** nail matrix. Presence of hypergranulosis, band-like infiltration of lymphocytes and histiocytes contacting the basal layer. Hematoxylin-eosin ×20. **C:** periungual skin. Presence of orthokeratotic hyperkeratosis with ridge flattening and lymphoid infiltration contacting the basal layer. Hematoxylin-eosin ×40.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Grover C, Kharghoria G, Baran R. Nail lichen planus: a review of clinical presentation, diagnosis and therapy. Ann Dermatol Venereol. 2022;149:150-64.
2. Iorizzo M, Tosti A, Starace M, Baran R, Ralph Daniel C, Di Chiacchio N, et al. Isolated nail lichen planus: an expert consensus on treatment of the classical form. J Am Acad Dermatol. 2020;83:1717-23.
3. Bunyaratavej S, Kiratiwongwan R, Suphatsathienkul P, Wongdama S, Leeyaphan C. Clinical features, and treatment outcomes of nail lichen planus: a retrospective study. JAAD Case Rep. 2021;17:43-8.
4. Ricardo JW, Lipner SR. Recommendations for treatment of nail lichen planus during the COVID-19 pandemic. Dermatol Ther. 2020;33:e13551.
5. Sakiyama T, Chaya A, Shimizu T, Ebihara T, Saito M. Spongiotic Trachonychia treated with topical corticosteroids using the paper tape occlusion method. Skin Appendage Disord. 2016;2:49-51.
6. Ujiie H, Shibaki A, Akiyama M, Shimizu H. Successful treatment of nail lichen planus with topical tacrolimus. Acta Derm Venereol. 2010;90:218-9.
7. Milani M, Adamo L. Successful treatment of nail lichen planus with a lacquer containing urea, keratinase, and a retinoid molecule: report of 10 cases. Case Rep Dermatol. 2022;14:43-8.
8. He J, Weng T, Zhu W, Yang Y, Li C. Alleviation of isolated nail lichen planus by the JAK1/2 inhibitor Baricitinib: a case report. J Dermatolog Treat. 2023;34:2274816.
9. Huang J, Shi W. Successful treatment of nail lichen planus with tofacitinib: a case report and review of the literature. Front Med (Lausanne). 2023;10:1301123.