Case Report
Central Eur J Paed 2024;20(2):xx-xx
DOI

Acral Peeling Skin Syndrome: A Rare Skin Disorder

Sofia Poço Miranda[1], Teresa Lopes Magalhães[2], Diana Bernardo[3], Susana Machado[3]

[1]Pediatrics Department, Unidade Local de Saúde do Alto Minho, Viana do Castelo, Portugal; [2]Pediatrics Department, Unidade Local de Saúde do Oeste, Caldas da Rainha, Portugal; [3]Dermatology Derpartment, Unidade Local de Saúde de Santo António, Porto, Portugal

Correspondence: *sofiapocomiranda@gmail.com*; Tel.: +351 258 802414

Received: September 5 2024; **Accepted**: October 10 2024

Abstract

Objective – We report the case of an 8-year-old girl with acral peeling skin syndrome. **Case Report** – A previously healthy 8-year-old girl presented with a history of flaccid bullous lesions on the plantar surface of her feet, and subsequent peeling and scarring since she was 12 months old. A biopsy of the plantar lesion was carried out and histological examination revealed an acral skin flap characterized only by the presence of an intracorneal bullous cleft, with hypogranulosis and focal parakeratosis. A genetic study was carried out, identifying two pathogenic heterozygous variants in the TGM5 gene. The clinical presentation, histological and genetic examination confirmed the diagnosis of acral peeling skin syndrome. **Conclusion** – Acral peeling skin syndrome is not a widely known pathology, which means that cases of acral peeling skin syndrome can be misdiagnosed as Epidermolysis bullosa simplex, especially when a genetic study is not available. Particularly in younger children, it is important not to underestimate the diagnosis of acral peeling skin syndrome, given the different prognostic implications between the two diagnoses.

Key Words: Peeling Skin Syndrome ▪ Acral Peeling Skin Syndrome ▪ Epidermolysis Bullosa Simplex.

Introduction

Peeling skin syndrome (PSS) is a heterogeneous group of rare, autosomal recessive disorders, involving mutations in the TGM5 gene, characterized by superficial, painless peeling and blistering of the skin without mucosal fragility (1, 2). It may have two distinct clinical presentations: the generalized variant and the acral peeling skin syndrome variant (APSS), a localized form, in which skin peeling is limited to the hands and feet (3, 4). The prevalence is unknown and Epidermolysis bullosa simplex (EBS) is an important differential diagnosis to consider (5). We report an 8-year-old girl with a case of APSS.

Case Presentation

A previously healthy 8-year-old girl was referred for a dermatology consultation for flaccid bullous lesions on the plantar surface of her feet, with subsequent peeling and scarring since she was 12 months old (Fig. 1 A and B). There was no history of trauma. The family history was negative and the girl had non-consanguineous parents.

A biopsy of the plantar lesion was carried out and histological examination revealed an acral skin flap, characterized only by the presence of an intracorneal bullous cleft, with hypogranulosis and focal parakeratosis (Fig. 2 and 3). There was no evidence of inflammation, subepidermal blistering, or blistering at other levels. A direct immunofluorescence study was carried out with antibodies to fibrinogen, C3, C4, IgA, IgG, and IgM, which did not reveal the presence of deposits. A genetic study was carried out, identifying two pathogenic variants in the TGM5 gene: c.337G>T p.(Gly113Cys), heterozygous - pathogenic; and c.1335G>C p. (Lys445Asn),

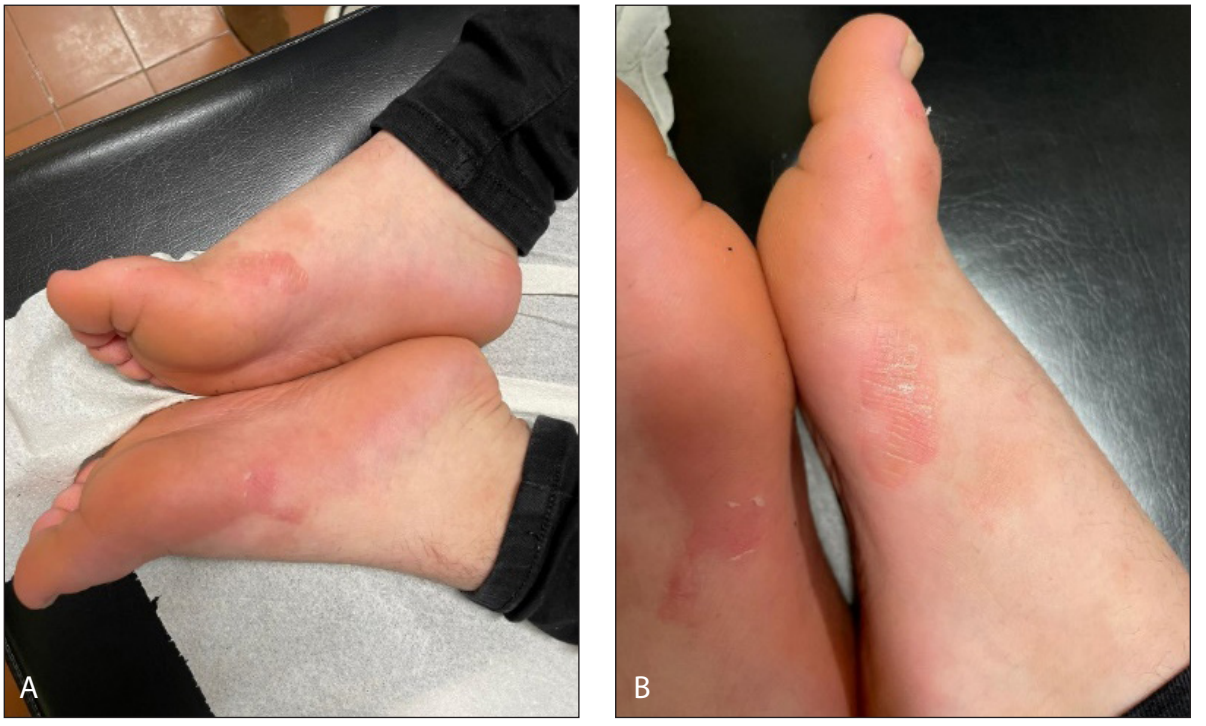

Fig. 1 *A and B: Lesions on the internal surface of both feet, with a peeling appearance, where they initially looked like blisters.*

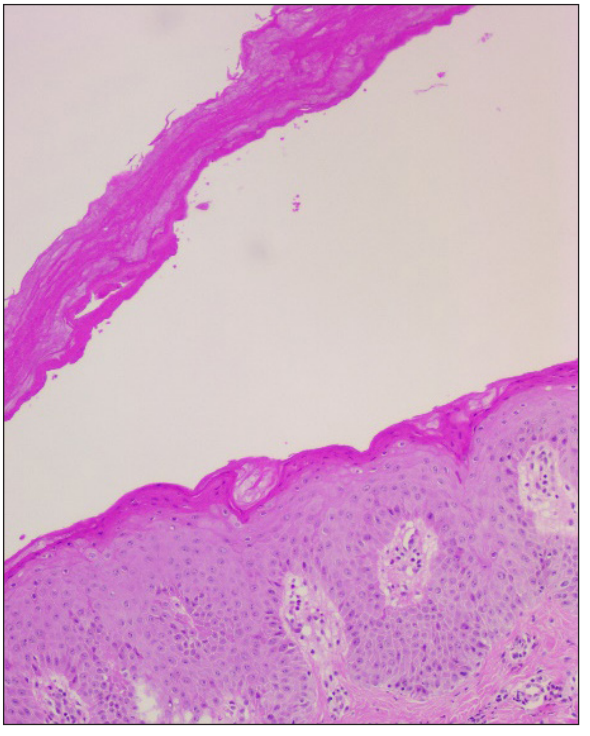

Fig. 2. *The skin biopsy reveals the presence of an intracorneal bullous cleft, without inflammatory content and with preserved epidermis at the base of the blister (hematoxylin-eosin 20×).*

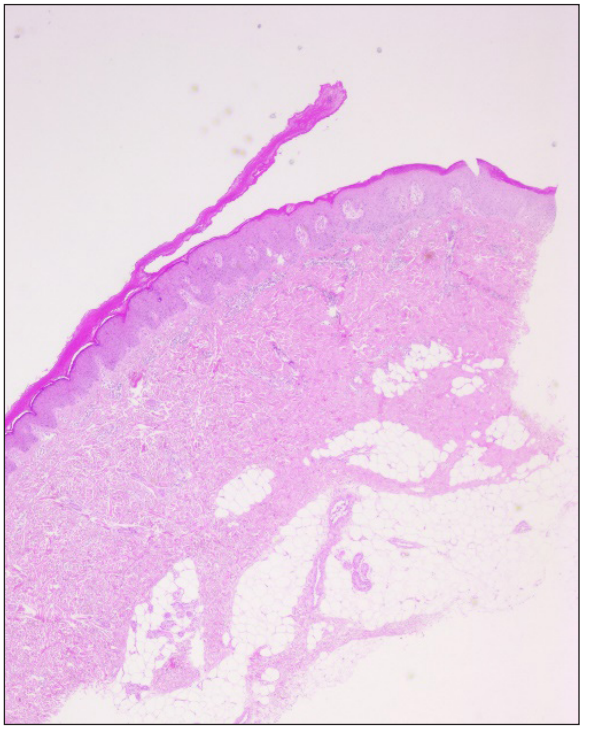

Fig. 3. *The epidermis shows agranulosis and parakeratosis and the roof of the blister consists exclusively of a compact hyperkeratotic horny layer (hematoxylin-eosin 100×).*

heterozygous - pathogenic, suggesting the probable diagnosis of APSS. The clinical presentation, histological and genetic examination confirmed the diagnosis of APSS.

Discussion

PSS was first reported in 1921 by Fox as "keratolysis exfoliativa congenital" (3, 6, 7). Later, in 1982, Levy and Goldsmith introduced the name "peeling skin syndrome" (1). More specifically, APSS is caused by biallelic (homozygous or compound heterozygous) mutations in the *TGM5* gene, encoding TGM5 (8). Transglutaminases are crucial for epidermal differentiation and are involved in the cross-linking of cornified cell envelope proteins through the formation of gamma-glutamyl-lysine isodipeptide bonds between adjacent polypeptides. In this sense, mutations in TGM5 lead to the complete abolition of cross-linking activity, resulting in the detachment of the stratum corneum from the underlying stratum granulosum at the site of activity and expression of TGM5. There is no correlation between the genotype and the severity phenotype between homozygous and compound heterozygous patients. Finally, homozygous mutations in the CSTA gene, which codes for cystatin A, a member of the family of inhibitor proteases expressed in the expressed in the cornified cell enveloper, have been reported in families with APSS without evidence of TGM5 mutations. Other mutations in the same gene have been implied in the pathogenesis of autosomal recessive exfoliative ichthyosis (8).

The precise incidence and prevalence of APSS are unknown due to underdiagnosis, frequent presentation in relatively mild forms, and the fact that it is easily misdiagnosed as other skin fragility disorders. The majority of reported patients are from European countries (8).

In infants and young children, APSS manifests clinically with blisters and erosions on the palms and soles, but not limited to the dorsal aspect of the hands and feet (9). In older children and adult APSS patients, peeling of the skin is the most prominent symptom, whereas blistering is less frequent (5). Environmental factors, such as high temperature, mechanical trauma (friction), humidity, and exposure to water, may exacerbate the symptoms (8, 10).

Most cases of APSS become evident at birth or in early childhood (8), as a similar case was found with presentation at 10 months of age (5). The history and physical examination may be suggestive of the presence of acral skin blistering and peeling in the absence of mucosal involvement and systemic manifestations, but a skin biopsy is essential for diagnosis. Suggestive histological findings are: hyperkeratosis, psoriasiform hyperplasia, hypergranulosis with keratinohyalin granules, and cleavage of the stratum corneum from the stratum granulosum, a key histological feature of PSS. Genetic studies can corroborate the diagnosis and identify mutations, taking into account the pattern of autosomal recessive heredity, with genetic variability (11). In the present case, histological analysis of the skin biopsy sample showed that the blister was not located at the subcorneal level, as is usual in APSS. The definitive diagnosis was made using a genetic study.

Differential diagnoses to consider include: other blistering exfoliative skin diseases, such as a localized form of EBS, keratolytic winter erythema, keratolysis exfoliativa, allergic contact dermatitis and dyshidrotic eczema (12). EBS can have a similar clinical presentation to APSS, with the formation of blisters and erosions on the palms and soles. Even though the blisters are also localized intraepidermally, they are located in the basal layer, and not in the upper epidermis, as in APSS, and usually occur after mechanical traumas (5, 8). Histopathological findings and a genetic study help to confirm the distinction between diagnoses (8). There is no specific treatment for APSS. Patients should avoid exacerbating factors. Daily topical application of emollients to affected areas may be beneficial (8). Parents should be informed of autosomal recessive inheritance and all patients and families should be referred for genetic counseling.

We consider this clinical case to be extremely relevant, given that APSS is not a widely known

pathology, which means that cases of APSS can be misdiagnosed as EBS (5), especially when a genetic study is not available. Particularly in younger children, it is important not to underestimate the diagnosis of APSS, given the different prognostic implications between the two diagnoses (5).

Conclusion

APSS is a rare heterogeneous group of rare, autosomal recessive disorders, involving mutations in the TGM5 gene, characterized by superficial, painless peeling and blistering of the skin without mucosal fragility, with a localized presentation, in which skin peeling is limited to the hands and feet. The prevalence is unknown and APSS is not a widely known pathology, which means that cases of APSS can be misdiagnosed as EBS, especially when a genetic study is not available. Particularly in younger children, it is important not to underestimate the diagnosis of APSS, given the different prognostic implications between the two diagnoses. We present a case of an 8-year-old-girl with APSS, in whom the histological examination of the biopsy of the bullous lesions showed the presence of an intracorneal bulla, not the most typical presentation of APSS, and the genetic study enabled the diagnosis to be made.

Authors' Contributions: Conception and design: SPM and TLM; Acquisition, analysis and interpretation of data: SPM, TLM, DB and SM; Drafting the article: SPM and TLM; Revising it critically for important intellectual content: SPM; Approved final version of the manuscript: SPM, TLM, DB and SM.

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

References

1. Levy SB, Goldsmith LA. The peeling skin syndrome. J Am Acad Dermatol. 1982;7(5):606-13. Doi: 10.1016/s0190-9622(82)70140-9.
2. Has C. Peeling Skin Disorders: A Paradigm for Skin Desquamation. J Invest Dermatol. 2018;138(8):1689-91. Doi: 10.1016/j.jid.2018.05.020.
3. Shwayder T, Conn S, Lowe L. Acral Peeling Skin Syndrome. Archives of Dermatology. 1997;133(4):535-6. Doi: 10.1001/archderm.133.4.535.
4. Hashimoto K, Hamzavi I, Tanaka K, Shwayder T. Acral peeling skin syndrome. J Am Acad Dermatol. 2000;43(6):1112-9. Doi: 10.1067/mjd.2000.103645.
5. Kavaklieva S, Yordanova I, Bruckner-Tuderman L, Has C. Acral peeling skin syndrome resembling epidermolysis bullosa simplex in a 10-month-old boy. Case Rep Dermatol. 2013;5(2):210-4. Doi: 0.1159/000354572.
6. Cabral RM, Kurban M, Wajid M, Shimomura Y, Petukhova L, Christiano AM. Whole-exome sequencing in a single proband reveals a mutation in the CHST8 gene in autosomal recessive peeling skin syndrome. Genomics. 2012;99(4):202-8. Doi: 10.1016/j.ygeno.2012.01.005.
7. Kharfi M, Khaled A, Ammar D, Ezzine N, El Fekih N, Fazaa B, et al. Generalized peeling skin syndrome: Case report and review of the literature. Dermatol Online J. 2010;16(3):1.
8. Sprecher E, Samuelov L. Peeling skin syndromes: UpToDate; 2024 [updated April, 2024. Available from: https://www.uptodate.com/contents/peeling-skin-syndromes?search=Peeling%20skin%20syndromes&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1#H109776716.
9. Kiritsi D, Cosgarea I, Franzke CW, Schumann H, Oji V, Kohlhase J, et al. Acral peeling skin syndrome with TGM5 gene mutations may resemble epidermolysis bullosa simplex in young individuals. J Invest Dermatol. 2010;130(6):1741-6. Doi: 10.1038/jid.2010.23.
10. Kharfi M, El Fekih N, Ammar D, Jaafoura H, Schwonbeck S, van Steensel MA, et al. A missense mutation in TGM5 causes acral peeling skin syndrome in a Tunisian family. J Invest Dermatol. 2009;129(10):2512-5. Doi: 10.1038/jid.2009.118.
11. Mathew R, Omole OB, Rigby J, Grayson W. Adult-onset acral peeling skin syndrome in a non-identical twin: a case report in South Africa. Am J Case Rep. 2014;15:589-92. Doi: 10.12659/AJCR.892110.
12. Sticova E, Květoň M, Dubská M, Kubátová A. Acral peeling skin syndrome: An underdiagnosed skin disorder. Indian J Dermatol Venereol Leprol. 2019;85(3):316-8. Doi: 10.4103/ijdvl.IJDVL_3_18.