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Papillon–Lefèvre Syndrome Mimicking Treatment-Resistant Psoriasis: A Case Report

Bashaer Almahdi[1], Warif Albogami[2], Hanadi Alsatti[1], Samaher Almahdi[3], Entesar Batouk[4]

[1.] Dermatology Department, Ministry of the National Guard - Health Affairs, Jeddah, Saudi Arabia. King Abdullah International Medical Research Center, Jeddah, Saudi Arabia. King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia.
[2.] Medical graduate, College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia.
[3.] Department of Preventive Dental Sciences, Division of Pedodontics, College of Dentistry, Jazan University, Jazan, Saudi Arabia.
[4.] Pediatric Rheumatology Department, Ministry of the National Guard - Health Affairs, Jeddah, Saudi Arabia. King Abdullah International Medical Research Center, Jeddah, Saudi Arabia. King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia.

Corresponding Author

Bashaer Almahdi

Dermatology Department, Ministry of the National Guard - Health Affairs, Jeddah, Saudi Arabia. King Abdullah International Medical Research Center, Jeddah, Saudi Arabia. King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia.

Keywords: Papillon–Lefèvre syndrome; CTSC gene; palmoplantar keratoderma; aggressive periodontitis; psoriasiform dermatitis; pediatric genodermatosis

Abstract:

Palmoplantar hyperkeratosis and early-onset aggressive periodontitis are the hallmarks of Papillon–Lefèvre syndrome (PLS), a rare autosomal recessive condition caused by pathogenic variants in the CTSC gene. We report a 9-year-old girl who was born to consanguineous parents and presented with progressive periodontal disease, nail dystrophy, and transgradient palmoplantar keratoderma. Based on clinical and histopathologic findings, she was initially misdiagnosed with psoriasis. Topical and systemic treatments were administered, with only mild improvement observed. A homozygous CTSC variant (c.899G>A; p.Gly300Asp) was subsequently found by whole-exome sequencing, confirming PLS. Partial clinical improvement was achieved with supportive dermatological care and multidisciplinary dental treatment. Early genetic diagnosis allows for appropriate management, and prevents unnecessary systemic immunosuppression. This case highlights the importance of considering PLS in children presenting with early-onset keratoderma and periodontal disease.

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Introduction

Papillon–Lefèvre syndrome (PLS) is a rare autosomal recessive genetic condition resulting from biallelic pathogenic mutations in the CTSC gene, which encodes cathepsin C, a lysosomal protease that plays a role in epithelial development and immunological modulation [1]. PLS affects 1 to 4 people per million worldwide [2]. More than 250 cases have been reported worldwide, with a higher

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frequency among certain populations in Saudi Arabia [3]. Parental consanguinity has been reported in around 20–40% of cases, with no clear gender predilection [2]. Cutaneous manifestations typically begin between 6 months and 4 years of age, aligning with the eruption of primary dentition, during which oral manifestations begin to develop [4]. PLS is marked by severe palmoplantar hyperkeratosis and early-onset, rapidly progressing periodontitis, which can lead to early loss of both primary and permanent teeth in children [5].

PLS development is influenced by genetic, immunological, microbiological, and environmental factors that impair host defense mechanisms by reducing the effectiveness of lymphocytes, polymorphonuclear leukocytes (PMNs), and monocytes [5]. As PLS demonstrates clinical and histopathological overlap with psoriasis and other hereditary palmoplantar keratodermas, it is prone to misdiagnosis, leading to delayed diagnosis and inappropriate treatment [6]. Histopathologic findings are nonspecific and include hyperkeratosis, parakeratosis, acanthosis, and mononuclear perivascular infiltration, which resemble psoriatic alterations [6]. Delayed recognition of dental manifestations can lead to severe periodontal deterioration; consequently, PLS may be misdiagnosed as other inherited keratodermas, such as Unna–Thost disease and Mal de Meleda [6]. This highlights the necessity for an interdisciplinary approach between dermatologists and dentists in achieving an accurate diagnosis [6].

We report a 9-year-old girl with early-onset transgradient palmoplantar keratoderma, nail dystrophy, and progressively worsening periodontal disease. The patient was initially treated with topical and biologic therapies for presumed psoriasis; however, the response was unsatisfactory. Whole-exome sequencing identified a homozygous pathogenic variation in the CTSC gene, confirming the diagnosis of PLS. Following genetic confirmation, the treatment plan was revised to incorporate comprehensive multidisciplinary dental and dermatologic care. Early initiation of appropriate management is essential for improving PLS outcomes.

Case Presentation

A 9-year-old girl, born to consanguineous parents, presented with a history of thick, scaly, erythematous hyperkeratotic plaques affecting both palms and soles since the age of one year. The lesions were progressive and associated with fissuring, mild pain, and pruritus. There was no history of recurrent infections or systemic illness. The family history was significant for inflammatory bowel disease in the father and congenital heart disease in a sibling. She had previously been evaluated by rheumatology for joint pain and by dentistry for recurrent dental discomfort and progressive tooth loss. Physical examination revealed well-defined scaly plaques over the elbows and knees, along with diffuse silvery hyperkeratotic plaques on the palms and soles extending to the dorsal aspects of the hands and feet with deep fissures [Figure 1]. The fingernails and toenails exhibited generalized dystrophy with subungual hyperkeratosis, without hyperhidrosis or malodor [Figure 2]. Oral examination showed generalized gingival inflammation, poor oral hygiene, mixed dentition, and severe caries involving the first permanent molars [Figure 3].

A diagnosis of palmoplantar psoriasis was initially established based on clinical features and histopathological findings consistent with psoriasiform dermatitis [Figure 4]. The patient was initially treated with topical calcipotriol, mometasone, and emollients, with mild improvement. Adalimumab (20 mg weekly) was administered for three months; however, due to inadequate response, the patient was shifted to ixekizumab (40 mg loading dose followed by 20 mg weekly) in combination with methotrexate (5–7.5 mg weekly) for presumed psoriatic arthritis. Despite prolonged systemic therapy, the response remained limited. Due to the early onset, treatment resistance, transgradient keratoderma, and severe periodontal disease, a syndromic keratoderma was hypothesized.

Whole-exome sequencing revealed a homozygous pathogenic CTSC mutation (c.899G>A; p.Gly300Asp), confirming the diagnosis of papillon–Lefèvre syndrome. Both parents were

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identified as heterozygous carriers. Ixekizumab was discontinued and the patient was maintained on methotrexate, urea-based keratolytics, calcipotriol, and emollients. Dental assessment revealed severe generalized periodontitis, secondary to PLS and a multidisciplinary plan was initiated. Follow up demonstrated partial improvement in the cutaneous lesions.

Discussion

The high prevalence of consanguineous marriage in Saudi Arabia contributes to a distinct genetic background compared with other populations [1,7,8]. Consanguinity is a well-established factor associated with increased homozygosity and an elevated prevalence of autosomal recessive disorders [9,17]. A recent study in molecular genetics revealed that more than 54% of reported hereditary illnesses are transmitted in an autosomal recessive manner [9]. In Saudi Arabia, greater caution is required to accurately identify autosomal recessive genodermatoses within this cohort [9].

Papillon–Lefèvre syndrome is a rare but clinically significant inherited keratinization disorder that typically manifests in early childhood with palmoplantar hyperkeratosis preceding dental complications [10–12]. This temporal discrepancy results in delayed diagnosis, as multiple studies have reported that PLS is often misdiagnosed as psoriasis due to similar clinical features, such as well-defined scaly plaques [12,13]. Histopathological examination is insufficient for the accurate diagnosis of Papillon–Lefèvre syndrome, as the cutaneous alterations—typically hyperkeratosis, parakeratosis, and acanthosis—are nonspecific and also observed in other psoriasiform and keratinization disorders [14,15]. In our case, reliance on biopsy findings led to a prolonged course of treatment for psoriasis.

The CTSC variant identified in this case (c.899G>A; p.Gly300Asp) has also been reported in other PLS cohorts and is associated with early disease onset and significant gingival complications [2,16,17]. The relationship between genotype and phenotype in Papillon–Lefèvre syndrome is not consistent, as individuals and families with the same CTSC mutations exhibit significantly diverse levels of clinical severity, indicating the influence of additional genetic and environmental factors [18]. Subsequent studies, including CTSC mutation analysis in many ethnic groups, have expanded the spectrum of mutations and demonstrated significant phenotypic variability, even among closely related affected individuals [19,20].

When cathepsin C is deficient, neutrophil serine proteases are unable to activate, impairing the body's innate immune defense and contributing to severe periodontal destruction [21]. In addition, cathepsin C is involved in epidermal development and desquamation in keratinocytes, and its deficiency leads to increased cellular proliferation and reduced apoptosis, resulting in chronic hyperkeratosis and fissuring observed in PLS [22]. The primary goals of treating PLS are to reduce aggressive periodontal destruction and lessen the severity of hyperkeratotic skin lesions, which requires cooperation between the child and their family [5]. Early treatment of periodontitis and strict adherence to preventive care programs are essential for preserving permanent teeth in children [5].

Comprehensive management of the condition requires a multidisciplinary approach involving a dermatologist, paediatrician, and dental specialists, particularly a periodontist and pedodontist [23]. The primary approach to managing cutaneous manifestations is the use of emollients; however, salicylic acid and topical corticosteroids are often used as adjuncts to enhance treatment efficacy [24]. Acitretin, etretinate, and isotretinoin are systemic retinoids that have been shown to be effective in managing both cutaneous and dental manifestations [24]. Oral acitretin therapy has been associated with a significant reduction in keratoderma and marked clinical improvement after approximately eight weeks of treatment [25]. Careful monitoring is essential during long-term acitretin therapy to detect potential adverse effects, including hepatic dysfunction, hyperlipidemia, skeletal abnormalities, and teratogenicity [26].

Conclusion

This case highlights the importance of maintaining a high index of suspicion for Papillon–Lefèvre syndrome in children presenting with early-onset, persistent palmoplantar keratoderma and severe

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periodontal destruction. The significant clinicopathologic overlap with psoriasis underscores the limitations of histopathology alone and emphasizes the value of molecular testing in establishing a definitive diagnosis. Early recognition facilitates prompt multidisciplinary management, reduces irreversible periodontal damage, and avoids unnecessary long-term immunosuppressive therapy.

Declarations

Patient Consent: The authors obtained written consent from patients for their photographs and medical information to be published in print and online, and with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors.

Conflict of Interest Statement: The authors declare no conflicts of interest.

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Author Contributions:

Bashaer Almahdi: Conceptualization, data collection, manuscript writing
Warif Albogami: Literature review, manuscript writing, critical revision of the manuscript
Hanadi Alsatti: Dermatology supervision, patient management, critical revision of the manuscript, and final approval.
Entesar Batouk: Rheumatology consultation, multidisciplinary patient evaluation, critical revision of the manuscript, and final approval.
Samaher Almahdi: Dental evaluation, interpretation of oral findings, preparation of the dental section of the manuscript

Ethics Approval: Written informed consent for publication of the patient's clinical information and clinical photographs was obtained from the patient's legal guardian.

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Figure Legends

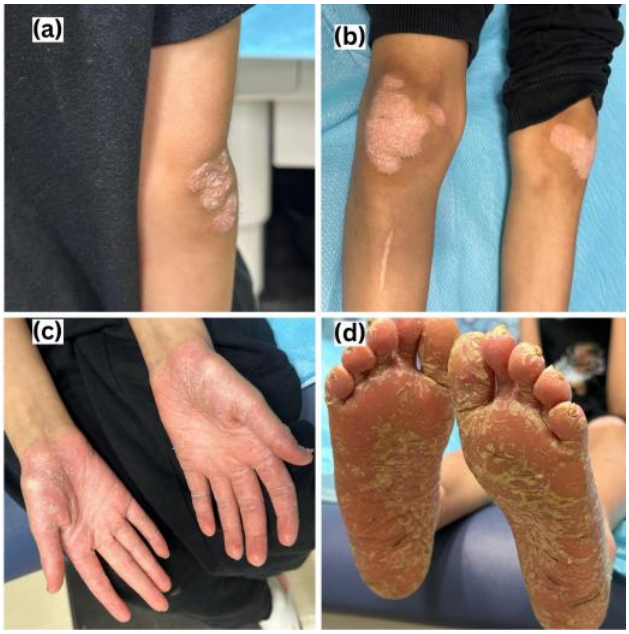

Figure 1: Well-demarcated erythematous scaly plaques involving the elbows and knees (a,b), Diffuse silvery hyperkeratotic plaques over the palms (c), and soles extending to the dorsal surfaces with deep fissure(d).

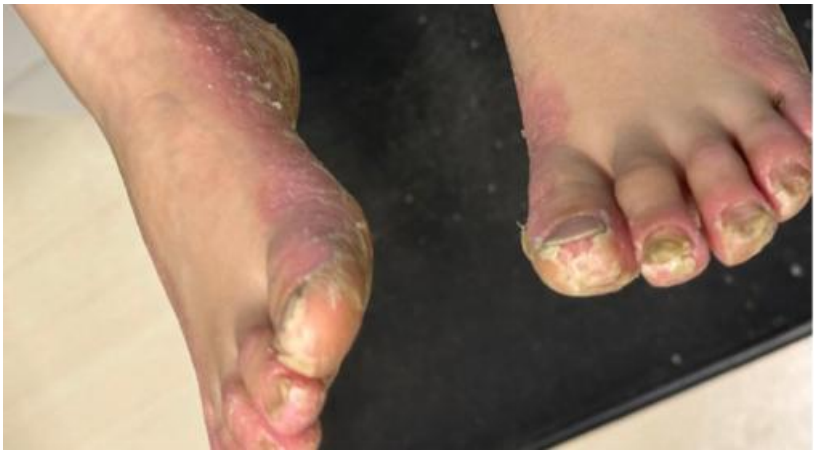

Figure 2: Diffuse nail dystrophy with prominent subungual hyperkeratosis involving multiple toenails.

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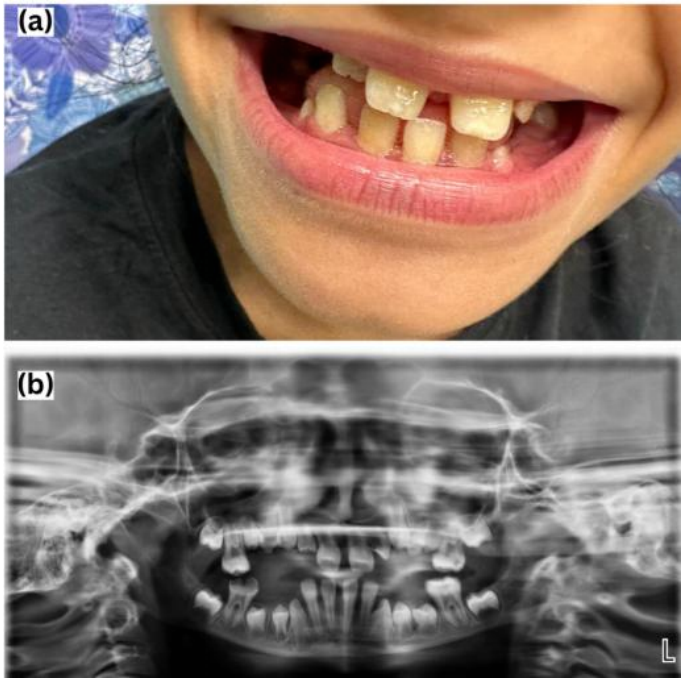

Figure 3: Extra-oral photograph (a) shows gingival inflammation with visible plaque accumulation, mixed dentition. The panoramic radiograph (b), revealed complete exfoliation of all primary teeth and demonstrated localized alveolar bone loss in lower lateral incisor and both mandibular molar (Furcation involvement in mandibular molars).

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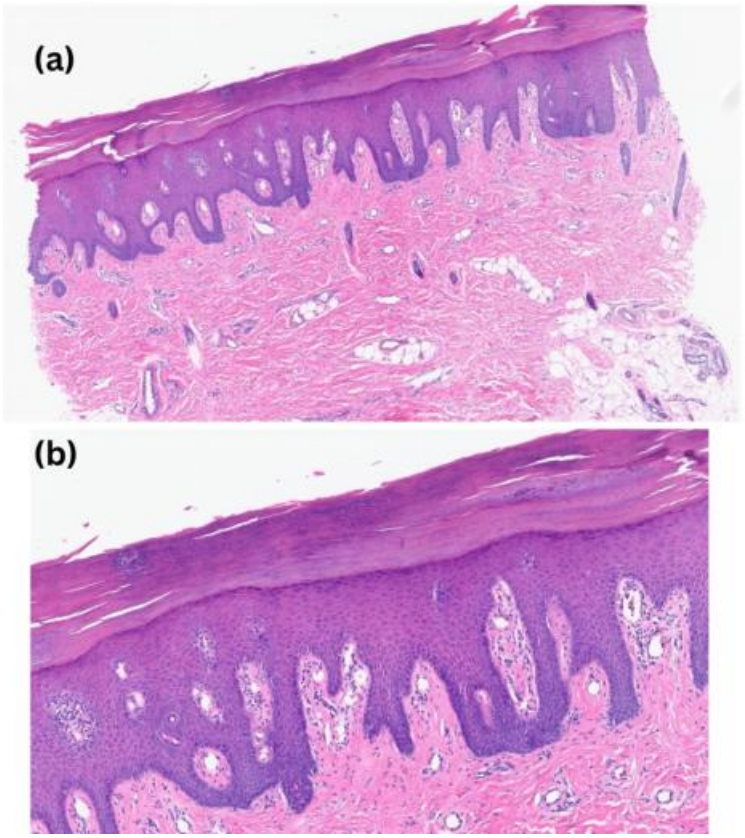

Figure 4: Low-power photomicrograph (a), (Hematoxylin and Eosin stain, ×40), showing psoriasiform epidermal hyperplasia with regular elongation of rete ridges, thinning of the suprapapillary plates, and overlying confluent parakeratosis. Higher-power photomicrograph (b), (Hematoxylin and Eosin stain, ×100) demonstrating diminished granular layer, neutrophilic collections within the stratum corneum (Munro microabscesses), and dilated capillaries within the dermal papillae