Case Report

Papillon-Lefèvre Syndrome: A Report of Four Cases and a Brief Review of the Literature

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Abstract

Papillon-Lefèvre syndrome (PLS) is a rare autosomal recessive genodermatosis characterized by palmoplantar hyperkeratosis and early loss of primary teeth and permanent teeth secondary to periodontitis, as well as disorders in neutrophil function and chemotaxis, recurrent infections, and internal organ abscesses. Topical moisturizers, keratolytic agents, and topical-systemic retinoids can be used for the treatment of palmoplantar keratoderma, and oral hygiene, antiseptic mouthwashes, systemic antibiotic treatments, and regular dentist follow-up are critical for periodontitis management. In this case report, we present the clinical features and treatments of four patients with PLS who were diagnosed based on physical examination and genetic analysis. We aim to increase the awareness of PLS among clinicians by describing the clinical and treatment characteristics of four patients with PLS.

Keywords: Genodermatoses, palmoplantar keratoderma, Papillon Lefèvre syndrome

Introduction

Papillon-Lefèvre syndrome (PLS) is a rare genodermatosis characterized by palmoplantar keratoderma and premature tooth loss. Patients with PLS often experience dysregulation in immune response and an increased frequency of bacterial infections because of the inactivation of neutrophil serine proteases. Treatment for palmoplantar keratoderma typically involves the use of topical moisturizers, keratolytic agents, and topical or systemic retinoids. Regular follow-up with a dentist is important for managing periodontitis in PLS patients.[1]

In this case report, we present the clinical features and treatments of four patients with PLS who were diagnosed based on physical examination and genetic analysis [CTSC (11q14.2) mutation]. With this case series, we aimed to add new patients to the current literature to increase the cumulative data of patients with PLS.

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Of the four patients analyzed, two were male, and the average age was 16 years. The patients were followed up for an average of 11 years (range: 5-20 years). All patients exhibited palmoplantar hyperkeratosis and history of tooth loss. One patient also presented with erythematous, scaly plaque lesions on the knee and elbow (Figure 1). All patients experienced symptoms such as itching and burning in the palmoplantar area. Additionally, 75% of the patients had a family history of PLS. Three of the patients were related, two were siblings, and one was their cousins. In terms of accompanying systemic comorbidities, one patient had cystic fibrosis, nephrolithiasis, and gynecomastia, while another patient had multiple liver abscesses and mental retardation. Biopsy of the patients' palmar regions revealed hyperkeratosis and spongiosis in the epidermis in all cases. All patients were treated with topical moisturizers and keratolytic. Three patients received

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acitretin treatment, and one patient could not be treated due to the presence of multiple liver abscesses and abnormal liver function tests. Instead, the patient received tazarotene cream. During follow-up, topical or systemic retinoid treatments effectively improved palmoplantar hyperkeratosis and enhanced the patients' quality of life.

The demographic, clinical, and histopathological characteristics of the patients are presented in Table 1.

The patients in this manuscript has given written informed consent to the publication of their case details.

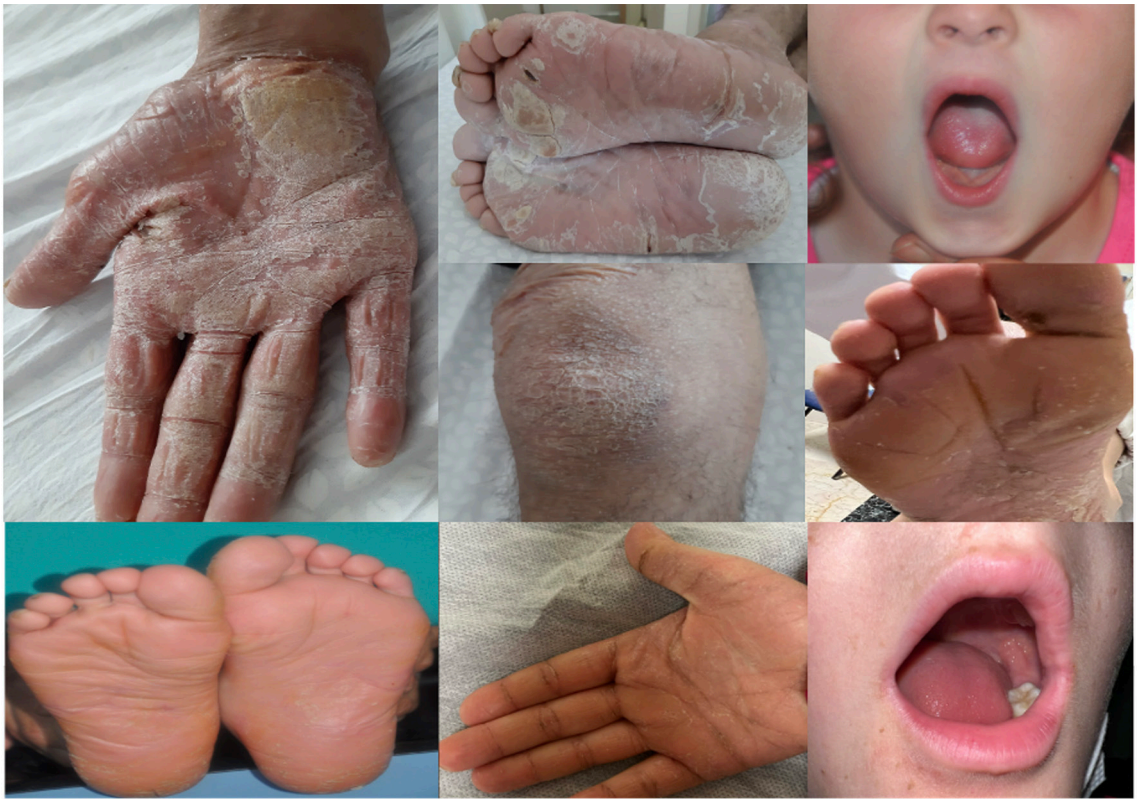

Figure 1. Clinical images of the lesions

Table 1. Demographic, clinical, and histopathological characteristics of the patients

Case	Age/sex	Age at diagnosis	Follow-up duration (year)	Family history	Dermatologic examination	Histopathologic analysis	Teeth loss	Comorbidity	Treatment
I	11/F	6	5	+	Erythema, hyperkeratosis in the palmoplantar area	Spongiotic dermatitis	+	-	Topical keratolytic, acitretin
II	15/M	4	11	+	Erythematous squamous plaque in the palmoplantar area	Spongiotic dermatitis	+	-	Topical keratolytic, acitretin
III	12/F	4	8	+	Erythema, hyperkeratosis in the palmoplantar area	Spongiotic dermatitis	+	Cystic fibrosis, nephrolithiasis, and gynecomastia	Topical keratolytic, acitretin
IV	26/M	6	20	-	Hyperkeratosis in the palmoplantar area, fissures, hyperkeratotic plaque in the knees and elbows	Spongiotic dermatitis	+	Multiple liver abcesses	Topical keratolytic, tazaroten

F: Female, M: Male

Discussion

PLS is a rare autosomal recessive genodermatosis caused by mutations in the *CTSC (11q14.2)* gene, which encodes the cathepsin C enzyme. Genetic, immunological, and microbiological factors contribute to the pathogenesis of PLS. Palmoplantar hyperkeratosis and early loss of primary and permanent teeth due to periodontitis are key features of the disease. Palmoplantar keratoderma and periodontitis typically develop simultaneously in patients aged between 1 and 4. However, there are cases of late-onset PLS without CTSC mutations.[1,2]

Palmoplantar keratoderma is characterized by widespread erythematous, hyperkeratotic plaques affecting the palms and soles, often leading to painful fissures that can interfere with daily activities. Patients with PLS may also exhibit hyperhidrosis, nail changes, and hyperkeratotic psoriasiform plaques on the knees and elbows.[1-4] Studies investigating the immunopathogenesis of PLS have identified activation of the T-helper 1 (Th-1)-Th-17 pathway and increased levels of interleukin-1 (IL-1) and IL-36 cytokines. It is thought that this cytokine profile may help explain how psoriasiform plaques located on the knees and elbows develop in patients and suggest that biological agents can be considered as potential treatment agents in resistant cases. Latour-Álvarez et al.[5] applied ustekinumab treatment (45 mg at weeks 0 and 4, then 45 mg every 8 weeks) to a 15-year-old girl with PLS who was resistant to topical steroid, phototherapy, isotretinoin, and acitretin treatments. The patients who received ustekinumab achieved regression of the erythematosquamous plaques and partial improvement of the palmoplantar keratoderma.[5,6]

Periodontitis presents as periodontal abscesses, halitosis, gum swelling, and difficulty in eating. Factors contributing to the development of periodontitis include impaired gingival sulcus epithelial permeability, decreased lymphocyte reactivation, impaired neutrophil chemotaxis, and an imbalance between pathogens and host immune response. Gram-negative anaerobic pathogens are considered the primary cause of periodontitis in PLS. Studies have shown elevated levels of IL-1β, IL-6, IL-8, and interferon-gamma in the gingival crevicular fluid of patients with PLS. Managing periodontal damage in PLS requires regular follow-up, oral hygiene maintenance, antiseptic mouthwash administration, and systemic antibiotic treatment. Intensive orthodontic treatment may be necessary during the growth period, and periodontal care can sometimes help preserve the patient's teeth.[7,8]

CTSC gene mutations can lead to neutrophil dysfunction, impaired chemotaxis, and recurrent infections, including internal organ abscesses in the liver and brain.[2] Patients with PLS should be monitored for the risk of pyogenic liver abscesses, especially when presenting with fever of unknown origin. *Staphylococcus aureus* is the most common causative agent of liver abscesses in PLS, usually occurring as a single abscess. Mental retardation, dura mater calcifications, growth retardation, hypothyroidism, atopic tendencies, and elevated immunoglobulin E levels are rare findings associated with this syndrome.[1-4] One of our cases had mental retardation and multiple liver abscesses.

Treatment options for palmoplantar keratoderma in PLS include topical moisturizers, keratolytic agents, and topical or systemic retinoids. Systemic retinoids have been shown to effectively reduce keratoderma, periodontal disease, and susceptibility to infection, making them a key therapeutic agent in PLS treatment.[1-4,6,9] A study by Leuenberger et al.[6] demonstrated that acitretin treatment decreased levels of IL-12B, IL-17C, IL-26, and IL-36 in a PLS patient. In cases where systemic retinoids cannot be used, such as in our case, topical retinoids can be a suitable alternative. Tazarotene, for example, regulates the proliferation and differentiation of keratinocytes and provides an additional anti-inflammatory effect, making it effective for treating keratoderma in PLS. Guldbakke et al.[10] used 40% urea cream and 0.1% tazarotene gel for palmoplantar keratoderma management after patient decline in oral retinoid treatment and achieved moderate improvement. Additionally, maintaining oral hygiene, using antiseptic mouthwashes, administering systemic antibiotics, and regular dental follow-up are crucial for managing periodontitis in the patients.[1,3] New studies on the *CTSC* gene indicate that there may be new possibilities for the treatment of the disease.[11]

Through this case report, we aimed to raise awareness about PLS among clinicians by presenting the clinical and treatment characteristics of four patients. Further studies and case series will contribute to our understanding of PLS pathogenesis and guide the development of new treatment options.

Ethics

Informed Consent: The patients in this manuscript has given written informed consent to the publication of their case details.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.C.E., E.A., Concept: Y.C.E., E.A., Design: Y.C.E., E.A., Data Collection or Processing: Y.C.E., E.A., Analysis or Interpretation: Y.C.E., E.A., Literature Search: Y.C.E., E.A., Writing: Y.C.E., E.A.

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