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Case Report

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Papillon-Lefèvre syndrome in early childhood: a case report with literature review

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ABSTRACT

Papillon-Lefèvre syndrome (PLS) is a rare genetic disorder with autosomal recessive inheritance, typically manifesting in childhood. The hallmark features include palmoplantar hyperkeratosis and premature loss of teeth. Additional associated findings may include psoriasiform plaques on the knees and elbows, hyperhidrosis, recurrent pyogenic infections, intracranial calcifications, and both physical and mental developmental delays. This case report presents a 5-year-old child who was admitted to the Faculty of Dentistry at Kırıkkale University with tooth loss and was subsequently diagnosed with PLS, accompanied by a review of the relevant literature.

Keywords: Papillon-Lefèvre syndrome, palmoplantar hyperkeratosis, tooth loss

INTRODUCTION

Papillon–Lefèvre syndrome (PLS), first described by Papillon and Lefèvre in 1924, is a rare hereditary disorder that manifests during childhood.[1] It is characterized by palmoplantar hyperkeratosis and premature loss of both primary and permanent dentition due to severe periodontitis. Although the precise pathogenesis of PLS remains incompletely understood, it is known to result from mutations in the cathepsin C (CTSC) gene, which follows an autosomal recessive inheritance pattern.[2] PLS is regarded as a subtype within the genetically and clinically heterogeneous group of palmoplantar keratodermas. Consanguineous marriages play a significant role in its occurrence, as the likelihood of inheriting the same defective *CTSC* allele from both parents increases in such unions. The estimated prevalence of PLS is between 1 and 4 cases per million individuals.[3,4]

This report presents a 5-year-old female patient who was admitted to the Faculty of Dentistry at Kırıkkale University with a complaint of tooth loss and was subsequently diagnosed with PLS after palmoplantar hyperkeratosis was detected during systemic evaluation. The aim of this report is to emphasize the importance of a thorough anamnesis and comprehensive systemic examination.

CASE

A 5-year-old female patient was admitted to the Faculty of Dentistry at Kırıkale University with a chief complaint of tooth loss. According to her parents, the patient had experienced spontaneous loss of teeth without any signs of dental caries, beginning at the age of two. Systemic evaluation revealed thickening of the skin on the palms and soles, for which she had been using topical treatments. The parents reported that hyperkeratosis and fissures on the palms and soles had first appeared when the child was one month old, and that regular use of dermatology-prescribed topical medications had resulted in significant improvement of the symptoms.

Family history revealed that the parents and two siblings were healthy, with no similar dermatologic or dental conditions, and that the parents were second-degree relatives.

Intraoral examination showed that all primary teeth, except for three molars, were missing. The remaining teeth exhibited gingival recession with root exposure and severe periodontal destruction. Radiographic evaluation demonstrated horizontal alveolar bone loss without evidence of root resorption (**Figure 1**). Based on these findings, the patient was referred to the Departments of Pediatrics and Dermatology with a preliminary diagnosis of PLS.

During pediatric evaluation, the patient was found to have been born via cesarean section with a birth weight of 2800 g following an uneventful pregnancy. There were no complaints during the neonatal period and no history of serious infections or additional diseases. Physical examination

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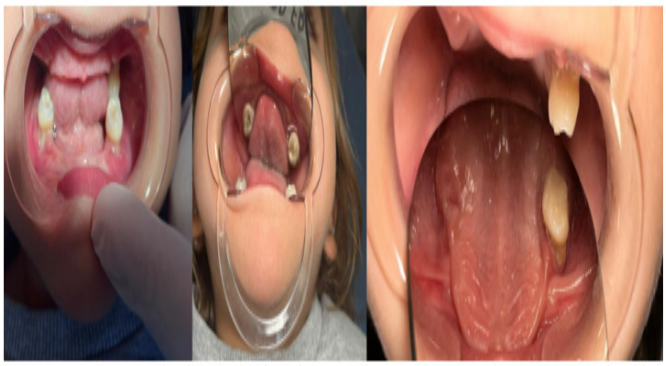

Figure 1. Intraoral photographs showing severe gingival recession, alveolar bone loss, and remaining primary molars in a 5-year-old patient with suspected Papillon-Lefèvre syndrome

revealed a height of 102 cm (3rd percentile) and a weight of 17 kg (25th-50th percentile). Since the results of investigations for short stature were within normal limits, it was considered that the patient's dental problems might have adversely affected her nutrition and, consequently, her growth. Therefore, dietary modifications were recommended. Mental development was assessed as normal, and no abnormalities were detected in other systemic examinations. Laboratory investigations were unremarkable except for a 25(OH) vitamin D level of 18 ng/ml. Echocardiographic evaluation revealed no pathological findings. The patient was subsequently referred to the Department of Medical Genetics for genetic counseling.

On dermatological examination, no remarkable findings were observed other than hyperkeratosis and fissures on the plantar surfaces. The skin appendages and mucous membranes appeared normal, and there were no pathological findings such as sweating abnormalities or arachnodactyly (Figure 2). A skin biopsy was obtained from the plantar region to differentiate among psoriasis, pityriasis rubra pilaris, and PLS.

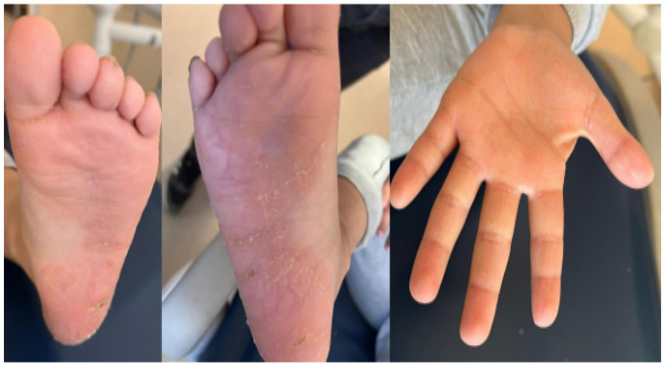

Figure 2. Palmar and plantar hyperkeratosis in a child with suspected Papillon-Lefèvre syndrome. Images show dry, thickened skin and fissures on the soles of the feet and mild hyperkeratosis on the palm

Histopathological examination revealed diffuse hyperkeratosis with focal areas of parakeratosis. Although the histopathological findings were not diagnostic for PLS, they excluded other dermatoses such as psoriasis, pityriasis rubra pilaris, and eczema. There were no acquired causes of keratoderma, such as dermatitis, chemical exposure, or drug use. Because early tooth loss accompanied keratoderma and no additional cutaneous findings were present, hereditary keratoderma disorders such as Mal de Meleda and Unna–Thost syndrome were considered unlikely.

Radiographs of the hands, feet, and long bones were obtained to evaluate for Haim–Munk syndrome, which is characterized by keratoderma and premature tooth loss and is regarded as a severe variant of PLS. No abnormalities were detected on radiography. DNA sequence analysis of the CTSC gene revealed a homozygous frameshift mutation (c.378delG). Based on these genetic and clinical findings, a definitive diagnosis of PLS was established.

For the treatment of keratoderma, topical corticosteroids and emollients containing 20% urea were prescribed. The family declined systemic therapy due to potential adverse effects. The patient continues to be followed regularly by the departments of dentistry, pediatrics, and dermatology.

DISCUSSION

PLS is a rare autosomal recessive disorder characterized by palmoplantar keratoderma and premature tooth loss resulting from severe periodontal destruction. Approximately 250 cases have been reported in the literature. Additional clinical manifestations may include intracranial calcifications, psoriasiform plaques over the knees and elbows, nail abnormalities, hyperhidrosis, recurrent pyogenic infections, and developmental delay in physical and mental growth. Although symptoms typically emerge between 6 months and 4 years of age, late-onset cases have also been described.[2-4]

The disease results from mutations in the CTSC gene located on chromosome 11q14–q21.[5,6] CTSC is a lysosomal cysteine protease that plays a key role in activating several serine proteases involved in immune and inflammatory responses. The CTSC gene is primarily expressed in epithelial tissues such as the palms, soles, knees, and keratinized oral gingiva, and is also present in osteoclasts.[6-9]

Premature loss of both primary and permanent teeth is a hallmark of PLS. Typically, complete loss of the primary dentition occurs by four years of age, whereas permanent teeth are lost by adolescence.[3] In our patient, tooth mobility and spontaneous exfoliation of deciduous teeth began around two years of age; at examination, only four molars remained. The primary cause of tooth loss in PLS is aggressive periodontitis.[10] Studies suggest that alterations in the oral microbiome contribute to the pathogenesis of periodontitis by promoting the proliferation of specific pathogenic species.[10-13] Other studies implicate immune dysfunction, citing impaired chemotaxis and phagocytosis of polymorphonuclear leukocytes (PMNLs), reduced integrin expression, and increased superoxide production.[14-17] However, some reports have demonstrated preserved PMNL chemotaxis and normal peripheral lymphocyte populations.[18-21] These findings support a multifactorial pathogenesis involving both microbial and host-related factors.

In young children presenting with early tooth loss, the differential diagnosis should include leukemia, neutropenia, hypophosphatasia, Langerhans cell histiocytosis, and Chediak–Higashi syndrome.[22-23] These conditions were excluded in our case based on clinical and laboratory evaluations.

Periodontitis has also been linked to systemic conditions such as cardiovascular disease. It is recognized as a risk factor for bacterial endocarditis and may contribute to valvular damage.[22,23] In our patient, both clinical and

echocardiographic evaluations revealed no cardiac abnormalities.

The cutaneous and dental manifestations of PLS may not appear simultaneously.[3] One study reported no correlation between the severity of dermatologic and periodontal involvement, noting that skin lesions do not regress with age.[24] In our patient, palmoplantar keratoderma began at one month of age and regressed notably after thİe first year of life.

Palmoplantar keratoderma, the primary cutaneous manifestation of PLS, typically develops between 6 months and 4 years of age. It presents as sharply demarcated, erythematous or yellowish hyperkeratotic plaques that may extend to the dorsal surfaces of the hands and feet. These lesions can impair manual function and cause painful fissures on the soles, leading to secondary infections and unpleasant odor.[2] Additional cutaneous findings may include psoriasiform plaques over the knees and elbows, thickened or fissured nails, and thinning of scalp hair.[3] In the absence of dental symptoms, these dermatologic features may lead to misdiagnosis as psoriasis, eczema, or dermatophytosis.[1] Our patient showed only mild plantar keratosis on examination, and histopathologic evaluation excluded other dermatoses. During infancy, when keratoderma was more pronounced, topical treatments were administered for presumed eczema and dryness.

Haim–Munk syndrome (HMS) and PLS are phenotypically related disorders caused by *CTSC* gene mutations.[25] Differentiation between the two may rely on identifying specific mutation types—such as the homozygous c.378delG (p.His127Metfs49)* variant detected in our patient—as well as assessing *CTSC* enzyme activity and exon copy number analysis. Although both disorders share similar genotypes, they exhibit distinct phenotypic features: onychogryphosis, pes planus, arachnodactyly, and acro-osteolysis are characteristic of HMS. In HMS, cutaneous and skeletal manifestations are more severe, whereas periodontal involvement tends to be milder compared with PLS.[26] PLS, generally associated with nonsense mutations in *CTSC*, is considered a milder form, while HMS represents a more severe clinical phenotype. Our patient exhibited no nail or skeletal abnormalities.[26]

Recurrent pyogenic infections due to PMNL dysfunction are common in PLS. Reported infections include cutaneous abscesses as well as hepatic, renal, and pulmonary involvement.[27,28] In patients with unexplained fever, hepatic abscess should be considered. Our patient had no history of recurrent or severe infections.

Although developmental delays in PLS have been reported, their association with the disease remains uncertain.[3] Our patient's cognitive development was normal. Her height was at the 3rd percentile and weight between the 25th and 50th percentiles. In the absence of familial short stature, vitamin D deficiency, anemia, or recurrent infections, it was considered that premature tooth loss might have adversely affected her nutrition and, consequently, her growth. In addition to nutritional consequences, early tooth loss can alter facial appearance, cause speech difficulties, and lead to psychosocial distress.[29] Psychological support by child psychiatrists should therefore be recommended. Early diagnosis and timely dental intervention are essential for achieving optimal physical and emotional development.

Intracranial calcifications represent another potential feature of PLS.[30] However, cranial imaging was not performed in our patient due to her young age and absence of neurological symptoms. PLS has also been associated with hearing loss, pseudoainhum, and ocular surface squamous neoplasia.[31-33] Although malignant cutaneous neoplasms are rarely observed, an increased incidence of malignant melanoma has been reported, particularly among Japanese patients.[26]

The prevalence of autosomal recessive disorders increases with consanguinity.[30] In this case, the patient was born to first-degree consanguineous parents. Genetic counseling was provided to the family following identification of the CTSC mutation. Accurate diagnosis and optimal management of PLS require a comprehensive, multidisciplinary approach involving dentistry, pediatrics, dermatology, and medical genetics, ideally complemented by child psychiatry and nutrition specialists. Treatment should be individualized according to clinical presentation and family circumstances.

Dental treatment options for PLS include oral hygiene recommendations, antibiotic therapy, prosthodontic rehabilitation, and implant placement. However, conventional periodontal therapy has generally been ineffective, as periodontitis in PLS is aggressive and leads to rapid destruction of the alveolar bone.[34] Due to severe bone loss, prosthetic rehabilitation remains a major challenge in these patients.

Dental management may include the use of osseointegrated implants, which represent the future rehabilitation plan for this case.[35] Following implant therapy, functional and esthetic oral rehabilitation can be achieved with a pediatric prosthesis. Regular follow-up appointments are essential to maintain oral hygiene, monitor implant stability, and ensure long-term success.

The treatment of palmoplantar keratoderma includes the use of topical emollients, corticosteroids, keratolytic agents, and systemic retinoids. Systemic retinoids such as isotretinoin, acitretin, and etretinate can lead to near-complete resolution of keratoderma and are also effective in reducing periodontitis and recurrent pyogenic infections.[36-38] For the management of periodontitis, initiation of systemic retinoid therapy is recommended after the eruption of permanent teeth.[36] However, the long-term use of systemic retinoids may be limited by adverse effects, including xerosis, cheilitis, musculoskeletal complications, and teratogenicity. Moreover, acitretin requires extended contraception for up to two years after discontinuation, which further restricts its use.[35]

In our patient, palmoplantar keratoderma showed marked improvement with topical therapies, and there was no indication for systemic treatment specifically targeting keratoderma. However, considering the potential benefits on periodontal disease, acitretin therapy was recommended to the family after consultation with the department of dentistry. After being informed about the possible benefits and adverse effects of systemic retinoid therapy, the family declined treatment. Regular follow-up with the departments of dentistry, pediatrics, and dermatology was therefore advised. Because of its rarity and multisystem involvement, the diagnosis of PLS is often delayed or overlooked.[39]

CONCLUSION

Early diagnosis, timely initiation of treatment, and regular multidisciplinary follow-up can significantly improve the patient's quality of life. Through this case report, we aim to emphasize the importance of detailed medical history taking, comprehensive systemic evaluation, and collaborative multidisciplinary care in patients presenting with findings involving multiple organ systems.

ETHICAL DECLARATIONS

Informed Consent

Informed consent was obtained from the legal guardians of the pediatric patient(s) described in this report. Where developmentally appropriate, assent was also sought from the child. The inclusion of vulnerable populations in this study adhered to national and international ethical guidelines. Extra care was taken to ensure voluntary participation, understanding, and protection of participant dignity and autonomy.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

Concept: T.B.K., E.H., C.Ş., M.E.A., A.A. T.Ö.; Design: T.B.K., E.H., A.A.; Control: T.B.K., M.E.A., A.A.; Data Collection and/or Processing: T.B.K., E.H., M.E.A., A.A.; Analysis and/or Interpretation: T.B.K., E.H., M.E.A., A.A.; Literature Review: T.B.K., E.H., M.E.A., A.A.; Article Writing: T.B.K., E.H., C.Ş., M.E.A., A.A.; Critical review: All authors.

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