

CASE REPORT

# Papillon-Lefevre Syndrome: A Novel Familial Presentation

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ABSTRACT

Papillon-Lefevre syndrome (PLS) is a condition characterized by dermatological manifestations and early onset periodontitis. The pathogenesis of PLS is secondary to mutation of the cathepsin C gene. Hence, the manifestations are expressed on the areas of the body covered by epithelium, such as palms, soles, knees and keratinized oral gingiva. Various immune cells, including polymorphonuclear leukocytes, macrophages, and their precursors are also affected leading to functional disability. PLS is an autosomal recessive condition and can occur in siblings born of consanguineous marriages. This report highlights a rare instance of two siblings of a family affected with Papillon-Lefevre syndrome.

**Keywords:** Cathepsin, Leukocyte, Mobility, Periodontitis, Keratosis.

CASE REPORTS

A 13-year-old female patient reported to us with a complaint of partially edentulous upper and lower arches since five years. Patient history revealed that her teeth had erupted normally but later on they became mobile and exfoliated. She also claimed that her deciduous dentition was lost completely before the age of seven.

The patient's family history revealed that she is a child born of consanguineous marriage and her elder brother also has a similar problem, but neglected to seek any treatment. The patient was otherwise normal and did not show any signs of systemic illness.

Extraoral examination of the patient did not show any notable changes. Examination of the palms and soles showed focal areas of keratinization, pigmented scales and deep fissuring (Figs 1 and 2). Intraoral examination showed missing 11, 21, 26, 31, 36, 41, 42, 46 and generalized grade III mobility (Fig. 3). Panoramic radiograph showed generalized horizontal bone loss extending upto the apices of the teeth and developing tooth buds of all third molars (Fig. 4).

The patient's brother on examination revealed marked reduction in lower facial height. Examination of the palms and soles showed thick, diffuse, dry keratotic plaques and areas of deeply pigmented scales with frequent areas of fissuring and crusting, which were pronounced over the lateral margins of the soles (Figs 5 and 6). Intraoral examination showed complete absence of upper and lower teeth. Resorption of the residual ridge was noted bilaterally in both the arches. The mucosa and the salivary flow were normal. Panoramic radiograph showed completely edentulous upper and lower arch and reduced alveolar bone height. There was no evidence of any impacted teeth (Fig. 7).

For both the patients, the lateral cephalograms did not show any evidence of calcifications. Complete hemograms did not



Fig. 1: Keratinization involving the palms



Fig. 2: Keratinization involving the soles of the feet



Fig. 3: Partially edentulous arch

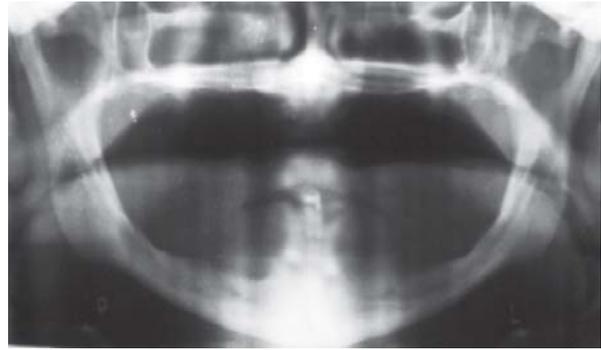


Fig. 7: OPG showing completely edentulous arch



Fig. 4: OPG showing partially edentulous arch



Fig. 5: Keratinization and crustings involving the palm



Fig. 6: Scaled skin

show any notable changes, and serum alkaline phosphatase and bilirubin levels were within normal limits.

Based on the history and clinical features, a provisional diagnosis of Papillon-Lefevre syndrome was arrived at. For both patients, thorough oral rehabilitation procedure was carried out and a dermatologist's opinion was sought for skin manifestations. Topical retinoic A application was advised by the dermatologist for palmoplantar keratosis. Follow-up examination after 15 days showed notable reduction in skin scaling and fissuring. The patient is being recalled for regular follow-up every month.

## DISCUSSION

Papillon-Lefevre syndrome (PLS), first described by two French physicians Papillon and Lefevre in 1924, is an extremely rare genodermatosis with predominant oral and dermatological manifestations.<sup>1-3</sup>

The exact etiology of PLS is not known, but it is believed as an autosomal recessive disorder with a gene frequency of 0.001.<sup>4</sup> Genetic analysis has mapped the major gene locus to chromosome 11q14.1-q14.3 with mutation and loss of function of cathepsin C gene in the homozygotes of PLS.<sup>1</sup> The cathepsin C gene encodes a cysteine-lysosomal protease also known as dipeptidyl-peptidase I, which functions to remove dipeptides from the amino terminus of the protein substrate.<sup>5,6</sup> It is hypothesized that the mutation in cathepsin C gene results in an altered immune response leading to defect in the neutrophil chemotactic and phagocytic function. It is postulated that the cutaneous lesions are secondary to expression of the mutated cathepsin C gene in the affected epithelium.<sup>7</sup> The periodontal manifestations can be attributed to impaired activity of T- and B-cell mitogens, abnormal neutrophil chemotactic and phagocytic function and bacterial infections.<sup>8</sup> However, the rapidity of the tooth loss in the order of its eruption in PLS is still not understood.<sup>9</sup>

PLS is usually considered to be associated with oral and dermal manifestations, however, there are reports with partial findings as well.<sup>9,10</sup> Such discordant expressions might be as a

result of epistatic interaction between the disease gene and other modifying genes.<sup>9</sup>

PLS has a prevalence of 1 to 4 cases per million persons.<sup>1-3,11</sup> Males and females are equally affected and there is no racial predominance.<sup>12</sup> Consanguinity is noted in approximately one-third of the cases.<sup>12-14</sup> The disorder is characterized by diffuse palmoplantar keratoderma and dramatically advanced periodontitis that is seen in both the deciduous and permanent dentitions.<sup>15</sup> The palmoplantar keratoderma typically has its onset as early as in the first year of life. The lesions typically present as white-yellow, brown or red plaques and patches that develop into crusts, cracks or deep fissures.<sup>1,2</sup> Initially, the sharply demarcated erythematous keratotic plaques may occur focally, but later they extend to involve the entire surface of the palms and soles, sometimes extending onto the dorsal surfaces of the hands and feet. Other less common sites of involvement include elbows, knees, legs, thighs, dorsal surface of the fingers, toes and rarely the trunk. Often, there is associated hyperhidrosis of the palms and soles resulting in a foul-smelling odor.<sup>1</sup> Nail changes are apparent in advanced cases and can manifest as transverse grooving and fissuring.<sup>16</sup> The findings may worsen in winter and be associated with painful fissures.<sup>17-19</sup>

The second major feature of PLS is severe periodontitis, which starts at age 3 or 4.<sup>17</sup> The development and eruption of the deciduous teeth proceed normally, but their eruption is associated with gingival inflammation and subsequent mobility and migration of the teeth. The resultant periodontitis is characteristically unresponsive to traditional periodontal treatment modalities and the primary dentition is usually exfoliated prematurely by age 4.<sup>15</sup> After exfoliation, the inflammation subsides and the gingiva appears healthy. However, with the eruption of permanent dentition, the process of gingivitis and periodontitis is usually duplicated and there is subsequent premature exfoliation of the permanent teeth as well.<sup>1</sup>

In addition to the dermatological and oral findings, patients may have decreased neutrophil, lymphocyte or monocyte function and showed increased susceptibility to bacterial infections leading to recurrent pyogenic conditions, such as pyoderma, furunculosis, pneumonia and hepatic abscesses. In many cases, pyogenic liver abscess is increasingly recognized as a complication of PLS associated with impairment of the immune system.<sup>17,20-21</sup> In addition, retardation of somatic development and ectopic calcifications of the falx cerebri and choroid plexus have also been reported.<sup>2,22</sup>

The clinical differential diagnosis includes Haim-Munk syndrome, prepubertal periodontitis and keratoderma palmoplantar of Unna-Thost syndrome and Meleda disease. Characteristically, the first two conditions are secondary to mutation of cathepsin C gene as in PLS. Others include acrodynia, hypophosphatasia, histiocytosis X, leukemia, cyclic neutropenia and Takahara disease, as all the above conditions show periodontal destruction and premature loss of teeth.

However, they can be easily differentiated from PLS by the absence of skin manifestations.<sup>22</sup>

The clinical features of Haim-Munk syndrome (HMS) include palmoplantar keratosis, progressive periodontal disease, recurrent skin infections and several skeletal malformations. In contrast to PLS, the cutaneous findings in HMS have been reported to be more severe and extensive whereas the periodontium is less severely affected. The skeletal malformations include acro-osteolysis, atrophic changes of the nails, arachnodactyly, and a peculiar radiographic deformity of the fingers consisting of tapered, pointed phalangeal ends, claw-like volar curve, and pes planus.<sup>13</sup>

Prepubertal periodontitis is characterized by rapidly progressive early-onset periodontitis, which may be localized or generalized. It may occur as a part of recognized syndrome or as an isolated non-syndromic disorder. The radiographic presentation of alveolar bone loss in prepubertal periodontitis in many cases appears similar to that observed in PLS, but it is differentiated from PLS by the absence of associated palmoplantar keratoderma. In contrast, palmoplantar keratoderma is seen in Unna-Thost syndrome and Meleda disease, which exhibit skin manifestations but not the oral changes.<sup>1</sup>

The histopathological features of PLS are usually nonspecific. The gingival epithelium may show hyperkeratosis, acanthosis, and occasional patches of parakeratosis. Exocytosis of inflammatory cells is seen in the periodontal pocket and the underlying connective tissue shows increased vascularity with a mixed inflammatory cell infiltrate consisting predominantly of polymorphonuclear leukocytes, lymphocytes, histiocytes and plasma cells.<sup>1,2</sup>

A multidisciplinary approach is important for the care of patients with PLS. Patients with mild dermatological manifestations are often treated with topical lubricants, keratolytic agents, such as salicylic acid or lactic acid, corticosteroids and antibiotics. In many instances, oral retinoids, including acitretin, etretinate, and isotretinoin are the mainstay of the treatment of both the keratoderma and periodontitis associated with PLS.<sup>17,23</sup> Effective treatment for the periodontitis includes extraction of the primary teeth combined with oral antibiotics and oral prophylaxis. Drugs that have been tried include erythromycin, metronidazole and amoxicillin. Treatment may be more beneficial if it is started during the eruption and maintained during the development of the permanent teeth.<sup>1</sup>

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