Oral and Dermatologic Findings in Two Siblings with Papillon-Lefèvre Syndrome: Review of the Literature

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Papillon-Lefèvre syndrome (PLS), first described in 1924(1), is a rare autosomal recessive disorder characterized by early onset palmoplantar hyperkeratosis and severe generalized destructive periodontitis leading to premature loss of both primary and permanent dentitions. PLS usually manifest itself between the ages of six months to four years, coinciding with the eruption of primary teeth. The proband becomes completely edentulous by the age of 15(2,3).

Gorlin et al. (4) in 1964 reviewed a total of 46 PLS cases described in the literature. They reported the occurrence rate of the syndrome in general population of 1-4 cases/million. In 1979, Haneke(5) reviewed a total of 124 cases and concluded that: 1) Males and females are equally affected; 2) There is no racial predominance of the condition; 3) Consanguinity is a feature in one-third of the cases; 4) There is increased susceptibility to infection in 25% of the cases, especially furunculosis, pyoderma, pyogenic liver abscess, and respiratory tract infection. Variable findings in the syndrome include intracranial calcification of the dura, retardation of somatic development and onychogryphosis(2-7). Up to 1995 more than 200 cases had been reported(2,3).

The first PLS report on an Arab was published in 1982, which described four Iraqi probands(8). Subsequently several reports on affected Arabs were published due to the increased awareness by both dentists and dermatologists of the oral and skin manifestations of the syndrome. In a recent review of the literature, Hattab and Amin(9) reported that one-third of the total PLS cases described (80 of 250 cases) were Arabs and 75% of them had a history of parental consanguinity. These findings are inconsistent with those reported by Haneke(5) on cases mainly derived from western communities. The association of PLS with consanguinity in particular ethnic groups suggests that genetic factors strongly contribute to the etiology of this syndrome and at least partly explain the relatively high incidence of the disease amongst Arabs. In this context it has been reported that consanguineous marriage in Arab communities accounts for one-third or more of the total marriages(10-12).

The exact causes of PLS are not well understood. Recent genetic analysis has mapped the PLS locus to chromosome 11q14-q21, which linked loss-of-function mutations in the cathepsin C gene with the etiology of the syndrome(13-15). Lack of cathepsin, a lysosomal protease enzyme, in PLS results in a reduced host response against virulent pathogens in dental plaque and other sites. An interesting feature of the cathepsin C gene is that mutations of this gene also result in two other closely related conditions, the Haim-Munk syndrome(16) and prepubertal periodontitis(17,18). A common clinical manifestation in all three syndromes is severe early-onset periodontitis. In addition to genetic alterations a number of environmental and host factors are involved in the pathogenesis of PLS periodontitis(2,3,9,19). Several mutations in this gene and variations in the clinical presentation of PLS have been reported recently(9,20,21).

This report describes two siblings with typical PLS who presented to the School Dental Clinic at Hamad Medical Corporation. To our knowledge this is the first Qatari family diagnosed with the syndrome.

Case Report:

Case 1:

W.A., a nine-year-old girl was first seen at the age of eight years with a chief complaint of "sore gums and teeth falling out". Examination revealed premature loss of primary teeth and severe periodontitis. A bilateral hyperkeratosis of the palms and soles was evident. The patient was diagnosed as having PLS.

The patient was the sixth of eight siblings, four girls and four boys. The younger brother was affected by the same syndrome. No one else in the family had similar manifestations. Pregnancy, labor, and delivery were normal. According to her
mother the skin of the palms and soles were red and rough at birth. The primary teeth had erupted at the expected date and she had full dentition by the age of three years. At approximately one year of age the gingivae around the erupted teeth became swollen and sore. A few months later the teeth became mobile and exfoliated one after another. There was no history of other serious illness or infection in areas other than the oral cavity. The development of the patient, both physically and mentally, was within normal limits.

Intraoral examination revealed complete loss of all primary teeth and erupted permanent incisors and first molars. The gingivae around the teeth were bright red, severely inflamed, swollen and tender. Multiple abscesses involving the marginal gingiva of the first molars were evident, with pus exuded from the periodontal pockets upon slightest pressure. The oral mucosa covering the edentulous area appeared normal (Figure 1). The teeth were mobile, drifted and extruded. The patient had difficulty chewing and offensive oral malodor was present. Submandibular lymph nodes were enlarged and tender.

Radiographic examination disclosed severe alveolar bone loss associated with all erupted teeth with no evidence of root resorption. The «floating» teeth showed extensive alveolar bone destruction. The unerupted teeth were in normal stages of development and present in their bony crypts with no sign of abnormal bone changes (Figure 2). One year later, the upper and lower left first permanent molars were exfoliated.

Dermatological examination revealed a bilateral and symmetrical hyperkeratosis of the palms and soles. Skin lesions were hyperkeratotic, erythematous, scaly and fissured with the soles more affected than the hands (Figures 3 and 4). No evidence of hyperkeratosis was found on her knees, elbows, and dorsal surfaces of the hands. Nails, sweating and hair were normal. The skin lesions aggravated during cold weather and at times of severe periodontal involvement. Thickening and cracking of the planter skin caused pain on walking.

The patient was placed on combined amoxicillin and metronidazole therapy (250 mg/three times daily for seven days)
every two to three months combined with scaling and root planing, oral hygiene instruction, and chlorhexidine mouthwash. The treatment reduced the symptoms but was ineffective in halting the progress of the periodontitis.

**Case 2:**

S.A., a five-year-old brother of Case 1, presented with complaints of teeth mobility, swollen and sore gingivae with difficulty in chewing. Medical and dental histories were, in general, similar to Case 1. He was born after an uneventful full-term pregnancy. The skin lesions were first noticed at birth when the palms and soles appeared red and roughened. No history of general serious infection was reported. His primary teeth started to erupt at the age of six months and he had his full dentition by the age of two and a half years. After teeth eruption, the gums became red, swollen, and bled easily, followed by teeth mobility and exfoliation. The boy was normally developed both physically and mentally. As in Case 1, hair growth, sweating and nails were normal.

Intraoral examination showed only primary canines and lower first molars present. The teeth were mobile, drifted, and extruded. The gingivae around the teeth were red, swollen, hemorrhagic and tender with gingival abscesses confined to the right upper canine and lower first molar (Figure 5). Gingival recession and heavy plaque accumulation were evident. The teeth were sensitive to touch and upon slight pressure pus exuded from the gingival abscesses. Offensive halitosis was present. Submandibular lymph nodes were palpable and tender. The teeth were extracted under antibiotic coverage. One year later the permanent first molars and lower central incisors erupted and the cycle of destructive periodontitis was repeated (Figure 6).

The skin lesions on the palms and soles were erythematous, hyperkeratotic, scaly, and cracked (Figure 7) without involving the knees and elbows. Seasonal variations of skin lesions were also noted in this patient and the severity of periodontitis coincided with the exacerbation of the cutaneous lesions.
Discussion:

PLS is inherited and appears to follow an autosomal recessive pattern with both parents phenotypically healthy and there being no family history of the disease other than in the affected siblings. Both parents must carry the autosomal gene for the syndrome to appear in their siblings. When two such carriers mate, there is a 25% chance of producing affected offspring. In this family, a brother and sister of six siblings had PLS exhibiting the typical clinical features. Hyperkeratosis of the palms and soles and generalized rapidly progressive periodontitis accompanied by severe alveolar bone destruction, leading to early loss of both primary and permanent dentitions. In both patients the skin lesions exacerbated at times of increased severity of periodontitis, subsided after exfoliation of teeth, and became aggravated during cold condition.

PLS should be differentiated from other conditions showing similar oral or cutaneous clinical features. Diseases with oral manifestations such as acrodynia, hypophosphatasia, histiocytosis X, leukemia, cyclic neutropenia, and Takahara’s syndrome are associated with periodontitis and premature loss of teeth. PLS was differentiated from them by the presence of the palmoplantar hyperkeratosis. PLS can also be distinguished from palmoplantar keratoderma of Unna Thost, mal de Meleda, Howel-Evans syndrome, keratosis punctata, keratoderma hereditarium mutilans (Vohwinkel’s syndrome) and Greither’s syndrome as these entities are not associated with periodontopathy.

Efforts to treat PLS have been traditionally directed either to reducing the hyperkeratotic skin lesions or halting the periodontal destruction. The therapeutic goal for skin lesions is to remove sufficient callus to preserve function and to relieve pain over pressure points from fissures and cracks. Treatments were based on topical application of lubricants, keratolytic agents; such as 6% salicylic acid (Keralyt gel) or 7-10% lactic acid in petrolatum, anti-inflammatory steroids, and antibiotics. Gentian violet, Castellani’s paint, or flexible collodion have been used to seal painful fissures. The therapeutic effects of these treatments were not satisfactory. Oral retinoids that have proven effective in the treatment of various types of keratinizing disorders have been incorporated in the treatment of PLS. Etretinate (a synthetic retinoid of acitretin; Tigason® is available in 10 and 25 mg capsules) has been successfully used for the treatment of palmoplantar keratoderma and periodontitis in PLS.

There are controversial reports of the effectiveness of systemic antibiotics combined with mechanical and chemical periodontal methods for the treatment of the periodontal component of PLS. Timanoff et al. reported that administration of tetracycline (250 mg t.i.d for one month) temporarily improved the condition but did not halt periodontal destruction. Preus reported successful treatment of periodontitis over a four and a half year follow-up in two siblings receiving tetracycline intermittently (2-4 weeks) in periods of exacerbation and continuously during the last two years of the study. He suggested that the combination of careful plaque control, periodontal surgery, and antibiotic therapy was important in successful treatment. Glenwright and Rock treated a case with penicillin, tetracycline and metronidazole at different times over eight years but did not arrest periodontal destruction of primary and permanent teeth. De Vree et al. followed two PLS siblings for 15 years and reported that continuous and intensive periodontal treatment along with systemic metronidazole (250 mg q.i.d for five days during periods of exacerbations) was successful in maintaining a number of permanent teeth in one patient but not able to prevent complete tooth loss in the other sibling. Successful treatment of PLS periodontitis has been reported using both amoxicillin or amoxicillin/clavulinate potassium (Augmentin®) and metronidazole (250 mg / t.i.d for 10 days) every six months followed by supportive periodontal therapy.

These conflicting findings on PLS management could be related to the severity of the condition, the age at which treatment was instituted, timing and duration of antibiotic therapy, professional supervision, follow-up evaluation period, and home care. Recently, osseointegrated implants have been used in PLS patients. Because of the complex etiopathogenesis of PLS, successful treatment of the periodontal component of this syndrome remains challenging.

References:

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Hattab F.N., et al.