

Papillon-Lefèvre syndrome: report of three cases in the same family

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SUMMARY: Keskin-Yıldırım Z, Şimşek-Derelioğlu S, Kantarcı M, Yılmaz Y, Büyükcavcı M. Papillon- Lefèvre syndrome: report of three cases in the same family. Turk J Pediatr 2012; 54: 171-176.

Papillon-Lefèvre syndrome is a rare autosomal recessive disorder caused by cathepsin C gene mutation leading to the deficiency of cathepsin C enzymatic activity. The disease is characterized by palmoplantar hyperkeratosis, periodontopathy and precocious loss of dentition, and increased susceptibility to infections. Pyogenic liver abscess is an increasingly recognized complication. Three cases of Papillon-Lefèvre syndrome in the same family are presented here. Two of the three siblings presented with characteristic manifestations of the syndrome. The third case had died previously due to liver abscess prior to a diagnosis of Papillon-Lefèvre syndrome.

Key words: Papillon-Lefèvre syndrome, hyperkeratosis, periodontopathy, liver abscess.

Papillon-Lefèvre syndrome (PLS) is an autosomal recessive disease that is characterized by symmetric palmoplantar keratodermatitis and severe periodontal destruction. The syndrome was first described by Papillon and Lefèvre in 1924¹. Genetic, immunologic and microbiologic factors are suggested as responsible for the initiation and progression of the disease². Genetic studies have shown that mutations in the major gene locus of chromosome 11q14 with loss of function of the cathepsin C gene are responsible for PLS^{3,4}. The cathepsin C gene is highly expressed in epithelial tissue such as the palms, soles, knees, and keratinized oral gingiva, which are commonly affected by PLS, and cells of the immune system⁵.

Papillon-Lefèvre syndrome (PLS) is classified as congenital defects of phagocyte number or function in primary immune deficiencies⁶. Immune dysregulation, due to a mutation in the cathepsin C gene, increases the risk of pyogenic infections in PLS patients⁷. Cathepsin C plays an important role in intracellular degradation of proteins and in activation of many serine proteases within immune/inflammatory cells, including polymorphonuclear leukocytes, monocyte-macrophages and mast cells. Neutrophils from patients with PLS do not

uniformly have a defect in their ability to kill *Staphylococcus aureus* and *Escherichia coli*, suggesting that serine proteases do not represent the major mechanism used by human neutrophils for killing common bacteria⁸.

In this report, the clinical presentation, differential diagnosis, therapeutic approach, and periodontal management of three siblings with PLS are discussed. They were born of first- degree consanguineous healthy parents.

Case Reports

Case 1

A nine-year-old girl presented with well-demarcated, yellowish, keratotic plaques over the skin of her soles extending onto the dorsal surfaces (Fig. 1). The remainder of her medical history was unremarkable. She had two brothers and three sisters. Two of her sisters and one brother were healthy; however, one sister (Case 2) and one brother (Case 3) had similar skin lesions.

On the physical examination, dystrophy and transverse grooving were present on her nails. Intraoral and panoramic examination showed permanent dentition with severe



Fig. 1. Keratotic plaques over the skin of Case 1.

gingival inflammation, deep periodontal pockets, severe bone destruction of the jaws, and discomfort on eating. Severe mobility affecting all the teeth and heavy deposits of plaque and calculus were also present (Fig. 2). All primary teeth were exfoliated. The panoramic and occlusal radiographs showed severe generalized destruction of alveolar bone around the permanent dentition, giving the teeth a “floating-in-air” appearance (Figs. 3, 4). Laboratory findings including complete blood count, liver function tests, total bilirubin, and alkaline phosphatase were normal.



Fig. 2. Intraoral view of Case 1.



Fig. 3. Panoramic radiograph showing generalized severe alveolar bone loss (Case 1).

Periodontal and prosthetic treatment was as follows: Teeth numbers 16, 26, 36, 46, 41, 42, 31, 32 had been extracted before presentation to our clinic. Following extraction of the periodontally unsalvageable teeth (11, 12, 21, 22, 33, 43, 45), she received scaling and adjunctive systemic antibiotics (amoxicillin + clavulanic acid for 10 days) (Fig. 5). In addition, she was advised to rinse with 15 ml benzydamine hydrochloride (approximately 1 tablespoon) every 1.5-3 hours as required for pain relief. The patient was instructed in oral hygiene, and in order to maintain vertical dimension and to provide esthetics, function and phonation, both maxillary and mandibular removable partial dentures were made. It was explained that the dentures would have to be remade eight months later in order to not block the growth of the jaw bones.

Case 2

This five-year-old girl was referred to us together with her sister (Case 1). The history



Fig. 4. Occlusal radiograph (Case 1).



Fig. 5. Intraoral view of Case 1 (after the extraction of unsalvageable teeth).

revealed early loss of her deciduous teeth after normal eruption and development of plantar hyperkeratosis at the age of two years. Cutaneous examination revealed plantar keratoderma, more on pressure areas with up to dorsolateral aspects (Fig. 6). Sweating and hair were normal. Intraoral and panoramic examination showed mixed dentition with severe gingival inflammation, deep periodontal pockets, severe bone destruction of the jaws, and discomfort on eating. As seen in her elder sister, severe mobility affecting all her teeth



Fig. 6. Keratotic plaques over the skin of Case 2.

and heavy deposits of plaque and calculus were also present. Most of the primary teeth were exfoliated; she only had four second primary molars (Fig. 7). The panoramic, occlusal and periapical radiographic examination showed severe generalized destruction of alveolar bone around the primary dentition, giving the teeth a "floating-in-air" appearance (Fig. 8). Mandibular incisors and first molar teeth showed early eruption. Other systemic examinations, routine laboratory investigations, and X-ray films of the skull and chest were normal.

Periodontal and prosthetic treatment was as follows: following extraction of the periodontally unsalvageable teeth (55, 65, and 85), she received scaling and adjunctive systemic antibiotics (amoxicillin + clavulanic acid for 10 days) (Fig. 9). In addition, spray form of benzydamine hydrochloride was applied directly on the inflamed tissue every 3 hours as required for pain relief. As in Case 1, in order to maintain vertical dimension and to provide esthetics, function and phonation, both maxillary and mandibular removable partial dentures were made. The patient was informed that the dentures would have to be remade six months later in order to not block the growth of the jaw bones.

Case 3

The information concerning this patient (brother of Cases 1 and 2) was obtained from the hospital records. An eight-year-old boy was referred to us with fever and pain in the right hypochondrium of two months' duration. There was no history of vomiting or jaundice. He was the second child of the family. On examination, he was febrile and had tachycardia and mild



Fig. 7. Intraoral view of Case 2.



Fig. 8. Panoramic radiograph showing severe generalized destruction of alveolar bone around the primary second molars, giving the teeth a "floating-in-air" appearance (Case 2).

pallor but no icterus. Abdominal examination showed a bulge on the lateral aspect of the right hypochondrium with tender hepatomegaly. The spleen was not palpable. He also had plantar keratoderma and loss of some dentition. Hematologic and biochemical investigations were normal except for leukocytosis (white blood cell: $24,800/\text{mm}^3$) and neutrophilia. Abdominal ultrasonography (US) showed well-defined hypoechoic lesions (abscesses) of varying size in the right lobe of the liver. Abdominal computed tomography (CT) showed abscess formation and subcapsular loculated fluid collection in the right lobe in the liver (Fig. 10). The patient was started on broad-spectrum antibiotics (cefotaxime, sulbactam and amikacin). Percutaneous aspiration under US guidance was performed and the aspiration material culture isolated *S. aureus*. His blood cultures were negative. He did not respond to medical treatment and died of septic shock.



Fig. 9. Intraoral view of Case 2 (after the extraction of unsalvageable teeth).

Discussion

Papillon-Lefèvre syndrome (PLS) is characterized by diffuse palmoplantar keratoderma and juvenile periodontitis¹. The diagnosis is mainly clinical. Variable clinical features and parental consanguinity suggest some heterogeneity and variable expression of the condition. There is evident consanguinity of parents in about one-third of the cases⁹. Since the parents of our patients had first-degree consanguinity, the children appear to have inherited the condition recessively. We were not able to perform genetic analysis for identifying the responsible mutation because of the low economic status of the parents; however, the dermatological, periodontal and radiological features strongly suggested the diagnosis of PLS.

One of the main features of the syndrome is symmetric palmoplantar erythematous hyperkeratotic plaques, which may also affect the elbows, knees and trunk^{2,10,11}. Hairs are usually normal, and nails may show onychodystrophy and transverse grooving. Claw-like phalanges with convex nails (arachnodactyly) and osteolysis described in PLS are perhaps its variants¹². Another form of the disease associated with palmoplantar keratosis and severe aggressive periodontitis has been named Haim-Munk syndrome. It differs from PLS in symptoms such as arachnodactyly, acroosteolysis and onychogryphosis¹³. Our patients had hyperkeratotic plaques only on the soles of both feet.

Another manifestation of PLS is premature loss of primary and permanent dentition due to progressive periodontitis¹⁰. Severe resorption of alveolar bone gives the teeth a "floating-in-air" appearance on dental X-ray film. Swelling of gums and severe periodontitis becomes evident in the first year of life itself, and loss of primary teeth occurs by the age of 3-4 years¹⁴. The periodontal inflammation subsides after exfoliation of the deciduous teeth. Our patients had gingival inflammation and tendency towards improvement after exfoliation of all teeth. The periodontitis in PLS is usually difficult to control. Effective treatment for the periodontitis includes extraction of the primary teeth combined with oral antibiotics and professional teeth cleaning. A course of antibiotics should be tried to control the active periodontitis in an



Fig. 10. Contrast-enhanced axial CT image show abscess formation (star) and subcapsular loculated fluid collection (f) in the right lobe in the liver (Case 3).

effort to preserve the teeth and to prevent bacteremia and subsequently pyogenic liver abscess^{7,14}. Treatment of periodontitis in our female patients was performed as mentioned above. However, the third one (Case 3) had not received any treatment for periodontitis. This may be one of the main causes leading to liver abscess in this patient.

The skin manifestations of PLS are usually treated with emollients. Salicylic acid and urea may be added to enhance their effects. Oral retinoids are the mainstay of the treatment of both the keratoderma and periodontitis associated with PLS¹⁵.

A rare finding in pediatric PLS cases is pyogenic liver abscess^{7,16-19}, which usually results from the seeding of the liver by pathogenic bacteria through a hematogenous route. The most common etiologic agent is *S. aureus*, and most often a solitary abscess is found²⁰. In PLS, the risk of pyogenic infections increases due to immune dysregulation resulting from mutations in the cathepsin C gene²¹. Microbiological studies have demonstrated *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Treponema denticola*, and *Rhizopus oryzae* organisms, suggesting that many pathogens may be involved in the disease process²¹. One of our cases (Case 3) had liver abscesses, and *S. aureus* was isolated from the aspiration material. Unfortunately, he died in spite of broad-spectrum antibiotic therapy.

Recurrent infections are relatively common in PLS. An estimated 17% of patients present

with marked predisposition to a variety of usually mild infections like skin pyodermas²². A number of cases having infected skin lesions were reported^{2,10,23}. We did not observe these findings in our patients, but they may be seen in the days ahead.

In conclusion, a multidisciplinary approach is important in the diagnosis and care of patients with PLS. PLS should be kept in mind in children with teeth having a “floating-in-air” appearance, and palmoplantar examination must not be omitted in those patients.

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