

Papillon–Lefevre Syndrome: A Case Report with Review of Literature

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Abstract : papillon-Lefèvre Syndrome (PLS) Is A Very Rare Autosomal Recessive Disorder Characterized By Palmoplantar Hyperkeratosis And Severe Early Onset Of Destructive Periodontitis Leading To Premature Loss Of Both Primary And Permanent Dentitions. Here We Are Presenting Case Report Of Siblings Who Presented With Palmoplantar Hyperkeratosis And Aggressive Periodontitis.

Keywords: Papillon-Lefèvre Syndrome, Periodontitis, Palmoplantar, Hyperkeratosis, Cathepsin C

I. Introduction

The Papillon-Lefevre Syndrome Was First Described In 1924 As A Rare Autosomal Recessive Genetic Disorder By Two French Physicians Papillon And Lefevre.[1] Characteristically It Is A Diffuse Hyperkeratosis Of Palm And Soles With Severe Periodontitis. Prevalence Of 1-4 Cases Per Million And Carrier Frequency Of 2-4 Per 1000 Population Is Reported With Equal Male And Female Predilection And No Racial Predominance.[2] In Literature Various Terminologies Have Been Used For PLS; Palmar-Plantar Hyperkeratosis With Severe Periodontal Destruction Involving Both Primary And Permanent Dentition, Palmoplantar Keratoderma With Periodontitis, Keratoris Palmoplantaris With Periodontopathia, Hyperkeratosis Palmoplantaris With Periodontitis.[3] The Recently Identified Genetic Defect In PLS Has Been Mapped To Chromosome 11q14–Q21, Which Involves Mutations Of Cathepsin C .[4] Studies In PLS Patients Have Shown More Than 90% Reduction In Cathepsin C Activity. Despite These Advances In

Characterizing The Genetic Basis Of The Syndrome, The Pathogenic Mechanisms Leading To The Periodontal Involvement Remain Elusive.[5] An Impaired Chemotatic And Phagocytic Function Of Polymorphonuclear Leukocytes (Pmns) Has Been Described In Many Reports. In Contrast To The, Above Studies, However, Reported Normal PMN Chemotaxis. Few Reports Have Addressed Lymphocyte Function In PLS.[6]

Periodontal Effects Appear Almost Immediately After Tooth Eruption When Gingiva Become Erythematous And Oedematous. Plaque Accumulates In The Deep Crevices And Halitosis Can Ensur. The Primary Incisors Are Usually Affected First And Can Display Marked Mobility By The Age Of 3 Years. By The Age Of 4 Or 5 Years, All The Primary

Teeth May Have Exfoliated [7]. Treatment With Oral Hygiene Instructions, Scaling And Root Planing Has Been Reported Unsuccessful[8]. Non-Surgical Treatment Combined With Use Of Systemic Antibiotics 21-24 And Additional Periodontal Surgery Has Also Been Reported To Fail. Following Such Tooth Loss, The Gingival Appearance Resolves And May Well Return To Health Only For The Process To Be Repeated As The Permanent Dentition Starts To Erupt. The Majority Of The Teeth Are Lost By The Age Of 14–15 Years.[7,8,9] Generally The Patient Consults Dentist First Because Of Premature Teeth Loss And Associated Problems. This Clinical Report Describes Such A Rare Condition With Special Attention On Its Diagnostic Characterization, Various Treatment Options And Prosthodontic Rehabilitation.

The Purpose Of This Paper Is To Demonstrate Clinical As Well As Radiological Features Of Papillon Lefevre Syndrome.

II. Case Report

A 9-year old female, Syrian immigrants in Greece was referred to my pediatric dental clinic, complaining of loose teeth, red bleeding gums and oral malodour. The patient presented with de-pigmented hair, white-pink skin, nystagmus and palmoplantar keratosis with normal nails.



Figure 1 a-b; Showing missing anterior teeth with red inflamed

The family history revealed consanguineous marriage of the parents. The parents and other family members were not affected. Pregnancy and delivery were normal. The mother had noticed skin lesions on the palms and soles of the children when they were 5 months old. **Figure .1 a-b** Intraoral examination revealed that the patient had poor oral hygiene with most of his teeth mobile (grades I and II); the gingiva was oedematous, inflamed and bled profusely when examined. The panoramic view showed generalized advanced bone loss. It was found that the teeth numbers; 16,26,36,46,41,42,31,32 was presents, but 55,54,53,63,64,65,74,73,83,84,85 all are lost. Mobility was present in all the permanent teeth that were present. The gingiva in relation to the existing permanent teeth was red, soft, and edematous, with deep periodontal pockets and bleeding on probing. OPG of the patient showed severe alveolar bone loss in relation to the existing permanent teeth up to the level of the apical third of roots, giving the teeth a “floating in air” appearance. **Figure.2**

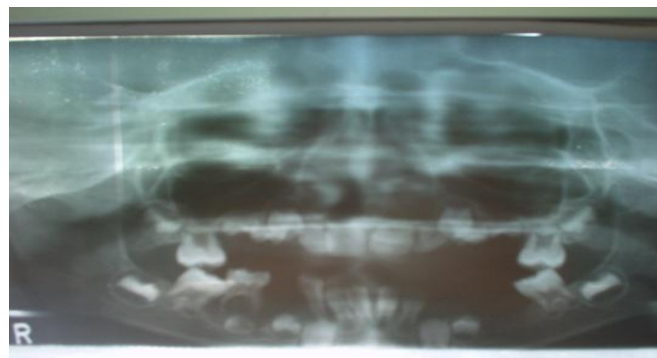


Figure 2: OPG showing severe loss of alveolar bone and teeth appear to be “floating in air.”

On extraoral examination, there were symmetrical, well-demarcated, keratotic, and confluent plaques affecting the skin of the palms and soles, which extended to the dorsal surface of the finger joints. The skin was dry and rough on palpation. The hair and nails appeared normal. **Figure .3,4**



Figure 3: Hyperkeratinization with keratotic plaque on the palmer surface of hand

The dermatologist prescribed an abdominal ultrasound and a skull x-ray; results from both examinations were normal with no hepatosplenomegaly and no dural calcifications, which are commonly found among PLS patients. The results from a complete blood count examination revealed an elevated erythrocyte sedimentation rate (ESR) count; (42 mm/h), suggesting an inflammation.



Figure 4: Keratotic plaque and hyperkeratinization of the palmar surface of feet

Treatment of the dermatology condition was conservatively planned, with emollients and keratolytics including salicylic acid; this postponed the use of oral retinoids including acitretin, etretinate and isotretinoin considering the patient's age and their side effects, such as hepatic and renal toxicity arising from the use of oral retinoids. As for dental care, we began by enforcing oral-hygiene related-habits; by teaching and encouraging the patient to brush his teeth and use mouth washes regularly. Full-mouth scaling followed by extraction of the painful mobile teeth was performed. Then, a combination of Augmentin (20–50 mg/kg/d) and Metronidazole (15–35 mg/kg/d) in divided doses was prescribed, every 8 h for 14 days, after which the patient was followed-up through monthly appointments.

In both case based on the history, clinical examination, and radiographic examination, a provisional diagnosis of Papillon-Lefèvre syndrome was made. For the conformation of the diagnosis, dermatological consultation was advised and blood samples were sent for genetic mapping. Result of the genetic mapping revealed For the conformation of the diagnosis, dermatological consultation was advised and blood samples were sent for genetic mapping. Result of the genetic mapping revealed abnormal gene at 11q14.1–q14.3 in both cases. This gene is commonly defective in patients with Papillon-Lefèvre syndrome, which confirmed the diagnosis of the case.

III. Discussion

PLS is an autosomal recessive inherited disorder, it means both parents will be phenotypically healthy and must carry the autosomal gene for the syndrome, no family history of the disorder except for the affected person and some siblings. PLS is suggested to be because of mutation in cathepsin C gene located on chromosome 11q14.1–q21 [10]. This cathepsin C gene encodes for cysteine lysosomal protease known as dipeptidyl-peptidase I. It removes dipeptides from amine terminals of the protein substrates. This gene is expressed in epithelial regions and in various immune cells like PMNLs, macrophages and their precursors. [11] In PLS, most severely affected regions are the keratinized gingivae of oral cavity, skin of palms and soles. Lysosomal protease enzyme plays an important role in maintaining the balance between oral microflora and immune system through protein degradation and proenzyme activation. Mutation in this enzyme lead to altered host response to pathogenic microorganisms in dental plaque. It is documented in literature that alterations in cathepsin C gene lead to pre pubertal periodontitis in PLS patients. [12] The characteristic dermatological lesions of symmetric palmoplantar keratosis of hands and feet including the dorsal surfaces of the extremities and others (elbows and knees) was first noticed at about the age of 2 years consistent with most reports in the literature. [1,5,7] These lesions have been reported to be more severe during cold weather as also evidenced in this case. [13] There was a positive history of manifestation of recurrent pyogenic skin infections since early childhood, a finding which was also demonstrated by Subramaniam et al. and could be attributed to the increased susceptibility to bacterial infections in these patients. Furthermore, the application of traditional ointment could also predispose the patient to recurrent skin infection and perhaps aggravated it. [14] Severe periodontal and alveolar bone destruction in children necessitates that a diagnosis should be reached to exclude any life-threatening disorders. These include leukaemia and neutropenias, where loosening of the teeth is an associated feature, along with extensive gingivitis, haemorrhage and ulceration. Other disorders where

premature loss of primary and/or permanent teeth occur include; hypophosphatasia, Langerhan's cell histiocytosis, Chediak–Higashi syndrome, acrodynia and acatalasia [15]. The patients discussed in this paper presented with prepubertal periodontal destruction with concomitant palmar-plantar hyperkeratosis diagnosed as PLS. Singh et al.[16] and Hattab et al.[17] attributed its etiology into three main factors which are reportedly responsible for the initiation and progression of this syndrome. These are inflammatory/immunology, microbiology, and genetic. An impairment of neutrophil chemotaxis, phagocytosis, and bactericidal activities accompanied by a decrease in natural killer cell mediated cell killing via myeloperoxidase deficiency and low integrin expression have been widely reported. In addition, there is functional impairment of the immunemediated mechanism of monocytic and lymphocytic cells to pathogens, depression of helper/suppressor T-cells ratio, elevation of serum IgG, and degenerative changes of plasma cells were identified. Furthermore, disruption of fibroblast and cementoblast function with defective periodontal ligament attachment and gingival epithelium has been observed the above mentioned have been widely reported in the literature as host contributory factor in the development of PLS.[16,17]

Another component of PLS may be radiographic evidence of intracranial calcification in choroid plexus and tentorium. Although this has been taken as cardinal feature, being inconsistent it is not considered important for the diagnosis. Histopathological examination reveals non-specific hyperkeratosis, acanthosis focal parakeratosis, psoriasiform hyperplasia, torturous capillaries in dermal papillae and superficial lymphocytic infiltration[18]

Immunologic, microbiologic, and genetic bases have been proposed. A decreased chemotactic and phagocytic function of neutrophils, myeloperoxidase deficiency, and low integrin expression has also been suggested as the possible pathogenesis. Capnophilic and facultatively anaerobic species mainly *Capnocytophaga* spp and *Streptococcus* spp, have also been demonstrated by microbiological studies[19]. Some previous case reports revealed that human herpes viruses (HSV) in concert with actinobacillus actinomycetemcomitans (AA) play an important role in the development of PLS periodontitis.[20]

Recently, the molecular basis underlying the etiopathogenesis of PLS has been established. A genetically demonstrated loss-of-function mutations affecting both alleles of the lysosomal protease CTSC gene in patients with PLS and subsequent dysregulation of localized polymorphonuclear leucocytes in inflamed periodontal tissues has been confirmed.[9,13] The CTSC gene, which is located on chromosome 11q14.1-q14.3 has endopeptidase activity, a lysosomal protein and is expressed in epithelial regions commonly affected by PLS including palms, soles, knees, and keratinized oral gingival.[12,13] Furthermore, high levels of expression of this gene have been found in various immune cells including polymorphonuclear leukocytes, macrophages, and their precursors.[9,10] lysosomal protease enzyme plays an important role in maintaining the balance between oral microflora and immune system through protein degradation and proenzyme activation. Hence, a mutation in this gene with consequent dysfunction of this enzyme leads to the altered host response to pathogenic microorganisms in dental plaque and periodontal pocket. It is documented in the literature that alterations in CTSC gene lead to prepubertal periodontitis in PLS patients.[21]

Gelmetti reported that retinoid therapy could positively influence the development of normal dentition in Papillon Lefevre Syndrome, if it is started during the eruption of the permanent teeth, and suggests that this result can be maintained for a long time even after stopping therapy.[22] Treatment consisted of extractions of periodontally involved teeth under antibiotic cover and treatment with etretinate resulted in a marked improvement of the palmar and plantar skin lesions.[23,24]

A multidisciplinary approach is important for the care of patients with PLS. The skin manifestations of PLS are usually treated with emollients. Salicylic acid and urea may be added to enhance their effects. Oral retinoids including acitretin, etretinate and isotretinoin are the mainstay of the treatment of both the keratoderma and periodontitis associated with PLS. Treatment may be beneficial if it is started during the eruption and maintained during the development of the permanent teeth.[23,24,25] 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 prevent bacteremia and subsequent pyogenic liver abscess. The risk of pyogenic liver abscess should be kept in mind in evaluating these patients when they present fever with unknown origin.[1,7,24,25] Because of the involvement of several structures a multidisciplinary approach is required in the management of patients with PLS. Patients were referred to the dermatologist for cutaneous lesion. For periodontitis, both the patients were prescribed appropriate antibiotics with 0.2% chlorhexidine gluconate mouth rinse and the patients were educated about importance of oral hygiene. Extraction of the mobile teeth with severe periodontitis was advised and the patients were referred to the prosthodontics for prosthesis fabrication. Presently patients are undergoing planned dental extractions with periodontal therapy & are kept on regular follow-ups.

Good dental care with the use of prophylactic antibiotics aims to minimize periodontitis and the loss of teeth by eradication of *A. actinomycetemcomitans* and *Capnocytophaga*. Alternatively, synthetic retinoids can be used for this purpose.[28]

Most patients end up losing all their teeth at an early age and are pretentied with prosthetic problems posed by severely atrophic thin alveolar ridges. Preprosthetic surgical techniques have been introduced as to aid retention and stability of dentures. Alternatively, dental implants that offer not only considerably better stability and retention of prosthesis but also improved comfort and masticatory efficiency along with satisfactory aesthetics are available. The use of titanium implants in patients with severe periodontitis has been reported, and the results indicate that periodontally compromised patients can be successfully treated using this method.

IV. Conclusion

Papillon Lefevre syndrome is an uncommon inherited disorder which shows both cutaneous and oral involvement affecting the social well-being of the patient. The dental surgeons and the der-matologist should be aware of this unusual entity so as to diagnose and manage promptly and accordingly. Combined cooperation from dermatologists, pediatrician, periodontists, and prosthodontists is critical for the overall care of patients suffering from PLS, which although a very rare condition, can lead to long-lasting psychological and social trauma to the growing patient.

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