Papillon-Lefèvre syndrome with albinism: A review of the literature and case report

MA Abu Al Ghanam¹*, MA Al Khawalde²

Abstract

Introduction
Papillon-Lefèvre syndrome is a rare autosomal recessive condition characterized by palmoplantar keratoderma and severe early onset of periodontitis. The palmoplantar keratoderma typically has its onset between the ages of 1 to 4 years. This article discusses cases of Papillon-Lefèvre syndrome with albinism.

Case Report
The first report of concurrence of Papillon-Lefèvre syndrome and type 1 oculocutaneous albinism in 2 brothers was described in previous literature in the year 2005. Albinism, derived from the Latin word ‘albus’, meaning ‘white’, is a group of inherited disorders in which melanin biosynthesis is reduced or absent. Several genes have been found to be responsible for albinism.

Conclusion
We hope that our report will aid in further investigation concerning PLS and the association between such variations and mutations of the CTSC causative gene.

Introduction
Papillon-Lefèvre syndrome (PLS) is a rare autosomal recessive condition characterized by palmoplantar keratoderma and severe early onset of periodontitis¹ described for the first time in the year 1924 by the French scientists Papillon and Lefèvre.

PLS is estimated to have a frequency of 1 to 4 occurrences per million individuals and greater than 300 cases have been reported worldwide⁵.

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Boys and girls are equally affected, with no racial predominance. The palmoplantar keratoderma typically has its onset between the ages of 1 to 4 years. The sharply demarcated, erythematous, keratotic plaques involve the entire surface of the palms and soles, sometimes extending onto the dorsal surface of the hands and feet²³.

The second major feature of PLS is severe periodontitis, which usually begins at the age of 3 or 4 years. The development and eruption of the deciduous teeth proceed normally, but their eruption is associated with severe gingival inflammation. The gingiva is bright red, oedematous, and bleeds easily. The periodontal pockets rapidly deepen, with severe loss of alveolar bone and marked fetor oris⁵⁶.

The aggressive inflammatory periodontal process then repeats itself after the eruption of the permanent teeth. In general, all or most of the permanent dentition is lost during the teenage years.

Conventional periodontal treatment usually fails in patients with PLS. To preserve alveolar bone, early extraction of periodontally involved permanent teeth has been considered as a mode of treatment⁶⁷.

Etiology and pathogenesis
Genetic
PLS is an autosomal recessive disorder. Recently, a few research groups have reported that loss of function mutations of the lysosomal protease cathepsin C gene (CTSC) are associated with PLS as well as other related conditions⁶⁷.

Immunologic
Another important etiologic factor is an alteration of the host defence owing to decreased function of lymphocytes⁸, polymorphonuclear leukocytes or monocytes⁵.

Microbial
Gram-negative microbial polysaccharides are generally recognized to be primary factors in the etiology of periodontitis, including periodontitis in PLS¹⁰⁻¹¹. Function tests showed reduced response to Staphylococcus species and Actinobacillus actinomycetemcomitans. Presence of virulent gram negative anaerobic pathogens were found at the site of lesion (plaque/periodontal pockets), such as Bacteroides gingivalis, Capnocytophaga species, spirochetes and Actinobacillus actinomycetemcomitans. Of all the pathogens, A.actinomycetemcomitans constituted more than 50% of the total colony-forming units¹¹.

There are also numerous virulence factors present, such as leukotoxin, collagenase, endotoxin, epitheliotoxins and a fibroblast-inhibiting factor, suggesting that PLS is mediated bacteriologically and therefore could be treated to show some improvement with antibiotics¹².

Variation in the clinical presentation of PLS has recently been observed. Willett et al. described a case with mild, late onset of periodontitis and early onset of palmoplantar hyperkeratosis¹３. Brown et al. presented 3 cases in which periodontal inflammation was relatively mild and both the periodontal and skin lesions were of late onset, starting around the third decade¹⁴.

The first report of concurrence of PLS and type 1 oculocutaneous albinism (OCA1) in 2 brothers was described in previous literature in the year 2005¹⁵.

Albinism, derived from the Latin word ‘albus’, meaning ‘white’, is...
a group of inherited disorders in which melanin biosynthesis is reduced or absent. Several genes have been found to be responsible for albinism. The current classification of albinism is determined by the affected gene, making the previously used terms, ‘partial or complete’ and ‘tyrosinase-positive or tyrosinase negative’ obsolete [16,17].

The gene for tyrosinase on chromosome 11q14-21 and the P gene on chromosome 15q11.2 are the most commonly affected genes; mutations on these genes cause OCA1 and ocular cutaneous albinism type 2 (OCA2), respectively.

Individuals with OCA1 typically have white hair at birth. Some individuals with a ‘leaky mutation’ (OCA1B) develop some melanin pigment in their eyelashes and hair over time, whereas others with OCA1A fail to develop any melanin pigment in their hair, skin or eyes during their lifetimes. Those with OCA2 are typically born with blond or red hair [18].

We report another case of PLS with albinism (OCA1).

**Case report**

A 10-year old male was referred to our periodontal clinic at Prince Hashem hospital, one of the Royal Medical Services hospitals of Jordan, complaining of loose teeth, red bleeding gums and oral malodour.

The patient presented with depigmented hair, white-pink skin, nystagmus and palmoplantar keratosis with normal nails (Figures 1, 2 and 3).

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 (Figure 4).

The dermatologist prescribed an abdominal ultrasound and a skull x-ray; results from both examinations were normal with no hepatospleno-megaly 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.

Ophthalmic examination showed that the patient had nystagmus, translucent irises and 6/18 and 6/24 level of visual acuity for both the right and the left eye, respectively.

The patient was the outcome of a full-term normal pregnancy, whose parents were related and had three other daughters and two other sons; none of them were affected with this condition, but our patient.

Treatment of the dermatologic 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 [19].

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 d, after which the patient was followed-up through monthly appointments.
Case Report

Discussion

The concurrence of two rare, recessive genetic conditions invites genetic investigation. Most possible explanations require that the underlying genes responsible for the two conditions should be located very close together on the same chromosome.

In the year 1989, mutations in the tyrosinase gene at chromosome 11q14.3 were identified as the cause of OCA. The genetic cause of PLS was identified only in the year 1999; Toomes et al. identified the genetic cause of PLS as a result of loss-of-function mutations in the CTSC. Mutations in the CTSC interestingly, also result two other closely related conditions, the Haim-Munk syndrome and pre-pubertal aggressive periodontitis.

Haim-Munk syndrome is also known as Cochin Jewish disorder or congenital keratosis palmoplantaris. It is characterized by red, scaly and thick patches of skin on the palms of the hands and soles of the feet (palmoplantar hyperkeratosis) that are apparent at birth along with frequent pus producing (pyogenic) skin infections, overgrowth of the fingernails and toe nails (onychogryphosis) and degeneration of the gums and bone surrounding the teeth (periodontosis) beginning in childhood.

PLS should be differentiated from other conditions showing similar oral or cutaneous clinical features. Diseases with oral manifestations such as acrodermatitis, hypophosphatasia, histiocytosis X, leukaemia, cyclic neutropenia and Takahara’s syndrome are associated with periodontitis and premature loss of teeth. PLS is differentiated from these other conditions 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 periodontal disease.

Combined co-operation from the dermatologist, the paediatrician and the dentist is critical for the overall care of patients suffering with PLS.

The conventional treatment of keratoderma was based on administration of anti-inflammatory emollients and keratolytic agents, such as topical steroids and salicylic acid. It was not until the development of retinoids in the early 1970s that the possibility of controlling PLS became promising. Etretinate, which is the ethyl ester of acitretin, an aromatic retinoid related to both retinoic acid and retinal was reported to be effective in the treatment of some types of palmoplantar keratoderma. The usage of oral retinoids have been reported to be effective in some patients with PLS. After 8 weeks of oral acitretin (10 mg) administration, improvement with marked reduction of keratoderma was observed in some patients. Side effects encountered due to the prolonged administration of etretinate are angular cheilitis, dryness of the lips, hair loss, arthralgias, tendinous and ligamentous calcifications and tenotogenicity. However, Balci et al. recently reported that the use of oral retinoids in the treatment of PLS-associated palmoplantar keratoderma is not curative. Treatment of the dental component of PLS is aimed at eliminating the reservoir of causative organisms. Some authors have claimed good results after the extraction of all the deciduous teeth allowing the permanent successors to erupt into an altered microbiologic environment.

During the past decades, several studies suggesting treatment options for PLS have been published. Ulbro et al. proposed a mode of periodontal therapy for patients with PLS (Table 1).

There are controversial reports regarding the effectiveness of systemic antibiotics combined with mechanical and chemical periodontal methods for the treatment of the periodontal components of PLS (Table 2).

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

Most patients end up losing all their teeth at an early age and are presented 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.

Further investigation concerning PLS and the association between such variations and mutations of the CTSC causative gene.

### Table 1: Suggested Mode of Periodontal Therapy for Patients with Papillon–Lefèvre Syndrome

<table>
<thead>
<tr>
<th>Deciduous dentition</th>
<th>Permanent dentition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral hygiene instructions and prophylaxis every third month</td>
<td>Oral hygiene instructions and prophylaxis every third month</td>
</tr>
<tr>
<td>Teeth with advanced periodontal disease: extraction</td>
<td>Mouth rinses twice daily with 0.2% chlorhexidine gluconate Teeth with moderate periodontal disease (bone loss, &lt;30% of the root length; probing pocket depth, &lt;5mm): dental scaling</td>
</tr>
<tr>
<td>Teeth with advanced periodontal disease: extraction</td>
<td>Prophylaxis once every month</td>
</tr>
<tr>
<td>All teeth should be extracted at least 6 months before eruption of the first permanent tooth; antibiotics should be given for 2 weeks after extraction</td>
<td>Antibiotic treatment for 4 w; recommended antibiotics: amoxicillin (20-50 mg/kg/day) + metronidazole (15-30 mg/kg/day) in divided doses every 8 h</td>
</tr>
<tr>
<td>Recommended antibiotics: amoxicillin-clavulanic acid, 20-40 mg/kg/day, in divided doses every 8 h</td>
<td>Teeth with advanced periodontal disease (bone loss, &gt;30% of the root length; probing pocket depth, &gt;6 mm): extraction</td>
</tr>
</tbody>
</table>

### Table 2: Studies on Effectiveness of Systemic Antibiotics in Treatment of Papillon–Lefèvre Syndrome Oral Manifestations

<table>
<thead>
<tr>
<th>Authors, year of publication</th>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinanoff et al, 1986</td>
<td>Administration of tetracycline (250 mg thrice daily for 28 days) followed by erythromycin (400 mg thrice daily for 28 days)</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Glenwright and Rock, 1990</td>
<td>Treated a case with penicillin, tetracycline and metronidazole at different times over 8 years</td>
<td>Ineffective</td>
</tr>
<tr>
<td>De Vree et al, 2000</td>
<td>Followed two Papillon-Lefèvre syndrome siblings for 15 years along with systemic metronidazole (250 mg four times daily for 5 days during periods of exacerbations)</td>
<td>Successful in maintaining a number of permanent teeth</td>
</tr>
<tr>
<td>Preus and Gjermo, 1987</td>
<td>Follow-up study period in two siblings receiving tetracycline intermittently (2-4 weeks) in periods of exacerbation and continuously during the last two years of the study</td>
<td>Successful treatment of periodontitis</td>
</tr>
<tr>
<td>Brown et al, 1993</td>
<td>Using tetracycline (250 mg four times daily for 3 weeks) combined with root planning and scaling</td>
<td>Favourable response</td>
</tr>
<tr>
<td>Eronat et al, 1993</td>
<td>Treated two cases (aged 7 and 9 years) with amoxicillin-clavulanic acid (augmentin) at a dosage of 1 g per day for 10 days every 6 months</td>
<td>No tooth loss was observed in either patient after more than two years of follow-up.</td>
</tr>
<tr>
<td>Bullon et al, 1993</td>
<td>Amoxicillin with clavulanic acid (500 mg thrice daily for 15 days) administered to a patient treated at regular intervals for 22 months</td>
<td>No response</td>
</tr>
<tr>
<td>Rüdiger et al, 1999</td>
<td>Using both amoxicillin and metronidazole (250 mg thrice daily for 10 days or 6 weeks) followed by supportive periodontal therapy every 3 to 4 months</td>
<td>Successful treatment</td>
</tr>
</tbody>
</table>

**Conclusion**

We presented a case of PLS and OCA1 concurrence, which manifested the typical features of these disorders in addition to common clinical features, and shared the same mutations of CTSC and tyrosinase genes. We hope that our report will aid in understanding and treating PLS and OCA1 better.

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Case Report

Abbreviations list
CTSC, cathepsin C gene; ESR, erythrocyte sedimentation rate; OCA1, type 1 oculocutaneous albinism; OCA2, type 2 oculocutaneous albinism; PLS, Papillon–Lefèvre syndrome.

Consent
Written informed consent was obtained from the patient for publication of this case study and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

References
34. Tinanoﬀ N, Tempro P, Maderazo EG. Dental treatment of Papillon–Lefèvre syndrome.

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Individuals with OCA1 typically have white hair at birth. Some individuals with OCA2, chromosome 15q11.2 are the most frequent genes, which melanin biosynthesis is reduced or absent. Several genes have been noted to be responsible for albinism.

Papillon–Lefèvre syndrome (PLS) is an autosomal recessive disorder of prepubertal periodontitis in 2 siblings with Papillon–Lefèvre syndrome (PLS). To preserve alveolar bone, early periodontal treatment is recommended. The palmoplantar keratoderma begins at the age of 3 or 4 years. The severe periodontitis, which usually begins on the palatal aspect of the dentition, tends to progress onto the dorsal surface of the palms and soles, sometimes extending onto the dorsal surface of the feet. Gingival inflammation is severe and associated with seeing gums and oral malodour.

The first report of concurrence of periodontitis and type 1 oculocutaneous albinism (OCA1) was described in 1970. In general, all or most of the permanent teeth have erupted and have been affected. Papillon-Lefevre syndrome may be progressive or rapidly deepen, with severe loss of alveolar bone.

There are also numerous virulence factors present, such as leukotoxin, chemotactic factors, proteases, lipases, and lipopolysaccharides. Presence of virulent gram negative anaerobic species, such as Actinobacillus actinomycetemcomitans. Of all the pathogens, Actinobacillus actinomycetemcomitans constituted more than 50% of the total microbial population in the gingival crevice.

Presence of virulent gram negative anaerobic species, such as Actinobacillus actinomycetemcomitans, was found in previous literature in the PLS. Enumerated factors include leukotoxin, chemotactic factors, proteases, lipases, and lipopolysaccharides. Presence of virulent gram negative anaerobic species, such as Actinobacillus actinomycetemcomitans, was found in previous literature in the PLS. Enumerated factors include leukotoxin, chemotactic factors, proteases, lipases, and lipopolysaccharides. Presence of virulent gram negative anaerobic species, such as Actinobacillus actinomycetemcomitans, was found in previous literature in the PLS. Enumerated factors include leukotoxin, chemotactic factors, proteases, lipases, and lipopolysaccharides.

In the PLS, the use of oral retinoids was postponed until the patient’s general condition was conservatively managed. Willett et al. described a case of PLS with albinism, which was followed-up through monthly appointments. In each case, a combination of augmentin was prescribed, every 8 h for 10 days. Then, a combination of augmentin and tetracycline was prescribed, every 8 h for 10 days. Thereafter, the patient was treated to show some improvement in periodontal parameters.

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