Case Report

Papillon-Lefevre syndrome: a rare case report and review of literature

白比隆—雷佛利症候群：一宗罕見病例報告及文獻綜述

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Papillon-Lefevre syndrome (PLS) is a rare genetically inherited autosomal recessive disorder. A 34-year-old woman presented with complaints of diffuse hyperkeratosis with scaling over both palms and soles with sclerodactyly of all fingers, increased sweating, loss of teeth with periodontitis and recurrent skin infections. History of first-degree consanguinity among the patients was present. Loss of teeth can be prevented by prompt administration of oral retinoids during the eruption of permanent teeth. Despite meticulous attention, many patients are still identified with PLS. Therefore, clinicians should be aware of this entity to avoid delay in diagnosis.

Keywords: Cathepsin C, hyperkeratosis, Palmoplantar keratoderma, Periodontitis, Pyoderma

Introduction

Papillon-Lefevre syndrome (PLS) is a rare autosomal recessive disorder characterised by periodontopathy, palmoplantar hyperkeratosis and severe early onset loss of deciduous and permanent dentition. It presents between the ages of one to five years and patients become edentulous by their early teens. The prevalence rate ranges from 1-4 cases per million individuals. Both men and women are affected equally without any racial or gender preponderance.

Multiple aetiological factors are implicated in the development of PLS. However, three main factors-
immunological, microbial and genetic factors are responsible for initiation and progression of PLS. Firstly, cellular immune defects with reduced phagocytic and chemotactic function of neutrophils, as well as other granulocytes are found in most of the patients. Secondly, pathogenic microorganisms such as *Actinobacillus actinomycetemcomitans*, *Capnocytophaga gingivalis*, *Fusobacterium nucleatum*, *Peptostreptococcus micros*, spirochetes and *Porphyromonas gingivalis*, act as the causative agents for periodontal problems in PLS.4 Another recently identified genetic defect in PLS patients is diminution in cathepsin C activity. The mutation in coding sequence of cathepsin C located on chromosome 11q14-q21 indicates PLS. The cathepsin C gene, also known as dipeptidyl-peptidase I, has endopeptidase activity. It is mostly expressed in the palms, keratinised oral gingiva, knees, and soles which are the most commonly affected areas in PLS. In addition, this gene is also expressed in many immune cells such as polymorphonuclear leukocytes, macrophages, and their precursors.3 Despite advances in characterising the syndrome, the pathogenic mechanisms involved in periodontal lesions still remain obscure. Various treatments including advice on oral hygiene, scaling, root planning, non-surgical treatment along with the use of systemic antibiotics, periodontal surgery have been tried but without success.3 We hereby report one case of PLS with the clinical characteristic features and a brief literature review.

**Case presentation**

A 34-year-old woman presented with complaints of skin thickening and fine scaling on the soles and palms with a foul smell, itching, and increased sweating since the age of two years. There was total loss of dentition and recurrent skin infections by the age of 10 years. History revealed similar complaints in her elder brother. History of first-degree consanguinity among the patients was present although both parents were healthy.

On clinical examination, diffuse hyperkeratosis with scaling was observed on both palms and soles extending over the margins and dorsa of the hands and feet (Figures 1 a-c). The presence of sclerodactyly of fingers of bilateral upper limb was also observed (Figure 1d). Oral cavity examination revealed loss of upper incisors and canines (left side) with periodontitis (Figure 2). Histopathological examination of epidermis showed hyperkeratosis, hypergranulosis, and acanthosis with regular elongation of rete ridges. Examination of the upper dermis showed a sparse lymphocytic infiltrate (Figure 3). These findings were consistent with palmoplantar keratoderma. Hence, the diagnosis of the PLS was made based on history, clinical, and histopathological features.

The patient was treated with oral isotretinoin 20 mg daily for one month together with 17% salicylic acid ointment. Systemic antibiotics were also given as advised by the dental department, along with dental advice. A significant improvement in hyperkeratosis and hyperhidrosis was observed after one month. Nevertheless, due to financial constraints, the patient stopped the treatment regimen and defaulted further follow-up.

**Discussion**

Papillon-Lefevre syndrome is generally considered as a manifestation of homozygosity of autosomal recessive genes. A 2.8-cm interval on chromosome 11q14 is mapped as a major gene locus for PLS. The mutational inheritance of cathepsin C gene is identified in homozygotes of PLS.6 Cathepsin C is one of the components required for T-cell activation. Recurrent pyogenic infection occurs due to neutrophil phagocytosis and impaired reactivity to T-cell and B-cell mitogens.7

Papillon-Lefevre syndrome generally starts in childhood with cutaneous lesions appearing with oral lesions. Cutaneous lesions, characterised by
Figure 1. (a) Diffuse hyperkeratosis with scaling over bilateral palms. (b) Diffuse hyperkeratosis with scaling soles extending over the margins. (c) Scaling extending over the margins and dorsa of feet. (d) Sclerodactyly of both hands.

Figure 2. Loss of teeth.

Figure 3. Hyperkeratosis, hypergranulosis, acanthosis with regular elongation of rete ridges with sparse lymphocytic infiltrate in upper dermis.
erythematous hyperkeratotic plaques, involve the entire surface of the palms and soles and sometimes extend onto the skin above the Achilles tendon and external malleoli (transgradiens). Hyperhidrosis of the palms and soles causes a foul smell. The psoriasiform plaques may also extend on to the elbows and knees and the condition may be associated with painful fissures, usually worsening during winter. The nails may also show transverse ridging and fissuring. Severe periodontitis and premature loss of primary and permanent dentition is also seen in PLS patients. All permanent teeth are usually lost between the ages of 14 to 16 years. The probable reasons of shedding of teeth are loss of alveolar bone, gingival infection, periodontal ligament destruction, and abscess formation. As a result of resorption of underlying alveolar bone, radiography shows a “floating in air” appearance of the tooth. The patient in this case also showed similar clinical and radiological characteristics. In addition to the oral and dermatological findings, there have been reports of decreased monocyte, lymphocyte or neutrophil function. In addition, pyogenic liver abscess, which is associated with impairment of immune system, has also been observed in a few cases.

The differential diagnosis includes three rare allelic variants of PLS: acrodynia, cyclic neutropenia, hypophosphatasia. However, this was not implemented in our study. The clinical features of muscle pain, insomnia, tachycardia, presence of erythrocytosis, psychological disturbances and premature teeth eruption along with dystrophic enamel differentiates PLS from acrodynia. The absence of palmoplantar hyperkeratosis differentiates cyclic neutropenia from PLS. The clinical features that differentiate hypophosphatasia from this disease include knock-knee, hypoplastic teeth, enlarged wrists, and phosphoethanolaminuria. Palmoplantar hyperkeratosis is not present in patients with cyclic neutropenia. Other conditions including Greither syndrome, keratosis punctate and Howel-Evans syndrome also can be included in differential diagnosis. Although palmoplantar hyperkeratosis may be present in these syndromes, periodontopathy is not observed in these cases.

Molecular genetic testing can be used to detect mutations in the Cathepsin C gene. This diagnostic service is available at specialised research laboratories. Genetic testing was not performed in this study due to low financial status of the parents. However, history, clinical, and histopathological features strongly supported the diagnosis of PLS. Furthermore, a consanguineous lineage has been defined for this syndrome. Similarly, in this case first-degree consanguinity was observed among the patients. Phenotypically, both the parents were healthy and no family history of this syndrome suggests an autosomal recessive genetic syndrome.

Patients with PLS should be managed with a multidisciplinary approach. Emollients, salicylic acid, and urea are involved in the treatment of skin manifestations. Oral retinoids including acitretin, isotretinoin and etretinate are mainly used to treat keratoderma and periodontitis. If the treatment is initiated before the onset of eruption of permanent teeth, normal dentition is expected for patients on treatment with retinoids. Treatment is more efficacious if it is continued during the development of permanent teeth. Shedding of the teeth can be delayed with advice on oral hygiene. A proper course of antibiotics should also be prescribed to preserve teeth, to control active periodontitis, to treat bacteraemia and pyrogenic liver abscess. Early extraction of infected teeth has also been recommended to avoid bone loss and allows protection of a solid base for implantation of artificial dentures. Furthermore, genetic counselling should also be given to the parents as well as caregivers of affected persons regarding the chances of passing the condition to their offspring.
Conclusion

Papillon-Lefèvre syndrome requires a multidisciplinary approach with dynamic participation of a dermatologist and dental surgeon. The current case report illustrates that continuous administration of isotretinoin along with salicylic acid and systemic antibiotics can improve the condition of the patient. Permanent loss of teeth can be prevented by prompt administration of oral retinoids during the eruption of permanent teeth. Despite meticulous attention, several patients are still identified with PLS. Therefore, prompt diagnosis and intervention is mandatory. A periodontist may be the first person to see and treat patients afflicted with unusual PLS, and therefore, greater awareness of this syndrome will be helpful in identifying more cases for further study. Hence, clinicians should be familiar with this condition to avoid delay in diagnosis.

References