Innovations

Papillon–Lefèvre syndrome – a case report and review of literature

Running title: Papillon - Lefèvre syndrome

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Received: 18 May 2022 A**ccepted:** 15 June 2022 **Published:** 30 June 2022

Abstract

Aim*: The aim of this paper is to briefly discuss about a 19-year-old male patient with Papillon-Lefèvre syndromewho also has an elder brother and a mother with similar condition and to enlighten the significance of eliciting family history, clinical examination, early diagnosis of oral complications such as premature exfoliation of teeth and severe periodontitis and proper management and follow up for a better quality of life.* ***Background:*** *Papillon-Lefèvre syndrome (PLS) is a rare, autosomal recessive inherited disorder which is characterized by palmoplantar keratosis, aggressive periodontitis, andpremature exfoliation of deciduous and permanent dentition. Numerous etiological factors namely genetic, immunological, or microbial are found to be associated with the syndrome. The incidence of PLS is found to be 1- 4/million with no sex and racial preponderance. In PLS, if both parents are carriers of the defective gene there is a 25% risk possibility for the children to be affected.* ***Method:*** *A thorough and a complete case history was obtained which includes the chief complaint, past medical and dental histories, family history, carrying out clinical and general examinations followed by advising the appropriate investigations namely, radiographic, biochemical, genetic, and histopathological and finally executing the custom-madetreatment for the patient wereperformed.* ***Conclusion:*** *Management of PLS requires a symptomatic and multidisciplinary approach with the help of a dermatologist due to cutaneous lesions and a dentist as both the dentition in the oral cavity are affected. This patient had undergone a complete evaluation performed by an oral physician who diagnosed the disorder, a periodontist who performed the periodontal treatment and a prosthodontist who provided an appropriate prosthesis for the patient. The patient was also referred to the dermatologist simultaneously for the cutaneous lesions.*

Keywords: *1.Aggressive periodontitis, 2.multidisciplinary management, 3.palmoplantar keratosis, 4.Papillon-Lefèvre syndrome, 5.PLS, premature exfoliation.*

Introduction

French physicians M.M. Papillon & Paul Lefèvre in 1924 described extensive trans gradient palmoplantar keratosis and premature exfoliation of primary and permanent dentitions in two siblings who were the off springs of a first-cousin mating. Later, this condition was coined as Papillon-Lefèvre syndrome (PLS), and more than 200 cases have been documented since then. (1,2)

PLS is inherited as an autosomal recessive disorder of keratinization, which is characterized by thickening of the palms and soles, redness, aggressive periodontitis which is caused by mutations in *cathepsin C* (CTSC) gene. The aetiology of PLS is not fully understood and it is believed to be either hereditary, acquired, or associated with other syndromes. In certain cases, PLS results from gene mutations on both the alleles of CTSC on chromosome 11q14.2, however most patients are homozygous for this mutation. Other clinical features include hyperhidrosis, arachnodactyly, intracranial calcification, increased susceptibility to infections, and even mental retardation reported in few patients. (2)

The skin lesions are in the form of erythema of the arms and soles most customarily precede keratoderma which later modify to unfold onto the dorsal surfaces, the Achilles tendon region and skin of the knees and elbows wherein they show up as psoriatic lesions. There is a tendency of recurrent pyogenic infections of the pores and skin (furuncles, gangrenous pyoderma) and abscesses of the kidney and liver, which is a result of Staphylococcus aureus and Escherichia coli.(3-7) Corsonwas the first person to describe about the intracranial calcifications, mainly seen across the cerebellar tentorium, falx cerebri and the choroid plexus of the lateral ventricle. (8) 25% of sufferers have an multiplied susceptibility to infections.(9) It is likewise conducive to greater common breathing and urinary tract infection. (10) There are some uncommon carcinomas reportedly associated with PLS, such as skin squamous cell carcinoma (SCC), malignant melanoma and albinism. (11-13)

The incidence of PLS is reported to be 1 - 4 per million as 2 - 4 people per thousand are found to be heterozygous for the gene causing PLS and thus becoming the carriers of this disorder. (14) There is no gender or geographic prediction of the disease reported in the literature. Higher frequency of occurrence reported in approximately 1/3rd of the cases in consanguineous offspring. (15)

Case report

A 19 year old male patient reported to the Department of Oral Medicine and Radiology at Saveetha Dental College and Hospital, Chennai with a complaint of missing teeth for the past 2 years. On probing further into the history it was reported that he had a normal eruption pattern of his deciduous teeth. At the age of four, there was a spontaneous mobility and exfoliation of all the deciduous teeth occurred. Concomitant with tooth exfoliation, he started developing itchy, scaly lesions on the palms and soles. He also revealed that the permanent teeth erupted at the appropriate age but at the age of ten, he developed mobility of permanent teeth also. First exfoliation of teeth started four years back with the mandibular anterior tooth and in two days the upper anterior teeth also exfoliated after a very mild trauma. The pattern of exfoliation according to the patient follows a pattern of eruption. The patient has been under dermatological care for skin lesions, but has not had any improvement.

On eliciting the family history, it was brought to our attention that the patient's parents have a consanguineous marriage and the patient has 2 elder brothers. The patient's mother and his second brother also reported to be present with the same conditions.

Clinical examination revealed bilateral hyperkeratosis of palms and soles seen as yellowish keratotic confluent plaques sparing other skin surfaces. Intraoral examination revealed generalized bleeding of gingiva on probing along with generalized gingival recession. Deep pockets measuring 7-8 mm were seen in 36,46,45,16,26. Multiple grade III mobile teeth were seen in 36,46,31,32,42,14,37,12 along with local factors. A periodontal abscess was noted in 46 measuring around 1*1 cm in size, pinkish red in colour with no pus or tenderness noted on palpation. (Figure 1)

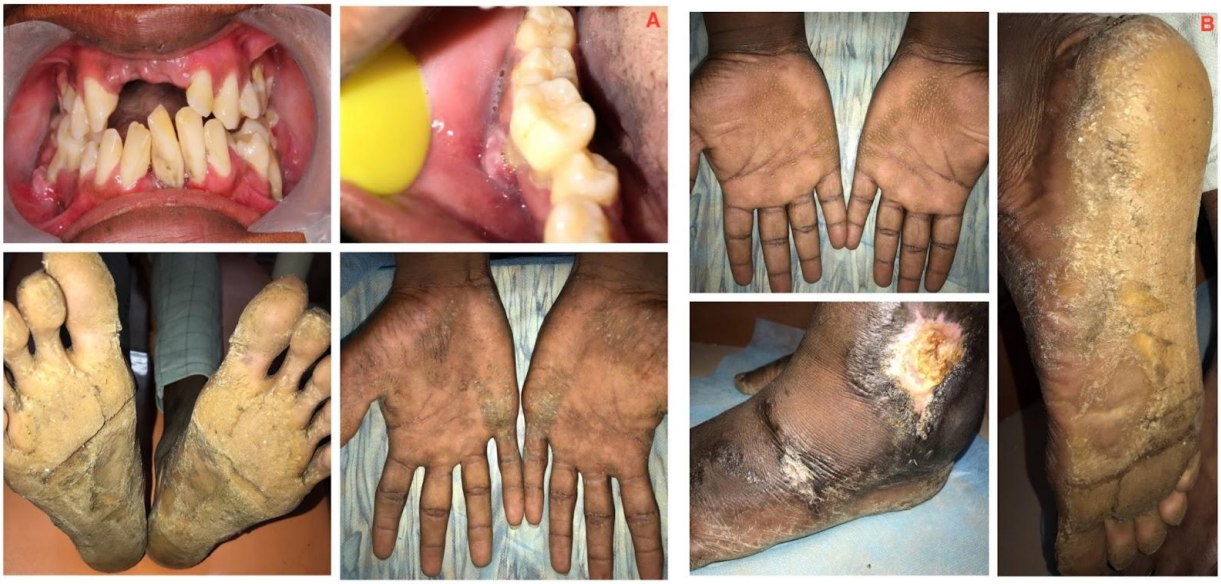

Figure 1: A (from right to left) - gingival abscess in relation to 46, intraoral frontal picture showing missing teeth, palmoplantar keratotic plaques in palms and soles of the patient. B (from right to left) - Palmoplantar keratotic plaques with crustation seen in the palms and soles of the patient's brother.

Investigations like routine hemogram, liver profile and radiographs were performed. Routine hemogram and liver function tests were all normal and within the limits. Panoramic imaging reveals missing teeth 11,12,21,41, tipping of 42,31 towards the midline, alveolar crest height below the CEJ level in all teeth with arch shaped bone loss suggestive of generalized vertical bone loss and ill-defined periapical radiolucency is seen in relation to 36,46 suggestive of periodontal abscess. (Figure 2)

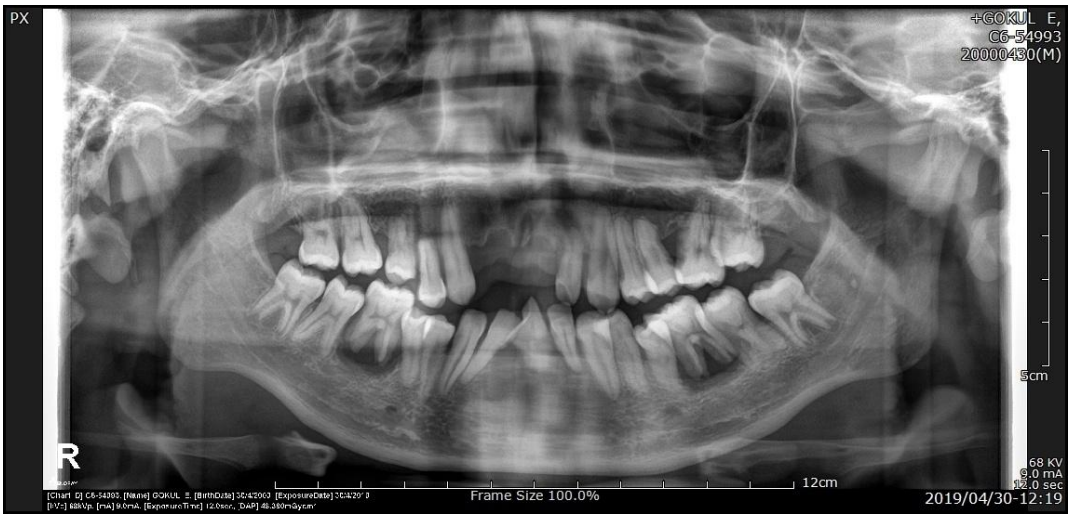

Figure 2: Panoramic radiograph of the patient prior to dental treatment.

The management of PLS requires a multidisciplinary approach. A team approach from a oral physician, oral surgeon, periodontist, prosthodontist and a dermatologist is required to improve the patient's quality of life. For this patient, complete subgingival scaling, root planning and flap surgery was performed in 16,26 and the teeth which had hopeless prognosis were extracted followed by removable prosthesis in the maxilla and mandible. (Figure 3) Patient was also advised to maintain oral hygiene and to be under regular follow - up.

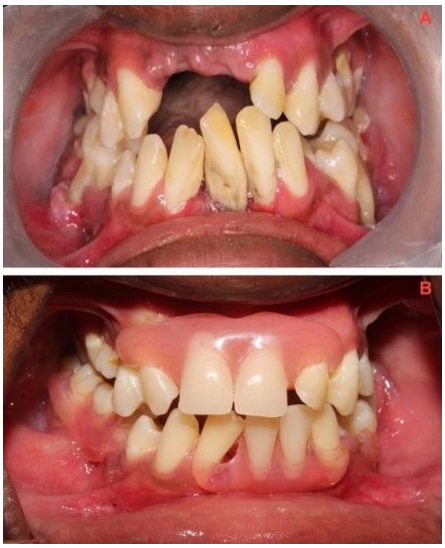

Figure 3: A - Preoperative intraoral picture showing aggressive periodontitis. B - Post treatment picture after extraction, periodontal management and removable prosthesis.

Discussion

Previous literature reveals that the prevalence of PLS have reported to be 1-4 cases/ million and the carrier frequency is 2-4/ 1000 individuals. There is an increase in the incidence noted in the Arabs and Indian population which highlights that our patients were all Indians and where from Tamil Nadu, the southern part of India. Till 2018, there have been more than 300 cases reported in the literature which are mostly reported by the dentists. (16) Consanguinity is a major etiological factor for PLS. In the pedigree analysis, it has been demonstrated that the patient's mother and second elder brother has PLS and the patient's first brother is a carrier of the PLS gene.

The PLS locus was discovered on chromosome 11ql4-q21 by Laass et al. (1997). (17) Later in 1999, two independent research groups discovered mutations in the gene linked to PLS and these have been linked to the loss of function of the cathepsin C enzyme, also known as dipeptidyl peptidase. (18,19) Cathepsin C (CTSC) is a lysosomal cysteine protease that partakes in a diverse variety of immune and inflammatory responses by activating an enzyme serine proteinases which is involved in the stimulation of phagocytic cells and T-lymphocytes, the activation of various inflammatory mediators and specific receptors, and the modulation of cytokine levels. CTSC gene expression was found to be high in a variety of immune cells and osteoclasts. (20) According to Rao et al. (1997), (21) the CTSC gene is normally expressed in epithelial regions that are frequently affected by PLS, such as the keratinized gingiva, palms, soles, and knee epidermis. According to Hewitt et al., a complete loss of function of CTSC is required for the aggressive periodontitis phenotype to manifest. Several mutations and polymorphisms in the CTSC gene have been identified in PLS gene polymorphisms from various ethnic groups. (21,22)

The dermatological management is to exfoliate enough callus to preserve function and relieve pain over pressure points caused by fissures and cracks. Treatments based on topical application of lubricants and keratolytic agents contained 5%-10% salicylic acid, 10% lactic acid, or 10% urea in a neutral base. Dermabrasion may aid in the penetration of topical agents into keratoderma lesions. (23) To seal painful fissures, gentian violet, Castellani's paint, or flexible collodions have been used. Retinoids are a group of drugs that include vitamin A and its natural and synthetic derivatives. Retinoids have been shown to improve skin cellular division and differentiation, cell surface alterations, immune defence, and wound healing. When applied topically, the skin's collagen deficiency is partially alleviated. Retinoids for topical use are available in cream, gel, and liquid forms. They work in tandem with topical antibiotics. Tretinoin was used to promote peeling of affected skin areas, but the treatment can irritate the surrounding skin. Oral retinoids have been shown to be effective in the treatment of a variety of keratinizing disorders, but long-term treatment is required. (24)

Periodontitis is a multifactorial disease characterised by the presence of numerous molecular species, including free radicals and reactive oxygen species (ROS). ROS are required in many metabolic pathways, but excessive production can cause cell damage. Oxidative stress occurs when ROS overwhelm the cellular antioxidant defence system, whether through an increase in ROS levels or a decrease in cellular antioxidant capacity. The first line of defence against microbial pathogens is neutrophils. (25) Periodontitis is caused by a failure to eliminate periodontal pathogens. Due to a lack of CTSC gene activity, neutrophil serine protease is deficient, resulting in a reduced ability of neutrophils to chemotaxis efficiently and an inability to generate neutrophil extracellular traps. This could explain the severe periodontitis seen in PLS. Hyperactive neutrophils produced more pro-inflammatory cytokines and had lower antimicrobial capacity. It also significantly contributes to oxidative stress and antioxidant deficiency. It is worth noting that, while systemic

immunodeficiency in PLS is relatively mild, with approximately 20% predisposed to recurrent infections, local periodontitis is extremely aggressive.

According to the current findings, PMN dysfunction is secondary to aggressive bacterial infection, which is influenced by the underlying loss of CTSC function and a deficiency in host defence mechanisms. The presence of virulent bacterial and viral infection in the periodontium, as well as the production of noxious enzymes and toxins such as leukotoxins, collagenase, proteases, endotoxin, and epitheliotoxin, indicates that PLS is bacteriologically mediated. (26) In our patient, periodontal management which includes subgingival scaling, root planning and flap surgery was done in relation to 16,26 followed by extraction of 31,36,42,46 as the teeth had poor prognosis to treatment. Later, the patient was given removable partial denture in the maxilla and mandible. The patient is under dermatologist supervision for cutaneous lesions.

Conclusion

Highlighting a rare case of Papillon-Lefèvre syndrome in a family presented with the cardinal clinical and radiographic features, and the sequence of progression which are important in identifying the disorder. A comprehensive management involving extraction, periodontal management and prosthesis was executed to this patient with regular follow up. The patient is also under management for cutaneous lesions by the dermatologist. The patient's brother and mother were also motivated to undergo the necessary dental and dermatological treatment to improve their quality of life.

Acknowledgement

The authors would like to thank the patient, his family and Saveetha Dental College and Hospital for all their help.

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