Papillon-Lefevre Syndrome Causing Social Stigma – A Case Report and Review

Smitha Rani Thada [1*], Keerthilatha M Pai [2]

[1]Reader (MDS), Department of Oral Medicine & Radiology, Manipal College of Dental Sciences, Manipal University, India
[2] Professor & Head (MDS), Department of Oral Medicine & Radiology, Manipal College of Dental Sciences, Manipal University, India

**** Corresponding Author:*** **Dr.Smitha Rani Thada,**
Flat no 204, Anand apartments, Karangalpady, Mangalore – 575003, Karnataka, India.
Mobile no – +919880813732 | Email: smitha.rani@rediffmail.com

Abstract

Background: Papillon-Lefevre syndrome is a rare autosomal recessive genetic disorder which is characterized by palmar plantar hyperkeratosis with precocious progressive periodontal disease that results in premature exfoliation of primary and permanent dentitions. Consanguinity of parents is evident in about one third of cases.

Context: Here we report a case of 22 year old male who presented with Papillon-Lefevre syndrome. The etiopathogenesis, investigations, differential diagnosis, complications and management of this syndrome are also discussed here.

Importance: It is a serious condition leading to social stigma as the individual suffering from this disorder often faces an edentulous state at a very early age. Early recognition and treatment especially with oral retinoids have shown promising results to some extent. However stem cell therapy can be expected to be a turning point in the dental treatment of such patients.

Key words: Aggressive periodontitis, palmar and plantar hyperkeratosis

Introduction

Papillon–Lefèvre syndrome (PLS) is characterized by keratosis palmoplantaris with periodontopathia. It is a rare autosomal recessive trait and parental consanguinity is demonstrated in 20 to 40% of cases.[1]PLS usually has its onset between 1 to 4 years of age. Males and females are equally affected without any racial predominance. Its prevalence is estimated to be 1 to 4 per million in the general population with a carrier rate of 2 to 4 per 1000.[1]

Case Report

A 22 year old male patient presented with a chief complaint of loosening of all his teeth since 10 years of age. He had to face social stigma since childhood because of the condition of his teeth. He had lost all his deciduous teeth by around 5-6 years of age and many of his permanent teeth were extracted due to mobility. Early loss and mobility of teeth hampered his psychological well-being and caused difficulty in speech, chewing and tooth brushing. Although he had undergone periodontal surgeries and replacement of the missing teeth, he was not satisfied with the results. He reported of consuming betel quid and alcohol to compensate his bad mouth odour. His medical history was non-contributory but his family history revealed that his parents had a consanguineous marriage. He gave no history of similar condition among his siblings or his relatives.

On general examination he was moderately built & adequately nourished. The most striking feature on extra oral examination was presence of symmetric, well-demarcated, yellowish, keratotic plaques over the skin of his soles and creases of his palms with areas of scaling of skin (Fig. 1). He reported of having developed fissures in skin of palms and soles when he was 10 years old that resulted in peeling off of skin leaving red thin skin underneath. His oral examination revealed poor oral hygiene with generalized gingival inflammation, recession & multiple periodontal abscesses (Fig. 2). He had multiple missing teeth with only 20 teeth (11, 12, 13, 17, 21, 22, 23, 28, 31, 32, 33, 35, 37, 38, 41, 42, 43, 44, 45, 47) present in his mouth having deep periodontal pockets and grade III mobility. Halitosis was significant. The fixed partial denture replacing missing teeth in the first and fourth quadrant were mobile.

OPG revealed multiple missing teeth and generalized severe interdental bone loss upto the apical third of the roots of all the remaining teeth, with increased spacing between the teeth. Fixed partial denture prosthesis were seen in the first and fourth quadrant. The mandibular left second molar showed a "Floating in space" appearance (Fig. 3). PA view of Skull showed no evidence of any calcifications of Falx cerebri. Routine haematological and biochemical investigations did not show any significant abnormalities except that the lymphocytes were slightly low (21.4%). Although the patient tested negative for HIV infection, his CD_3 and CD_4 counts were low.

The features of severe aggressive periodontitis associated with Palmo – Plantar keratosis prompted a clinical diagnosis of Papillon Lefevre Syndrome. The skin condition was confirmed by dermatologist as palmar plantar hyperkeratosis. Due to the severe periodontal destruction in all the teeth, it was decided to carry out total extraction and replacement with complete dentures.

Discussion

Papillon Lefèvre syndrome (PLS) was first described by two French physicians Papillon and Lefevre in 1924.[2] The disease is characterized by diffuse palmoplantar hyperkeratosis and juvenile periodontitis.[3] Palmoplantar hyperkeratosis usually manifests during first 4 years of life. The sharply demarcated erythematous keratotic plaques may occur focally, but usually involve the entire surface of palms and soles, sometimes extending onto the dorsal surfaces

of hands and feet.[3] Often, there is associated hyperhidrosis of palms and soles resulting in a foul-smelling odor.[4] Well-demarcated psoriasiform plaques occur on the elbows and knees. The findings may worsen in winter and be associated with painful fissures.[5]The second major feature of PLS is severe inflammation and degeneration of structures surrounding and supporting the teeth (periodontium), which starts at 3 or 4 years of age and affects both the deciduous and permanent teeth. It characteristically is unresponsive to traditional periodontal treatment modalities. Primary teeth frequently become loose and fall out by 4 years of age. After exfoliation, the inflammation subsides and gingiva appears healthy. However, with the eruption of permanent dentition the process of gingivitis and periodontitis is usually repeated and without treatment, there is subsequent premature exfoliation of permanent teeth. The teeth erupt normally but are soon lost, and by age of 14 years patients are usually edentulous, although the third molars are sometimes spared.[6] But in our patient all the remaining permanent teeth were so severely periodontally compromised that even after appropriate periodontal treatments we were not able to save any of his teeth for him. All of them had to be extracted and rehabilitated with prosthesis.

Etiopathogenesis –The genetic basis for most PLS appears to be mutations affecting both alleles of cathepsin C gene (CTSC), located on chromosome 11q14-q21 encoding a lysosomal protease in the interval between D11S4082 and D11S931.[7] The CTSC gene (11q14.2) spans 4.7 kb and is encoded by seven exons. CTSC also known as dipeptidyl peptidase I (DPPI) is a lysosomal exo-cysteine protease belonging to peptidase C1 family. It has four independent active sites each containing an essential cysteine within a papain-like domain. It coordinates for activation of many serine proteases in immune/inflammatory cells and it removes dipeptides from the free N-terminus of protein and peptides. It also encodes a polypeptide chain that folds into an exclusion domain, a propeptide, and two papain-like domains.[5]

CTSC is seen at high levels in polymorphonuclear leukocytes, alveolar macrophages, skin, kidney, and placenta, and at moderate or low levels in a variety of other organs. It plays a major role in the cleavage of some hormones like glucagon, gastrin and angiotensin II, and the activation of granule serine proteases from cytotoxic T lymphocytes, natural killer cells, mast cells (tryptase and chymase), and neutrophils (cathepsin G and elastase).[5]

Biochemical assays of cathepsin C indicate that germline missense and truncatingmutations in the gene encoding cathepsin-C are associated with PLS. Mutations appear to either affect the active site structure and/or cause problems in folding and aggregation of the CTSC[8] and this dramatically reduce its enzymatic activity. Seventy-seven distinct CTSC mutations have been identified, most of which are missense mutations that alter protein folding and function.[5] Heterozygous carriers of the mutation have approximately 50% of enzymatic activity, while subjects in whom both cathepsin C alleles are mutated (Homozygous) show less than 10% of normal activity in hydrolysis of the synthetic substrate glycylL-arginine-7-amino-4-methylcoumarin.[9] The majority of patients with PLS are reported to be homozygous for the same cathepsin C mutations inherited from a common ancestor and are recessive in nature. Parents and siblings are heterozygous for cathepsin-C mutations and they do not show either palmoplantar hyperkeratosis or severe early onset periodontitis characteristic of PLS.

PLS is caused by more or less complete loss of CTSC activity, but the phenotype is still somewhat variable, and may include only palmoplantar keratosis or only prepubertal perio-

dontitis. Thus, PLS should be part of the differential diagnosis of any individual or family presenting with either palmoplantar keratosis alone or severe early-onset periodontitis alone.[8]

In our case, genetic testing could not be performed to identify the gene mutation because of his low economic status, but dermatological, periodontal, and radiological features strongly suggested the diagnosis of PLS. Moreover, consanguineous descent was also reported by our patient. Phenotypically, the parents were healthy and there was no family history of the disease, suggesting an autosomal recessive pattern of inheritance.

Despite these advances in characterizing the genetic basis of the syndrome, the pathogenic mechanisms leading to juvenile periodontitis is not well understood but is now thought to be related to an abnormal immune system and to invading bacteria in the cementum of the teeth. Various immunologic defects have been described. Fifty percent of patients are immunocompromised showing decreased neutrophil, lymphocyte or monocyte functions.[7] The Major Histocompatibility Complex (MHC) loci span nearly 3.6 Mb, and contains the most polymorphic human genes, with strong linkage disequilibrium. CTSC deficiency in PLS results in decreased peripheral T lymphocyte subpopulation (CD3+ CD4+), and hence show an increased susceptibility to recurrent suppurative infections which is also reflected in our case. MHC products, known as Human Leukocyte Antigens (HLA) class I (A, B and C) and class II (DP, DQ and DR), play a key role in antigen presentation to T-cells during elicitation of adaptive immune responses. Several works have attempted to associate HLA alleles with PLS and severe periodontitis, but showing no particular association of HLA alleles with PLS. However one of the study [8] showed the association of the HLA-DRB1*11 allele with this syndrome and another study showed PLS individuals were deficient of serine proteinases in polymorphonuclear neutrophils (PMNs). Serine proteinases and serine proteinase-derived peptides are supposed to play an important role in the elimination of bacteria mediated by PMNs, the absence of protein and protein activity of serine proteinases found in the PLS patients could explain their predisposition to periodontal infections.[10]

Microbiological studies have demonstrated Actinobacillus actinomycetem comitans, Porphyromonas gingivalis, Fusobacterium nucleatum, and Treponema denticola organisms, suggesting that many pathogens may be involved in the disease process.[11] A. actinomycetem comitans plays a significant role in the pathogenesis and progression of the rapid periodontal breakdown seen in PLS.[12]

Other associated features and complications: Calcification of the falxcerebri and the choroid plexus, and retardation of somatic development are often associated feature.[13] It has been suggested that 20–25% of patients show an increased susceptibility to infections, of which otitis media is a common example.[13]Additional symptoms and findings may include frequent pyogenic skin infections, nail dystrophy, and hyperhidrosis.[14] Patients with PLS seem to be particularly predisposed to develop pyogenic liver abscess.[15] The investigations including radiographic analysis, complete blood count, liver function transaminase levels, total bilirubin, alkaline phosphatase, urine analysis along with clinical findings is usually sufficient to establish the diagnosis of PLS but however genetic testing will help in establishing the accurate diagnosis by differentiation from various other syndromes

associated with similar features.

Treatment: A multidisciplinary approach is important. Palmoplantar keratosis is usually treated with topical emollients. Salicylic acid and urea can be added to enhance their effect. The periodontitis in PLS is usually difficult to control, however, the disease may be arrested by combined mechanical and antibiotic periodontal treatment. Teeth with moderate periodontal disease must be treated with dental prophylaxis once a month along with systemic antibiotics (Amox + Metronidazole) for 4 weeks. Teeth that are highly mobile and those that are affected with severe periodontal disease must be extracted and in young patients extraction of the primary teeth 6 months prior to eruption of permanent first molars combined with oral antibiotics and professional teeth cleaning may help in preservation of permanent teeth. Oral hygiene instructions and prophylaxis every 3 months with use of 0.2% chlorhexidine rinses twice a day is equally important. And most importantly intensive maintenance therapy and microbiological monitoring and treatment of the infection with A. actinomycetemcomitans completes the effective treatment for PLS. Oral retinoids, such as acitretin, etretinate, and isotretinoin, have been reported to be beneficial in treating both the cutaneous and dental defects in Papillon-Lefevre syndrome.[14] An important point to note is that if retinoid therapy is started during the eruption of the permanent teeth, it can result in the development of normal dentition.[16] It is highly debatable whether implants should be used in PLS patients. On the one hand, impairment of the immune system in PLS patients puts the patients at risk of peri-implantitis and implant loss that cannot be controlled. On the other hand, in spite of every effort being made to prevent it, these patients often lose their teeth at an early age, which has orthodontic, physiognomic and hence, psychological consequences.[17]

Conclusion

Papillon Lefevre syndrome thus results in social stigma as the individual suffering from this disorder often faces an edentulous state at a very early age. Hence the recognition, identification, and clinical assessment of this condition is of great importance. Genetic counselling with a multidisciplinary treatment approach should be our prime objective.

Conflict of Interest: None declared.

References

1. Kaustubh Suresh T, Bhongade M L, Pretti C, Shweta K, Priyanka J, Somnath B. K.et.al. “Genetic Mapping in Papillon-Lefèvre Syndrome: A Report of Two Cases”. Case Reports in Dentistry, Volume 2013, Article ID 404120, 4 pages, http://dx.doi.org/10.1155/2013/404120.

2. Papillon MM, Lefèvre P. Two cases of family symmetrical keratoderma palmar and plantar (disease of Meleda) in the brother and the sister. Coexistence in both cases of serious dental deteriorations. Bull Soc Fr Dermatol Syphiligr. 1924;31:82–7.
3. Margi VB, Nilam AB, Vishal NS, Neeta VB. Papillon-lefevre syndrome: Case series and review of literature. J Indian Soc Periodontol. 2013 Nov-Dec; 17(6): 806–811. doi: 10.4103/0972-124X.124530.
4. Shahbaz AJ, Amor K. Papillon-Lefèvre syndrome: Case report and review of the literature. Dermatology Online Journal; 2004, 10 (1): 13.
5. Romero-Quintana JG, Frías-Castro LO, Arámbula-Meraz E, Aguilar-Medina M, Dueñas-Arias JE, Melchor-Soto JD. et.al. Identification of novel mutation in cathepsin Cgene causing Papillon-Lefèvre Syndrome in Mexican patients. BMC Medical Genetics 2013, 14:7, http://www.biomedcentral.com/1471-2350/14/7.
6. Hart TC, Walker SJ, Bowden DW, Hart PS, Callison SA, Bobby PL. et.al. An integrated physical and genetic map of the PLS locus interval on Chromosome 11q14, Mammalian Genome 2000, 11, 243–246.
7. Dhadke SV, Kulkarni PM, Dhadke VN, Deshpande NS, Wattamwar PR. Papillon Lefevre Syndrome. JAPI; March 2006, 54, p 246 – 247.
8. Hewitt C, McCormick D, Linden G, Turk D, Stern I, Wallace I.et.al. The Role of Cathepsin C in Papillon-Lefe`vre Syndrome, Prepubertal Periodontitis, and Aggressive Periodontitis. Human Mutation 2004, March 23(3):222 - 228.
9. Zhang Y, Lundgren T, Renvert S, Tatakis DN, Firatli E, Uygur C.et.al. Evidence of a founder effect for four cathepsin Cgene mutations in Papillon-Lefèvre syndrome patients. J Med Genet 2001;38:96–101.
10. De Haar SF, Jansen DC, Schoenmaker T, De Vree H, Everts V, Beertsen W. Loss-of-function Mutations in Cathepsin C in Two Families With Papillon-Lefèvre Syndrome are Associated With Deficiency of Serine Proteinases in PMNs. Human Mutation; Mutation in Brief #714 (February 2004) Online page 1-7.
11. Robertson KL, Drucker DB, James J, Blinkhorn AS, Hamlet S, Bird PA microbiological study of Papillon-Lefèvre syndrome in two patients. J ClinPathol 2001;54:371–376.
12. Nagaveni NB, Suma R, Shashikiran ND, Subba VR. Papillon-Lefevre syndrome: Report of two cases in the same family. J Indian SocPedod Prevent Dent - June 2008; 78-81. http://www.www.jisppd.com
13. Acun Kaya F, Seyfioglu Polat Z, Akuzumbaran E, Tekin GG. Papillon-Lefevre Syndrome-3 Years Follow up: A Case Report. International Dental and Medical Disorders ISSN 1308-1322, December 2008; 1(1): 24 – 28.
14. Dhanawade SS, Shah SD, Kakade GM. Papillon- Lefevre Syndrome with Liver Abscess. Indian Pediatr 2009; 46: 723 – 725.
15. Almuneef M, Khenaizan SA, Ajaji SA, Anazi AA. Pyogenic Liver Abscess and Papillon-Lefèvre Syndrome: Not a Rare Association. Pediatrics Vol. 111 No.1 January1, 2003 pp.e85-e88 (doi: 10.1542/peds.111.1.e85).
16. Anshu S, Soheyl S, Sanjeev KJ, Rajdeep B. Papillon Lefevre syndrome: Bridge between Dermatologist and Dentist. J ClinExp Dent. 2010; 2(1):e43-6.
17. Nickles K, Schacher B, Ratka-Kruger P, Krebs M, Eickholz P. Long-term results after treatment of periodontitis in patients with Papillon–Lefevre syndrome: success and failure. J ClinPeriodontol 2013; 40: 789–798. doi: 10.1111/jcpe.12120.

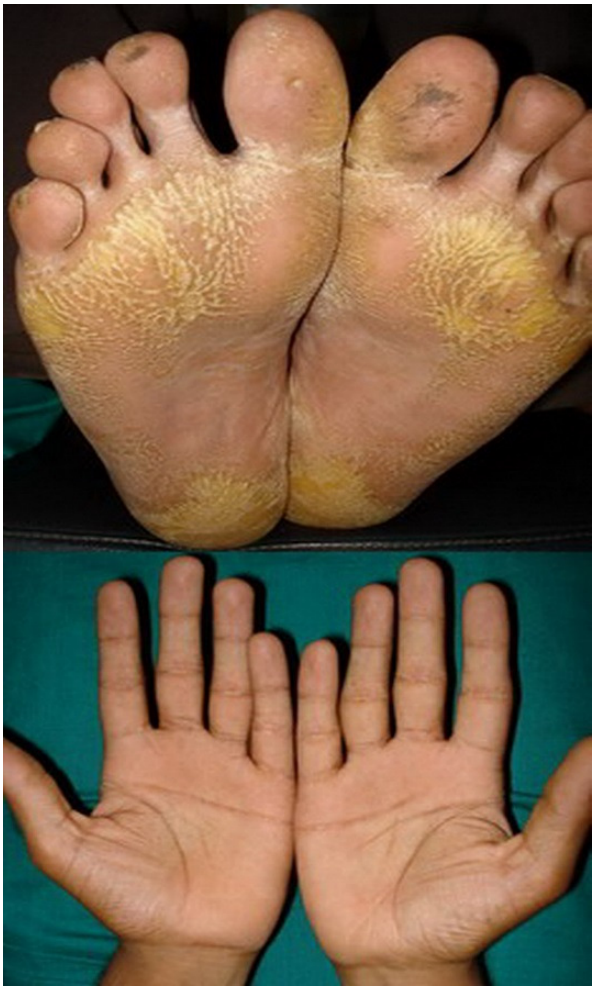

Figure 1: Palmoplantar keratosis appearing as symmetric, well-demarcated, yellowish, keratotic plaques over the skin of his soles and creases of his palms with areas of scaling of skin seen.

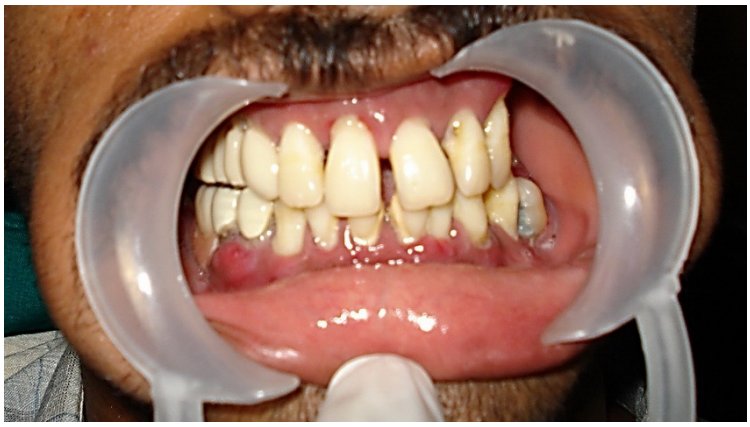

Figure 2: Generalized gingival inflammation, severe recession, spacing between all his teeth and multiple periodontal abscesses.

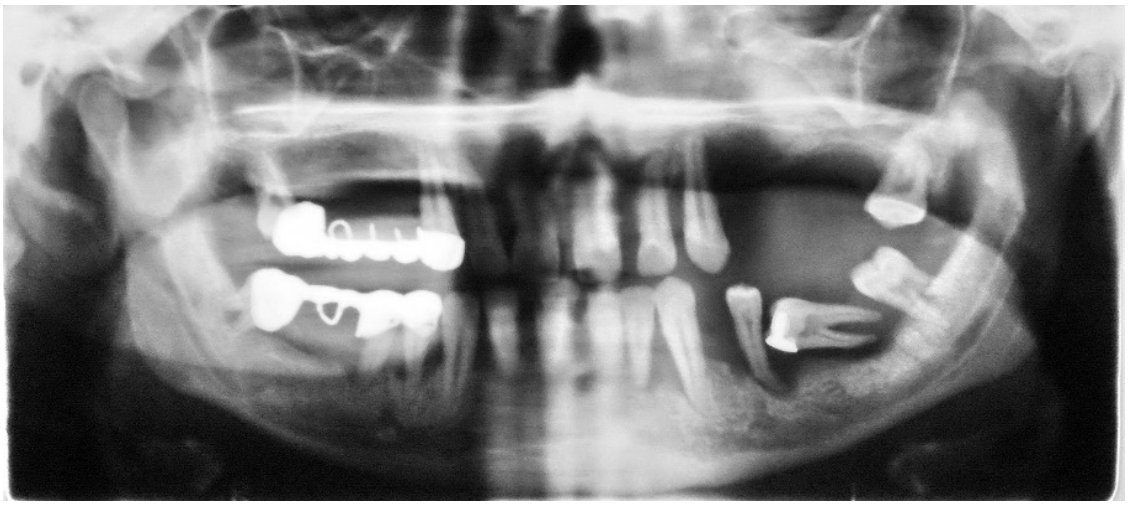

Figure 3: OPG revealed multiple missing teeth and generalized severe interdental bone loss till apical third of the roots of all the remaining teeth, with increased spacing between the teeth. Fixed partial denture prosthesis seen in the upper and lower right posterior region. "Floating of tooth in air" appearance of 37 was seen.