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Review article

Papillon-Lefèvre Syndrome. All about palms, soles and gums: a brief review

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Abstract

Papillon-Lefèvre syndrome (PLS) is an autosomal recessive disorder of keratinization characterized by palmoplantar keratoderma and periodontitis with subsequent loss of teeth. The exact etiology of the diseases remains to be unraveled. Nonetheless cathepsin C gene mutations may be involved. The present review focuses on the recent advances about role of cathepsin C gene in the causation of PLS and other disorders.

Introduction

Papillon-Lefèvre syndrome (PLS) is a rare autosomal recessive disorder affecting children between the ages of 1-4 years.[1,2] It was first described by two French physicians, Papillon and Lefèvre in 1924. With a prevalence of 1-4 cases/million, it equally affects both sexes without any racial predominance. PLS presents as diffuse palmoplantar keratoderma (PPK) and a rapidly progressive juvenile periodontitis with subsequent loss of both primary and secondary dentitions. The PPK usually appears between the ages of 1-4 years, is characterized by well-demarcated erythematous, keratotic plaques that usually involve the entire surface of the palms (**Figure 1**) and soles (**Figure 2**) and may transgress onto the dorsa of the hands and feet.[3] In advanced cases, achilles tendons may also be involved. Well-circumscribed psoriasiform plaques may occur on the elbows and knees.[4] A foul smelling odor may result from the hyperhidrosis of the palms and soles.[2] The aggressive periodontitis which affects both the primary and secondary dentitions, usually starts between the ages of 3-4 years.[4] The eruption of primary dentition is associated with gingivitis and subsequent periodontitis that leads to premature exfoliation of the dentition. Apparently, after exfoliation the gingiva appears healthy; but with the eruption of secondary dentition the whole process of inflammation and periodontitis is repeated with subsequent loss of the dentition (**Figure 3**). The patient is usually edentulous by the age of 15 years, but third molars may be spared.[5] The degree of skin involvement is not related to the level of periodontitis. Associated nail changes consist of dystrophy and transverse grooving.[6] An increased susceptibility to infections resulting in subsequent recurrent pyogenic infections of the skin is attributed to decreased neutrophil and lymphocyte functions.[7] The impairment of the immune function may also lead to recurrent pyogenic liver abcesses in PLS patients.[7] A radiographic evidence of intracranial calcification may also be noted in some patients.[8] Histopathology of the affected skin usually reveals hyperkeratosis, parakeratosis, acanthosis and perivascular infiltration of

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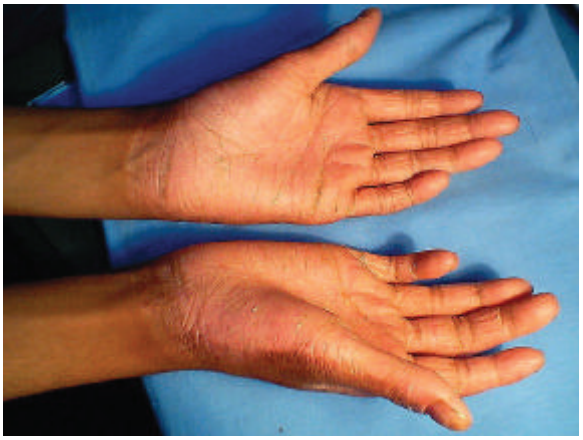

Figure 1 Diffuse palmar keratoderma in PLS.

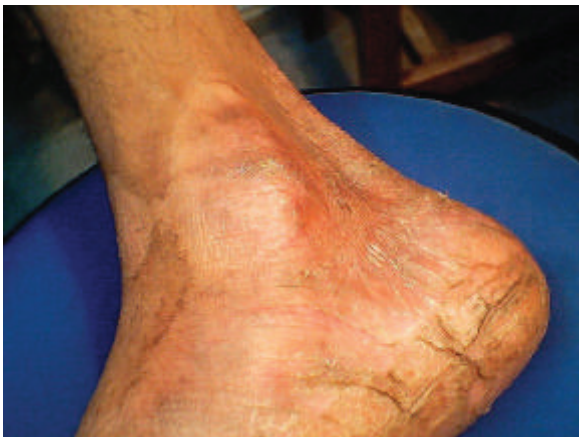

Figure 1 Diffuse plantar keratoderma with fissuring in PLS. The keratoderma is encroaching on the dorsum, as well.

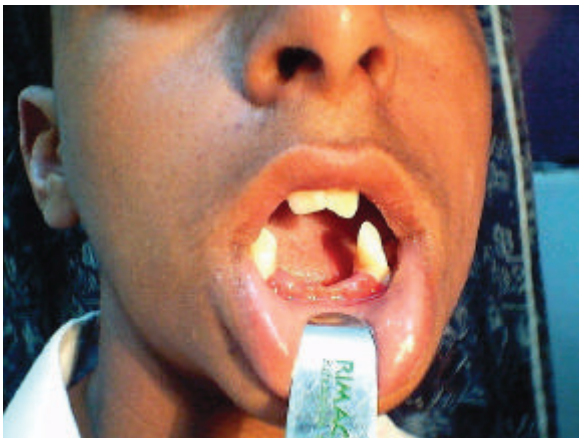

Figure 3 Loss of permanent teeth following periodontitis in PLS.

inflammatory cells.[9] A few cases of late onset variation of PLS without any underlying CTSC gene mutations have also been described in the literature.[10]

Cathepsin C gene mutations associated with PLS

The cathepsin C gene (CTSC) which is located on chromosome 11q14 encodes a cystein lysosomal protease that functions by removing dipeptides from the amino terminal of the protein substrate. Its main functions are thought to be protein degradation and pro-enzyme activation in addition to its immunological role.[11] It also has endopeptidase activity. The CTSC gene is over 46 kb long and consists of 7 exons and 6 introns.[12] The gene is expressed in epithelial regions that are usually affected by PLS including palms, soles, knees and keratinized oral gingiva. It is also expressed in polymorphonuclear leukocytes, macrophages and their precursors. Several mutations have been reported in the CTSC gene in individuals from diverse ethnic groups. The total number of mutations in the CTSC gene described to date is 41 with 17 mutations being located in exon 7. Although the etiology of PLS is not well-established, recently two research groups reported an association of PLS with loss of function mutations affecting both the alleles of the CTSC gene.[5,12] Interestingly, CTSC gene mutations have also been reported in Haim-Munk syndrome and prepubertal periodontitis. Severe early onset periodontitis is a common manifestation of all three disorders and they seem to be allelic variants. Approximately one-third of the families show consanguinity.[2] Moreover, all PLS patients are homozygous for the same CTSC gene mutations which are inherited from a common ancestor. Heterozygous carriers either do not show the

PPK or early onset periodontitis. The periodontitis and increased susceptibility to various infections has also been attributed to impaired immunity resulting from dysfunction in neutrophil motility and bactericidal function.

Other disorders associated with CTSC gene mutations

As mentioned earlier, two other rare disorders namely Haim-Munk syndrome and prepubertal periodontitis have also been found to be associated with CTSC gene mutations. Haim-Munk syndrome is an autosomal recessive genodermatosis that was first reported in 1965.[13] It is characterized by congenital PPK and progressive early onset periodontitis. Other features associated with Haim-Munk syndrome include arachnodactyly, acro-osteolysis, atrophic changes of the nails, and a radiographic deformity of the fingers. The cutaneous findings in this syndrome are reported to be more severe in contrast to PLS. A mutation of CTSC gene affecting a highly conserved amino acid residue has also been identified in Haim-Munk syndrome.[14] CTSC gene mutation has also been found to be associated with prepubertal periodontitis which is characterized by rapidly progressive form of early onset periodontitis resulting in the destruction of the periodontium of the primary and secondary dentitions. It may be localized or generalized and may present as an isolated disorder or as part of a recognized syndrome. Both the patterns of familial transmission have been described for prepubertal periodontitis.[14]

Treatment

Topical emollients with or without salicylic acid and/or urea are usually prescribed to treat the keratoderma of PLS symptomatically[7] but the mainstay of the treatment of both keratoderma and periodontitis are oral retinoids. If instituted early in the course of the disease, especially during the eruption of the secondary dentition, oral retinoids including acitretin, etretinate and isotretinoin could result in normal dentition.[15] It is no doubt a challenging task to treat the periodontitis but extraction of the primary dentition combined with oral antibiotics could help.[7,16]

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Pakistan Association of Dermatologists is holding its Silver Jubilee Conference at Karachi from 9th to 12th December, 2004. JPAD will publish a special issue on this historic occasion. Readers are requested to fully contribute about the achievements/challenges to dermatology in Pakistan, and history of and achievements by their departments. Manuscripts should reach the Editorial Office by 30th June, 2004.