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CASE REPORT

Papillon–Lefevre syndrome: Reporting consanguinity as a risk factor

Aasim Farooq Shah [a,*], Pradeep Tangade [a,1], Swatantra Agarwal [b,2]

[a] Department of Public Health Dentistry, Kothiwal Dental College & Research Centre, Kanth Road, Moradabad 244001, Uttar Pradesh, India
[b] Department of Prosthodontics, Kothiwal Dental College & Research Centre, Kanth Road, Moradabad 244001, Uttar Pradesh, India

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KEYWORDS

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Abstract Papillon–Lefevre syndrome (PLS) is an autosomal recessive genetic disorder characterized by palmoplantar hyperkeratosis associated with severe early-onset periodontitis and premature loss of primary and permanent teeth. This report describes two cases of PLS in 28-year-old female and 16-year-old male siblings with consanguineously married parents. The patients presented to the Department of Public Health Dentistry of a dental education and research institute in India with thickening, flaking, and scaling of the skin on the palms and soles of the feet. On oral examination, the female patient presented completely resorbed maxillary and mandibular alveolar ridges with retention of only the third molars. The male patient retained only teeth 18, 13, 28, 38, and 45. Based on complete histories and clinical examination findings, a final diagnosis of PLS was made and treatment was initiated using an interdisciplinary dental approach in both cases.

1. Introduction

Papillon–Lefevre syndrome (PLS) is a type IV palmoplantar keratosis (Papillon and Lefevre, 1924; Stevens et al., 1996). The etiology of PLS appears to be genetic in most cases, characterized by mutations affecting both alleles of the cathepsin C gene (CTSC) on chromosome 11q14. Most patients with this syndrome are homozygous for these CTSC mutations (Hart et al., 1999, 2000; Toomes et al., 1999). The disorder can be hereditary, acquired, or associated with other syndromes. PLS is autosomal recessive, and consanguinity has been demonstrated in 20–40% of patients (Kaya et al., 2008; Zhang and Lundgren, 2001). Several previous reports have described PLS in the children of consanguineously married parents (Khan et al., 2012; Varsha and Nilesh, 2010). Consanguineous marriage is a cultural practice with ancient roots, and 20% of the world's population currently lives in communities that prefer this form of marriage (Modell and Darr, 2002). Arab countries have the highest rates (20–50%) of consanguineous marriage in the world (Vardi-Saliternik et al., 2002).

In 1924, the French physicians Papillon and Lefevre described a condition characterized by palmoplantar hyperkeratosis, severe early-onset periodontitis, and premature loss of primary and permanent teeth in a brother and sister

* Corresponding author. Mobile: +91 9456910498.
E-mail addresses: dr_aasimshah@yahoo.com (A.F. Shah), ptangade@rediffmail.com (P. Tangade), drswatantra@yahoo.co.in (S. Agarwal).
[1] Mobile: +91 9997466339; fax: +91 0591 2452996.
[2] Mobile: +91 9837043736.

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(Ashri, 2008; Hattab and Amin, 2005). Frequent pyogenic skin infection, nail dystrophy, and hyperhidrosis are also commonly associated with PLS (Bergman et al., 1988). Patients with PLS also typically show the underlying disease associated with functional or quantitative neutrophil abnormalities, and 50% of patients are immunocompromised (Van-Dyke et al., 1984). PLS affects both sexes equally. The estimated prevalence of this syndrome is 1–4 per million in the general population, and its carrier rate is 2–4 per 1000 (Angel et al., 2002). Several other disorders, such as Feer's syndrome, palmoplantar ectodermal dysplasia, and Haim–Munk syndrome, have similar clinical features (Ashri, 2008; Singla et al., 2010). The present report describes two classical cases of PLS in a 28-year-old woman and a 16-year-old boy with consanguineously married parents.

2. Case reports

2.1. Case 1

A 28-year-old woman (Fig. 1c) presented to the Department of Public Health Dentistry, Kothiwal Dental College and Research Centre, Moradabad, Uttar Pradesh, India, with the

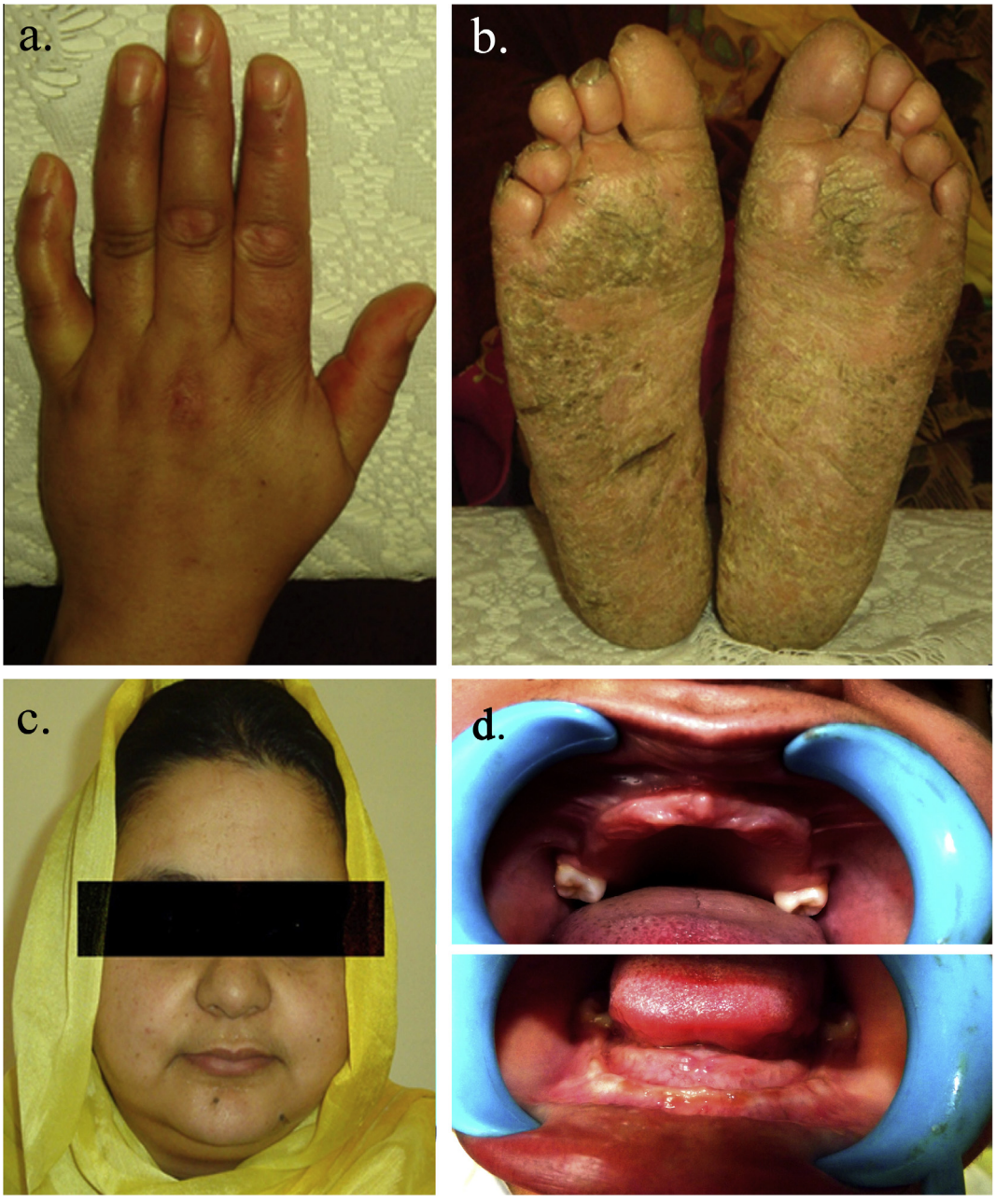

Figure 1 Colour slides of Case 1 (a & b) showing thickening, flaking, scaling, psoriasiform, erythematous, yellowish, keratotic plaques over the skin (c) presenting the facial profile (d) intraoral photograph revealing all third molars are present also the partially edentulous alveolar ridges with normal overlying mucosa.

chief complaint of premature loss of permanent dentition. She was the first child of healthy consanguineously married parents. Collection of a detailed family history revealed that the patient's grandparents were also consanguineously married and that her siblings exhibited similar clinical signs. The patient's dental history indicated that her deciduous teeth had erupted normally, but had exfoliated gradually by the age of 3–4 years. Her permanent teeth were also lost prematurely, soon after normal eruption. The patient also reported cycles of skin lesion exacerbation and remission and multiple infections since early childhood, resulting in regular visits to dermatologists. General examination showed persistent thickening, flaking, and scaling of the skin of the patient's palms and soles of the feet (Fig. 1a and b), associated with swollen and friable gingiva since the age of 4 years.

Symmetrical, well-demarcated, psoriasiform, erythematous, yellowish keratotic plaques covered the soles of her feet and extended onto the dorsal surfaces (Fig. 1a and b). Dystrophy and transverse grooving of the nails, more pronounced on the toenails than on the fingernails, was also present. The skin of the patient's left and right palms, elbows, and knees was exfoliating, and the underlying skin appeared red and shiny, suggestive of keratoderma.

Intraoral examination revealed retention of only the four third molars and complete resorption of the edentulous portion of the mandibular/maxillary ridge, with normal mucosa (Fig. 1d). None of the third molars showed mobility or was associated with gingival inflammation. An orthopantomograph confirmed alveolar resorption and the presence of only the third molars (Fig. 2).

Laboratory investigations, such as a complete blood count, blood chemistry profile, and liver function tests, produced results within normal limits. Immunological studies revealed low CD3+ and CD4+ counts. Based on the patient's history and clinical findings, PLS was diagnosed and consanguinity was proposed as a high-risk factor.

After explaining all possible treatment modalities to the patient, a treatment plan was initiated. Considering her sociodemographic and economic profile, treatment included the fabrication of full dentures. The maxillary third molars were not extracted to aid denture retention; the patient was advised to visit the clinic every 3 months for monitoring of these teeth.

2.2. Case 2

A 16-year-old male patient (Fig. 3c) presented to the Department of Public Health Dentistry of the Kothiwal Dental College and Research Centre complaining of esthetic problems and difficulty eating for 1 year due to the loss of permanent teeth. He was the brother of the patient described in case 1, the second child of healthy consanguineously married parents. The patient had a history of skin thickening and scaling on the palms and soles of the feet since early childhood. His past medical and dental history revealed frequent upper respiratory infection, early exfoliation of the deciduous dentition, and loss of all permanent teeth by the age of 14 years due to excessive mobility.

Physical examination revealed well-demarcated, yellow keratotic plaques on the bilateral palms and soles of the feet (Fig. 3a and b), extending onto the dorsal surfaces of the hands and feet. The patient's knees and elbows were also affected, but to a lesser degree than the palmoplantar surfaces.

Intraoral examination showed that teeth 18, 13, 28, 38, and 45 were present (Fig. 3d). The gingiva surrounding these teeth appeared normal, except for that around tooth 45, which exhibited grade I mobility. No other tooth showed mobility or was associated with gingival inflammation. Edentulous portions of the alveolar ridges were completely resorbed.

Hematological examination revealed a hemoglobin concentration of 10.0 g/dl, total leukocyte count of 9200 x 10^9/L, and erythrocyte sedimentation rate of 20 mm/h. Biochemical findings were within normal limits. Based on patient's history and clinical and laboratory findings, PLS was diagnosed and consanguinity was considered to be a high-risk factor.

Considering patient's sociodemographic profile, treatment included the extraction of tooth 45 and fabrication of dentures for resorbed alveolar areas. Teeth 18, 13, and 38, which were stable, were retained to aid denture retention. The patient was advised to visit the clinic at 3-month intervals for the assessment of tooth stability.

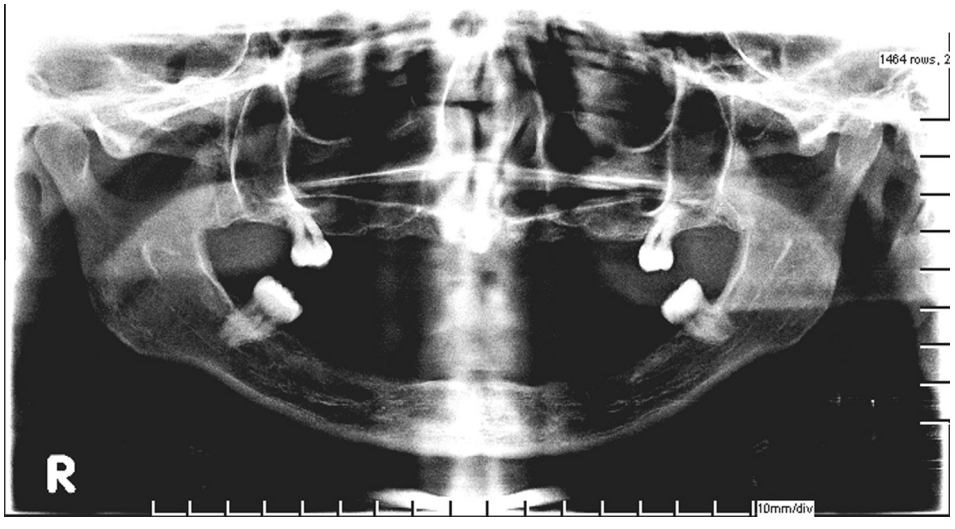

Figure 2 Radiograph (Orthopantomograph) of Case 1 showing edentulous alveolar ridges with presence of all third molars.

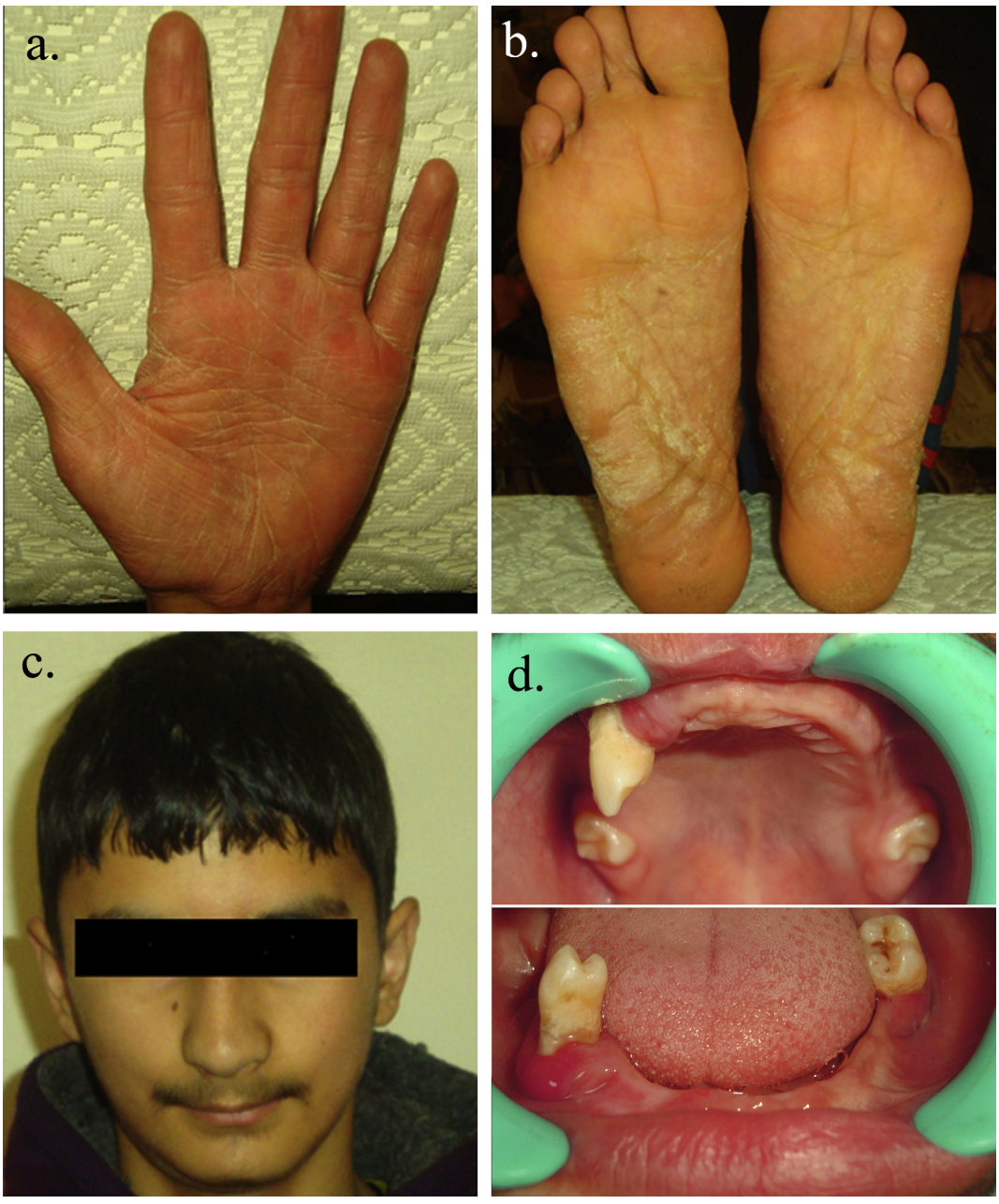

Figure 3 Colour slides of Case 2 (a & b) showing well-demarcated, yellow keratotic plaque on palms and soles (c) presents the facial profile of case 2 while (d) presents intraoral picture revealing presence of both maxillary and one mandibular third molars, upper right canine and lower right premolar with receded as well as inflamed gingiva, edentulous alveolar ridges with normal overlying mucosa can also be seen.

3. Discussion

PLS is a rare disorder with autosomal recessive inheritance, meaning that both parents of affected individuals are phenotypically healthy and a family history of the disease is lacking, except often in siblings.

Several authors have documented cases of PLS characterized by late-onset periodontitis and early-onset palmoplantar hyperkeratosis or, more generally, skin manifestations (Brown et al., 1993; Bullon et al., 1993; Willett et al., 1985). Numerous authors have also reported cases of PLS with clinical features similar to those described in the present report (Almuneef et al., 2003; Khan et al., 2012; Papillon and Lefevre, 1924; Varsha and Nilesh, 2010) and/or occurring in siblings (Angel et al., 2002; Bullon et al., 1993; Hattab and Amin, 2005; Sharma et al., 2013; Ullbro et al., 2003).

Three main factors have been proposed to underlie the initiation and progression of PLS: (1) impairment of neutrophil chemotaxis, phagocytosis, and bactericidal activities with decreased cell migration (Liu et al., 2000; Lundgren et al., 2005); (2) the presence of virulent Gram-negative anaerobic pathogens (*Actinobacillus actinomycetemcomitans*) in periodontal plaque and pockets (Bergman et al., 1988; González et al., 1997); and (3) a defect of immune-mediated mechanisms

involving reduced lymphocyte response to pathogens, decreased helper/suppressor T-cell ratio, poor monocytic function, elevated serum immunoglobulin G level, and degenerative changes in plasma cells (Pilger et al., 2003). The CTSC gene responsible for PLS is located on chromosome 11q14-21, where it encodes a lysosomal protease in the interval between D11S4082 and D11S931.

Patients with PLS always exfoliate deciduous teeth prematurely, after which gingival inflammation subsides and the gingiva appears healthy. However, gingivitis and periodontitis recur with the eruption of permanent teeth, often leading to premature exfoliation of all teeth except the third molars. Mercury intoxication (Feer's syndrome) may also cause premature loss of deciduous and/or permanent teeth, but it can be distinguished from PLS because it is characterized by red desquamation, often involving both extremities, erythrocyanosis, muscle pain, insomnia, sweating, tachycardia, and psychic disturbances (Singla et al., 2010). PLS can also be differentiated from other syndromes causing palmoplantar hyperkeratosis, such as Howel–Evans, Greither's, and Vohwinkel syndromes, as none of these conditions presents with periodontitis (Kaur, 2013).

In patients with PLS, routine blood investigations and liver function tests usually yield values within normative ranges. Neutrophil counts, lymphocyte counts, and/or monocytic function are decreased in some patients (Almuneef et al., 2003). Histopathological examination may reveal acanthosis, nonspecific hyperkeratosis, psoriasiform hyperplasia, focal parakeratosis, tortuous capillaries in dermal papillae, and/or superficial lymphocytic infiltration (Shah and Goel, 2007; Yagmur et al., 2004). Immunological function is occasionally impaired, likely due to insufficiency of cathepsin C, which is essential for granzyme B activation and natural killer cell activity; such impairment is usually associated with increased susceptibility to pyogenic skin infection (Lundgren et al., 2005; Meade et al., 2006; Ullbro et al., 2003).

Oral retinoids, such as acitretin, etretinate, and isotretinoin, have been reported to be beneficial in the treatment of PLS (El-Darouti et al., 1988; Lundgren et al., 1996). The initiation of retinoid therapy during permanent tooth eruption can aid normal development of the dentition (Bergman et al., 1988; Lundgren et al., 2005; Pilger et al., 2003; Vardi-Saliternik et al., 2002). Emollients are used to treat the skin manifestations of this syndrome. A multidisciplinary approach is always important for the care of patients with signs of PLS.

As described in a previous report, the incidence of PLS has increased recently (Singla et al., 2010). Because this syndrome involves permanent destruction of dentition, usually at an early age, dentists play an important role in diagnosis and treatment. Thus, dentists should be familiar with the etiology and management of PLS. Dermatologists and pediatricians can also help to save the permanent dentition of affected individuals through early diagnosis and prompt referral to dentists.

4. Ethical clearance

This work was approved by the Ethics Committee of Kothiwal Dental College and Research Centre Moradabad, India and informed written consent was acquired from both the patients separately after explaining to them the purpose of the discussion. All procedures followed the ethical principles and guidelines established under the Declaration of Helsinki.

Conflict of interest

The authors declare that there is no financial interest associated with the aforementioned materials/persons used within this study and declare no conflicts of interest.

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