Rare disease

Initial expression of the Papillon-Lefèvre syndrome in consanguine family

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A rare case of Papillon-Lefevre syndrome is discussed with clinicoradiological presentation. The purpose of the case report is to make the medical community aware of this rare syndrome and its association with consanguinity. Papillon-Lefevre syndrome is an extremely rare genodermatosis of autosomal-recessive inheritance which usually manifests itself between the ages of 6 months to 4 years characterised by diffuse palmoplantar hyperkeratosis (keratoderma), and rapidly progressive and devastating periodontitis, affecting the primary as well as permanent dentition. Papillon-Lefevre syndrome results from a combination of host and bacterial factors, including recessive gene, consanguinity, specific periodontal pathogens and lack of thorough oral hygiene. The present case report describes Papillon-Lefevre syndrome and its association with consanguinity in a 3-year-old girl.

BACKGROUND

Papillon-Lefevre syndrome (PLS) is a very rare syndrome of autosomal-recessive inheritance characterised by palmer–plantar hyperkeratosis and early onset of a severe destructive periodontitis, leading to premature loss of both primary and permanent dentitions. The prevalence of PLS is estimated to be 1–4 cases per million and about 300 cases have been reported worldwide, out of which only few cases had consanguineous parents.

The purpose of the following case report is to make the dentist aware of this very rare syndrome associated with Consanguine Family.

We would also like to emphasise the need to investigate the palmer–plantar hyperkeratosis, periodontopathic microflora, neutrophil function test, intracranial ectopic calcification, type 1 oculocutaneous albinism along with consanguinity when examining a case of severe destructive periodontitis.

CASE PRESENTATION**Complaint and history**

A 3-year-old girl reported with a chief complaint of early loss of teeth. Clinical history revealed that she had normal eruption of deciduous teeth at chronological age of 8–9 months. Left upper and right lower central incisors spontaneously exfoliated 2 months prior to the patient's reporting date.

Medical history was non-contributory. The family history revealed consanguineous marriage of the parents. The parents and other family members were not affected. Natal history revealed uneventful full-term pregnancy and delivery. The patient had normal physical and mental development with normal gait and speech.

Clinical assessment

Dermatological examination revealed dry skin with hyperkeratotic plaques present on palms and soles, also extending onto the dorsal surface of hands and feet. The skin lesions aggravated during cold weather and the patient experienced pain on walking. There was neither anomalous involvement of hair or nail nor any involvement of knee, elbow or pyogenic infection.

Intraoral examination significantly showed premature loss of left upper and right lower central incisors along with recession of gingiva in right and left upper lateral incisors. Gingival inflammation, deep periodontal pockets, mobility of teeth, deposits of plaque and halitosis were evident. Oral mucosa covering the edentulous region in relation to right upper and lower central incisors appeared normal while left upper central incisor region showed healing socket. Submandibular lymph nodes were not palpable.

INVESTIGATIONS**Radiological investigations**

Orthopantomograph showed generalised horizontal bone loss. Initial calcifications of permanent teeth were in accordance with normal developmental pattern.

Skull radiographs did not reveal any intracranial ectopic calcifications.

Laboratory investigations

Routine blood investigations and liver function tests, total bilirubin and alkaline phosphatase were found to be within normal range.

Serum immunoglobulin G (IgG) level was elevated while values of IgM, IgA were found to be within normal range.

Results of the neutrophil function test showed defective phagocytosis of *Candida albicans* and chemotactic activity of neutrophilic granulocytes.

Microbiological examination

Escherichia coli and *Streptococcus mitis* microflora was isolated from the plaque culture.

Histopathology

Owing to the patient's age, parents did not agree for biopsy, despite counselling.

DIFFERENTIAL DIAGNOSIS

The following differential diagnosis of osteolytic diseases was considered before arriving at a final diagnosis:

- ▶ Haim-Munk syndrome (HMS)
- ▶ Prepubertal periodontitis
- ▶ Takahara's syndrome
- ▶ Leukaemia
- ▶ Howel-Evans syndrome
- ▶ Keratoderma hereditarium mutilans (Vohwinkel's syndrome)
- ▶ Greither's syndrome

TREATMENT

Thorough ultrasonic scaling and curettage was carried out following which she did not turn up for follow-up.

OUTCOME AND FOLLOW-UP

Patient did not come for follow-up visit.

DISCUSSION

PLS, first described in 1924 by two French physicians Papillon and Lefevre, is an extremely rare genodermatosis of autosomal recessive inheritance.¹ It usually manifests itself between the ages of 6 months to 4 years characterised by diffuse palmoplantar hyperkeratosis (keratoderma), and rapidly progressive and devastating periodontitis, affecting the primary as well as permanent dentition.^{2 3}

Recently, variation in the clinical presentation of PLS has been observed namely parental consanguinity, ectopic calcification of dura, type 1 oculocutaneous albinism (OCA1), hyperhidrosis of palm and sole, mild mental retardation, frequent pyogenic skin infections and liver abscesses.^{2 4} Genetics have studied the PLS locus and mapped this to chromosome 11q14–q21, recently it was discovered that PLS patients have loss-of-function mutations in their Cathepsin C (CTSC) gene. This CTSC gene is involved in protein degradation and proenzyme activation.⁵

The development and eruption of the teeth in the PLS proceed normally but are associated with the periodontitis, which causes premature loss of deciduous and permanent teeth. The hyperkeratosis of the skin is known to be present in pressure areas such as palms, soles, knuckles, ankles, elbows and knees. The level of periodontal infection and the degree of dermatological involvement are not inter-related.^{6 7}

The present report describes a rare case of PLS in a 3 year-old girl born to consanguineous parents.

Oral manifestations of PLS appears between the ages of 6 months to 4 years, almost simultaneously with the

onset of palmoplantar hyperkeratosis, the degree of dermatological involvement may not be related to the level of periodontal infection.^{2 7}

The development and eruption of the deciduous teeth in PLS proceed normally. Usually, the teeth are normal morphologically although microdontia, root resorption and incomplete root formation are reported in a few cases. The eruption is associated with gingival inflammation and subsequent rapid destruction of the periodontium. The primary dentition usually exfoliates prematurely by the age of 4 years.⁶ After exfoliation, the inflammation subsides and the gingiva appears healthy.⁷ However, with the eruption of the permanent dentition the process of gingivitis and periodontitis is usually repeated and there is premature exfoliation of the permanent teeth, leading to complete loss of permanent dentition by adolescence.⁵

Rapidly progressive periodontitis is commonly associated with pathologically deep pockets, severe alveolar bone loss and teeth mobility, along with plaque accumulation, gingival abscesses, purulent exudates and halitosis.

PLS shows an association with complex subgingival flora including anaerobic and aerobic species of periodontal pathogens. *Capnocytophaga* and *Streptococcus* species including *Streptococcus constellatus*, *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus sanguis*, species of *Neisseria* and *Bacillus*, *Prevotella intermedia*, *Prevotella melaninogenica*, *Prevotella nigrescens*, *Peptostreptococcus* species, *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* are mainly seen but no particular periodontopathogen is invariably associated with PLS.^{5 8} However, in this case *E coli* and *S mitis* microflora was isolated from the plaque culture.

Human cytomegalovirus (HCMV), a herpes virus genomic sequence, detected by PCR identification, occurs with elevated frequency and also contributes to severe types of periodontal diseases including PLS.⁹ HCMV infection alters the immune control of resident microorganisms and is important in a multistage pathogenesis of periodontitis involving viral activation, periodontopathic bacteria and host immune responses. In this case, the PCR was not done to detect HCMV genomic sequence.

The sharply demarcated erythematous keratodermal plaques may occur focally, but usually involve the entire surface of the palms and soles, sometimes extending onto the dorsal surfaces of the hands and feet. It is often associated with hyperhidrosis of the palms and soles, resulting in a foul odour.¹⁰ Well-demarcated psoriasisiform plaques may be present on the elbows and knees.

Skin lesions may appear as white, light yellow, brown or red plaques; the findings may worsen in winter and undergo crustation, cracking, and painful deep fissuring. Infection may superimpose on the defective skin, resulting in the formation of abscesses.

Pyogenic liver abscess is increasingly recognised as a complication of PLS associated with impairment of the immune system. However, in our case, IgG level was elevated but finding of pyogenic liver abscess was not seen.

The exact cause of the periodontal disease and increased susceptibility to infection in PLS have not been found but it has been attributed to decrease neutrophil phagocytosis, bacterial infection and impaired reactivity to T-cell and B-cell mitogens.¹¹

Figure 1 Clinical picture showing premature loss of teeth.

Figure 2 Showing hyperkeratotic plaque on palms.

Figure 3 Hyperkeratosis on the dorsal surface of feet, soles and planter.

Nail changes are apparent in advanced cases of PLS characterised by as transverse grooving and fissuring, but in our case no such changes were observed.

Radiographically, PLS is characterised by generalised loss of alveolar bone. Severe resorption of alveolar bone gives the teeth a 'floating-in-air' appearance on dental radiographs. Gorlin *et al*¹¹ have suggested dural calcification as a third component of the syndrome. Reyes observed radiographic evidence of intracranial calcification. Recently, par-entel consanguinity is also observed as a characteristic of this disorders.¹²

In this case, ictopic intracranial calcifications were also not evident on the skull radiographs.

Histopathological findings of affected skin consist of hyperkeratosis, occasional patches of parakeratosis, acanthosis and slight perivascular inflammatory infiltrate.¹⁰

The mutations of CTSC gene also result in two other closely related conditions: the HMS and prepubertal/aggressive periodontitis. A common clinical manifestation in all these conditions is severe early-onset periodontitis.

HMS is an ethnically specific disorder described only in Jews of South Indian origin (the so-called Cochin Jews).¹³ HMS also exhibits arachnodactyly, acroosteolysis, atrophy of nails and deformity of the phalanges in the hands, the cutaneous findings are more severe and extensive, while periodontitis is less severely affected than in PLS.¹¹

None of these features were found in the present case.

The absence of palmoplantar keratoderma in the pre-pubertal periodontitis differentiates it from the PLS.

PLS should be differentiated from other conditions showing similar oral or cutaneous clinical features. Diseases with oral manifestations such as acrodynia, hypophosphatasia, histiocytosis X, leukaemia, cyclic neutropenia and Takahara's syndrome are associated with periodontitis and premature loss of teeth. PLS was differentiated from them by the presence of the palmoplantar hyperkeratosis (figures 1–4).

PLS can also be distinguished from palmoplantar keratoderma of Unna Thost, mal de Meleda, Howel-Evans syndrome, keratosis punctata, keratoderma hereditarium mutilans (Vohwinkel's syndrome) and Greither's

Figure 4 Orthopantomograph showing severe bone loss.

syndrome as these entities are not associated with periodontopathy.²

Learning points

- It can be accepted that Papillon-Lefèvre syndrome (PLS) is an extremely rare condition of autosomal-recessive inheritance characterised by palmer–plantar hyperkeratosis and early onset of a severe destructive periodontitis, leading to premature loss of both primary and permanent dentitions.
- Consanguinity seems to be a notable prerequisite for PLS.
- Recently reported findings such as ectopic calcification of dura, type 1 oculocutaneous albinism, hyperhidrosis of palm and sole, mild mental retardation, frequent pyogenic skin infections, liver abscesses, consanguinity and loss of function mutations in Cathepsin C gene have made the variable clinical presentation of PLS, so a wide array of differential diagnosis should be taken into consideration.
- Although the characteristic findings of PLS can be easily diagnosed, they are often overlooked. Therefore, medical and dental professionals should be aware of this rare syndrome and provide the long-term periodic follow-up.

Competing interests None.

Patient consent Obtained.

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