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Papillon-Lefèvre syndrome: a case report and review of the literature

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Resumen

Título: Síndrome de Papillon-Lefèvre: caso clínico y revisión bibliográfica

Describimos el caso clínico de un niño de 9 años y medio afecto de periodontitis e hiperqueratosis desde los 5 años de edad. Queremos destacar la afectación generalizada de toda la dentición, las alteraciones inmunológicas encontradas y la discreta afectación dermatológica, siendo el cuadro estomatológico el que identifica en su mayor parte la enfermedad. El tratamiento precoz con acitretino puede mejorar tanto la evolución de las lesiones dérmicas como de la periodontitis.

Palabras clave

Síndrome Papillon-Lefèvre, periodontitis, hiperqueratosis palmoplantar

Abstract

We report the case of a nine-and-a-half-year-old boy who had had periodontitis and hyperkeratosis since the age of five. We describe the involvement of the entire dentition, the associated immunological disorders, and the discrete cutaneous findings. This disease is chiefly identified by its stomatologic features. Early treatment with acitretin can improve the outcome of both the skin lesions and the periodontitis.

Keywords

Papillon-Lefèvre syndrome, periodontitis, palmoplantar hyperkeratosis

Introduction

Juvenile periodontitis is a rare disease characterized by rapid loss of the tissues in which the periodontal tissue is inserted (alveolar bone and periodontal ligament), during or immediately after the emergence of the primary dentition. It is generally associated with anaerobic subgingival flora (*Capnocytophaga*, *Actinobacillus* and bacteroids) and situations in which the child's immune system is compromised, particularly if there are neutrophil disorders, as in Down's syndrome, diabetes mellitus, Chediak-Higashi syndrome and cyclic neutropenia.

It is highly unusual in preschool-age children with deciduous teeth. In slightly older children, it may be localized in the permanent incisors and first molars or be generalized. Both forms can be associated with palmoplantar hyperkeratosis, in which case, they constitute Papillon-Lefèvre (P-L) syndrome, which leads to the premature loss of all the teeth except, on some occasions, the lower middle incisors. This syndrome was described by Papillon and Lefèvre in 1924[1] in a brother and sister who presented palmoplantar hyperkeratosis and widespread destruction of the tissues supporting the dentition, which was subsequently lost. Its incidence has been estimated to be between one and four cases per million in the general population.[2,3] Boys and girls are equally affected and there is no racial predominance.[4,5] It is transmitted as an autosomal recessive trait, and parental consanguinity exists in 33% of cases.[4] The prevalence of carriers is calculated to be 2-4 per thousand population.[2]

Case report

The patient was a boy aged nine-and-a-half years, born of a normal first pregnancy. His parents were not consanguineous, his psychomotor development had been unremarkable and there was no relevant family history, except for periodontitis in his paternal grandmother. At the age of five years, he presented gingival bleeding and multiple dental abscesses in gingiva, episodic fever, asthenia, sialorrhoea and difficulty with mastication. Laboratory studies included a full blood count with erythrocyte sedimentation rate and uric acid, calcium, iron, bilirubin, alkaline phosphatase, transaminase and antistreptolysin antibody levels; the only finding of note was an elevated sedimentation rate (22 in the first hour and 42 in the second). The culture of a specimen taken from the bottom of the periodontal pocket demonstrated the presence of gram-positive bacilli, diphtheroid bacilli and *Streptococcus viridans*. Gingival biopsy revealed the presence of chronic nonspecific inflammation compatible with prepubertal periodontitis.

Sixteen months later, he presented a second episode, again with diffuse abscesses throughout the oral cavity accompanied by spontaneous gingival bleeding, fever and asthenia. Given

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the severity of these symptoms, some deciduous teeth were extracted (we do not know precisely which teeth were removed, as the procedure was carried out by another specialist and the parents do not remember the details).

After another symptom-free period, lasting 17 months, the problems described above recurred, affecting all the teeth. The culture of another specimen taken from the periodontal pocket yielded results similar to those of the previous one and the biopsy findings again proved to be nonspecific. Physical examination showed a well-nourished child whose height and weight were within normal limits. He was found to have periodontal inflammation and hyperkeratotic lesions on elbows, knees (figure 1) and, to a lesser extent, on the palms and soles. Further laboratory studies were performed, including full blood count, sedimentation rate, antinuclear antibodies (ANA), anti-smooth-muscle antibodies (ASM), anti-mitochondrial antibodies (AMA), immunoglobulins, and cellular immunity tests. The sedimentation rate was 19 in the first hour and 50 in the second. The following immunologic findings were worthy of note: elevated IgA (475 mg/dL), an increase in absolute values of CD4+ and CD45R+ cells and, thus, in suppressor-inducer activity, and lymphoblast transformation test results at the lower end of the normal range.

Stomatological examination revealed the presence of mixed dentition. Around the teeth, we observed hyperplastic gingivitis, with spontaneous bleeding on palpation and exudation of a substance that was either purulent-looking or serous, according to the site (figure 2). Both the deciduous and permanent dentition exhibited grade I-II mobility. Bacterial plaque was also present around both primary and secondary teeth.

Orthopantomography (figure 3) also demonstrated the presence of mixed dentition, drawing attention to the severe vertical alveolar bone resorption in a number of teeth, mainly in the first permanent molars. The maxillary basal bone did not appear be affected by osteoporosis or by any other calcification disorder.

He was being treated with Levamisol to boost his immune system, and oral hygiene measures were prescribed by his stomalogist. At last visit, he had dental abscesses and periodontitis that do not impair mastication, and his permanent dentition is still complete.

Review

P-L syndrome is an unusual hereditary (recessive autosomal) disorder that is characterized by diffuse palmoplantar keratoderma and premature loss of teeth.

The cause of the P-L syndrome is not well understood, but it has been reported that loss-of-function mutations affecting both alleles of the cathepsin C gene, located on chromosome 11q14.1-q14.3, are associated with this syndrome.[6,7] The cathepsin C gene is expressed in epithelial regions commonly affected by P-L syndrome, such as palms, soles, knees, and keratinized gingiva. It is also expressed in diverse immune cells (polymorphonuclear leukocytes, macrophages and their precursors). The lack of functional cathepsin C in P-L syndrome may

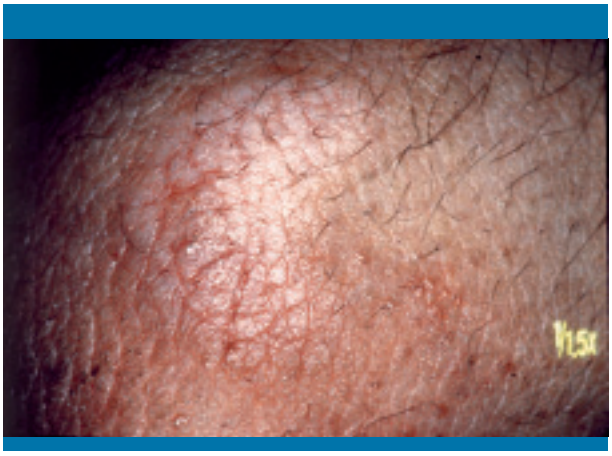

Figure 1.

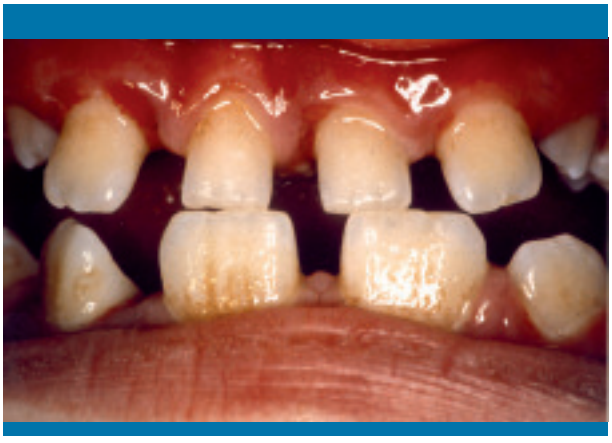

Figure 2.

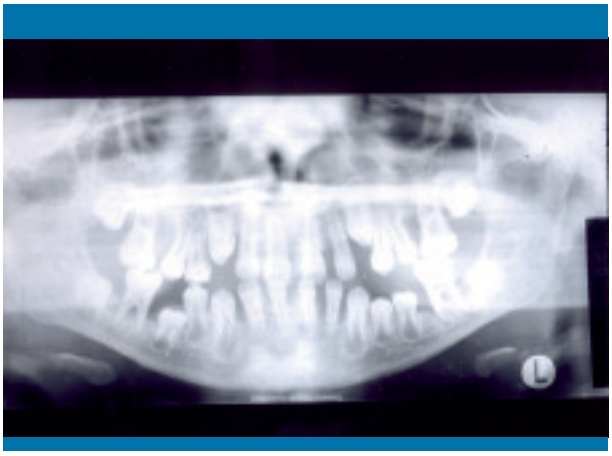

Figure 3.

be associated with a reduced host response against microoganisms in dental plaques and perhaps at other sites.[8] A possible role of *Actinobacillus actinomycetemcomitans* has been reported in P-L syndrome periodontitis.[9]

Cutaneous manifestations

Periodontitis generally precedes hyperkeratosis, which tends to develop towards the fourth year of life,[2] although, occasionally, the two can occur simultaneously. In some cases, the symptoms may be so mild that the patient scarcely mentions them to the paediatrician. Palmoplantar hyperkeratosis has been described in association with several diseases, which usually have an autosomal dominant pattern of heredity. Mal de Meleda[10] also involves palmoplantar keratoderma, which appears around the age of 2 or 3 years, with smooth or irregular hyperkeratosis. It is progressive by nature (progrediens) and tends to invade surrounding regions (transgrediens); unlike P-L syndrome, however, it is not accompanied by periodontal disease. It is also an autosomal recessive trait.

Palmoplantar keratoderma (hyperkeratosis or excessive thickness of the stratum corneum) may be confluent and/or punctate lesions, and can spread from the palms and soles (transgrediens). The hyperkeratosis is generally not severe, but may worsen if the periodontal involvement becomes more marked. Confusion with psoriasis is possible.

Stomatological features

Once the teeth have emerged, buccal disorders appear, generally coinciding with the onset of the cutaneous manifestations. There is gingival inflammation and reddening and a pronounced bleeding tendency. The eruption of deciduous teeth is practically normal, until the first primary molar appears; at this point, the destruction of the periodontium begins. The teeth are affected in order of eruption, avulsion being preceded by the formation of a large periodontal pocket. By the age of 4 to 5 years, all the deciduous teeth have been lost, and the gingiva returns to normal. After a time, the process is repeated when the permanent dentition erupts. All the dentition is lost, with widespread bone destruction, by the age of 15 to 18 years. The gingiva appears to be normal, but radiologic examination reveals loss of alveolar bone. The affected teeth show different degrees of mobility depending on the severity of alveolar bone loss.

Premature loss of the deciduous teeth also occurs in other diseases, such as acrodynia (mercury poisoning), hypophosphatasia (autosomal recessive alkaline phosphatase deficiency) and acatalasaemia or Takahara's disease (progressive gangrenous lesions affecting gingiva and alveolar bone, also an autosomal recessive trait). Severe periodontal diseases also develop at an early age in children with cyclic neutropenia.

Other disorders have been associated with P-L syndrome, such as mental retardation, ectopic intracranial calcifications, ungual dystrophy, a 20% decrease in susceptibility to infections,[3] and arachnodactyly with a peculiar deformity of the terminal phalanges,[11] none of which were encountered in this case.

The skin is the most common site of infection, with pyoderma (also known as pyodermatosis) being present in 20% of cases.[12] The internal organs (liver, kidney, lung) and abdominal cavity are much less frequently affecte.[13] This patient did not present an increase in susceptibility to infections in the areas mentioned, only recurrent dental abscesses.

The immunologic disorders observed include functional alterations of the polymorphonuclear cells, with defective adhesion,[11] leukocyte motility and bactericidal capacity,[14] and low response of the T and B cells to mitogens.[15] In this case, the immunologic abnormality encountered was an increased suppressor-inducer activity, due to an increase in both CD4+ and CD45R+ cells, and a rise in the IgA levels. The results of the lymphoblastic transformation test fell at the lower end of the normal range.

Synthetic retinoids (vitamin A analogs) have proved to be effective in treating keratinisation disorders (lamellar ichthyosis, Netherton's syndrome, mal de Meleda and juvenile pityriasis rubra pilaris). The influence of retinoids on infectious complications of Papillon-Lefèvre syndrome is controversial. Some authors report complete remission of pyoderma,[11] while others claim that infections were precipitated by the use of these drugs. Various synthetic retinoids, such as isotretinoin, etretinate and acitretin have been used. The major secondary effects are: embryotoxicity, bone toxicity (hyperostosis, accelerated ossification, etc.), hepatotoxicity in patients with preexisting liver damage, cheilitis and dryness of the mucosa, erythema and erosions of the distal regions of the limbs, reversible hair loss, and reversible paronychia. Etretinate can be tolerated at higher doses than isotretinoin without producing bone toxicity. Acitretin accumulates less and is eliminated more rapidly than etrinate. Radiologic monitoring is necessary during treatment in order to prevent bone complications from arising. The bone toxicity of acitretin and etretinate are still not precisely known.

After around two months of treatment with acitretin, the dermal lesions improve; this improvement is maintained throughout the period of treatment, but the lesions tend to reappear once treatment is discontinued. The best results seem to be obtained with etretinate. At the same time, the periodontal disease can be considerably mitigated and, subsequently, no teeth are lost. If, therefore, treatment with acitretin is started before the permanent teeth erupt, at around the age of five-and-half, the normal adult dentition can be preserved.[10] Furthermore, the dental manifestations may remain asymptomatic once treatment has been completed. The pathological bases and the mechanism by which retinoids influence the development of a normal periodontium are not known. There may be some relationship to the regulatory effect of collagen turnover.[12]

Our patient was not treated with retinoids because the cutaneous lesions were so mild that they hardly troubled the patient until we started to investigate his history. Moreover, he first consulted us at the age of 9, when his permanent teeth had already erupted.

Appropriate systemic antibiotic therapy should also be administered,[16] in agreement with the antibiogram performed at the peak of the episode. The oral bacterial flora should be checked at each visit. Eradication of *A. actinomycetemcomitans* has been shown to play a role in the successful treatment of periodontitis.[17,18] Treatment to boost the immune response may help to reduce the number of infections in internal organs and skin, as well as in the mouth. In our patient, Levamisol was administered to this end.

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