A New Family with Papillon-Lefèvre Syndrome: Effectiveness of Etretinate Treatment

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GOAL

To describe Papillon-Lefèvre syndrome and the efficacy of etretinate.

OBJECTIVES

1. To discuss the epidemiology, inheritance, and clinical appearance of Papillon-Lefèvre syndrome (PLS).
2. To outline possible etiologies including the differential diagnosis of PLS.
3. To describe the different therapies and their efficacy with special focus placed on the retinoid etretinate.

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Papillon-Lefèvre syndrome is characterized by the association of palmoplantar hyperkeratosis, severe periodontitis, and early loss of deciduous and permanent teeth. We report two patients from the same family, aged 21 and 30 years, who were unaware of their pathology; one was successfully treated with etretinate.

Inherited palmoplantar keratodermas (PPK) are a heterogeneous group of disorders of keratinization, characterized by erythema and hyperkeratosis of the palms and soles, which can be distinguished from each other on the basis of histopathologic findings (the presence or absence of epidermolysis), on the aspect of the palmoplantar lesions (diffuse, focal, or linear), by the presence of other associated abnormalities, and the pattern of inheritance.[1] Among PPK, the so-called Papillon-Lefèvre syndrome (PLS) received particular attention and was distinguished from the Meleda disease because of the peculiar association of palmoplantar hyperkeratosis transgrediens and severe periodontitis with precocious loss of deciduous and permanent teeth.[2,3]

Although an important causative role was assigned to hypovitaminosis A in the past, consequent to a general deficit or to a tissue-altered metabolism,[2] it is now known that PLS is an inherited autosomal recessive disorder that affects both genders equally and does not show ethnic preferences. Its gene has been mapped to the chromosomal region 11q14.[4]

Papillon-Lefèvre syndrome is usually considered to be a rare disease, with a prevalence estimated between 1 and 3 per 1,000,000 people; however, more than 200 patients have been reported in the literature.[4] Parental consanguinity is found in approximately 40% of cases.[5] Its first clinical sign is the occurrence during the first 4 years of life of palmoplantar hyperkeratosis, which follows a short erythematous phase. The margins of

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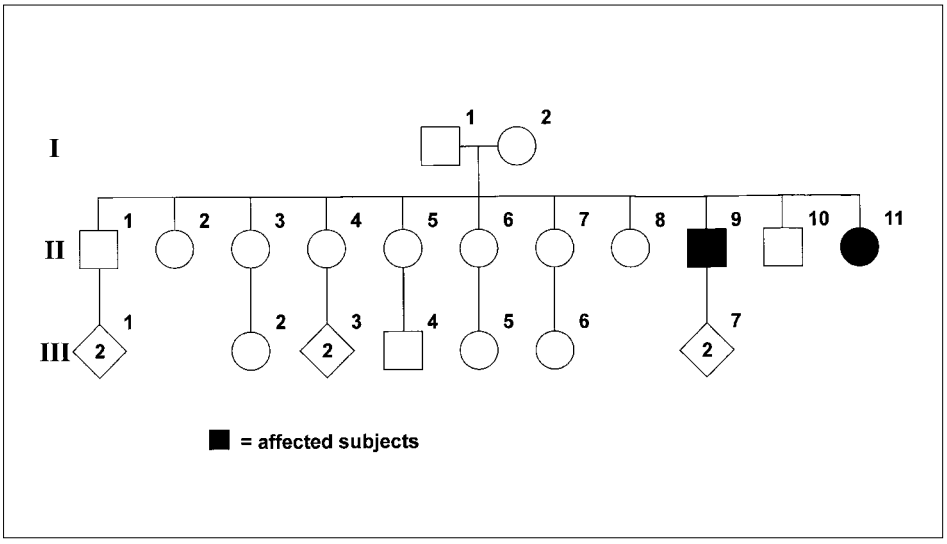

FIGURE 1. Family tree.

the lesions are well-defined and erythematous; erythroderma is often intense. During winter, the lesions tend to become dry and to cause painful fissures with bleeding and inflammation. Usually, the plantar regions are more severely involved than other areas, and this can cause difficulty in walking. Later in life, the normal skin sulci become marked and the cutis can assume a parchment-like quality.

It is important to emphasize that PLS can involve skin regions other than the palmar and plantar areas; a differential diagnosis with psoriasis is necessary when PLS affects the volar surface of the wrists, forearms, elbows, trunk, pretibial regions, or knees. However, in PLS, scales are small and thin, whereas in psoriasis they are large and lamellar. Often, hyperkeratosis is associated with hyperhidrosis and this combination causes an unpleasant smell (bromhidrosis). Follicular hyperkeratosis sometimes affects limbs, and PLS can also occur in association with acro-osteolysis, arachnodactyly,[6] and mental retardation.[2,3] Cutaneous annexes also can be involved resulting in thin hair and various nail abnormalities (horizontal grooves or streaks, spooning, brittleness, pitting, anonychia, and dystrophy).

The second major feature of PLS consists of severe gingivostomatitis and periodontitis, which start at 3 to 4 years of age. The teeth are structurally normal and erupt at the expected age and in the normal sequence. The phlogosis starts at the end of the eruption of the last deciduous teeth and leads to a complete loss of them. Permanent teeth also erupt normally and, again, when the last ones erupt the periodontitis reappears. By the age of 13 to 14 years, patients affected by PLS are edentulous. Rarely, PLS can occur in patients aged 20 to 40 years with a relatively mild course.[7] Some patients can have calcification of the dura,[2] falx cerebri, tentorium cerebelli, and choroid plexus.[8] Increased susceptibility to infections has also been reported.[9]

In this paper, we report 2 patients from a family of 11, who reached the ages of 21 and 30 years, respectively, without the knowledge of being affected by such a disease.

Case Reports

Case I—A 30-year-old man was the 9th child born from consanguineous parents (first-degree cousins) in a family of 11 (Figure 1). The palmar and plantar regions presented symmetrical diffuse erythema and marked hyperkeratosis. Numerous pits were evident over the thenar and hypothenar eminences, volar surface of some fingers, some fingertips, and over his plantar hyperkeratosis, which was surrounded by macerated skin consequent to hyperhidrosis (Figure 2).

Rosy-colored patches over the dorsal surface of the hands and the metacarpal-phalangeal and interphalangeal joints were clearly evident and mildly scaling. Hyperkeratosis of the feet also extended over the dorsal surface of toes and the Achilles tendons. Fingernails were affected by trachyonychia, while the first toenail of the right foot showed onychogryphosis.

Histologic examination of the palmar skin showed thickening of the epidermis, hypergranulosis, hyperkeratosis, and mild mononuclear cell infiltrate of the papillary dermis (Figure 3).

Palmoplantar hyperkeratosis had affected the patient since he was a child, causing intense pain because of the occurrence of deep fissures during winter. Moreover, phlogistic processes of the oral cavity had caused the loss of both deciduous and permanent teeth; thus, he became edentulous at the age of 12 and since that time has needed dentures. All routine

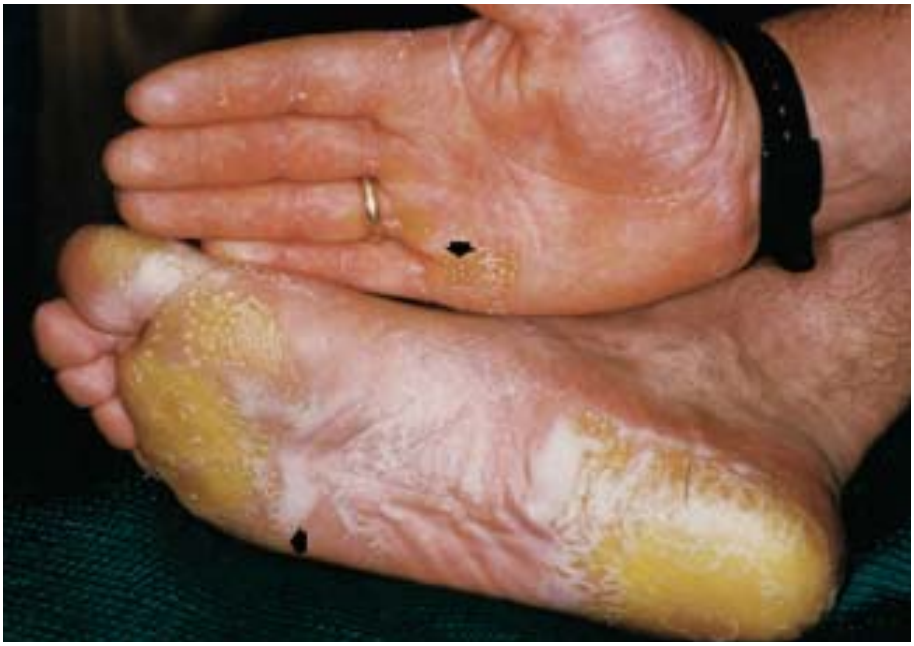

FIGURE 2. Case I. Marked palmoplantar hyperkeratosis with numerous evident pits (arrow).

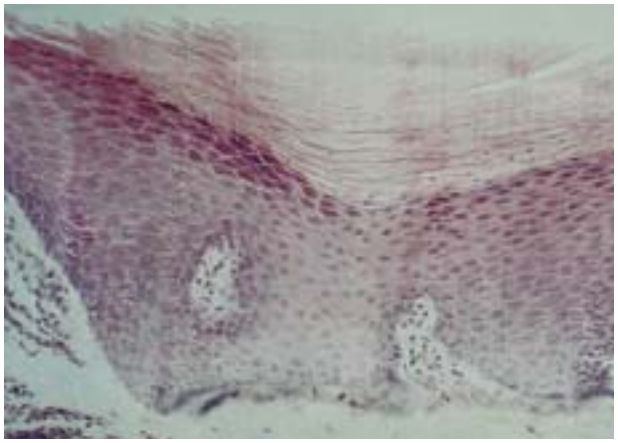

FIGURE 3. Case I. Histologic examination of palmar skin shows thickening of epidermis, hypergranulosis, hyperkeratosis, and mild infiltrate of mononuclear cells in the papillary dermis.

blood examinations were within the normal limits. Skull radiography also gave normal results. These findings led to a diagnosis of PLS.

Treatment with etretinate (50 mg/day) for 9 months was initiated, and his skin lesions showed a marked improvement. This improvement was evident during the first weeks of treatment (Figure 4). During this period, all blood analyses remained within the normal range, and no phlogistic processes occurred. This patient was only affected by a mild cheilitis.

We suspended therapy for 3 months, corresponding to the summer period, in order to avoid photosensitivity, which has already been reported to complicate this drug therapy.[10] During this last period, the patient utilized keratolytic and emollient agents, alternatively, with satisfactory control of his hyperkeratosis.

Case II—A 21-year-old woman was the 11th child from the same family of Case I. She was affected by palmoplantar hyperkeratosis transgrediens, and no pits or nail abnormalities of the hands or feet were evident.

Histologic examination of the palmar cutis showed hyperkeratosis, hypergranulosis, and acanthosis. Hyperkeratosis started in her childhood, and severe inflammation of the oral cavity caused the precocious loss of deciduous and permanent teeth. She had become edentulous a few weeks before her presentation (Figure 5). All routine blood analyses were within the normal limits, and skull radiography was normal. None of the other siblings were affected by PLS (Figure 1).

After being informed about the teratogenic effects of etretinate, she decided not to be treated because she planned to become pregnant.

Comments

The etiopathogenesis of the severe periodontitis in PLS is still poorly understood. It is likely that dystrophic-degenerative processes, associated with phlogistic and systemic factors, might cause a progressive atrophy of paradental tissues and the early loss of deciduous and permanent teeth.

Following the discovery of gram-negative anaerobic agents and other microorganisms that are exclusively pathogenic for periodontal tissues in deep periodontal pockets, saliva, oral mucosa, and tooth roots, a role for such infectious agents in PLS has been proposed, but is still in need of clarification.[7,11] Addi-

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FIGURE 4. Case I. Aspect of the plantar skin after treatment.

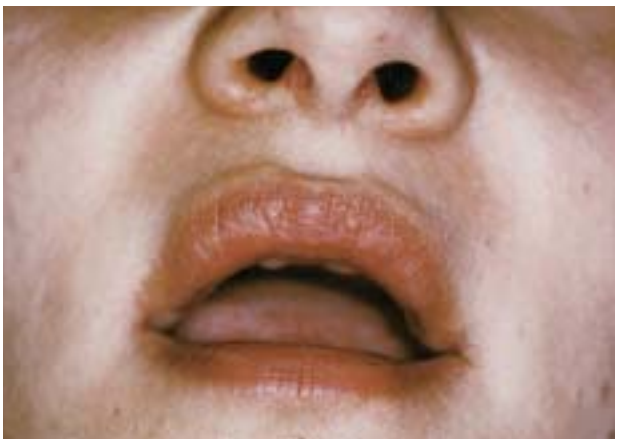

FIGURE 5. Case II. Lack of teeth in a 21-year-old woman.

tionally, the existence of a dyskeratosis of the gingival junctional epithelium with reduced efficiency of the barrier function and an increased permeability to periodonto-pathogenic bacteria and their toxic products has been suggested.[11] Finally, the immunologic disequilibrium, already reported in PLS, might further predispose patients to infections[9,12,13]

For the differential diagnosis, PPK of Unna-Thost and Meleda disease can be distinguished from PLS, because the former do not show dental problems.[1] The Haim-Munk syndrome, characterized by congenital palmoplantar keratosis, progressive periodontal destruction, recurrent pyogenic skin infections, arachnodactyly, and claw-like deformations of the terminal phalanges, can be distinguished from PLS by the severity and extension of the skin manifestations, and by the later onset. The periodontum also is less severely affected in this disease.[4,6] On the other hand, conditions that are associated with gingivitis and cause premature exfoliation of the teeth, including acrodynia, acatalasia, histiocytosis X, leukemia, Chédiak-Higashi syndrome, juvenile periodontitis, hypophosphatasia, cyclic neutropenia, congenital neutropenia, and Takahara's syndrome, can be ruled out because the characteristic palmoplantar hyperkeratosis is absent.[1, 5]

In the past, both dermatologic and periodontal therapies were ineffective; steroids as well as salicylic acid and emollients were used topically.[14] More recently, synthetic retinoids have proven to be effective in PPK[10] and, particularly in PLS, where etretinate,[8,13-15] acitretin,[16] and isotretinoin[17] have been employed. They are capable of regulating cell proliferation and differentiation, particularly in keratinizing epithelia, and they can modify immune responses. Moreover, the retinoids may have auxiliary functions in antibody production and effects on various functions of granulocytes and monocytes. Thus, etretinate may reduce susceptibility to infections in PLS.[10] In fact, in a follow-up study of 10 years, etretinate administration, at the time of permanent teeth eruption, proved to be effective in modulating the course of periodontitis and in preserving teeth.[15] Usually, etretinate is well tolerated by patients and may only cause mild cheilitis.[10] However, inhibition of the migration of neutrophilic granulocytes and impairment of the motility of monocytes *in vitro* have been demonstrated during treatment with etretinate.[10] Tosti *et al*.[18] reported two liver abscesses caused by pyogenic bacteria in one patient being treated with etretinate. Most probably, in this patient, the drug administration activated a latent deficit of polymorphonuclear chemotaxis. Thus, suspending treatment in the summer might have a double basis: avoid photosensitization and reduce risk of infection.

In conclusion, it seems important to underline the need for a multidisciplinary approach in the diagnosis of a complex syndrome such as PLS, careful genetic counseling, and early treatment with retinoids, which can significantly reduce the risk of odontic consequences.

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Dr. Schepis reports no conflict of interest.