Homozygous Palmoplantar Keratoderma Type Bothnia Improved by Erythromycin: A Case Report

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Sir,

Hereditary palmoplantar keratodermas (PPKs) are a clinically and genetically heterogeneous group of mostly rare disorders with the unifying trait of hyperkeratosis on palms and soles. In northern Sweden diffuse palmoplantar keratoderma is more frequent than in other parts of the world with a reported prevalence of 0.3–0.6% among school children (1, 2). The overwhelming majority of PPK cases in Sweden are attributed to the autosomal dominant PPK type Bothnia (PPKB) (3) with only a few identified cases of autosomal recessive PPK (4). Furthermore, the first two cases of epidermolytic PPK in Sweden have only recently been described (5), even though this is the predominant variant of PPK worldwide.

All PPKB patients examined genetically share the same haplotype for the disease region on chromosome 12q1, indicative of a common genetic origin of this disorder. However, the actual PPKB mutation has not yet been identified, although a large number of candidate genes have been scrutinized for mutations. Due to the high frequency of PPKB in northern Sweden there are families where both parents are affected by PPKB, but so far no report has been presented of a more severe clinical presentation of PPK in children from such families. Here we report on the first case of PPKB shown to be homozygotic for the disease region on chromosome 12q1. This homozygotic patient was more severely affected than other PPKB patients examined (3), nevertheless she showed a discernible long-term improvement after a course of erythromycin treatment.

CASE REPORT

An 18-year-old woman was referred to our department for evaluation of distressing PPK. Thickening of palmar skin was first observed at the age of 4 and upon water exposure a white spongy appearance was evident on palms and soles. At the age of 12 there was a marked deterioration, the skin changes became more conspicuous with striking hyperkeratosis appearing also on the dorsal aspects of finger and toe joints. Subsequently, distal onycholysis appeared on some toenails and anti-fungal treatment with terbinafine orally at 0.25 g daily was prescribed for 3 months. The nail condition improved but there was no amelioration of the skin. The patient was extremely unhappy with her condition and to avoid exposure of her hands she withdrew from other people. On examination the patient showed a more prominent PPK than usually seen in PPKB with a thin erythemathous rim surrounding the hyperkeratotic skin (Fig. 1a, b). Hyperkeratosis was also present on the dorsal aspects of toe and finger joints. However, no additional skin changes were detected. The mother, father and sister of the proband also showed signs of PPKB, although their skin alterations were less prominent. On account of our previous observations in PPKB patients, erythromycin 0.5 g twice daily for 1 month was prescribed to the proband. The treatment resulted in an obvious improvement with thinner and softer skin and a less conspicuous phenotype. However, 3–4 months after erythromycin treatment the patient experienced a relapse. The patient has received a few more courses of erythromycin, the interval between them has varied from 4 months up to more than 1 year. Each course has led to improvement followed by some relapse (Fig. 1c, d), but the skin condition has never deteriorated to the pre-treatment state. As a result of her improved condition the patient is now more outgoing and less apprehensive about the appearance of her hands.

Histopathological examination of punch biopsies from the proximal-ulnar site of palmar skin of the patient and her father showed orthohyperkeratosis without signs of epidermolytic hyperkeratosis or fungal infections. After informed consent blood samples were obtained from the proband and her family, genomic DNA was extracted and microsatellite analysis was performed according to standard procedures. The family members were genotyped with DNA markers covering the PPKB locus region on chromosome 12q1 and haplotypes were constructed. Haplotype analysis of the proband revealed a homozygous domain of approximately 5 Mb, whereas the affected relatives of the proband were heterozygotic for the PPKB region (Fig. 2).

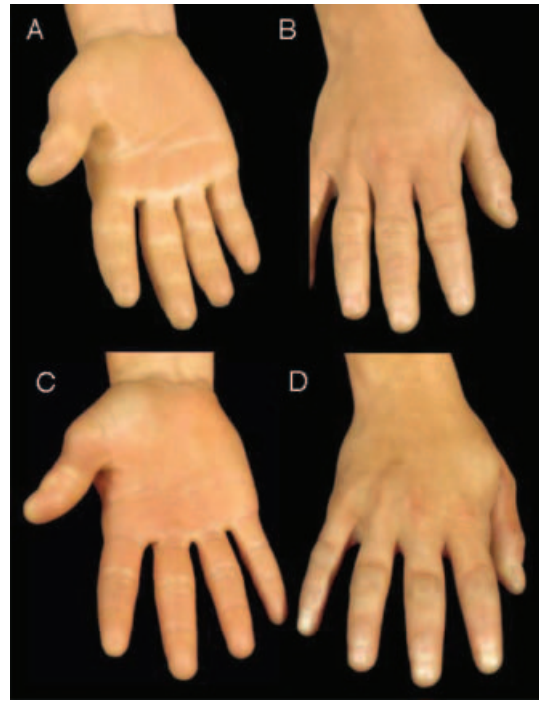

Fig. 1. Appearance of the right hand of the patient before the first (a, b), and 4 months after the second (c, d) erythromycin treatment.

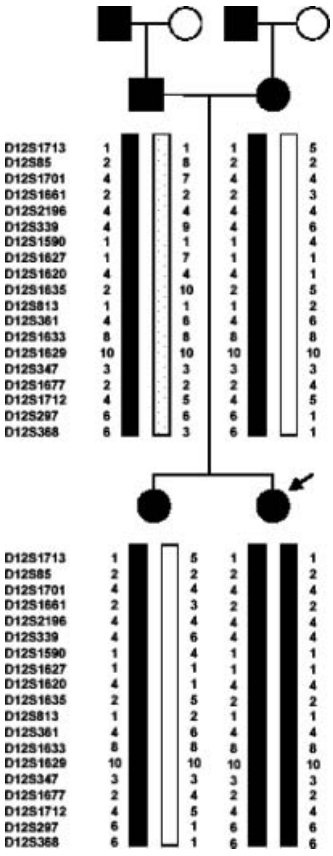

Fig. 2. Pedigree of the family of the homozygotic palmoplantar keratoderma type Bothnia (PPKB) patient. Haplotypes of the PPKB region on chromosome 12q1 are given with the markers in centromeric to telomeric order (http://genome.ucsc.edu).

DISCUSSION

In this report we describe the first case of a PPKB patient genetically shown to be homozygous for the PPKB chromosomal region. In a disorder with strict dominant inheritance, homozygotic and heterozygotic individuals should not differ in clinical expression. However, there are several examples of partly dominant diseases where the homozygotes are more severely affected than individuals carrying only one disease allele (6). In order to establish whether the more severe phenotype is due to the homozygotic state of the disease locus or to other factors it will be necessary to examine more patients homozygotic for PPKB.

There is no known curative treatment for PPKB. Although anti-mycotic treatment, especially when given orally, often results in improvement this is usually temporary. Some patients consider moisturizing agents useful, whereas topically applied retinoic acid has been tried without benefit (7). Systemic retinoid treatment has been dissatisfying, as the patients experienced that the skin became too sensitive and unsuitable for manual work. Surprisingly, several patients with PPKB have reported improvement after 10–30 days on oral erythromycin given for infectious diseases or the keratoderma (Lundström, unpublished observation). In particular, the white, spongy appearance of the palmoplantar skin after immersion in water became less pronounced but thinning and softening of the skin have also been reported by the patients. Usually the improvement lasts for months to years.

As PPKB is not an infectious disease it is reasonable to assume that some mechanism other than the antibiotic effect of erythromycin is responsible for the observed improvement. Apart from the antimicrobial potency, a range of antibiotics including the macrolide erythromycin has been shown to modify host functions, especially those related to immunomodulation and anti-inflammatory effect (8, 9). However, there are no data supporting PPKB as an immunological disorder and the patients do not show any obvious signs of inflammation, as long as they do not contract fungal infections.

Another effect ascribed to some macrolide antibiotics is antiproliferation (10, 11). However, in PPKB such a mode of action seems unlikely as there is no evidence for hyperproliferation in PPKB, which is regarded as a retention hyperkeratosis (12). Thus, the mechanisms responsible for the observed improvement after erythromycin treatment remain obscure.

A controlled clinical trial needs to be done to confirm the beneficial effect of erythromycin on PPKB patients.

ACKNOWLEDGEMENTS

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Presence of *Demodex* in Follicular Hyperkeratotic Spicules on the Face. A Casual Association?

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Sir,

Follicular hyperkeratotic spicules (FHS) are a rare cutaneous disorder characterized by the presence of follicular, keratotic, horny spicules, mainly on the face. They have been described as idiopathic and associated with a variety of conditions including chronic renal failure, Crohn's disease and malignant diseases. They should be differentiated from the pseudohyperkeratotic spicules of the face, which correspond to cryoprecipitates in association with a monoclonal gammopathy (1), and pityriasis folliculorum, which associates the follicular plugging with a diffuse facial erythema and burning or itching sensations (2). The pathogenesis of FHS is unknown. Recently, it has been suggested that *Demodex* mites might play a role in the aetiology of these lesions, although this fact remains controversial (3).

CASE REPORT

We describe here a 76-year-old woman diagnosed with hypertension, diabetes mellitus and polycythaemia rubra vera treated with oral hydroxyurea from February 1999 until October 2001. She was admitted to our department with a 2-year history of multiple asymptomatic follicular hyperkeratotic spicules on her face that had appeared in November 2001. No treatment had been applied. She did not have atopic history, photosensitivity or any systemic symptoms. She washed her face daily with water and denied using make-up, creams or oils. Examination revealed multiple spicules with a horny appearance in the follicular openings of the face, particularly on the frontal and temporal regions, cheeks, chin and ears (Fig. 1). No erythema or telangiectasia was observed. No lymphadenopathy was present. Microscopic examination of four biopsies from the spicules demonstrated follicular hyperkeratotic plugs with *Demodex* mites occupying the follicular infundibula in all of them (Fig. 2). A mild lymphocytic cell infiltrate around each follicular infundibulum was observed. A biopsy from apparently healthy skin on the temporal region showed similar histopathological changes although slightly less pronounced. Laboratory investigations disclosed a mild thrombocytosis and hyperglycaemia. Serum and urine immunoelectrophoresis were normal. Autoantibody screen showed positive ANA (titre 1:160) and

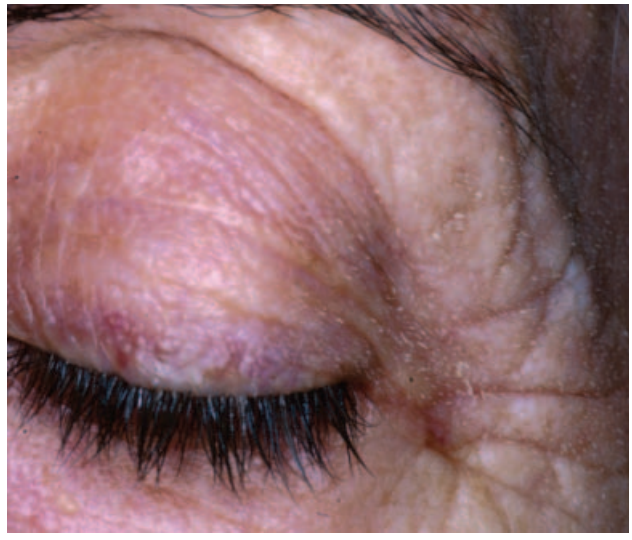

Fig. 1. Spicules with horny appearance in the follicular openings.

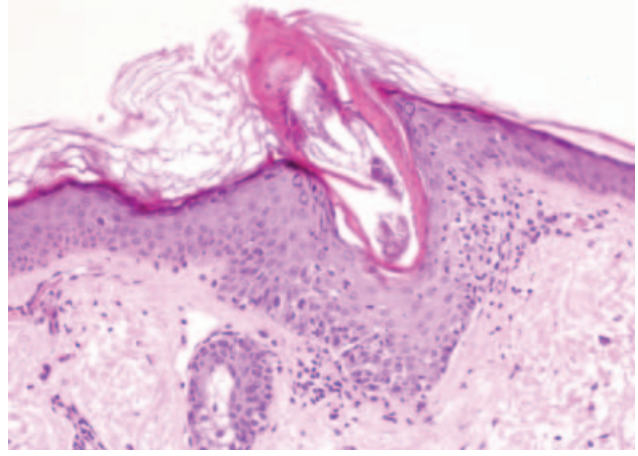

Fig. 2. Follicular hyperkeratotic plugs with *Demodex* mites.