CASE REPORT

Mal de Meleda: a report of two cases of familial occurrence

Mal de Meleda: relato de 2 casos de ocorrência familiar

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Abstract: Mal de Meleda is a rare transgressive palmoplantar keratoderma with an estimated prevalence of 1 in 100,000 individuals. It was first described in 1826 by Stulli on the island of Mljet. Its autosomal recessive inheritance was described in 1938, and the defective gene was localized to chromosome 8qter in 1998. Clinical features are the result of abnormal palmoplantar keratinization and include severe symmetrical transgressive hyperkeratosis and erythema of the feet and hands in a glove-and-sock pattern. Genetic counseling is mandatory in cases of consanguinity. We report two cases of familial occurrence in the offspring of consanguineous parents.
Keywords: Keratoderma, palmoplantar; Keratoderma, palmoplantar, diffuse; Nails

Resumo: Mal de Meleda é uma ceratodermia palmoplantar transgressiva rara, com prevalência estimada de 1:100.000 habitantes, descrita em 1826 por Stulli, na Ilha de Meleda. A herança autossômica recessiva foi descrita em 1938 e a alteração gênica no lócus 8qter, documentada em 1998. As principais manifestações clínicas decorrem da alteração da ceratinização palmoplantar. Há intensa hiperceratose transgressiva com eritema também no dorso das mãos e pés com distribuição em luvas e botas O aconselhamento genético faz-se necessário, sobretudo nos casos de consanguinidade. Nosso objetivo é relatar 2 casos de ocorrência familiar de pais consanguíneos.
Palavras-chave: Ceratodermia palmar e plantar; Ceratodermia palmar e plantar difusa; Unhas

INTRODUCTION

Mal de Meleda is a rare autosomal recessive skin disease characterized by transgressive palmoplantar hyperkeratosis. Features may also include lichenoid lesions, brachydactyly and nail dystrophy. The disease has a high morbidity and significantly impairs quality of life. Here we describe the cases of two patients from the same family with typical clinical pictures and a history of consanguinity between the parents. The cases illustrate a rare genodermatosis that should be part of the differential diagnosis of palmoplantar keratodermas.

CASE REPORT

CASE 1: A white, female, 62-year-old patient born of healthy first cousins who was born and still living in Mogi das Cruzes presented with a complaint of desquamation and thickening of the skin on the palms of her hands and soles of her feet since birth. The clinical picture had worsened, with involvement of the dorsa of the feet and hands. She complained of intense sweating and fetid, painful lesions but denied any comorbidities or other systemic alterations. She reported that her parents had had 6 children, 3 of

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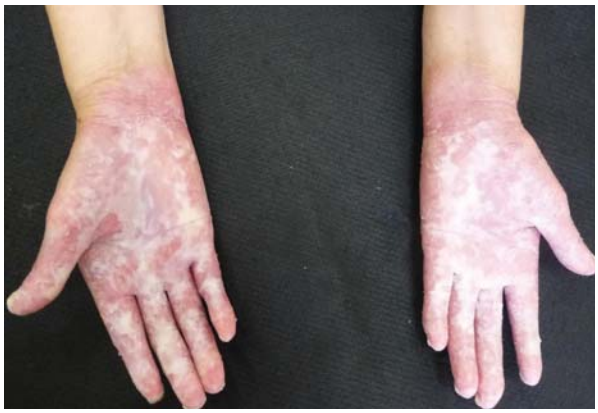

Figure 1: Intense hyperkeratosis producing a yellowish color interwoven with an erythematous border in the palmar region of patient 1

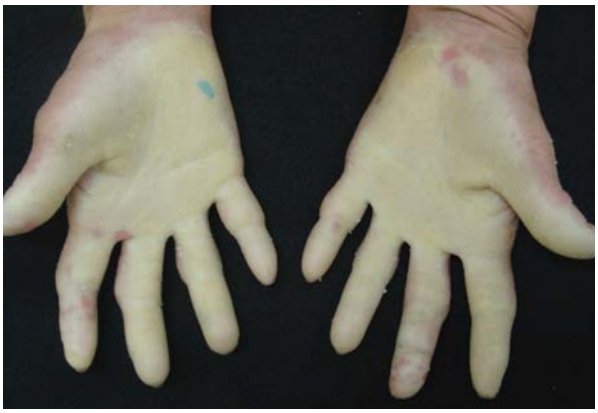

Figure 3: Palmar hyperkeratosis in patient 2 with the same appearance as in patient 1

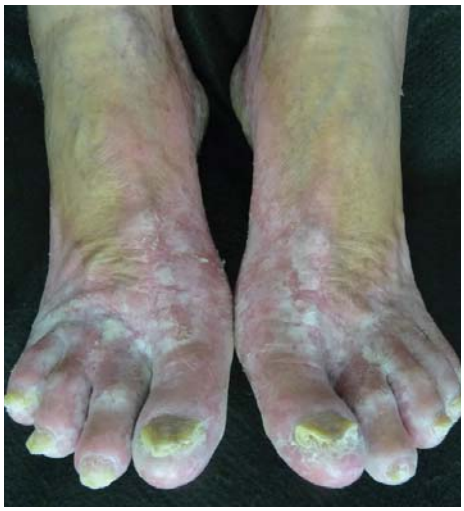

Figure 2: Plantar hyperkeratosis extending to the dorsal region as an intense yellowish hyperkeratosis on an erythematous base in patient 1. Hyperkeratosis of the nails can also be observed

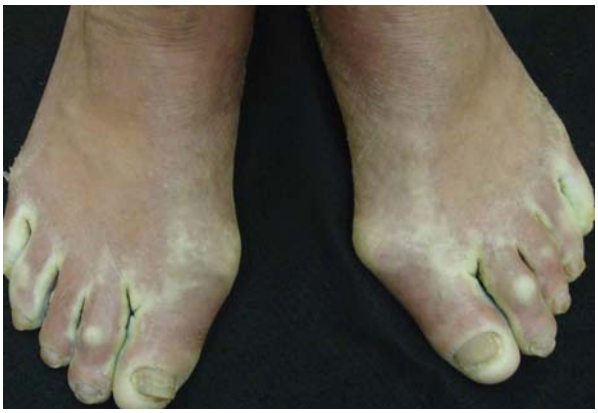

Figure 4: Intense hyperkeratosis with a yellowish appearance in the interdigital region extending on an erythematous base to the dorsal region and nail dystrophy and hyperkeratosis in all the toes in patient 2

whom were healthy and 3 of whom suffered from the disease (her, the patient in case 2 and another sibling, who had died of another cause). Dermatological examination revealed intense transgressive whitish-yellow palmoplantar hyperkeratosis with maceration, and erythema extending to the dorsa of the feet and hands. Hyperkeratosis of the nails on all the fingers and toes was also present (Figures 1 and 2). Laboratory tests were normal. A clinical diagnosis of Mal de Meleda was made. However, the patient refused any specific treatment (systemic retinoids) and chose treatment with emollients.

CASE 2: BDC, 72 years old, female, sister of patient 1, born and living in Mogi das Cruzes presented with a complaint of desquamation on her feet and hands since birth and the development of painful fissures. She also complained of excessive sweating and lesions with a fetid odor but denied any lesions on other parts of her body. She has diabetes mellitus (which is being treated with glibenclamide 5 mg 3 x/day) and hypothyroidism (which is being treated with Puran T4 50 μg/day). On examination the patient was found to have transgressive palmoplantar hyperkeratosis with a yellowish paraffin-like color. Foul-smelling interdigital fissures and maceration were present. All the nails were affected by dystrophy. Laboratory tests were normal. Mal de Meleda was diagnosed and treatment with acitretin and emollients was started.

DISCUSSION

Mal de Meleda is classified as a rare transgressive palmoplantar hyperkeratosis with an estimated prevalence of 1 in 100,000 individuals. Also known as keratosis palmoplantaris transgrediens of *Siemens, it was first observed by Luca Stulli in 1826 on the island of Meleda (Mljet) in Dalmatia, which was on a Mediterranean trade route in the Middle Ages.* [1,2] Nearly all the described cases are of descendants of individuals from this region, but the disease has also

been described in America and Africa. [3,4,5] For more than 50 years it was thought to be a form of Hansen's disease. However, Hovorka and Ehlers noticed that it was not an infectious disease and used the term "Mal de Meleda". The first epidemiological study was carried out by Kogoj. [6-8] The autosomal recessive inheritance of the disease was described in 1938, and in 1998 mutations were identified in the ARS B gene on chromosome 8q24.3, which codes for SLURP-1 (the secreted Ly-6/uPAR protein related to mammals). [1,9-11] SLURP1 is a late marker of epidermal differentiation, and there is a correlation between its location in the stratum granulosum and the a-7 acetylcholine nicotinic receptor. [9-12] In addition, this receptor is present in eccrine sweat glands and ducts, whose secretions are regulated by the cholinergic system. Interestingly, patients with Mal de Meleda generally suffer from hyperhydrosis and have hypertrophic sweat glands. [12-13] Mutations in SLURP1 would therefore appear to lead to alterations in the sweating process. [10] To date, 14 different mutations have been described. [9-12,14] All the individuals affected with these mutations were homozygous, except for one who was heterozygous. [9]

The main clinical features are the result of abnormal keratinization, characterized by differentiation of the keratinocytes in the stratum granulosum, leading to the formation of a palmoplantar hyperkeratotic covering. There is intense transgressive hyperkeratosis and erythema extending to the dorsa of the hands and feet in a glove-and-sock pattern. Hyperhydrosis is also present and may be accompanied by bromhidrosis and painful fissures. Other findings include nail dystrophy affecting all the toes and fingers, brachydactyly, lichenoid eruption and contracture of the fingers with functional loss. [2,8,15]

Mal de Meleda must be differentiated from other syndromes that present with diffuse palmoplantar keratoderma. This can be difficult because of the broad spectrum of clinical manifestations. Observation of any associated lesions and the inheritance pattern can help in the differential diagnosis. Transgrediens et progrediens palmoplantar keratoderma (Greither's syndrome) can present with similar manifestations to those of Mal de Meleda, but it has an autosomal dominant inheritance pattern and progressive evolution and presents with epidermolysis. The location of the mutation is the subject of controversy. Papillon-Lefèvre syndrome, an autosomal recessive condition, is the result of a mutation in the cathepsin C gene located on chromosome 11q14 and is characterized by diffuse keratodermia together with gingivitis, early loss of teeth, periosteal changes and intracranial calcifications. [15] Richner-Hanhart syndrome is characterized by keratodermia, mental retardation and elevated tyrosine and tyrosine metabolite levels. [6] A mutation in the first extracellular domain of connexin 26 causes Vohwinkel's syndrome, an autosomal dominant condition characterized by mutilating palmoplantar keratodermia, which can progress to spontaneous amputation, alopecia, ichthyosis and deafness.[6] Unna-Thost syndrome is characterized by diffuse non-transgressive palmoplantar keratodermia with an autosomal dominant inheritance pattern and a mutation in the keratin 9 gene. [8] Naxos disease is an autosomal dominant condition caused by a deletion in the plakoglobin gene on chromosome 17q21, which presents with non-transgressive keratodermia in association with arrhythmogenic right ventricular cardiomyopathy and woolly hair. Huriez syndrome, an autosomal dominant condition, is caused by a mutation in a gene mapped to chromosome 4q23 and presents with diffuse palmoplantar keratodermia accompanied by sclerodactyly, atrophy and koilonychia. Deafness, leukonychia and keratodermia with knuckle pads characterize Bart-Pumphrey syndrome, an autosomal dominant condition caused by a mutation in the connexin 26 gene. Other types and variations are described in the literature and should be considered in a differential diagnosis. [2,9]

Before retinoids became available, treatment was with emollients and keratolytics. Currently, the most effective treatment is with acitretin, which is effective primarily in improving the hyperkeratosis and has little effect on the erythema. Treatment duration is not defined and continuous use is recommended. Patients should undergo laboratory tests at three-month intervals. [7] Genetic counseling is required, particularly in cases of consanguinity. [5,7]

Mal de Meleda is a rare genetic dermatosis and is still very difficult to treat. The introduction of retinoids as a treatment option led to a partial improvement, and this form of treatment should be recommended unless there are contraindications. The aim of this article was to describe a rare genodermatosis that should be included in the differential diagnosis of palmoplantar keratodermias. ❑

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