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Title: A case of Mal de Meleda in whom a novel gene mutation was identified

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Abstract

Mal de Meleda, otherwise known as keratoderma palmoplantaris transgrediens, is a rare type of autosomal recessive palmoplantar keratoderma. A 19-year-old male patient presented with a congenital yellowish discoloration and thickening of both palms and the soles of the feet. His family history revealed no consanguinity between the mother and father, and that he had three healthy brothers. Second and third degree relatives also exhibited similar skin findings in five females and one male. From the isolated DNA samples, the extrinsic regions of the SLURP1 gene were screened using sequence analysis and Sanger sequencing was performed with the 3130 Sequence Analyzer.

Results of this analysis show that, a p.Arg 96 Pro (R96P) (c.287 CGA>CCA) homozygous missense point mutation was detected on the SLURP 1(a secreted toxin-like mammalian lymphocyte antigen 6/urokinase-type plasminogen activator receptor-related protein 1) gene of the patients, while heterozygous p.Arg 96 Pro (R96P) (c.287 CGA>CCA) mutation was detected in the mother, father and brothers. Our search of the human genome mutation database (HGMD) and previous literature revealed no previous report of this mutation in Mal de Meleda. In conclusion, we report this case due to the identification of a novel gene mutation in a patient with Mal de Meleda, a palmoplantar keratoderma.

Key Words: Mal de Meleda, palmoplantar keratoderma**,** SLURP1.

Introduction

Mal de Meleda, otherwise known as keratoderma palmoplantaris transgrediens, is a rare type of autosomal recessive palmoplantar keratoderma [1]. It was first described in 1826 in a patient in Mljet, formerly known as Meleda Island in the Adriatic Sea. The prevalence of this extremely rare disease is 1/100000 [2,3]. Since its description in 1826, the disease has been reported in at least 19 countries apart from Croatia. These include Algeria, Chile, China, Germany, India, Indonesia, Italy, Japan, Korea, Laos, Libya, The Netherlands, Pakistan, Saudi Arabia, Scotland, Sweden, Tunisia, Turkey and the United Arab Emirates [2].

We report a case of a 19-year-old male patient diagnosed with Mal de Meleda and in whom a novel gene mutation was identified.

Case Presentation

A 19-year-old male patient presented with a congenital yellowish discoloration and thickening of both palms and the soles of the feet. His only other symptoms were hyperhidrosis and mal odor in the hands and feet. His previous medical history was unremarkable. His family history revealed no consanguinity between the mother and father, and that he had three healthy brothers. Second and third degree relatives also exhibited similar skin findings in five females and one male. The patient's family tree is shown in Fig. 1. No pathology was observed at systemic examination. Dermatological examination revealed bilateral palmoplantar pointed pits, maceration and malodor between the toes on slightly erythematous yellowish hyperkeratotic areas extending to the dorsal aspect of the hands

and feet (Fig. 2). Examination of hair, teeth and mucosa was unremarkable. Subungual hyperkeratosis and dystrophic changes were determined in the nails. The hands and toes were free of contractures and no limitation of motion was observed. Routine laboratory analyses were within normal limits. Hyphae and spores were observed at direct KOH analysis of samples prepared from the palms and soles of the feet and from the nails. Informed consent form was obtained from the patient. Punch biopsy was obtained from the hyperkeratotic lesion. Light microscopy revealed hyperkeratosis on the surface. Thickening of the granular layer and marked psoriasiform hyperplasia of the epidermis were observed. Mild perivascular mononuclear inflammatory cellular infiltration was observed in the superficial dermis (Fig. 3).

Mal de Meleda was diagnosed based on the clinical and histopathological findings. Moisturizers and topical antifungal medications were prescribed for the hyperkeratotic lesions.

We collected blood samples from four individuals, including our patient, and performed genomic DNA isolation. Three pairs of primers were used for the SLURP1 gene. These primers included; 1F: 5'GAACAGTGAGTTCCCCAGTG 3', 1R: 5'CACTGAGAATGAGGAGGGTG 3', 2F: 5'GATGTCAGCGAGACTCCTTC 3', 2R: 5'CAGGACTGGGTCTCTGAG 3', 3F: 5'GAACAGGGATCACAGGGAG 3', 3R: 5'GTCATGTCCACTCTTGGCTT 3', respectively. From the isolated DNA samples, the extrinsic regions of the SLURP1 gene were screened using sequence analysis and Sanger sequencing was performed with the 3130 Sequence Analyzer.

Results of this analysis show that, a p.Arg 96 Pro (R96P) (c.287 CGA>CCA) homozygous missense point mutation was detected on the SLURP1 gene of the patients, while heterozygous p.Arg 96 Pro (R96P) (c.287 CGA>CCA) mutation was detected in the mother, father and brothers (Fig. 4). Our search of the HGMD (human genome mutation database) and previous literature revealed no previous report of this mutation in Mal de Meleda.

Discussion

Mal de Meleda, a hereditary palmoplantar keratoderma, is characterized by symmetrical palmoplantar keratoderma and hyperkeratosis covering the dorsal surface of the hands and feet in glove-sock form occurring at birth or within a few years after birth [3]. Apart from these findings, patients have also presented with findings such as hyperhidrosis in the palms and soles of the feet, pointed pits in palmoplantar keratoderma areas, perioral erythema, brachydactyly, nail disorders, progressive, conical, thinning, contracture and pseudoarthritic developments on the fingertips, and

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cleft palate [3-5]. Our patient presented with hyperhidrosis in the palms and soles of the feet, pointed pits in palmoplantar keratoderma areas, and subungual hyperkeratosis.

Autosomal recessive palmoplantar keratodermas should be considered at differential diagnosis of Mal de Meleda. Among these, the Papillon-Lefèvre syndrome is characterized by periodontitis and premature tooth loss [6]. Our patient's teeth were normal in appearance. Hyperkeratosis, which was observed on the dorsal surfaces of our patient's hands and feet and mild erythema also help to differentiate it from the autosomal dominant Thost-Unna keratoderma [3]. The absence of mental retardation and corneal dystrophy distinguished it from Richner-Hanhart syndrome, while the absence of periorificial verrucous papules and hyperkeratosis distinguished it from Olmsted syndrome. Honeycomb pattern and star-like hyperkeratosis, deafness, spontaneous amputations and the absence of ichthyosis distinguished it from the autosomal dominant Vohwinkel syndrome, the absence of concomitant esophageal malignancy and oral mucosal lesions distinguished it from Howel-Evans syndrome, while the absence of woolly hair and cardiac anomalies helped to distinguish it from Mal de Naxos [2,5-8].

In 2001, the pathogenesis of Mal de Meleda was reported to be due to the ARS (component B) gene mutation encoding SLURP1 in the chromosome 8q24.3 region [9]. In addition to its role as a neuromodulator regulating epidermal homeostasis, the SLURP1 protein is also known to inhibit the secretion of tumor necrosis factor alpha from macrophages during wound healing. These roles also explain the hyperproliferative and inflammatory processes reflected in the clinical manifestation of Mal de Meleda [1]. Examination of the DNA material obtained from the patient's blood sample revealed a p.Arg 96 Pro (c.287 CGA>CCA) homozygous missense mutation in the SLURP1 gene. No case of Mal de Meleda with this mutation was encountered in our scan of the previous literature.

Mal de Meleda, with its chronic course, is difficult to treat. Topical keratolytic agents are usually employed [7]. Treatment with systemic retinoids, 5-fluorouracil infusion, and bath PUVA has also been reported to be very effective [10,11]. However, symptoms may resurface when treatment is discontinued. Treatment should be supplemented with antibacterial and antifungal medication due to the increased risk of bacterial and fungal infections in these patients [1]. Topical antifungal therapy was administered in our case because hyphae and spores were observed at direct KOH analysis prepared from the palms and soles of the feet, and also from the nails.

We report this case due to the identification of a novel gene mutation in a patient with Mal de Meleda, a palmoplantar keratoderma.

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Figure 1: Pedigree

Figure 2: Bilateral palmoplantar pointed pits on slightly erythematous yellowish hyperkeratotic areas extending to the dorsal aspect of the hands and feet.

Figure 3: Light microscopic image of the lesion showing hyperkeratosis on the surface, thickening of the granular layer and marked psoriasiform hyperplasia (hematoxylin-eosin staining, x40).

Figure 4: Sanger Sequence heterozygote image (mother, father and brothers) (above)/ Sanger Sequence homozygote image of the patient (below)

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