Mal de Meleda (MDM) is a rare autosomal recessive inflammatory keratoderma, characterized by diffuse erythema and hyperkeratosis of the hands and feet that appears soon after birth and progressively extends to the dorsal aspect of the hands and feet and around the wrist and ankles. In addition, there are erythematous hyperkeratotic plaques over the joints, perioral erythema, brachydactyly and nail abnormalities. The palmo plantar keratoderma (PPK) is usually associated with hyperhidrosis and superinfection resulting in malodorous maceration. The hyperkeratosis of the hands typically causes conical tapering and constriction of fingers with severe functional restriction of the hands and sometimes spontaneous amputation of the digits.

Although MDM is mainly reported from the island of Meleda/Mljet, it has been observed in other parts of the world, including the Mediterranean countries, middle East, Taiwan and Americas. The disease locus of MDM has been mapped to chromosome 8qter, and in recent studies, homozygous mutations in the ARS (component B) gene have been identified in families with this disorder. In this report, we describe the clinicopathologic findings of a Taiwanese woman with MDM in whom homozygous missense mutation in the ARS gene was detected.

Case Report

The proband, a 27-year-old female, presented with PPK that appeared soon after birth. The family reported no known consanguinity. She was the only affected member in the family. On examination, the patient had marked erythema and hyperkeratosis of the hands and feet in a glove-and-stocking distribution, accompanied by malodor (Fig.). The hyperkeratotic areas showed a prominent background erythema. In addition, large erythematous keratotic or scaly plaques were present over the joints (knees and elbows) and thighs. The keratoderma of the hands was most severe and caused conical tapering of fingers with reduced mobility of the hands. The nails were thickened. Widespread mottled hyperpigmentation was noted symmetrically over the extremities. She had normal sweating. No abnormalities of the eyes, teeth and hair were found. She showed no signs of delayed psychomotor development.

Biopsy of a hyperkeratotic lesion revealed marked hyperkeratosis with parakeratosis, psoriasiform epidermal hyperplasia with hypergranulosis and a sparse superficial perivascular predominantly lymphocytic infiltrate. Electron microscopy showed marked thickening of the stratum corneum with parakeratosis. Some corneocytes contained lipid vacuoles. Small aggregates of lamellar bodies were noted in the intercellular spaces in the first few layers of the corneocytes. These findings are consistent with MDM. Biopsy of a hyperpigmented macule showed slight psoriasiform hyperplasia with basal hyperpigmentation and some pigmented dendritic melanocytes in the epidermis without melanocytic proliferation. The keratoderma improved after treatment with acitretin 20 mg/day.
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Genomic DNA was extracted from whole blood. The 3 exons of the ARS gene were amplified by polymerase chain reaction using previously described primers.7 Automated sequencing revealed a homozygous G→A transition at nucleotide 256 in exon 3 of the proband, predicting a conversion of a glycine (GGG) to an arginine (AGG) at amino acid 86 (G86R). The mutation was confirmed by both forward and reverse sequencing. Both parents and 2 of the 3 sisters of the patient were carriers of the same mutation.

Discussion

The phenotypic hallmark of MDM is the presence of transgressive PPK. Transgressive PPK can also be observed in Naxos disease (PPK with cardiac abnormalities and woolly hair) and Papillon-Lefevre syndrome (PPK with periodonopathia). However, these other forms of PPK can be distinguished from MDM based on their associated clinical features.10,11

The present family is the second pedigree with MDM reported from Taiwan. These 2 pedigrees appear unrelated. In addition to the keratoderma, our patient manifested widespread mottled hyperpigmented macules. Review of the clinical photos of the patients from the first pedigree revealed similar macules on the forearms in 1 of the affected sisters. Whether this pigmentary anomaly is a clinical manifestation of MDM remains to be determined.3

The ARS (component B) gene encodes secreted lymphocyte antigen-6/urokinase-type plasminogen activator receptor-related protein-1 (SLURP-1).7 To date, 10 different mutations in the ARS gene have been reported.7–9,12 The nucleotide 256 in exon 3 may represent a mutation hot spot, since 256G>A mutation has been reported 3 times (in the present pedigree, a Palestinian pedigree and a Turkish pedigree5) and 256G>C mutation has been reported once in Turkish pedigree.3

The pathogenesis of abnormal keratinization and local inflammation in MDM is still not clear. The process of keratinization and desquamation of the epidermis is very complex and requires precise coordination and sequential regulation of multiple genes. SLURP-1 is expressed in the skin, exocervix, gums and esophagus by immunostaining.13 The protein is secreted by cultured keratinocytes, and its expression is regulated by retinoic acid, epidermal growth factor and interferon-γ. The tissue localization and the association with MDM suggest that SLURP-1 is implicated in maintaining the physiologic and structural integrity of the epidermis.

SLURP-1 belongs to the Ly-6/uPAR superfamily of receptor and secreted proteins, which participate in signal transduction, immune cell activation or cellular adhesion.14,15 SLURP-1 is structurally related to snake neurotoxins and Lynx1 (an endogenous toxin-like modulator of nicotinic acetylcholine [ACh] receptors)16 which suggests that SLURP-1 may act as a ligand for a neuronal ACh receptor. ACh is remarkably abundant in the epidermis and other types of surface epithelium. In keratinocytes, neuronal nicotinic ACh receptors (nAChR) have been shown to control cell viability, proliferation, differentiation and motility.17 The ACh signaling through α7 nAChR channels appears essential for epidermal homeostasis.18 Chimienti et al reported that SLURP-1 acts as a neuromodulator of the human α7 nAChRs of keratinocytes, and suggested that SLURP-1 is likely to be essential for both epidermal homeostasis and inhibition of tumor necrosis factor-α release by macrophages during wound healing.15 This may explain both the hyperproliferative as well as the inflammatory phenotype of MDM.15

Further research of factors involved in regulating α7 nAChR signaling pathway in the skin may facilitate development of specific treatment to reduce the
keratoderma and the associated inflammation in MDM.

**ACKNOWLEDGMENT:** This study was supported by grant NSC91-2314-B006-112 from the National Science Council, Taiwan.

**References**