



# Mal de Meleda: A late-diagnosed family with a pathogenic variant not reported from Turkey

*Mal de Meleda: Türkiye'den daha önce bildirilmemiş mutasyona sahip ileri yaşta tanı alan bir aile*

● Zeynep Karaca, ● Savaş Yaylı\*, ● Sevgi Bahadır\*

Kars Harakani State Hospital, Clinic of Dermatology, Kars, Turkey

\*Karadeniz Technical University Faculty of Medicine, Department of Dermatology, Trabzon, Turkey

## Abstract

Mal de Meleda (MDM), also called keratoderma palmoplantaris transgrediens, is a rare autosomal recessive palmoplantar keratoderma with an estimated prevalence of 1:100,000. Genetic mutations affecting SLURP-1 play a role in MDM. It typically starts shortly after birth and is characterized by hyperkeratosis extending from the palmoplantar region to the dorsal surfaces that worsens with age. MDM can lead to severe functional limitations involving the hands and feet and psychosocial problems. The rarity of the condition can lead to misdiagnoses and unsuitable treatments, with MDM commonly mistaken for psoriasis due to the involvement of the elbows and knees. This report presents the case of a family affected by MDM who had a pathogenic variant previously not reported in Turkey, been followed up with the diagnosis of psoriasis for several years, and received a late diagnosis where systemic acitretin achieved satisfactory clinical improvement.

**Keywords:** Mal de Meleda, palmoplantar keratoderma, SLURP1, rare diseases, autosomal recessive diseases

## Öz

Keratoderma palmoplantaris transgrediens olarak da bilinen Mal de Meleda (MDM), tahmini prevalansı 1:100.000 olan nadir görülen ve otozomal resesif geçiş gösteren bir palmoplantar keratodermadır. SLURP-1 genetik mutasyonları, MDM'de rol oynar. Tipik olarak doğumdan kısa bir süre sonra başlar. Palmoplantar bölgeden dorsal yüze ilerleyen ve yaş ile kliniği kötüleşen hiperkeratoz ile karakterizedir. Hastalık el ve ayaklarda ciddi işlevsel bozukluğa ve psikososyal problemlere yol açabilir. Çok nadir olduğundan hastalar yanlış tanı ve tedaviler alabilmektedirler. Diz ve dirsek tutulumu nedeniyle psoriasis ile karıştırılabilmektedir. Bu olgu sunumunda, daha önce Türkiye'den bildirilmemiş patojenik varyanta sahip olan ve uzun yıllar psoriasis tanısı ile takip edilen, geç tanı alan ve sistemik asitretin ile tatmin edici klinik iyileşme sağlanan MDM tanılı aile sunulmaktadır.

**Anahtar Kelimeler:** Mal de Meleda, palmoplantar keratoderma, SLURP1, nadir hastalıklar, otozomal resesif hastalıklar

## Introduction

Mal de Meleda (MDM) is a rare palmoplantar keratoderma (PPK) that starts immediately after birth and usually worsens with age, potentially leading to severe functional limitations involving the hands and feet<sup>1</sup>. It shows an autosomal recessive (AR) pattern of inheritance with an

estimated prevalence of 1 in 100,000<sup>1,2</sup>. Due to being rare, MDM can commonly be overlooked, misdiagnosed, and inappropriately treated. This case report aimed to present a family with a pathogenic variant not previously reported in Turkey who received a late diagnosis to demonstrate the significance of genetic diseases in clinical dermatology practice.

**Address for Correspondence/Yazışma Adresi:** Zeynep Karaca MD, Kars Harakani State Hospital, Clinic of Dermatology, Kars, Turkey  
Phone: +90 530 512 75 45 E-mail: zeynepkaraca.zk90@gmail.com **Received/Geliş Tarihi:** 10.05.2020 **Accepted/Kabul Tarihi:** 05.10.2020  
**ORCID:** orcid.org/0000-0002-3333-7027

## Case Report

A 58-year-old male patient with palmoplantar thickening and erythema since childhood presented to the outpatient clinic with recently developed pruritus. The patient's parents, sister, and children were healthy; however, his two brothers had similar symptoms since childhood. The patient did not have a history of consanguinity among his parents and had been followed up for palmoplantar psoriasis since childhood. The patient had been treated for psoriasis, unsatisfactorily, and sought treatment only for a recent pruritus onset. Dermatological examination revealed well-circumscribed erythema and scaling extending from the palms and soles of the hands and feet to the dorsal surfaces, wrists, and ankles and diffuse, yellow-white hyperkeratotic plaques in the palmoplantar region. Additionally, the patient had developed koilonychias and subungual hyperkeratosis, well-circumscribed erythematous-squamous plaques on the knees and elbows, sclerosis toward the fingertips, and flexion contracture of the hand (Figure 1). The patient did not have comorbid diseases. Palmoplantar, knee, and elbow involvement supported the diagnosis of psoriasis; however, diffuse hyperkeratosis instead of the typical squamous pattern and sclerotic appearance of the fingers suggested PPK. The biopsy revealed severe hyperkeratosis, acanthosis, an increase in the granular layer, and spongiosis in the epidermis, all of which were evaluated as compatible with PPK. The patient was suspected to have MDM and was initiated on acitretin at 25 mg once daily (qd). Moreover, the KOH preparation of the shave biopsy obtained from the

well-circumscribed erythematous lesions in the hands and feet revealed fungal hyphae. The patient was initiated on itraconazole at 200 mg by mouth (PO) twice daily. After 1 week of treatment, the pruritus regressed almost completely. The patient's two brothers (aged 52 and 50 years), who had as well been diagnosed with psoriasis but had not received any treatment, had similar clinical presentations (Figure 2). They were correspondingly initiated on acitretin at 25 mg PO qd. A sample from the 50-year-old brother underwent DNA sequence analysis for pathogenic variants in the *SLURP1* gene with a preliminary diagnosis of MDM. The results revealed c.211C>T (p.Arg71Cys) in both alleles, a variant that is not found in the ClinVar database and which was considered to be pathogenic. The symptoms of all three patients had regressed after 1 month of acitretin treatment. By the end of the third month, hyperkeratosis had reduced almost by half. Informed consent were obtained from all patients.

## Discussion

MDM was first described by Croatian scientist Luca Stulli in 1826<sup>1</sup>. MDM has been shown to be present in at least in 20 countries (i.e., Algeria, Taiwan, China, Germany, India, Indonesia, Italy, Japan, Australian, Korea, Libya, Netherlands, Pakistan, Croatia, Scotland, Sweden, Tunisia, Turkey, UEA, and USA) and to affect at least 19 ethnic populations<sup>2</sup>. The first cases in Turkey were reported in 1970. Majority of the reported cases were diagnosed during the first 20 years of life<sup>3</sup>.



**Figure 1.** Well-circumscribed erythema; scaling extending from the palms and soles of the hands and feet to dorsal surfaces, wrists, and ankles; and diffuse, yellow-white hyperkeratotic plaques in the plantar region (a, b), transgradient involvement in the dorsa of hands (c), and well-circumscribed erythematous-squamous plaques on the knees (d)



**Figure 2.** (a-c) Similar clinical involvement in the middle and (d-f) younger siblings

The disease begins in the form of well-circumscribed “glove and stocking” erythema which becomes hyperkeratotic over time and often takes a progredient course. The palmoplantar lesions are transgradient and can extend to the dorsa of the fingers in children and to the dorsal surfaces of the hands and feet in adults<sup>1</sup>. Other symptoms include hyperkeratotic lesions on the knees and elbows, perioral erythema, nail dystrophy, and clubbing of the fingers. Moreover, the disease has been described in association with pseudoainhum and spontaneous autoamputations<sup>4</sup>. Histological findings of MDM include non-epidermolytic hyperkeratosis and acanthosis in the epidermis and perivascular lymphocytic infiltrate in the dermis<sup>2</sup>. Histopathology results suggested PPK in our first patient; hence, we did not require a skin biopsy for the other two patients due to the similar clinical findings noted and preliminary diagnosis of MDM.

The diagnosis of MDM includes clinical presentation, family history, and genetic analysis<sup>1</sup> and should consider concomitant cutaneous and extracutaneous findings<sup>5</sup>. The differential diagnosis should assess PPK<sup>6</sup>. PPK of the Gamborg-Nielsen type is an AR inherited condition caused by *SLURP1* gene mutations and has a clinical presentation similar to and represents a variant of MDM. It is separated from MDM due to its less severe phenotype, i.e. milder hyperkeratosis, no nail involvement, and no distant hyperkeratosis<sup>7</sup>. Papillon-Lefèvre syndrome (PLS) is another AR inherited PPK characterized by aggressive progressive periodontitis and early loss of permanent teeth. PLS is caused by loss-of-function mutations in the *CTSC* gene, which encodes cathepsin C<sup>8</sup>. Naxos syndrome is an AR inherited genodermatosis that is characterized by wooly hair, ventricular arrhythmias marked by ventricular extrasystoles and tachycardia, and cardiac anomalies accompanied by palmoplantar hyperkeratosis<sup>9</sup>. Tyrosinemia type 2 (Oculocutaneous tyrosinemia or Richner-Hanhart syndrome) is focal

palmoplantar hyperkeratosis with an AR pattern of inheritance that is accompanied by corneal opacity or ulcers, mental retardation, and elevated tyrosine levels<sup>10</sup>. MDM syndrome is differentiated from classic Vohwinkel syndrome by the absence of starfish-shaped keratoses on the joints, honeycomb palmoplantar keratosis, and hearing impairment<sup>11</sup>. Greither’s disease has several clinical similarities with MDM syndrome; however, in Greither’s disease, the palms and soles may be spared, the inheritance pattern is autosomal dominant, and the typical nail changes observed in MDM are absent<sup>12</sup>. Further, Olmsted syndrome is a palmoplantar hyperkeratosis characterized by periorificial fissures and plaques that may be accompanied by alopecia, pruritus, and leukoplakia, follicular keratosis, and erythromelalgia at varying frequencies<sup>13</sup>. The scleroatrophic syndrome of Huriez follows an AD inheritance, presents with palmoplantar keratosis, congenital scleroatrophy of distal extremities, and hypoplastic nail changes, and the involved skin may develop squamous cell carcinoma<sup>14</sup>. Additionally, Howel-Evans syndrome is a rare form of AD inherited PPK that is associated with esophageal cancer<sup>15</sup>. Additional complaints or symptoms besides cutaneous findings were not noted in our patients. The clinical findings including well-circumscribed “glove and stocking” hyperkeratosis, sclerotic appearance of the fingers, nail involvement, and erythematous hyperkeratotic plaques on the knees and elbows supported the diagnosis of MDM.

Currently, the molecular analysis and identification of the relevant gene allow for definitive diagnosis in most PPKs<sup>5</sup>. The disease has been linked to pathogenic variants in the *ARS (Component B)-81/S* gene (LY6LS) on chromosome 8, also known as *SLURP1*<sup>2,6</sup>. In addition to being an epidermal neuromodulator, *SLURP1* prevents the secretion of tumour necrosis factor alpha from macrophages during wound healing. This explains the hyperproliferative and inflammatory processes associated with the clinical presentation of the MDM<sup>6</sup>.

MDM has been shown to be associated with at least 20 pathogenic variants of *SLURP1*. Most affected individuals are homozygous for pathogenic variants, and there are few cases who were reported to have compound heterozygous pathogenic variants. The most recurrent pathogenic variant is c.82delT (p.Cys28fs32X) that has arisen in 23 kindred from six ethnic groups in six Mediterranean countries (i.e., Algeria, Croatia, Turkey, Scotland, Tunisia, and Italy). The pathogenic variants that have been previously reported from Turkey include c.129C>A (p.C43X), c.256G>C 1 (p.Gly86Arg), c.286C>T (p.Arg96X), and c.293T>C (p.Leu98Pro). Our patient had the c.211C>T (p.arg71cys) pathogenic variant, which has previously been reported in Japanese patients but not in Turkey<sup>2</sup>.

PPKs are not life-threatening; however, they reduce acral function and cause pain and significantly impact the patient’s quality of life. The patients can be recommended personalized shoes, analgesics, or topical anesthetics to facilitate activities of daily living<sup>5</sup>. Anti-fungal and antibacterial treatments can be used to address the increased risk of infection<sup>6</sup>. Our patient had developed a secondary fungal infection, which was treated with systemic itraconazole.

Patients can be recommended to bathe daily and maintain hand and foot care and mechanical lesion removal. Additionally, regular moisturizing, applying keratolytics (such as urea or salicylic acid), and wet dressing can help alleviate symptoms<sup>1,5</sup>. Studies have reported that 5-Fluorouracil infusion and bath-PUVA have been successful for the symptomatic treatment of MDM<sup>6</sup>. Systemic retinoids, especially

acitretin, can significantly improve complaints<sup>5</sup>. Acitretin achieves clinical improvement by normalizing epidermal cell proliferation, differentiation, and cornification. However, it has significant side effects that limit its use, including cheilitis, hepatotoxicity and lipid dysregulation, and teratogenicity. Women taking acitretin should use contraceptives for 2-3 years after the discontinuation of treatment. Alitretinoin (9-cis-retinoic acid) is a novel retinoid that has been reported to successfully treat MDM. It is considered to have more potent anti-inflammatory and immunomodulatory effects compared to other retinoids and to cause fewer side effects and requires only 1 month of contraception for women of childbearing age after the cessation of treatment<sup>16</sup>. Our patients benefited from acitretin treatment and resumed treatment. Complaints tend to recur after the mentioned PPK treatments are discontinued<sup>6</sup>. The literature reports full-thickness skin grafting to yield encouraging results with no recurrence after a certain period of follow-up<sup>1</sup>. Surgical treatment can be tried for pseudoainhum that does not respond to treatment<sup>5</sup>. In addition to functional impairments, MDM is associated with psychosocial problems due to its physical appearance, prompting patients to live secluded lives and abandon seeking treatment. They are subjected to a stereotypical stigma by society who may consider the condition infectious. All these factors require an ethical and professional approach<sup>17</sup>.

## Conclusion

MDM is a rare genetic disease that affects functionality and mental state. Early diagnosis is critical to reduce its psychosocial effects by early and efficient treatment options. To the best of our knowledge, this is the first case report identifying the c.211C>T (p.Arg71Cys) pathogenic variant in Turkey.

### Ethics

**Informed Consent:** Informed consent were obtained from all patient.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Z.K., Concept: Z.K., S.Y., Design: Z.K., S.Y., S.B., Data Collection or Processing: Z.K., Analysis or Interpretation: Z.K., S.Y., S.B., Literature Search: Z.K., Writing: Z.K., S.Y.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

## References

- Perez C, Khachemoune A: Mal de Meleda: A focused review. *Am J Clin Dermatol* 2016;17:63-70.
- Radiono S, Pramono ZAD, Oh GGK, Surana U, Widiyani S, Danarti R: Identification of novel homozygous SLURP1 mutation in a Javanese family with Mal de Meleda. *Int J Dermatol* 2017;56:1161-8.
- Ayman T, Yerebakan O, Yilmaz E: Mal de Meleda: A review of Turkish reports. *J Dermatol* 2000;27:664-8.
- Guerra L, Castori M, Didona B, Castiglia D, Zambruno G: Hereditary palmoplantar keratodermas. Part I. Non-syndromic palmoplantar keratodermas: classification, clinical and genetic features. *J Eur Acad Dermatol Venereol* 2018;32:704-19.
- Guerra L, Castori M, Didona B, Castiglia D, Zambruno G: Hereditary palmoplantar keratodermas. Part II: syndromic palmoplantar keratodermas - diagnostic algorithm and principles of therapy. *J Eur Acad Dermatol Venereol* 2018;32:899-925.
- Gurel G, Cilingir O, Kutluay O, Arslan S, Sahin S, Colgecen E: Patient with Mal de Meleda in whom a novel gene mutation was identified. *Eurasian J Med* 2019;51:206-8.
- Kastl I, Anton-Lamprecht I, Gamborg Nielsen P: Hereditary palmoplantar keratosis of the Gamborg Nielsen type. Clinical and ultrastructural characteristics of a new type of autosomal recessive palmoplantar keratosis. *Arch Dermatol Res* 1990;282:363-70.
- Machado RA, Cuadra-Zelaya FJM, Martelli-Júnior H, et al: Clinical and molecular analysis in papillon-lefèvre syndrome. *Am J Med Genet A* 2019;179:2124-31.
- Li GL, Saguner AM, Fontaine GH: Naxos disease: from the origin to today. *Orphanet J Rare Dis* 2018;13:74.
- Madan V, Gupta U: Tyrosinaemia type II with diffuse plantar keratoderma and self-mutilation. *Clin Exp Dermatol* 2006;31:54-6.
- Saleh D, Tanner LS: Vohwinkel Syndrome. 2020 Feb 5. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan.
- Athanikar SB, Inamadar AC, Palit A, Sampagavi VV, Deshmukh NS: Greither's disease. *Indian J Dermatol Venereol Leprol* 2003;69:292-3.
- Agarwala MK, George R, Pramanik R, McGrath JA: Olmsted syndrome in an Indian male with a new de novo mutation in TRPV3. *Br J Dermatol* 2016;174:209-11.
- Lee YA, Stevens HP, Delaporte E, Wahn U, Reis A: A gene for an autosomal dominant scleroatrophic syndrome predisposing to skin cancer (Huriez syndrome) maps to chromosome 4q23. *Am J Hum Genet* 2000;66:326-30.
- Sroa N, Witman P: Howel-Evans syndrome: A variant of ectodermal dysplasia. *Cutis* 2010;85:183-5.
- Bakija-Konsuo A, Zitinski M, Fatovic-Ferencic S: Mal de Meleda: A great imitator. *Clin Dermatol* 2019;37:175-81.
- Park HK, Kim EJ, Ko JY: Alitretinoin: treatment for refractory palmoplantar keratoderma. *Br J Dermatol* 2016;174:1143-4.