Case Report

Expanding the Geographic Spectrum: First Documentation of Mal de Meleda in Three Siblings from Pakistan – A Case Series

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Abstract

Mal de Meleda (MdM) is a rare autosomal recessive palmoplantar keratoderma caused by SLURP-1 gene mutations. It typically presents in early childhood with waxy, yellowish thickening of palms and soles that may extend to the dorsal surfaces. We report the first familial case series of MdM in Pakistan, involving three female siblings aged 11, 11, and 9 years. All showed varying degrees of transgradient hyperkeratosis, nail changes, and hyperhidrosis. Family history revealed consanguinity and a similarly affected paternal aunt. Based on clinical findings, a diagnosis of MdM was made. Management included topical keratolytics, antibiotics, and in one case, systemic therapy. This series underscores the phenotypic variability of MdM, emphasizes the diagnostic value of family history, and contributes to the expanding geographic understanding of this genodermatosis.

Keywords: Geographic Spectrum, Documentation, Mal de Meleda, Three Siblings.

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Introduction

Mal de Meleda (MdM), also known as keratoderma palmoplantaris transgrediens, is a rare autosomal recessive form of palmoplantar keratoderma caused by biallelic mutations in the SLURP-1 gene on chromosome 8.[1] MdM commonly presents in early childhood, initially with erythema that evolves into thickened, waxy, ivory-yellow malodorous plaques affecting the palms and soles.[2] These plaques often extend to the dorsal aspects of the hands and feet in a "glove-and-stocking" distribution and may lead to circumferential digital constriction (pseudoainhum).[3]

First described by Luko Stulli in 1826 on the island of Mljet, Croatia, MdM has primarily been reported in endemic regions around the Mediterranean Sea. For over half a century, it was misdiagnosed as leprosy until Hovorka and Ehlers identified it as a non-infectious condition, coining the term 'Mal de Meleda,' which remains in use today. This case series presents three Pakistani female siblings with sharply demarcated thickened plaques on their palms and soles, extending to the dorsal surfaces of the hands and feet . Family history in the paternal aunt (within a consanguineous family) identifies this as the first Pakistani familial case of MdM to our knowledge, and among the most remote from the endemic region. This report aims to expand the understanding of the pheno-typic variability and geographical distribution of MdM, emphasizing its clinical diversity. The cases were first seen in early 2024. The patients are lost to follow-up.

Case Reports

Patient "Ms. A"

An 11-year-old Pakistani girl, born via cesarean section as part of a twin birth, presented with a lifelong history of thickened, yellowish skin on the

palms and soles, beginning symmetrically at the fingertips and toe tips at 6 months of age and gradually spreading in a transgradient "glove-and-socks" distribution (Figure-1). Symptoms worsened in winter, with tingling pain, sensory loss, difficulty walking, and significant weight loss over the last six months. She also reported palmoplantar hyperhidrosis and heat intolerance, which exacerbated her discomfort. Examination revealed sharply demarcated hyperkeratotic plaques extending to the dorsal hands, feet, wrists, ankles, and Achilles tendon region; elbows, knees, and perianal region were spared. Nail abnormalities included koilonychia, transverse ridging, erythronychia, and half-and-half nails. After a 6-minute water immersion test, the skin appeared spongy white without papules, followed by fissuring. Sclerodactyly limited daily activities and contributed to pain (Figure-2).

The patient's medical history included recurrent infections, particularly maceration between finger webs, without any history of blistering, hearing loss, or dental anomalies. Family history revealed a similarly affected paternal aunt. Two younger sisters had milder forms, and parental consanguinity was present. Based on clinical features and family history, a diagnosis of Mal de Meleda (MdM)—a rare autosomal recessive palmoplantar keratoderma—was made. Laboratory investiga-

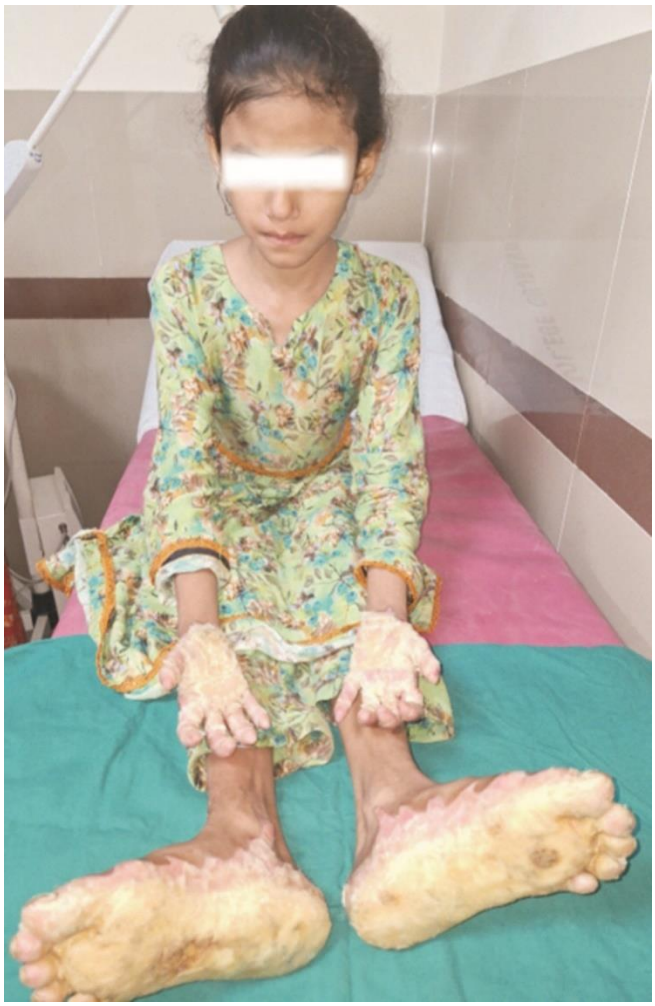

Figure 1: *Diffuse, yellow, waxy hyperkeratotic plaque with a red, scaly border over the palms and soles, presenting in a glove-and-stocking distribution.*

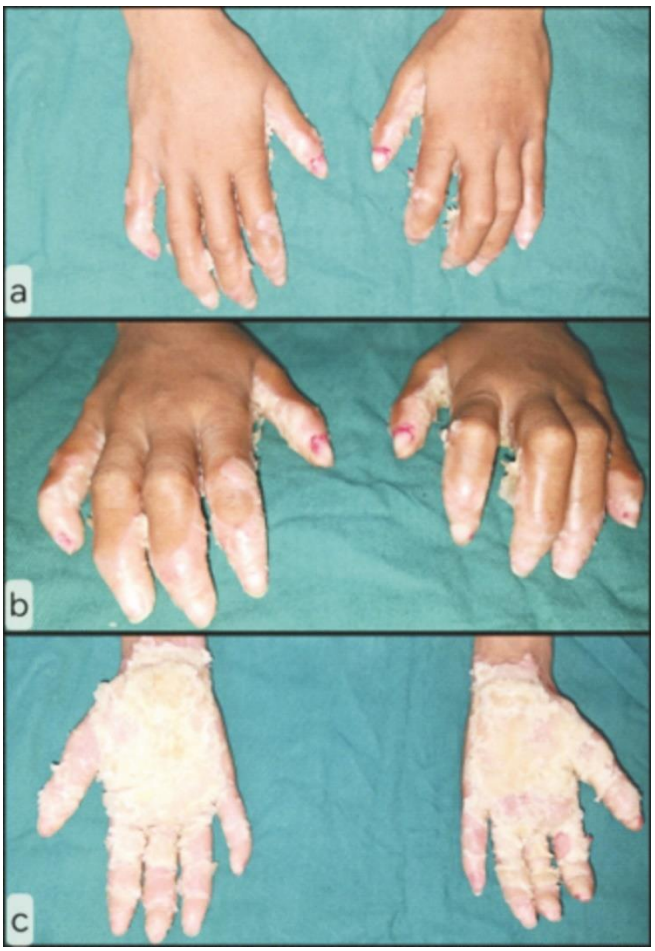

Figure 2: ***(a)****; Fingers show flexion contracture. There is circumferential hyperkeratosis, leading to sclerodactyly and digital constrictions.* ***(b)*** *Nail changes include hyper-curvature, koilonychia, transverse ridging, erythronychia, and half-and-half nails (normal RFTs).****(c);*** *Diffuse yellow, waxy hyperkeratotic plaques on the palms with scaly borders, loss of dermatoglyphs, and pseudoainhum. Lesions extend onto the dorsal aspects of both hands*

tions showed elevated triglycerides for age (148 mg/dL) with normal cholesterol (108 mg/dL), and no other significant findings.

Treatment included topical fusidic acid 2% and terbinafine for secondary infections; a mixture of 5% salicylic acid and 10% urea in petroleum jelly twice daily for hyperkeratosis; and a 1:1 mix of liquid paraffin and petroleum jelly for hydration. Systemic therapy comprised oral itraconazole 100 mg once daily, levofloxacin 250 mg once daily, syrup Co-amoxiclav 312.5 mg twice daily, ibuprofen for pain, and cetirizine at bedtime for pruritus. Despite this regimen, the patient experienced persistent symptoms, emotional distress, insomnia, irritability, school dropout, and social isolation, highlighting the profound psychological and functional burden of the disease.

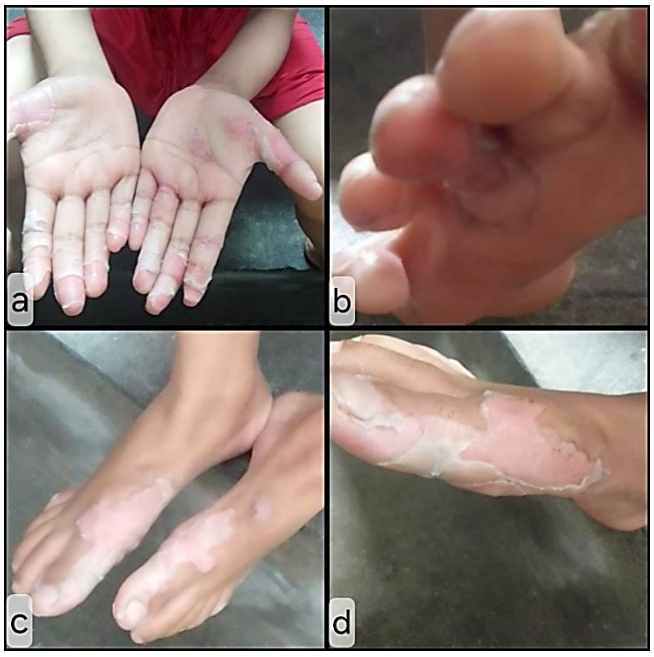

Figure 3 (a–d)**:** *Sharply demarcated, thickened plaques with peeling on palms and soles.*

Patient "Ms. B"

An 11-year-old female, twin of Patient Ms. A, presented with thickened yellowish plaques on palms and soles, first noted at age 7 on finger and toe tips. Progression was gradual, without hyperhidrosis. Examination revealed well-demarcated transgradient hyperkeratosis with a "glove-and-stocking" distribution (figure-3), nail ridging, and thickening. No infections, blistering, dental, auditory, or developmental abnormalities. School attendance continued with minimal social discrimination. Diagnosed clinically as Mal de Meleda (MdM); managed with topical therapies only.

Patient "Ms. C"

A 9-year-old female, youngest sibling of Patients Ms. A and Ms. B, showed milder transgradient hyperkeratosis starting at age 7. Lesions involved palms, soles, and dorsal aspects of hands/feet (Figure-4). She reported hyperhidrosis and malodor but no pain, fissures, or systemic features. Nails showed mild transverse ridging. Water immersion test revealed white sponginess. No periorificial hyperkeratosis, alopecia, infections,

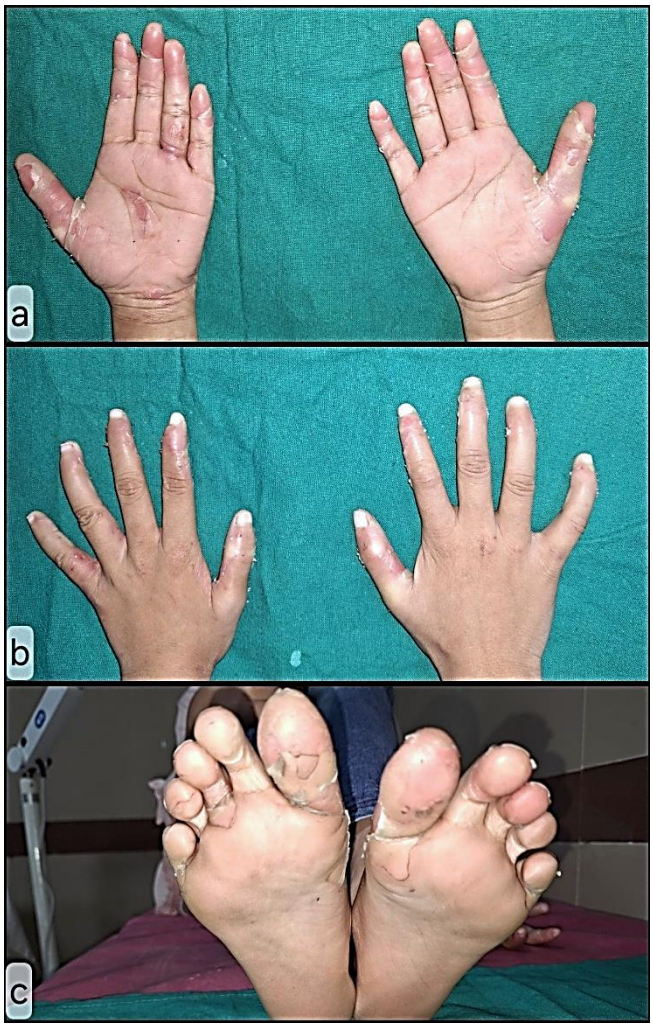

Figure 4 (a, b, c): *Yellow, thickened skin with peeling on the palms and soles.*

Table 1: *Stepwise Management Approach For Palmoplantar Keratoderma.*[10]

Step	Considerations
1. General Measures	– Weekly soaks + mechanical debridement (pumice/callus file). – Fissures: Razor debridement + bedtime occlusive Vaseline dressings. – Footwear, hygiene. – Emollients to reduce dryness/fissures. – Treat bacterial/fungal infections.
2. Topical Therapies	– Keratolytics: Urea 10–40%, SA 6–12%. – Combo: Urea + salicylic acid or lactic acid. – Retinoids (tazarotene/tretinoin): Mild PPK; combine with oral for severe. – Steroids: Inflammatory PPK, esp. with keratolytics. – Vit D3 analogs: ~50% response; combine with oral retinoids. – Dermabrasion: Enhances topical absorption. – PUVA.
3. Systemic Therapies	– Retinoids (acitretin > isotretinoin), low-dose (≤25 mg/d) for hyperkeratosis/contractures. – Monitor for hepatotoxicity, hyperlipidemia, teratogenicity (esp. acitretin: 3-year contraception). – Blistering forms: Start low to avoid erosions.
4. Surgical Care	– Debridement for hyperkeratosis/pseudoainhum prevention. – Surgical release or excision + grafting in advanced cases. – CO_2 laser: Limited benefit.
5. Physiotherapy	– Prevent contractures, maintain joint mobility.
6. Follow-up & Monitoring	– Monitor treatment response, side effects, infections, erosions.
7. Genetic Counseling	– Discuss risks, family planning.
8. Emerging Therapies	– siRNA: Targets keratin mutations. – Readthrough drugs (e.g., topical gentamicin): Promising in Nagashima-type.

leukokeratosis, blepharitis, corneal dystrophy, delayed growth, hearing/dental issues, eosinophilia, or lipid abnormalities. Social stigma due to skin appearance noted despite school attendance. Diagnosis of MdM made based on clinical features and family history; only topical treatment was given.

Discussion

Mal de Meleda (MdM) is a rare autosomal recessive palmoplantar keratoderma (PPK) first described on Croatia's Meleda island in 1826. It is caused by biallelic mutations in the SLURP1 gene, which encodes the secreted Ly6/uPAR-related protein-1, essential for regulating keratinocyte differentiation and immune function in the epidermis. Loss of SLURP1 function disrupts skin barrier integrity, leading to hyperkeratosis, inflammation, and fissuring.[4] The most common mutations—c.82delT, p.Arg96, and p.W15R—are more prevalent in Europe and Mediterranean populations, suggesting a founder effect.[5] Clinically, MdM presents with transgrediens (extension beyond palms and soles), pseudoainhum (constrictive bands), painful fissures, and secondary infections.[6] Unlike epidermolytic forms such as Vörner and Greither syndromes, MdM is non-epidermolytic. The differential diagnosis includes other mutilating PPKs with transgrediens and pseudoainhum, notably Vohwinkel syndrome (GJB2, with deafness), Olmsted syndrome (TRPV3, with periorificial keratoderma), and Greither syndrome (epidermolytic).[7] Genetic confirmation of SLURP1 mutations is ideal for accurate diagnosis, prognosis, and family counseling due to the autosomal recessive inheritance and risk in consanguineous families.[9] New therapies under investigation include siRNA targeting keratin gene mutations, particularly effective in pachyonychia congenita (KRT6A), and read through agents like topical gentamicin, which show promise in Nagashima-type PPK.[8,10] A deeper understanding of SLURP1-related pathways

may support targeted therapeutic interventions, including immune modulation and keratinocyte differentiation control, with gene therapy offering potential future options.

Limitations include clinical-only diagnosis without SLURP1 genotyping (cost-prohibitive) and loss to follow-up.

Written consent for participation and publication of clinical details and images was obtained from the patients' guardians.

Conclusion

This case series highlights three siblings with varying severity of Mal de Meleda, a rare autosomal recessive disorder. Their presentations reflect the phenotypic variability of the disease, from severe hyperkeratosis with hyperhidrosis to milder keratosis without hyperhidrosis. This series underscores the importance of family history and consanguinity in the diagnosis and provides further insight into Mal de Meleda.

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Author's Contribution

YS: Conceived, designed, edited the manuscript, given final approval of the version to be published, critical revisions.

NS: Manuscript writing, final approval of the version to be published.

AS: Manuscript writing, final approval of the version to be published.

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