SHORT COMMUNICATION

# Mal de Meleda: Diagnostic Work-up and Therapy with Low-dose Acitretin

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Keratosis palmoplantaris transgrediens et progrediens is a rare autosomal recessive hyperkeratotic skin disorder (estimated prevalence 1/100,000), first described in 1826 by Luko Stulli as "Mal de Meleda" on the Adriatic island of Mljet (Meleda) in Southern Croatia (1). It belongs to the heterogeneous group of hereditary palmoplantar keratodermas (PPKs) which can be focal or diffuse with or without extracutaneous manifestations (i.e. syndromic) and variable prognosis. An exact diagnosis followed by genetic counselling is important for the patient and affected family. However, given the diversity of hereditary PPKs and their rareness, making the correct diagnosis and choice of optimal therapy might be challenging.

## CASE REPORT

An 82-year-old Caucasian male presented with a history of palmoplantar hyperkeratosis since early childhood with extension to the dorsal aspects of the feet and hands and progression with age. He had a history of type 2 diabetes, arterial hypertension, chronic kidney disease and age-related macular degeneration. His ancestry search back to the year 1700 and his 5 own children (4 sons, 1 daughter) did not reveal a PPK or other dermatological diseases.

Clinical examination revealed plaque-like yellowish and waxy palmoplantar hyperkeratosis with adjacent sharply demarcated, fine scaly erythema, which extended to the forearms and lower legs in a cuff-like (gloves and socks) distribution (**Fig. 1**a–d). In addition, nail dystrophy (Fig. 1e) and malodour was found. Total-body skin examination, including oral cavity, teeth and scalp hair, revealed no pathological findings. A punch biopsy from plantar skin revealed hyperkeratosis, mild hypergranulosis and a discrete perivascular inflammatory infiltrate in the superficial dermis, but no epidermolysis. Fungal culture from palmoplantar skin revealed *Trichophyton verrucosum*.

Based on the early onset of disease, clinical presentation with palmoplantar transgredient and progressive hyperkeratosis and likely autosomal recessive inheritance, a hereditary PPK, specifically keratosis palmoplantaris transgrediens et progrediens (Mal de Meleda) was suspected. This clinical diagnosis was later confirmed by detecting a homozygous *SLURP-1* gene mutation.

The patient received intensive topical treatment, including keratolytic agents, tretinoin and class III steroids. In addition, he carefully removed hyperkeratotic skin after a daily hand and foot bath, sometimes with support of a skin fraze. The *Trichophyton* superinfection was treated with topical econazole and systemic terbinafine (250 mg/day for 4 weeks).

As acitretin is generally reported to be beneficial for hereditary PPKs, including Mal de Meleda (2–4), and the patient previously experienced dysaesthesia and excessive palmoplantar desquamation at higher doses (20–30 mg/day), low-dose acitretin was initiated at 10 mg/day. Two months later, the patient showed significantly reduced palmar hyperkeratosis and reduced area and intensity of erythema on the forearms and lower legs, with continuous improvement over 6 months (Fig. 1f–i). Furthermore, nail dystrophy and overall desquamation diminished. Low-dose acitretin treatment was well tolerated and continued without development of dysaesthesia or laboratory parameter abnormalities for up to 12 months along with topical treatment. This therapy resulted in an improvement in the patient's quality of life from 0–1/10 numerical analogue scale (NAS) to 8–9/10 NAS.

## DISCUSSION

PPKs comprise a heterogeneous group of genetic skin diseases. An accurate patient and family history, together with thorough examination of the skin, is essential to make the correct diagnosis. The key diagnostic criteria include:

- Clinical presentation: (*i*) pattern of palmoplantar involvement (diffuse, punctate or focal hyperkeratosis); (*ii*) extension of hyperkeratosis to the dorsal aspect of hands and feet (transgrediens); (*iii*) progression during life (progrediens); (*iv*) presence of constriction rings (mutilating PPKs).
- Absence or co-occurrence of additional cutaneous or extracutaneous features: (*i*) non-syndromic isolated PPKs; (*ii*) non-syndromic PPKs with additional cutaneous features (complex PPKs); (*iii*) syndromic PPKs with extracutaneous manifestations.
- Mode of inheritance.
- Histopathology: presence/absence of epidermolysis.

In the current patient, additional cutaneous or extracutaneous manifestations were lacking, hence a complex or syndromic PPK was excluded. Due to the negative family history, an autosomal recessive inheritance or a spontaneous mutation was assumed, although the latter seemed unlikely as the patient had 5 healthy biological children.

As differential diagnosis, a PPK Unna-Thost-Vörner (epidermolytic, non-transgredient) or the transgredient and progressive PPK Greither were excluded due to clinical manifestation and mode of inheritance (dominant); thus, an autosomal recessive transgredient and progressive isolated PPK, such as PPK type Nagashima or Mal de Meleda, was likely (5). Since the Nagashima type is present only in Asians, keratosis palmoplantaris transgrediens et progrediens (Mal de Meleda) remained the final suspected clinical diagnosis in the current patient.

As in this case, Mal de Meleda manifests soon after birth with diffuse transgredient palmoplantar hyperkeratosis and erythema that progresses with age (progrediens). Furthermore, hyperkeratotic plaques on elbows and

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**Fig. 1. Clinical images at first presentation with:** (a, d) diffuse waxy palmoplantar hyperkeratosis with transgredient, (b, c) sharply demarcated erythema in a gloves and socks distribution, (e) nail dystrophy, and (f, i) clinical presentation after 6 months of therapy with considerable reduction in palmoplantar hyperkeratosis, (g) nail dystrophy, and (f–i) overall erythema and desquamation.

knees, nail dystrophy, perioral erythema, angular cheilitis, digit tapering, hyperhidrosis, microbial superinfections and malodour can be present. Rarely, pseudoainhum and melanoma can occur in affected areas (6, 7). In contrast to other hereditary PPKs, epidermolysis is lacking (5). The first 3 causative mutations were identified in 2001 in the secreted mammalian Ly-6/uPAR-related protein 1 (*SLURP-1*) gene of which one is a single nucleotide deletion (c82delT) that was also detected in the current patient (8). To date, at least 20 different mutations in the *SLURP-1* gene are known to cause Mal de Meleda, and, among others, a novel missense mutation was detected in a 27-year-old Austrian patient of Turkish origin in 2011 (9). SLURP-1 is a regulator of epidermal homeostasis, and its mutation impairs keratinocyte differentiation due to decreased transglutaminase 1, keratin 10, p21 and caspase 3, leading to hyperparakeratosis (10). Furthermore, *SLURP-1* controls inflammatory cytokines, such as tumour necrosis factor (TNF)-α, interleukin (IL)-1 or IL-6 (11, 12).

The therapeutic management of hereditary PPKs, recently reviewed by Bodemer et al. (13), aims at symptom relief, as a curative approach is currently not available. While international therapeutic guidelines are lacking due to the rareness of the disease, common approaches include topical keratolytic, anti-inflammatory and skin care agents, regular mechanical debridement and consequent therapy of bacterial/fungal superinfections (13). Systemic therapy includes oral retinoids, although worsening, especially in epidermolytic PPKs, may occur.

Isotretinoin, acitretin and alitretinoin in doses between 20 and 50 mg/day have been reported efficient after 3–4 months of therapy in PKKs including Mal de Meleda (2, 14, 15); however, with blistering, dryness and skin tenderness or severe diffuse hair loss as side-effects. A retrospective study in 30 patients with another plantar keratoderma (pachyonychia congenita) by Gruber et al. (4) revealed low-dose (<25 mg/day) acitretin for a longer duration (>5 months) being more beneficial than higher doses (>25 mg/day) for a shorter time (≤5 months) and more efficient than isotretinoin. Our observation is in agreement with a successful treatment of a less severe PPK (punctate PPK type 1) with low-dose acitretin (10 mg/day) (3). Thus, low-dose (i.e. 10 mg/day) acitretin therapy combined with consequent topical treatment represents an efficient and well tolerated long-term therapeutic approach for Mal de Meleda.

*The authors have no conflicts of interest to declare.*

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