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Refractory disseminated superficial actinic porokeratosis effectively treated with cholesterol/lovastatin cream: a case report

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Dear Editor,

Disseminated Superficial Actinic Porokeratosis (DSAP) is an autosomal dominantly inherited disorder of epidermal keratinization, with local autoinflammatory features. Recently, gene mutations in mevalonate kinase (MVK) pathway have been implicated in the pathogenesis of DSAP, linear porokeratosis and porokeratosis *palmaris et plantaris disseminata*[1-4].

MVK pathway plays a pivotal role in human physiology and disease, underlying multiple conditions of dermatological interest, such as HyperImmunoglobulin D Syndrome (HIDS) and Congenital Hemidysplasia with Ichthyosiform nevus and Limb Defects (CHILD) syndrome.

In DSAP and related porokeratotic disorders, cutaneous lesion development requires: i) an inherited monoallelic germline mutation in MVK genes, ii) a second hit somatic mutation at keratinocyte level with subsequent clonal expansion. Diseased keratinocytes account for the central, moderately atrophic portion of each lesion, while the characteristic peripheral ring (cornoid lamella) consists of a mixture of second-hit and naïve cells[5]. The resulting cholesterol-depleted phenotype is speculated to display higher susceptibility to ultraviolet A (UVA)-induced apoptosis, hence the relationship with sunlight exposure[1]. Moreover, local mevalonate accumulation may promote training of innate immune cells via Insulin-like Growth Factor 1 Receptor (IGF1-R) and mammalian Target Of Rapamycin (mTOR) activation and epigenetic phenomena, leading to an autoinflammatory microenvironment[4]. An analogous mechanism at a systemic level is believed to be responsible of HIDS autoinflammation[6].

Pathogenesis-based therapeutic approaches include topical Cholesterol/Lovastatin[7] and topical Lovastatin monotherapy[8]. The rationale of the former consists in simultaneously impairing intermediate metabolites formation in mutated cells and replenishing them with the final product. *In vitro*, statins inhibit keratinocyte proliferation, through complex cell cycle regulation. Surprisingly, replenishment with cholesterol - but not with MVK pathway intermediates - rescues the defect, at least partially[9]. Statin monotherapy also seems to be an option, possibly leveraging the anti-inflammatory consequences of mevalonate pathway inhibition[7].

Efficacy appears to be higher in DSAP, with a more modest response in linear porokeratosis and porokeratosis *palmaris et plantaris disseminata*[7].

Herein, we report a case of DSAP successfully treated with a fixed combination Cholesterol/Lovastatin galenic cream.

A healthy 66-year-old man with a 40-year history of clinically evident DSAP came in for consultation at the outpatient service of our Dermatology Clinic. The patient complained of occasional itch but was otherwise asymptomatic. His condition had proven refractory to several previous treatments, including vitamin D analogues, 5-fluorouracil cream and photodynamic therapy.

On physical examination, numerous red-brownish lesions could be documented, with a distribution favoring distal extremities. Dorsal surfaces of both forearms were particularly affected. On closer inspection, a typical, net, circular border with a rim of scale was appreciated, as well as the tendency towards central atrophy (Fig. 1 A, C). A biopsy was performed. Histopathological examination revealed the pathognomonic cornoid lamella peripherally and epidermal atrophy towards the center. The patient did not consent to genetic testing. Thus, the diagnosis of DSAP was confirmed on clinicopathological grounds and a therapeutic trial with once daily, fixed combination Cholesterol (2%)/Lovastatin (2%) galenic cream was initiated. At a two-month follow-up visit, marked improvement of the cutaneous picture was noticed, with visible reduction of lesional extent and number (Fig. 1 B, D).

Despite outstanding advancement in our understanding of porokeratotic disorders, exact molecular knowledge of their pathomechanisms still eludes us. However, current evidence seems to have finally provided clinicians with viable and effective approaches to this otherwise notoriously treatment-resistant condition.

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Figure 1. Clinical appearance of the *right* forearm before (A) and after (B) 2 months of treatment; clinical appearance of the *left* forearm before (C) and after (D) 2 months of treatment.