Topical atorvastatin in the management of porokeratosis

Dear Editor,

Porokeratosis is a heterogeneous group of disorders of keratinisation with disseminated superficial actinic porokeratosis (DSAP) being the most prevalent form.[1] Lesions appear as asymptomatic or itchy brown papules or plaques on photo-exposed regions with an atrophic or hypopigmented centre and a border looking like a raised railroad track. Though the exact pathogenesis is not known, interference of mevalonate kinase pathway in cholesterol synthesis has been shown to play some role. There are multiple therapeutic options for porokeratosis like cryotherapy, photodynamic therapy, LASERs, topical imiquimod, topical 5-fluorouracil, oral retinoids, topical steroids and vitamin D analogues, but these are not much effective and are costly. Recent research has demonstrated that treating porokeratosis with topical lovastatin and cholesterol can be effective.[2,3]

A 66-year-old male presented with multiple itchy brownish lesions over face, trunk and extremities of one year duration. On examination, multiple brownish papules and annular plaques were seen over the above-mentioned areas with central atrophy and thin raised thread-like border the size of 0.5–1 cm and minimal scaling. Figure 1a and 1b demonstrates baseline clinical images of annular plaques over trunk and forearms respectively. Histopathological examination of skin biopsy from the border of one of the lesions revealed focal invagination of epidermis with a column of parakeratosis, hypogranulosis and apoptotic keratinocytes (coronoid lamella). Figure 2 illustrates histopathological changes seen in this patient. With the diagnosis of dissemination superficial porokeratosis (DSP), the patient was started on low-dose acitretin 10 mg daily but with minimal improvement even after one year of therapy. Thereafter, the patient was counselled regarding the possible usefulness of topical statins in his skin disease. Since topical lovastatin is not commercially available, we decided to compound topical 2% atorvastatin cream in our pharmacy. It was prepared by mixing crushed tablets of atorvastatin 20 mg (10 tablets)

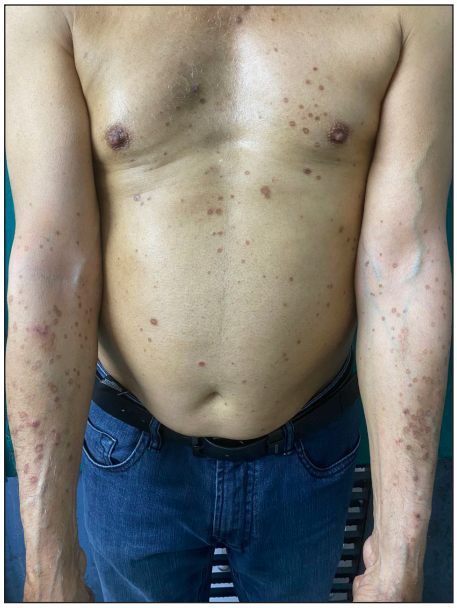

Figure 1a: At baseline, there are multiple brownish papules and annular plaques over the trunk and forearms.

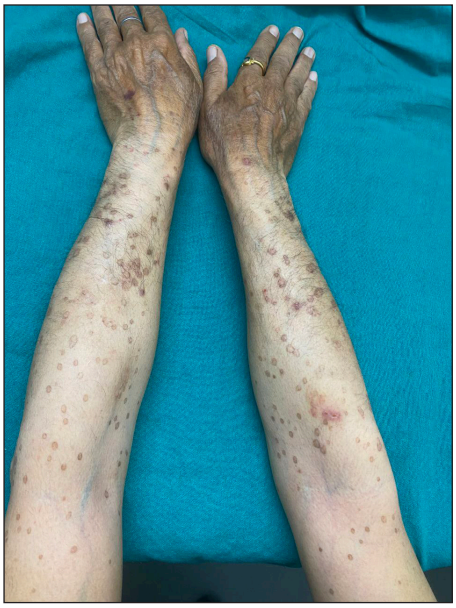

Figure 1b: Lesions with central atrophy and thin raised thread-like border.

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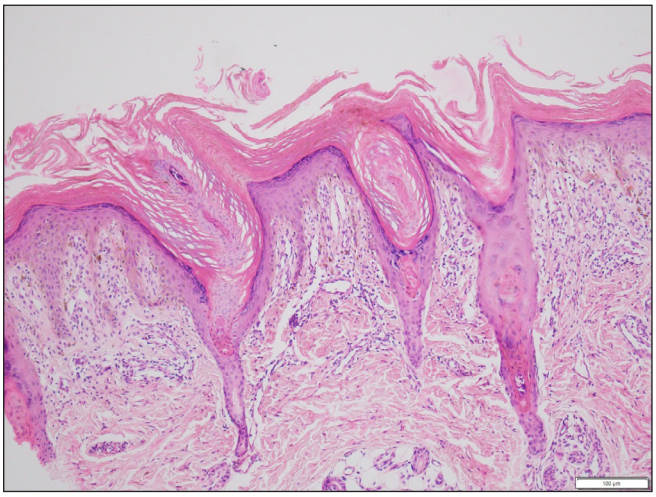

Figure 2: Histopathological examination of skin biopsy from the border of one of the lesions revealed focal invagination of epidermis with a column of parakeratosis, hypogranulosis and apoptotic keratinocytes (coronoid lamella) (Haematoxylin and eosin stain, 100x).

in 10 gms of white paraffin wax, making it 2% atorvastatin cream. We advised the patient to apply half a fingertip unit of cream to bigger lesions (approximately 2 cm), which is changed appropriately to lesional size. After one month of treatment with the combination of oral acitretin with 2% atorvastatin cream, the patient reported 40% improvement in itching; hence oral acitretin was discontinued. At the end of four months of therapy, there was complete resolution of pruritis and few lesions started to resolve. Figure 3a and 3b illustrates flattening of all lesions and 20% resolution of old lesions after 6 months of treatment. The patient reported an overall improvement in the quality of life. No adverse effects were observed.

Porokeratosis is a disorder of keratinisation; the exact pathogenesis is not known. Recent studies show that germline mutations involving genes encoding like mevalonate kinase (MVK), phosphomevalonate kinase (PMVK), farnesyl diphosphate synthase (FDPS) and mevalonate diphosphate decarboxylase (MVD) play key roles in the disease pathogenesis.[4] Loss of function of any of these genes can cause cholesterol deficiency and also accumulation of toxins leading to premature apoptosis and dysregulated keratinocyte differentiation.[5] There are few studies which have used topical lovastatin or simvastatin with cholesterol, based on the fact that statins block hydroxymethylglutaryl-CoA (HMG CoA) enzyme which prevents the accumulation of toxic end products and helps cholesterol in accessing keratinocytes for efficient transepidermal incorporation. These studies showed complete resolution of symptoms and partial to near complete resolution of lesions in two months. None of the studies showed complete resolution of lesions.[2] Various recent case series published on the role of topical statins in porokeratosis are summarised in Table 1. These findings were similar to our observations.

It can be hypothesised that by obstructing the defective pathway, toxic end products are prevented from building up and keratinocyte differentiation dysregulation is avoided. Because of this, the lesions have partially resolved. Further exploration regarding proper dosing and duration of topical statins and their efficacy in maintaining long-term remission has to be done. From our observation, we conclude that topical atorvastatin can be a cheap and effective modality in the treatment of extensive porokeratosis leading to significant improvement in the patient's quality of life. Topical statins with or without cholesterol can be combined with other therapies such as LASERs, which have shown promising outcomes for better cosmetic benefits.

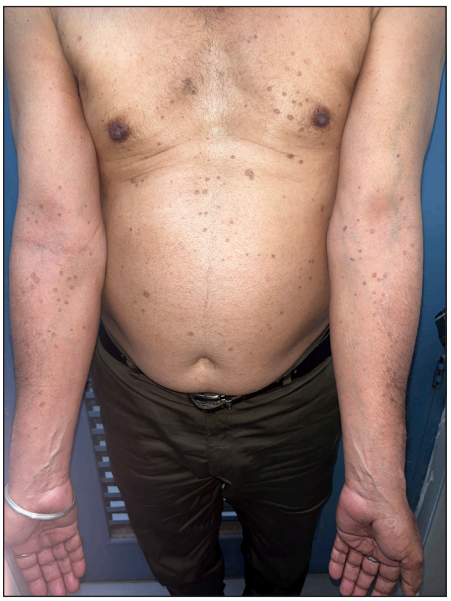

Figure 3a: Decrease in the number of lesions over the trunk and upper limbs 6-months post treatment.

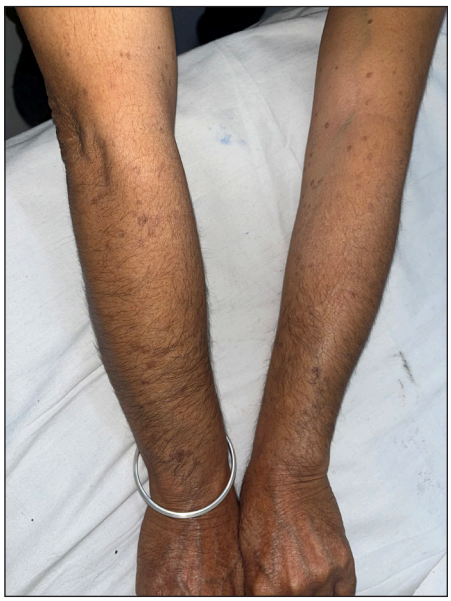

Figure 3b: Forearms post therapy at six months.

Table 1: Summary of various studies on the role of topical statins in porokeratosis

Authors	Type of topical statin	Results
Atzmony L *et al.*[2]	Topical lovastatin + cholesterol, eight patients	Near-complete clearance of DSAP in four weeks and moderate improvement of porokeratosis palmaris et plantaris disseminata lesions and linear porokeratosis.
Byth LA *et al.*[3]	Topical simvastatin + cholesterol, eight patients	Improvement in DSAP lesion number, erythema and scaling on treated limbs compared with controls in six weeks.
Albanell F *et al.*[6]	Topical simvastatin in two refractory porokeratosis phytotropica patients	In 26 months, 50% reduction in the size of lesion and there was sustained response for two years.
Santa Lucia *et al.*[7]	Topical lovastatin+ cholesterol versus topical lovastatin alone, 12 patients in each group	The disease severity decreased by 50% points on the DSAP-GASI; ($P < .001$) in the lovastatin cholesterol group and 51.4% in the lovastatin group. There was no statistically significant difference between the groups.

DSAP-GASI: disseminated superficial actinic porokeratosis

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Net Letter

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Summary: Porokeratosis is a heterogeneous group of keratinisation. We had a 66-year-old male with disseminated superficial porokeratosis (DSP) who was treated with acitretin for one year. Due to non-responsiveness, he was treated with topical atorvastatin 2% once daily application. There was complete resolution of pruritic. In four months, there was flattening of all lesions and resolution of 20% of lesions was seen by six months. Mutation in mevalonate kinase pathways causes toxin accumulation and cholesterol deficiency, leading to keratinocyte dysregulation. Statins block these pathways, preventing toxin accumulation and partial resolution of porokeratosis.