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Oral Statin Therapy in KRT16- and KRT17-Associated Palmoplantar Epidermal Differentiation Disorder (Pachyonychia Congenita)

Running head: Oral statins for KRT16/KRT17-pEDD-PC

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Ethics statement: The patients have given written informed consent to the publication of their case details.

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Abstract

Palmoplantar epidermal differentiation disorder associated with pachyonychia congenita (pEDD-PC) is a rare autosomal dominant skin disorder caused by pathogenic variants in keratin genes, including *KRT6A*, *KRT6B*, *KRT6C*, *KRT16* and *KRT17*. While statins have been reported to alleviate symptoms in *KRT6A*-pEDD-PC, their efficacy in other subtypes remains unclear. We report six adult patients, including four with *KRT17* variants and two with *KRT16* variants, who underwent off-label oral statin therapy. Statins were administered for at least six months following dose stabilization. Although the treatment was well tolerated in most cases, no significant clinical improvement in plantar calluses or pain was observed. All patients discontinued therapy due to insufficient efficacy. Our findings indicate that oral statin therapy may offer limited benefit in *KRT16*/*KRT17*-pEDD-PC and suggest the potential importance of early intervention and genotype-specific therapeutic strategies.

INTRODUCTION

Palmoplantar epidermal differentiation disorder associated with pachyonychia congenita (pEDD-PC)[1], formerly known as pachyonychia congenita, is an autosomal dominant skin disorder characterized by nail dystrophy, plantar calluses, and sebaceous cysts (steatocystoma multiplex). Diagnosis of pEDD-PC is based on clinical findings and/or identification of a heterozygous pathogenic variant in one of five keratin genes associated with the disease: *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, and *KRT17*, encoding keratins 6A, 6B, 6C, 16, and 17, respectively. The disease is further subclassified into *KRT6A/KRT6B/KRT6C/KRT16/KRT17*-pEDD-PC, according to the specific gene variant present in each patient.

pEDD-PC imposes substantial psychological and economic burdens on affected individuals, primarily due to severe plantar pain from calluses. Accordingly, there is a growing need for treatments that effectively alleviate this pain and improve patients' quality of life. Various therapeutic agents have been explored for pEDD-PC, including reports demonstrating the efficacy of oral statins, which are hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, in treating patients with *KRT6A*-pEDD-PC[2, 3, 4]. Here, we present our experience with oral statin therapy in adult patients from one *KRT17*-pEDD-PC family and one *KRT16*-pEDD-PC family.

MATERIALS AND METHODS

Off-label oral statin therapy was administered to four patients with *KRT17*-pEDD-PC (Patients 1-4), each harboring a heterozygous c.296T>C (p.Leu99Pro) variant in *KRT17* from a single family[5], and two patients with *KRT16*-pEDD-PC (Patients 5-6), each harboring a heterozygous c.374A>G (p.Asn125Ser) variant in *KRT16*, also from a single family (**Table 1**). The off-label use of statins and data collection were approved by the Institutional Review Board of Hokkaido University Hospital (#92), Hokkaido University Graduate School of Medicine (#14-063), and National Cheng Kung University Hospital (B-BR-110-100, NCKUH-11104017). The study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from the subjects prior to data collection.

Treatment was primarily with rosuvastatin. Rosuvastatin was initiated at 5 mg/day and gradually increased to 10–20 mg/day, with monthly blood tests to monitor blood counts, creatine kinase, liver function, and renal function. Approximately six months after dose stabilization, the size and pain intensity of plantar calluses were evaluated. Pain intensity was assessed using the visual analog scale (VAS). Only Patient 6 received a different regimen: pitavastatin 2 mg/day for 6 months followed by atorvastatin 10-20 mg/day for 15 months.

RESULTS

All patients completed at least six months of oral statin treatment following dose stabilization. Patients 2-4 were able to increase the rosuvastatin dose to 20 mg. Patient 1 required a dose reduction to 10 mg due to elevated serum creatine kinase levels when the dose was increased to 15 mg. The final dose for Patient 5 was also 10 mg. Patients 2-6 did not experience any adverse effects. Table 1 summarizes the VAS scores of all patients before and after the treatment, showing no substantial improvement. Similarly, the clinical manifestations of the plantar calluses remained largely unchanged in all cases (**Figure 1**). Given the limited efficacy, oral statin treatment was discontinued.

DISCUSSION

pEDD-PC-associated genes encode stress-induced keratin proteins, which serve as crucial intermediate filaments in areas subjected to mechanical stress. Dominant negative effects resulting from heterozygous variants in these keratin genes are thought to compromise the mechanical stability of epithelial cells, such as those in the

nail unit and palmoplantar epidermis. Statins may alleviate these effects by reducing the expression of *KRT6A*.

The most commonly used treatment for plantar pain in pEDD-PC is mechanical shaving of the calluses. This method, also used for calluses in the general population, has the advantage of being easily administered in any setting; however, its efficacy is temporary. Traditional topical treatments, including keratolytics, emollients, retinoids, and steroids, are not highly effective. Systemic administration of retinoids can inhibit hyperkeratosis, but long-term use is often limited by adverse effects.

In recent years, several new treatments have been reported, including intradermal injection of botulinum toxin[6] and oral erlotinib[7], partly due to the efforts of Pachyonychia Congenita Project (PC Project), an international patient advocacy organization. Rapamycin has been shown to selectively inhibit *KRT6A* expression in cultured human keratinocytes, and its topical application improved symptoms in two pEDD-PC cases. However, according to a press release from Palvella Therapeutics, a phase 3 trial using topical rapamycin did not meet a primary endpoint, which was a daily patient-reported outcome measure[8]. Furthermore, although systemic rapamycin has shown symptom improvement in pEDD-PC patients, treatment discontinuation is often necessary due to adverse effects[9]. As a specific treatment, injection of siRNA targeting the pathogenic

KRT6A variant mRNA, without affecting wild-type *KRT6A,* has shown improvement in calluses in a *KRT6A*-pEDD-PC patient[9].

Simvastatin, an HMG-CoA reductase inhibitor, reduces *KRT6A* gene expression by binding to a specific site in its promoter region[10]. This *KRT6A* inhibition by statins is partially dependent on the Stat1 transcription factor. Our rationales for oral statin therapy for *KRT16*/*KRT17*-pEDD-PC patients include: 1) previously reported efficacy in *KRT6A*-pEDD-PC patients[2, 3, 4], 2) heterodimer formation of keratins 6 and 16[11], and 3) STAT1-dependent regulation of *KRT17* expression[12]. Although some patients showed a mild reduction in VAS scores, all eventually discontinued treatment due to unsatisfactory outcomes. The limited efficacy may be attributed to minimal (direct or indirect) effects of statins on *KRT16*/*KRT17* expression, insufficient drug concentration at the target site, or it may reflect the older age of our patients compared to previously reported pediatric and young adult *KRT6A*-pEDD-PC cases[2, 3, 4]. Statins may be more effective when initiated at earlier ages[13]. Additionally, Nrf2, a known inducer of both *KRT16* and *KRT17* expression[14], is activated by statins[15]. This raises the possibility that the Nrf2-mediated upregulation of *KRT16* and *KRT17* may have offset their suppression caused by the mechanism described above. One of the limitations of this case series is its small size. It remains uncertain whether the same lack of efficacy

would be observed in other families with KRT16/KRT17-pEDD-PC. Our study suggests that therapies other than oral statins may be more beneficial for adult patients with *KRT16*/*KRT17*-pEDD-PC.

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FIGURE LEGENDS

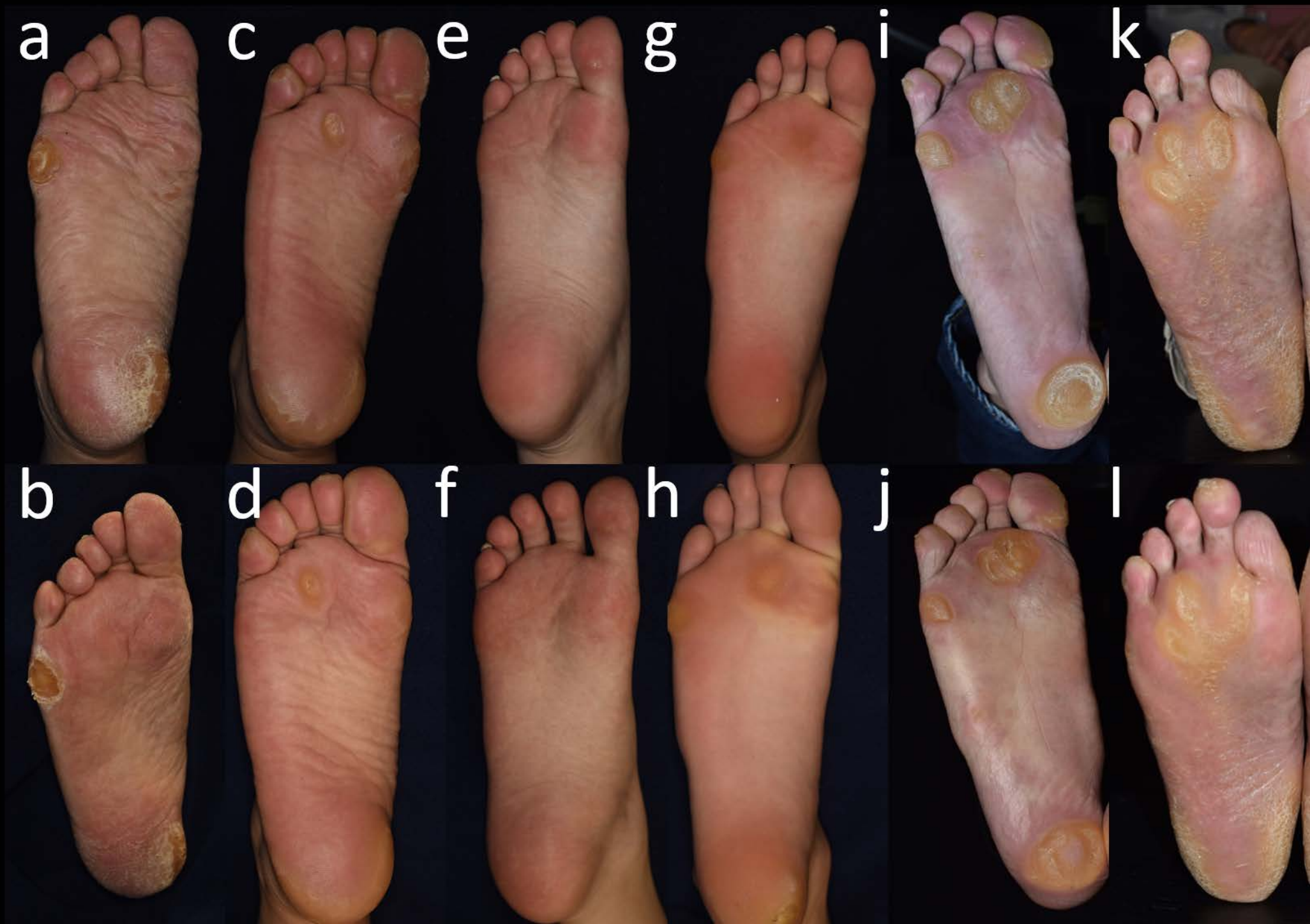
Fig. 1. Clinical manifestations before and after oral statin therapy.

(**a, b**) Patient 1; (**c, d)** Patient 2; (**e, f**) Patient 3; (**g, h**) Patient 4; (**i, j**) Patient 5; (**k, l**) Patient 6. Images before treatment (**a, c, e, g, i, k**); after (**b, d, f, h, j, l**) treatment.

Table. 1. Overview of pEDD-PC patients treated with statins.

	Family 1				Family 2	
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age/Sex	80/M	54/F	21/F	17/M	30/M	54/F
Variant	Heterozygous c.296T>C in *KRT17*				Heterozygous c.374A>G in *KRT16*	
Pre-treatment VAS score	6.4	7.3	10	8.4	4.5	Moderate to severe pain†
Post-treatment VAS sccore	4.4	7.0	3.5	5.9	8	No improvement†

†VAS score not documented in the medical record.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