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Case Report: Insights Through Translation Science | Full Access

Pachyonychia congenita: a case report of a successful treatment with rosuvastatin in a patient with a *KRT6A* mutation

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Summary

Pachyonychia congenita (PC) is a rare autosomal dominant disorder characterized by nail dystrophy and palmoplantar keratoderma with severe plantar pain affecting quality of life. There is no effective treatment. Heterozygous mutations in the keratin genes *KRT6A*, *KRT6B*, *KRT6C*, *KRT16* and *KRT17* have been reported as a cause of PC. Herein we present a female patient with an amino acid substitution mutation in *KRT6A* (c.1381G>A, p.Glu461Lys in exon 7) and classic features of PC associated with oral leucokeratosis and follicular hyperkeratosis. We also demonstrate successful treatment of the patient with rosuvastatin. A 3.6-mm reduction in plantar callosity thickness was demonstrated by sonography. Our patient also experienced significant pain relief that allowed her to increase physical activity (Children's Dermatology Life Quality Index score dropped nine points following treatment). Collectively, these improvements suggest that rosuvastatin may offer a promising treatment for PC.

What's already known about this topic?

Pachyonychia congenita (PC) is an autosomal dominant disease characterized by nail dystrophy and painful plantar keratoderma.

Keratolytics, emollients, retinoids and steroids have been used for treatment but with limited benefits.

What does this study add?

A patient with PC who had a *KRT6A* mutation was treated with rosuvastatin with significant improvement in plantar hyperkeratosis and pain.

Statins could be a promising treatment for PC with long-term safety, but further studies are needed.

Pachyonychia congenita (PC) is a rare autosomal dominant disorder characterized by plantar pain, nail dystrophy with subungual hyperkeratosis and palmoplantar keratoderma. Other features include oral leucokeratosis, follicular keratotic papules and cysts. The current classification of PC is based on the underlying mutation in specific keratin genes (*KRT6A*, *KRT6B*, *KRT6C*, *KRT16* and *KRT17*), and each subtype gives rise to a spectrum of symptoms.[1], [2] Herein, we present a case of PC with a mutation in *KRT6A* that responded to treatment with oral rosuvastatin.

Case report

An 8-year-old female patient presented to our clinic with painful plantar hyperkeratosis and thickened nails with a progressive course since early infancy. She was the second child of distantly related parents with no history of genetic disease. She had an uncomplicated birth and her early developmental milestones were normal. Nail abnormalities were the first features that became apparent, followed by plantar hyperkeratosis that covered both her feet gradually worsening and causing considerable pain upon walking. She was initially treated with oral acitretin 10 mg per day for 10 months, which exacerbated her pain necessitating discontinuation of the drug and treatment with emollients and keratolytics only. At that point, examination revealed focal yellow hyperkeratotic plaques and deep fissures that were more prominent on the heels and metatarsal areas. Her fingernails had a wedge-shaped hypertrophy at the distal end with a mild brown discoloration. Involvement of the palms and toenails was less severe. The child also had follicular hyperkeratotic papules over her extremities and white plaques on the buccal mucosa. These clinical features were consistent with PC.

To elucidate the underlying genetic basis of PC in this family, the patient and her parents were referred for genetic counselling and testing. Following acquisition of informed consent in accordance with the Declaration of Helsinki principles, peripheral blood samples were obtained from the patient and her parents, and DNA was extracted. Capture-based target enrichment of samples prior to next-generation sequencing (NGS) was performed using the Roche NimbleGen

capturing method. Targeted sequencing of PC-associated genes was performed on the Illumina platform, a disease-specific gene-targeted NGS panel for identification of pathogenic variants in PC. This panel covers four distinct genes, i.e. *KRT6A*, *KRT6B*, *KRT16* and *KRT17*. The patient was found to have a heterozygous mutation in *KRT6A*; NM_005554: c.1381G>A, NP_005545: p.Glu461Lys. This sequence variant was absent in 119 654 alleles in the control population (ExAC.broadinstitute.org) and 1000 Genomes (www.1000genomes.org). Furthermore, the bioinformatics programs MutationTaster, CADD, PolyPhen2 and SIFT predicted the variant to be pathogenic or damaging. In addition, segregation analysis of the variant in the family with polymerase chain reaction followed by Sanger sequencing showed that the mutation was absent in both parents and was present as heterozygous in the proband consistent with a *de novo* autosomal dominant *KRT6A* mutation, thus confirming the diagnosis of PC.

The impact of the disease was evaluated by the Children's Dermatology Life Quality Index (CDLQI) and the callosity thickness was assessed by ultrasound. The CDLQI score was 22 and the maximum callosity thickness on her left heel was 1.54 cm.

We started treatment with oral rosuvastatin (5 mg per day). The patient was routinely evaluated for drug side-effects. Some improvement with less fissuring and blistering was noted after 4 weeks of treatment (Fig. 1a). After 6 months of treatment the patient reported a marked decrease in pain and reduction in blister formation. The plantar lesions showed partial improvement with fewer scales and fissures, and the CDLQI had dropped to 13, a decrease of nine points (Fig. 1b). On ultrasound examination, the maximum thickness on her left callus was 1.18 cm, representing a 23.4% decrease (Fig. 2). After 6 months the patient stopped taking rosuvastatin for 3 weeks. There was a marked increase in pain and, to a lesser degree, hyperkeratosis on both feet; however, clinical improvement was observed after readministration of rosuvastatin.

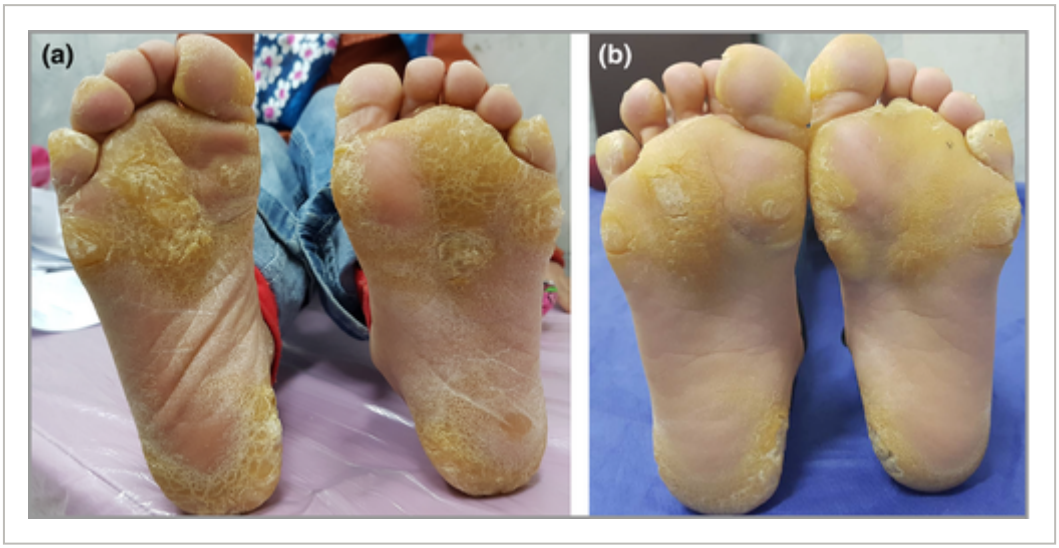

Figure 1

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Clinical findings in the patient with pachyonychia congenita. (a) Thick yellow hyperkeratotic plaques and deep fissures were prominent on the heels and metatarsal areas at 4 weeks and (b) after 6 months of rosuvastatin treatment. Marked reduction in scaling and fissures was noted on both feet.

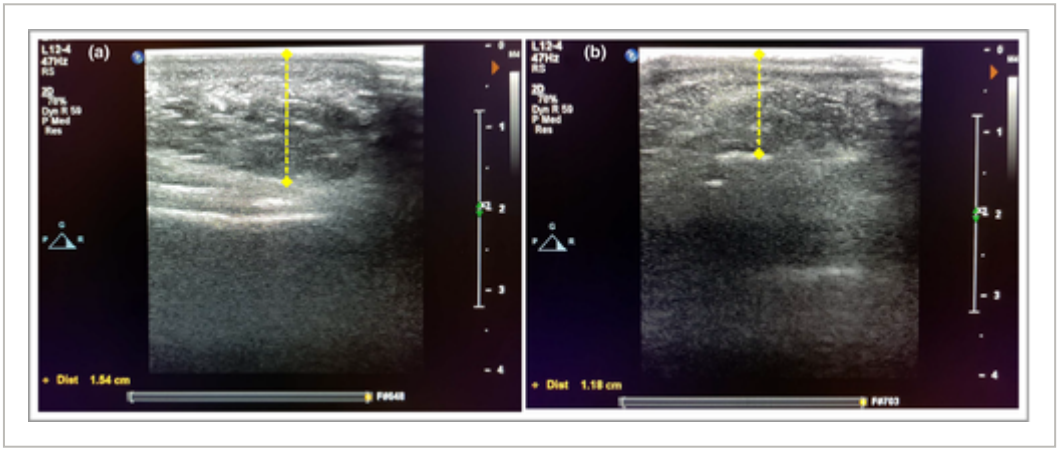

Figure 2

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Maximum callosity thickness on the patient's left heel (a) before and (b) after the treatment with rosuvastatin. A 3.6-mm reduction in callosity thickness was demonstrated by sonography. The yellow lines delineate the thickness of the callus.

Discussion

Mutations in five different keratin genes have been reported to cause PC.[3] Mutation analysis in our case revealed a G-to-A transition in codon 1381 of *KRT6A*, which results in substitution of glutamic acid by lysine in keratin 6A (c.1381G>A, p.Glu461Lys on exon 7). The corresponding sequence variant has been reported in the *KRT6B* gene,[2] further supporting the pathogenicity of the *KRT6A* mutation.

As painful plantar keratoderma is the most debilitating manifestation of PC, treatment options mainly focus on these lesions.[4] The most effective treatment so far is mechanical debridement of the calluses.[5] Topical regimens, such as keratolytics, emollients, retinoids and steroids, are used but have limited benefits.[5] In addition, topical sirolimus has been trialled in two patients with PC who had painful calluses.[6] The treatment resulted in thinning of keratoderma, rapid improvement of pain and ability to ambulate. Oral retinoids reduce hyperkeratosis by suppressing keratin production but they are ineffective in pain reduction.[7] Finally, intralesional injections of botulinum toxin and a mutation-targeted siRNA have been tested in a limited

number of patients with successful regression of callus and lessening of pain in the treated area.[8], [9]

Zhao *et al*. found that simvastatin, and also compactin, a precursor of statins, can decrease the transcription of the *KRT6A* gene by binding to a specific site in its promoter region in an *in vitro* model.[10] Based on their study and on previous suggestions that the use of statins may be beneficial in the treatment of PC,[11] we hypothesized that statins could be beneficial in the treatment of our patients. The best statin available for use in paediatric patients is rosuvastatin, which was started at a low dosage. No side-effects were noted. The patient reported a significant improvement in pain, hyperkeratosis, blistering and follicular keratosis.

Our observations in one patient suggest that statins could be a promising treatment for plantar keratoderma and associated pain in PC. The long-term use of statins, and rosuvastatin in particular, has been reported to be safe in familial hypercholesterolaemia, and they do not demonstrate a reduction in efficacy over time.[12], [13] It is possible that statins could effectively alleviate the main symptoms of PC that impact patients' quality of life but the efficacy and long-term safety of statin use in the treatment of PC needs to be demonstrated in future clinical trials.

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Supporting Information

Filename	Description
bjd17276-sup-0001-PowerpointS1.pptx application/mspowerpoint, 23.7 MB	**Powerpoint S1** Journal Club Slide Set.

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