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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

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THERAPEUTIC HOTLINE

First case of pachyonychia congenita in the Czech Republic

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ABSTRACT: Pachyonychia congenita (PC) is a rare autosomal dominant skin disorder characterized predominantly by hypertrophic nail dystrophy, oral leukokeratosis, and painful palmoplantar keratoderma. It is associated with a mutation in one of five keratin genes, KRT6A, KRT6B, KRT6C, KRT16, or KRT17. The International PC Research Registry (IPCRR) confirms that as of January 2014 there have been 547 cases of PC genetically confirmed. It is estimated that there are between 2000 and 10,000 cases of PC in the world. However, the exact prevalence of PC is not yet established. We report a case of PC-K6a, p.Arg164Pro, in a 40-year-old man. Initially he was diagnosed with onychomycosis and was treated with systemic antifungals. This is the first genetically confirmed case of PC in the Czech Republic.

KEYWORDS: keratinizing disorder, nail dystrophy, pachyonychia congenita, systemic antifungals

Case report

A 39-year-old man was referred to our department by his general practitioner with discolored and thickened toenails and fingernails. The discoloration was present since 3 years of age. Over time the nails thickened and became deformed. At least three times in a month he suffered bacterial superinfection of the nail folds followed by onycholysis, accompanied by occasional pain and difficulty in holding small objects. An initial diagnosis of onychomycosis was made, and several times he had potassium hydroxide examination and fungal cultures were conducted, each time though with a negative result. After the patient underwent systemic antifungal treatment three times for 3 months, each with no improvement, further investigations were conducted.

Following a full clinical examination, it was noted that there were abnormalities to his skin, its appendages, and mucous membranes. There was thickening and hardening of four fingernails with brown and yellowish discoloration of their free edges. In comparison, all toenails were affected

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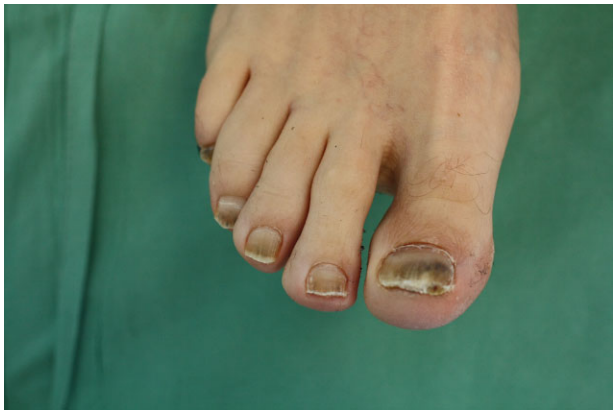

FIG. 1. Dystrophy of the patient's toenails.

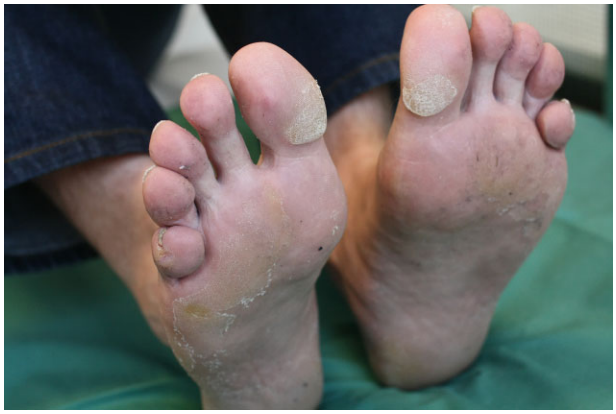

FIG. 2. Plantar keratoderma in a patient.

(FIG. 1). The nail plates were thickened with black, brown, and yellowish discoloration. Moreover, there was mild plantar keratoderma (FIG. 2). It appeared in his teens but has never caused any pain. There was also some mild oral leukokeratosis mainly on the tongue. Otherwise physical examination was without any pathology.

A full family history was also taken and it was found that other family members had similar symptoms, indicating this was likely an autosomal dominant disorder. The patient's paternal grandmother and his father had similar changes to the fingernails and toenails with mild keratoderma. Moreover, the patient's two daughters, age 6 and 4, have fingernail and toenail changes. Their toenails are thickened with yellowish discoloration of their free edges (FIG. 3). Their fingernail plates also have a yellowish discoloration of their free edges. Both girls do not as yet have any changes on the soles and do not have involvement of the oral mucosa.

The most likely diagnosis was the rare keratin disorder, pachyonychia congenita (PC). Genetic testing was performed by the Pachyonychia

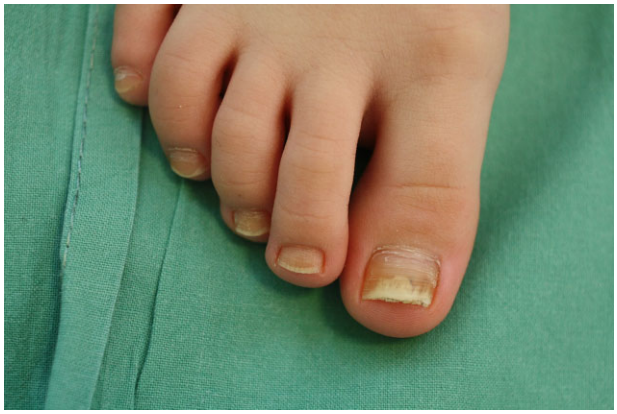

FIG. 3. Dystrophy of the toenails in one of the patient's daughters.

Congenita Project. For the International PC Research Registry (IPCRR), the patient completed a detailed questionnaire, provided clinical photos, and underwent a clinical consultation by phone. Genomic DNA was extracted from saliva collected in a DNA sample collection kit. The PC-associated keratin genes were amplified by polymerase chain reaction (PCR) and the PCR products directly sequenced (1). A mutation was identified in K6a, p.Arg164Pro; c.491G>C, confirming the clinical diagnosis of PC. This mutation is at the start of the helix initiation motif domain located in the 1A domain of the keratin 6a protein and has been previously reported in only two kindreds (2,3).

Discussion

Pachyonychia congenita is a group of autosomal dominant disorders caused by mutation in one of five keratin genes: KRT6A, KRT6B, KRT6C, KRT16, or KRT17 (4–6). Previously classified as PC-1 and PC-2, clinical and molecular data on more than 500 patients (7) have shown more overlap between the clinical features of the two subtypes than thought. A new classification system is now used of PC-K6a, PC-K6b, PC-K6c, PC-K16, and PC-K17. Characteristics common to all forms are hypertrophic nail dystrophy and painful focal plantar keratoderma. Other features found include extensive cysts of all types, follicular hyperkeratosis, palmar keratoderma, and oral leukokeratosis. Although some with PC have little or no nail involvement, hypertrophic nail dystrophy of the hands and feet is the most prominent symptom in the vast majority of patients with PC. They usually develop at, or soon after, birth and present as discolored, thickened nail plates. Thickened toenails seem to be more

frequent than fingernails (6). It could be due to the greater trauma exerted from shoes.

According to Eliason et al., KRT6A mutation carriers seem to be 11.1 times as likely to have all 10 toenails affected than carriers of other mutations. What more, it looks like KRT6A mutation carriers have the earliest average onset of nail symptoms at about 4 months of age (6).

Patients with mutations in KRT6A seem to have more extensive disease compared with the patients with mutations in KRT16. They experience earlier onset, more extensive nail involvement, and higher prevalence of oral leukokeratosis, cysts, and follicular hyperkeratosis (8). Both PC-K6a and PC-K16 patients usually experience extreme pain from the plantar keratoderma. That is why the case of our patient with very subtle symptoms is so unusual. So far there have only been two other cases described with the same mutation K6a, p.Arg164Pro (2,3). In the first case, the patient had nail changes and plantar keratoderma with persisting palmoplantar erythema. In the second case, members of three generations had only subtle nail changes with plantar hyperkeratosis limited to the pressure areas of the soles.

It is interesting that individuals within a family with the same mutation and between individuals from different families but with the same mutation can vary in the severity of the clinical phenotype. Some of this may be due to environmental factors including lifestyle, occupation, care of their condition, as well as due to genetic variation – polymorphisms. It is important to stress that PC can be easily misdiagnosed as onychomycosis. From the example of our patient, we can presume that many patients with PC may never reach the right diagnosis and may be repeatedly treated as fungal infection. On the other hand, PC patients can get nail infections and may need antibiotics or antifungals to treat the infections. These will not improve the abnormalities of the nail due to PC but will treat the secondary infection. It is important for PC patients, especially in young children, to recognize when they have an infection and to get the appropriate treatment.

Currently there is no specific and effective therapy for patients with PC. In a small group of patients, the botulinum toxin was successfully used to relieve pain from plantar keratoderma (9). According to the latest studies, mechanical/surgical options are preferred by patients over medical therapies. Carriers of KRT16 and KRT6a mutations are more likely to benefit from keratolytics than carriers of mutations in KRT17 (10). Presently there are many studies, for example with siRNA and topical rapamycin, being conducted to find an effective treatment for PC (7).

Conclusion

This case highlights the importance of a full clinical examination and a detailed family history to determine the underlying cause of a patient's symptoms and features. This is essential to (i) determine the likelihood of a genetic condition and to aid in genetic counseling and (ii) determine the most appropriate treatment.

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