CHAPTER **37**

PACHYONYCHIA CONGENITA: A Case Report and Review of a Rare Genetic Disorder

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INTRODUCTION

Pachyonychia congenita (PC) is a rare autosomal dominant genodermatosis with an estimated incidence of only 5,000 to 10,000 reported cases worldwide (1). This disorder is most often caused by heterozygous mutations in any one of the genes encoding the differentiation-specific keratins K6a, K6b, K6c, K16, or K17. The most common clinical findings of PC include hypertrophic nail dystrophy, palmoplantar keratoderma, plantar pain, oral leukokeratosis, and epidermal cysts (2). This article reports a patient presenting with genetically confirmed PC who was treated conservatively. A thorough review of the most recent literature and findings of PC will also be presented.

CASE REPORT

A 15-year-old male, accompanied by his parents, presented to the clinic with a chief complaint of plantar pain, thickened nails, and palmoplantar callosities. The patient was an active member of the high school baseball team and was on his feet often for activities of daily living. Even with these painful lesions he has maintained a high level of performance and is an excellent pitcher. The parents of the patient noticed callus formation on his plantar feet by age 3 and subsequently began manually debriding the calluses biweekly. At age 7, the patient underwent genetic screening for which he tested positive for a mutation in the keratin gene (*KRT)* 6b. This genetic screening confirmed a diagnosis of pachyonychia congenita 6b (PC6b) and the patient was part of the International PC Research Registry (IPCRR) provided through the patient advocacy group PC Project. The patient and his family denied any known family history of PC and the patient had an otherwise unremarkable past medical history, past surgical history, family medical history, social history, and review of systems. The patient denied any allergies and current medications.

Physical examination of the patient revealed hyperkeratotic lesions to the plantar medial heel, plantar medial first metatarsal head, plantar second metatarsal head, plantar fifth metatarsal head, medial interphalangeal joint of the hallux, distal and medial second digit, and distal fifth digit of the right foot (Figure 1). Hyperkeratotic lesions presented in the same locations on the left foot with an additional hyperkeratotic lesion at the lateral aspect of the interphalangeal joint of the hallux (Figure 2). All hyperkeratotic lesions of the feet were tender upon palpation. Hypertrophic nail dystrophy was observed to the first, second, and fifth digits of the right foot and to the first and fifth digits of the left foot (Figure 3). Milder hyperkeratotic lesions were present on the hands at the medial second metacarpal head, palmar fifth metacarpal head, and distal third digit of the right hand and at the lateral palm, medial second metacarpal head, palmar third metacarpal head, palmar interphalangeal joint of the first digit, distal interphalangeal joint of the third digit, and palmar middle phalanx of the fourth digit of the left hand (Figure 4). No hypertrophic nail dystrophy was noted to the nails of the hands. The oral mucosa was unremarkable and no epidermal cysts were identified. The vascular, muscular, and neurological examinations of the feet were unremarkable. Shave biopsies of the hyperkeratotic lesions of the feet were sent to a pathological lab and results confirmed proliferation of keratin.

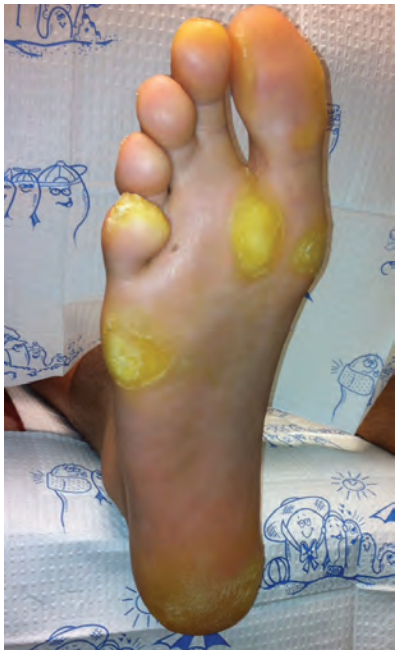

Figure 1. Initial presentation of patient with Pachyonychia congenital. Right foot, plantar.

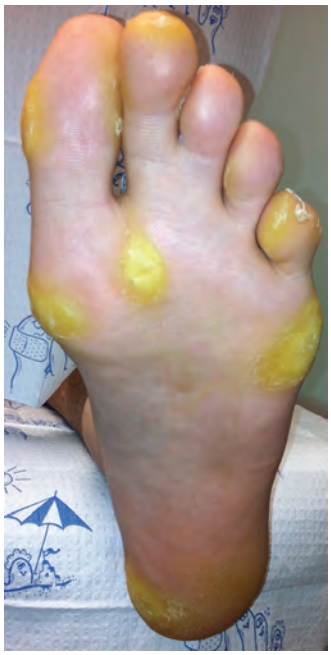

Figure 2. Left plantar foot.

Treatment of the patient consisted of palliative care for the callosities and thickened nails of the feet. Nails and calluses of the feet were debrided and a keratolytic cream was dispensed to the patient for daily application to the hyperkeratotic lesions. Accommodative orthotics were dispensed to the patient to offload pressure to the lesions on his feet. The patient returned to the clinic 1 month after his initial visit to obtain another set of accommodative orthotics. At this time, the patient was pleased with the relief provided by the orthotics and admitted to wearing them in his sneakers at all times. The patient was instructed to return to the clinic every 2 months for palliative care and orthotic adjustment for best outcome.

DISCUSSION

History of PC

PC was first described in 1904 by Muller (3). However, the ectodermal defects of PC were presented by Jadssohn and Lewandowsky in 1906 and by Jackson and Lawler in 1951 (4,5). Thus, historically PC has been subdivided into two major phenotypic subtypes, PC-1 or Jadassohn-Lewandowski type, and PC-2, or Jackson-Lawler type. PC-1 was associated with mutations in *KRT6A* and *KRT16*, while PC-2 was associated with mutations in *KRT6B* and *KRT17* (6). These PC subtypes were created on the basis of subtle differences in phenotype of the disorder, such that patients with PC-1 were reported to have more prominent oral leukokeratosis (4) and patients with PC-2 were reported to have cysts and natal teeth (5). Although this simple classification of PC would improve the ability to predict phenotypic prognosis without genetic testing,

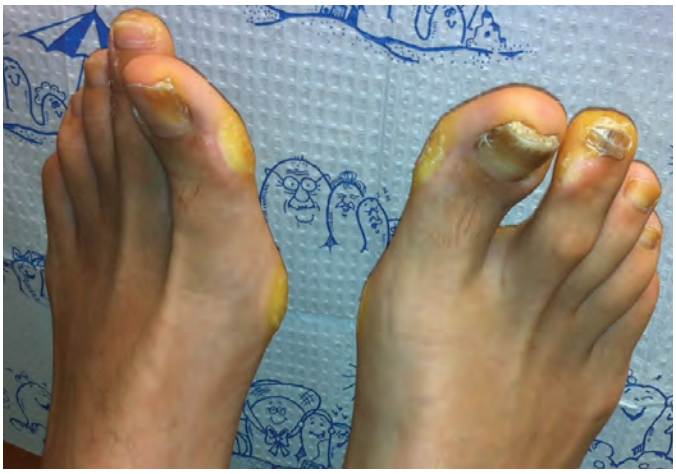

Figure 3. Hypertrophic toenails.

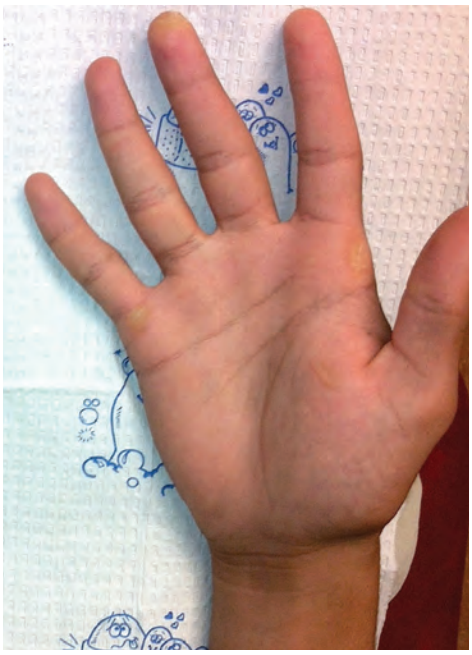

Figure 4. Palmar hands of patient.

significant overlap in clinical features of the two subtypes of PC have been reported (7). Furthermore, Spaunhurst et al (8) found that patients with *KRT6A* and *KRT16* mutations have significantly different manifestations of the disease and should be classified separately from each other. Therefore, the PC-1/PC-2 classification system does not represent a rational or clinically useful classification.

With recent reports and studies indicating overlap between PC subtypes, a new classification system based on the specific keratin defect of PC was adopted. Data from the International PC Research Registry, provided by the PC Project were used to formulate this new and current classification system of PC. Currently, a diagnosis of PC-6a, PC-6b, PC-16, and PC-17 represents mutations in the *KRT6A*, *KRT6B*, *KRT16*, and *KRT17* genes, respectively (9).

The most recent addition to this classification is PC-6c, which indicates a mutation in the *KRT6C* gene (10). A diagnosis of PC-U corresponds to a mutation in an unknown gene in an individual with classical clinical findings of PC found in the absence of a known PC keratin gene mutation (9). This classification allows clinicians to provide more accurate prognosis and subsequent treatments for patients with PC.

Role of Keratin in PC

The existing 54 human keratins belong to the intermediate protein family, which consists of at least six types–keratins make up the type I and type II intermediate filament proteins (11). Keratins are the intermediate filament proteins specifically expressed by the epithelial cells, in which they form a dense cytoplasmic network. The primary functions of the keratin cytoskeleton are to provide mechanical strength and resilience to epithelial cells and tissues to withstand everyday stress and physical trauma. Disruption of this cytoskeleton leads to extreme fragility of the epithelial tissues in which the mutated keratin is expressed (12). Keratins associated with PC may be located in the basal or suprabasal layers of palmoplantar skin, epidermal appendages, and oral mucosa (7). Thus disruption of the cytoskeletal function through mutation in PC manifests as cytolysis and hyperkeratosis, specifically in the palmoplantar epidermis, nail bed, mucosae, and pilosebaceous unit (13).

Clinical Presentation of PC

PC is determined by the location and nature of the causative mutation, as well as other unknown genetic and environmental factors. Patients with PC consistently present with a triad of features, including nail dystrophy, focal palmar/plantar keratoderma, and pain (14). In addition to this triad of features, other common features of the disorder are follicular keratosis, oral leukokeratosis, pilosebaceous cysts, and natal or prenatal teeth (2, 15). Less common findings include ear pain, hoarseness, hyperhidrosis, and alopecia (7, 9). A rare, yet life-threatening finding is laryngeal obstruction (16). There are reports in the literature of corneal findings, deafness, skeletal abnormalities, mental retardation, diabetes, early menarche, and cataracts. However, these reports included individuals who had not yet been genetically tested for PC and can now be eliminated from the list of PC manifestations (17).

The development of symptoms varies from patient to patient, but the development of hypertrophic nail dystrophy, palmoplantar keratoderma, and plantar pain develop at about the same ages in PC patients. Hypertrophic nails usually develop just after birth and hyperkeratosis of the plantar surfaces usually develop when the child starts ambulation. At one point, 20-nail dystrophy was thought to be required for phenotypic diagnosis of PC, but the presence of toenail dystrophy with plantar keratoderma and plantar pain in patients older than three years is a much more sensitive means of clinically diagnosing PC (9). Until PC is genetically confirmed, differential diagnoses of the aforementioned symptoms should include onychomycosis, oral candida albicans, epidermolysis bullosa simplex, familial onychogryphosis, palmoplantar keratoderma striata, and Clouston syndrome (18).

The most problematic symptom reported by PC patients is focal plantar keratoderma associated with severe pain. The pain is often out of proportion to the extent or duration of the callus, suggesting that the mechanism is not the result of pressure from the callus itself. The reason for the plantar pain is not fully understood, but thought to be related to deep blister formation beneath the callus that develops over pressure points of the plantar surfaces. PC patients report plantar pain to be highly debilitating such that the pain may limit mobility and social interaction, as well as the ability to find and maintain work (9).

Treatment Options

No specific treatment for PC exists as each patient presents with a unique array of symptoms and thus a treatment must be designed on an individual basis. The most often employed methods of treatment for PC center on symptomatic relief, hygienic grooming practices, and treatment of secondary infection when indicated. For palmoplantar keratoderma, such treatments include emollients, custom-made orthotics, keratolytics, soaking, debridement of the hypertrophic skin, antibiotic cream, salicylic acid, steroids, and pain medications. Furthermore, treatments for hypertrophic nails include filing/grinding/cutting, moisturizers, nail avulsion, and surgical removal of the nail bed. Other studied treatments include Botulism toxin, Rapamycin, Simvastatin, Retinoids, and siRNA, but these treatments are not readily available to patients and are still undergoing clinical studies. Thus far, Simvastatin and Rapamycin have been shown to selectively block K6a expression in human keratinocytes (19,20). Use of Rapamycin showed improvement of symptoms in PC patients, which suggests that Rapamycin, or its analogs, may be a therapeutic option, but all patients discontinued the drug due to its side effects (20). Currently mechanical/surgical options are preferred over medical therapies in PC patients (21).

Retinoids are of continued interest as a treatment for pachyonychia as these drugs are known to act via retinoic acid response elements (RAREs), which are present in the keratin gene promoters, and inhibit gene expression. In a study by Gruber et al (22), use of Retinoids caused a thinning of calluses, however many patients discontinued the oral Retinoids due to adverse effects outweighing the benefits. Although all patients reported the presence of side effects, this study demonstrated a potential advantage of treatment with lower doses of the retinoid aciretin for

longer duration as compared with retinoid therapy with higher doses, shorter duration, and isoretinoin (22).

The most promising research for PC treatment seems to be the development of small interfering RNAs (siRNAs). Humans have three copies of nearly identical *KRT6* genes, encoding the K6a, K6b, and K6c proteins. Mouse knockout studies strongly suggest that the loss of one of these keratins may be tolerated without adverse effect (23, 24). In turn, carefully designed siRNAs have been shown to potently and specifically silence mutant keratin alleles differing from the wild type by a single point mutation (25, 26). However, major obstacles exist for siRNA delivery to the skin, including that delivery of functional siRNAs to skin involves stratum corneum penetration and keratinocyte uptake followed by incorporation into the RNA-induced silencing complex (27). In a study by Hickerson et al (27), intradermal injections of siRNAs into PC patient foot lesions resulted in improvement, but the pain associated with administration to the callosities necessitated oral pain medication and regional nerve blocks to make treatment tolerable (28). This pain prevents administration of siRNAs with hypodermic needles from being a viable treatment option, but research into the use of dissolvable microneedle arrays has proven successful in the transgenic mouse model and may prove successful in human PC patients (29).

PC is a rare disorder with symptoms that overlap those of several other disorders, making diagnosis a challenge. The importance of genetic testing in patients with the triad of toenail dystrophy, plantar keratoderma, and plantar pain must be stressed as genetic testing is the only way to confirm that the disorder is actually PC. Genetic confirmation of PC aids in genetic counseling and clinical prognoses, which are important to obtain the best outcome for the patients. Furthermore, identification of mutations is especially important for the design of future mutation-specific and/or gene-specific therapies (30).

Unfortunately, several challenges still remain in the realm of PC. There remains an incomplete understanding of PC, particularly with the cause of plantar pain. Also, the relatively small number of PC patients, and even smaller number of those patients who contain the same mutation, make clinical trials and their statistical validity difficult. Despite these challenges, research is ongoing with new interest in use of spliceosome-mediated RNA trans-splicing (SMaRT) and induced pluripotent stem (iPS) cells as possible future treatments for PC patients.

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