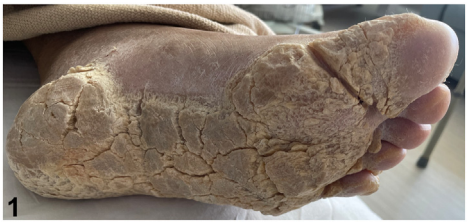
Painful thickened skin on the soles of the feet

Lowell T. Nicholson, MD, Christina Topham, MD, Julia Curtis, MD, and Lauren M. Madigan, MD

Key words: genodermatoses; nail dystrophy; pachyonychia congenita; palmoplantar keratoderma.



CASE PRESENTATION

A 45-year-old man from Tonga was noted to have thick, scaly skin on both feet. He reported a 20-year history of painful calluses and fissures on the soles, as well as nail thickening and intermittent white patches in the oral cavity. On physical examination, there was thick, yellow-colored hyperkeratotic scale projecting from the plantar aspects of both feet (Fig 1), hypertrophic nail dystrophy, and wedge-shaped subungual hyperkeratosis (Fig 2).

Question 1: Which of the following investigations would be most useful in establishing the correct diagnosis?

A. Skin scraping for potassium hydroxide

B. Skin biopsy

C. Nail clipping for histology and culture

D. Genetic testing

Answers:

A. Skin scraping for potassium hydroxide — Incorrect. Nail dystrophy and subungual hyperkeratosis can be seen in dermatophyte infection though the chronicity, severity, and associated keratoderma make this unlikely as the primary diagnosis.

B. Skin biopsy — Incorrect. Biopsy of hyperkeratotic regions will demonstrate histopathologic findings suggestive of pachyonychia congenita (PC), such as atypical keratinocytes with pale cytoplasm and eosinophilic inclusions; however, genetic testing remains the gold standard for diagnosis.[1,2]

C. Nail clipping for histology and culture — Incorrect. Onychomycosis can mimic the nail changes seen in PC and dermatophyte infection can complicate PC secondarily, but nail fungus alone does not explain the chronic, severe presentation described previously.

D. Genetic testing — Correct. PC is an autosomal dominant genodermatosis caused by mutations in keratins 6A, 6B, 6C, 16, and 17.[1,2] Although generally suspected based on clinical findings alone, molecular genetic testing should be performed to

From the Department of Dermatology, University of Utah School of Medicine, Salt Lake City, Utah.

Funding sources: None.
IRB approval status: Not applicable.
Prior presentation: This article has not been presented previously.
Patient consent: Consent was obtained for the publication of medical information and patient photographs.

Correspondence to: Lowell T. Nicholson, MD, Department of Dermatology, 30 North 1900 East SOM 4A330, Salt Lake City, UT 84132. E-mail: lowell.nicholson@hsc.utah.edu, Twitter: @lowellthorndike.

JAAD Case Reports 2022;29:146-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2022.09.011

confirm the diagnosis and identify the causative keratin mutation.[1,2] In our patient, genetic testing was performed and revealed a mutation in the keratin gene KRT16.

Question 2: Which of the following is not commonly associated with the diagnosis pictured here?

A. Oral leukokeratosis

B. Alopecia

C. Pilosebaceous cysts

D. Follicular keratoses

Answers:

A. Oral leukokeratosis — Incorrect. Oral leukokeratosis is a classic finding in PC and presents as white-gray, hyperkeratotic plaques, most commonly on the buccal mucosa but can also involve the tongue, palate, mucosal lips, larynx, and upper airway.[1,2] Involvement of the airway can cause acute airway obstruction in young children.[1]

B. Alopecia — Correct. Alopecia is not a typical finding in patients with PC but can be associated with a variety of other genodermatoses, including Clouston syndrome. Clouston syndrome, or hidrotic ectodermal dysplasia, classically presents with micronychia or anonychia, cone-shaped nails, palmoplantar hyperkeratosis, and sparse, fragile hair that progresses to alopecia by adulthood.[1]

C. Pilosebaceous cysts — Incorrect. Patients with PC frequently develop multiple cutaneous cysts.[1,2] Pilosebaceous cysts — including steatocystomas and vellus hair cysts — and epidermal inclusion cysts develop during adolescence and continue into adulthood.[1,2]

D. Follicular keratoses — Incorrect. Follicular keratoses at sites of friction, most commonly on the elbows and knees, are another finding commonly observed in pachyonychia congenita.[1,2]

Question 3: Which abnormal gene product is implicated in the most likely diagnosis?

A. Keratins 6, 16, and/or 17

B. Connexin 30

C. Transient receptor potential cation channel

D. Keratins 5 and 14

E. Various proteins involved in telomere maintenance

Answers:

A. Keratins 6, 16, and/or 17 — Correct. PC is inherited in an autosomal dominant fashion and results from mutations in 1 of 5 genes encoding epidermal keratins — KRT6A, KRT6B, KRT6C, KRT16, and KRT17.[1,2] Spontaneous mutations in epidermal keratins occur in about one-third of patients with PC.[1]

B. Connexin 30 — Incorrect. Clouston syndrome is an autosomal dominant disorder resulting in mutations in GJB6 gene which encodes connexin 30.[3] Both palmoplantar hyperkeratosis and nail dystrophy of Clouston syndrome can mimic PC but the partial or total alopecia is lacking in patients with PC.[1]

C. Transient receptor potential cation channel — Incorrect. Olmsted syndrome is a very rare keratinizing disorder that presents with palmoplantar keratoderma and periorificial keratotic plaques.[1] The autosomal dominant form of Olmsted syndrome is caused by a gain of function mutation in the TRPV3 gene which encodes transient receptor potential cation channel, subfamily V, member 3.[4]

D. Keratins 5 and 14 — Incorrect. Abnormal keratins 5 and 14 are implicated in epidermolysis bullosa simplex.[5] Epidermolysis bullosa simplex manifests as blisters and hyperkeratosis of the palms and soles but lacks the classic wedge-shaped nail dystrophy of PC.[1] Additionally, palmoplantar blisters are not typical in PC, which can be another differentiating factor between the 2 entities.

E. Various proteins involved in telomere maintenance — Incorrect. Dyskeratosis congenita (DC) is a genetically heterogenous disorder with multiple potential mutations all resulting in impaired telomere maintenance.[6] This condition presents clinically as a triad of nail dystrophy, leukoplakia, and reticulated hyperpigmentation or poikiloderma.[1] While both pachyonychia congenita and DC can have associated nail dystrophy and white patches/plaques of the oral mucosa, several key differences separate the conditions including distinctive nail dystrophies (omega nail in pachyonychia congenita vs longitudinal striation and/or brittleness in DC), the absence of palmoplantar hyperkeratosis in DC, and reticulated hyperpigmentation, which is present in DC but not PC.

Abbreviations used:

DC: dyskeratosis congenita
PC: pachyonychia congenita

Conflicts of interest

None disclosed.

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