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Comparative Study of High-Resolution Multifrequency Ultrasound of the Plantar Skin in Patients with Various Types of Hereditary Palmoplantar Keratoderma

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Key Words
High-resolution multifrequency ultrasound · Palmoplantar keratoderma · Pachyonychia congenita

Abstract
Background: High-variable-frequency ultrasound is used as an imaging tool for various cutaneous disorders. We utilized this tool in pachyonychia congenita (PC) patients, who typically present with plantar hyperkeratosis and often severely debilitating pain, compared to patients with epidermolytic palmoplantar keratoderma (EPPK) and mal de Meleda (MDM). ***Objective:*** To ascertain the feasibility of ultrasound technology for the diagnosis of PC. ***Methods:*** The study included a total of 16 patients, 7 with PC, 5 with EPPK and 4 with MDM, who underwent ultrasound examination of the plantar skin with high-resolution multifrequency ultrasound equipment. ***Results:*** Ultrasound scans performed over the proximal and distal plantar foot calluses in PC patients demonstrated hyperechoic dots and lines within the epidermis compatible with hyperkeratosis, engorged varicose veins in the dermis and an anechoic layer interposed between the epidermis and the dermis, corresponding to blister fluid below the calluses. In contrast to PC patients, patients with MDM and EPPK demonstrated no blisters. ***Conclusion:*** PC patients, as opposed to a group of patients with MDM and EPPK, displayed subepidermal blistering beneath their calluses. This finding may help in the diagnosis of PC and in partially explaining plantar pain as part of PC symptomatology.

Introduction

Pachyonychia congenita (PC) is a very rare autosomal dominant keratinizing disorder estimated to affect between 5,000 and 10,000 people worldwide [1].

Heterozygous mutations in one of five keratin genes, *KRT6A*, *KRT6B*, *KRT6C*, *KRT16* and *KRT17*, encoding keratins K6a, K6b, K6c, K16 and K17, respectively, are responsible for this genodermatosis [1, 2]. These mutations result in fragility of the epithelial cells and tissues associated with cell cytolysis and hyperkeratosis [2–4]. Although early studies identified genotype-phenotype correlations between mutations in given genes and clinical manifestations, more recent data have cast serious doubts regarding the validity of this classification scheme, leading to the development of a new classification system for PC, based solely on molecular criteria and recognizing five types of PC: PC-K6a, PC-K6b, PC-K6c, PC-K16 and PC-K17 [1, 2].

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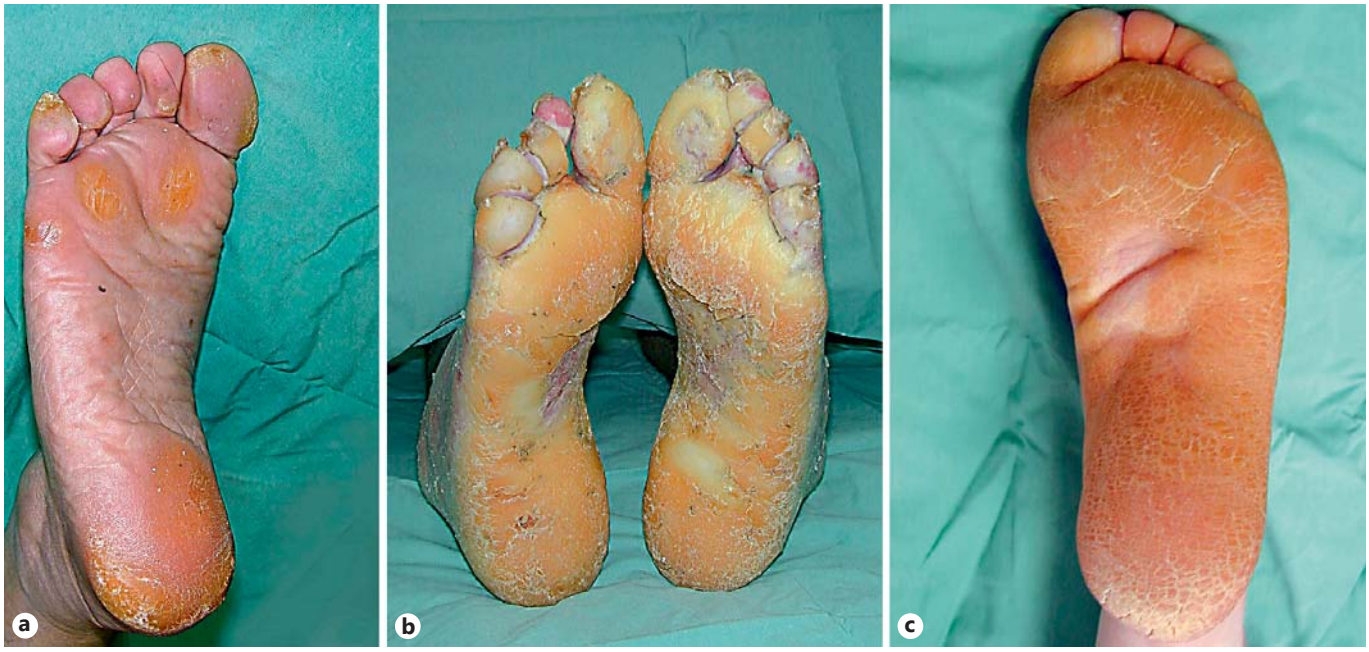

Fig. 1. Plantar keratoderma in a patient with PC (**a**), MDM (**b**) and EPPK (**c**).

The clinical manifestations of PC are multifaceted and involve the palmoplantar skin, nails, pilosebaceous unit, oral mucosa and teeth [1, 2]. Interestingly, a large-scale phenotypic and molecular study of the disease has revealed that despite the name of the syndrome, nail involvement is not universal in PC [1]. In contrast, palmoplantar involvement is universally found in adult PC patients whose diagnosis has been confirmed at the molecular level [1, 5]. In fact, some patients solely manifest thickening of the plantar skin surface, which may under certain circumstances lead to confusion with other forms of hereditary palmoplantar keratoderma [6]. A very typical feature of plantar hyperkeratosis in PC patients is the existence of severely debilitating pain, confining many patients to wheelchairs from childhood [1, 5, 6]. The reported severity of plantar pain often bears little correlation to the extent of the callus, what could indicate that factors other than pressure from the callus itself may contribute to the pain [1, 7].

Recently, high-variable-frequency ultrasound has been recognized as a highly discriminative imaging tool for a wide range of cutaneous disorders [8, 9]. This technology enables to demonstrate the characteristics of the skin layers and structures of the normal skin as well as skin lesions and adjunct contiguous tissues. It allows for the accurate high-resolution imaging of the epidermis, dermis and hypodermis and of the nail bed, as well as deeper layers such as muscles, tendons and even bones. Color duplex examination allows visualization of blood flow, distinguishing between arterial and venous flow, and calculation of flow velocity and resistance index in the arterial flow [8].

The aim of the present study was to ascertain the potential value of this technology in the diagnosis of PC. We identified features found in PC, as opposed to mal de Meleda (MDM) and epidermolytic palmoplantar keratoderma (EPPK), which shed light upon the pathogenesis of plantar pain in this disorder.

Methods

Patients

The study included a total of 16 patients, 7 with PC, 4 with MDM and 5 with EPPK. There were 13 females and 3 males, aged 2–64 years, with an average age of 25.5 years. The 7 PC patients included 5 women and 2 men, aged 17–64 years, with an average age of 36.7 years. In the MDM group there were 3 females and 1 male, aged 5–37 years, with an average age of 22.5 years, and in the EPPK group there were 5 female patients, aged 2–24 years, with an average age of 12.4 years. All patients were diagnosed based on clinical (fig. 1), histopathological and molecular findings (table 1). All patients provided informed consent to undergo ultrasound examination according to a protocol approved and reviewed by the

Table 1. Patient clinical, molecular and ultrasound features

Disease	Phenotype	Age (sex)	Gene (mutation)	Blisters	Varices
PC	FNEPPK + cysts + neonatal teeth	31 (M)	*KRT17* (p.N92S)	1	1
PC	FNEPPK + cysts	64 (M)	*KRT17* (p.N92S)	1	1
PC	FNEPPK + leukokeratosis + vellus hair cysts	56 (F)	*KRT6a* (p.N171S)	1	1
PC	FNEPPK + leukokeratosis + vellus hair cysts	23 (F)	*KRT6a* (p.N171S)	1	1
PC	FNEPPK + leukokeratosis + vellus hair cysts	18 (F)	*KRT6a* (p.N171S)	1	1
PC	FNEPPK	17 (F)	*KRT16* (c.R127C)	1	1
PC	FNEPPK	48 (F)	*KRT16* (c.R127C)	1	1
MDM	PPK	37 (M)	*SLURP1* (p.G86R)	0	0
MDM	PPK	5 (F)	*SLURP1* (p.G86R)	0	0
MDM	PPK	23 (F)	*SLURP1* (c.del82T)	0	0
MDM	PPK	25 (F)	*SLURP1* (p.G86R)	0	1
EPPK	EPPK	2 (F)	*KRT9* (p.N161S)	0	0
EPPK	EPPK	4 (F)	*KRT9* (p.N161S)	0	0
EPPK	EPPK	24 (F)	*KRT9* (p.N161S)	0	0
EPPK	EPPK	22 (F)	*KRT9* (p.R163W)	0	0
EPPK	EPPK	10 (F)	*KRT9* (p.R163W)	0	0

FNEPPK = Focal non-epidermolytic palmoplantar keratoderma; PPK = palmoplantar keratoderma.

Institutional Helsinki Committee and by the National Committee for Genetic Studies.

Ultrasound

Skin ultrasound examination of plantar calluses was performed with a high-resolution multifrequency 5–17 MHz linear array transducer (IU22 Philips, Philips Medical Systems, Bothell, Wash., USA). A large amount of gel was applied, and in some cases a gel pad was used to obtain a good acoustic window and proper focus location, thus improving the skin images. Gray scale slices and color and spectral Doppler examination were performed.

All patients had an ultrasound of the proximal, middle and distal plantar foot on each side and were examined for the presence of blisters and varices beneath calluses.

Statistical Analysis

Statistical analysis for the presence of blisters and varices was performed using Fisher's exact test.

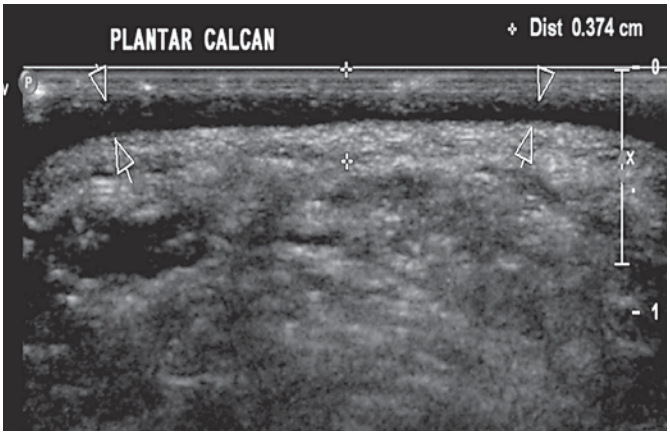

Fig. 2. Ultrasound scan performed over the calluses at the proximal plantar foot in a PC patient demonstrates an anechoic layer interposed between the epidermis and the dermis (arrows), representing blisters of fluid below the calluses. The whole skin thickness is 0.374 cm (cursors).

Results

Ultrasound scans performed over the calluses of all PC patients demonstrated an anechoic layer interposed between the epidermis and the dermis at the proximal and distal plantar foot on each side, corresponding to blister fluid below the calluses (fig. 2, table 1). The width of this layer varied from an average of 1.2 mm at the proximal plantar area (fig. 3a) to 3.2 mm at the distal plantar area (fig. 3b).

The whole epidermis-dermis width, including the anechoic layer, reached an average of 3.7 mm proximally (fig. 3a) and 5.3 mm distally (fig. 3b), compared to 1.5–2 mm at the middle plantar area, where the skin is normal (fig. 3c), as is also demonstrated on a panoramic view of the plantar foot (fig. 4). Additional findings in PC patients included hyperechoic dots and lines within the epidermis, corresponding to areas of hyperkeratosis (fig. 5),

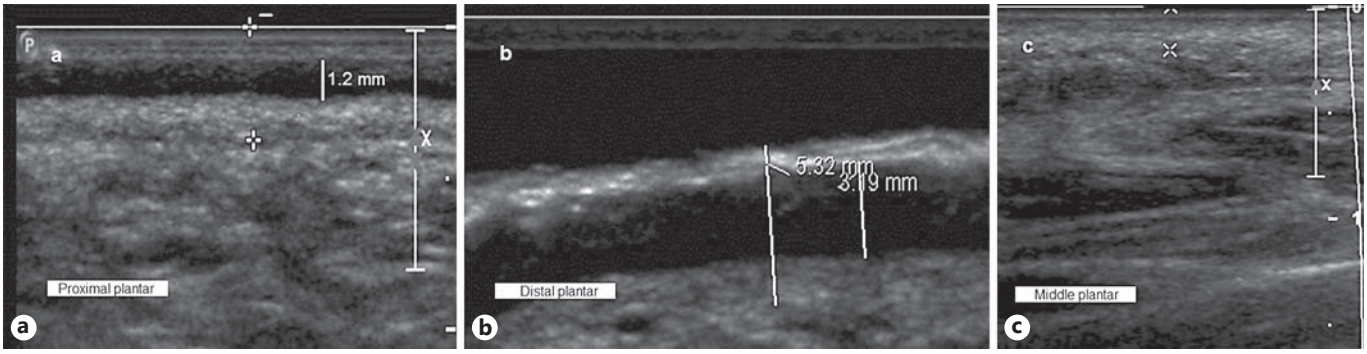

Fig. 3. Ultrasound scans over the plantar skin foot at different levels in a PC patient. The width of the anechoic layer interposed between the epidermis and the dermis varies from 1.2 mm at the proximal plantar area (**a**) to 3.2 mm at the distal plantar area (**b**). The whole epidermis-dermis width, including the anechoic layer, was largest at the distal plantar area, reaching an average of 5.3 mm (**b**). Normal skin is demonstrated at the middle plantar area (**c**).

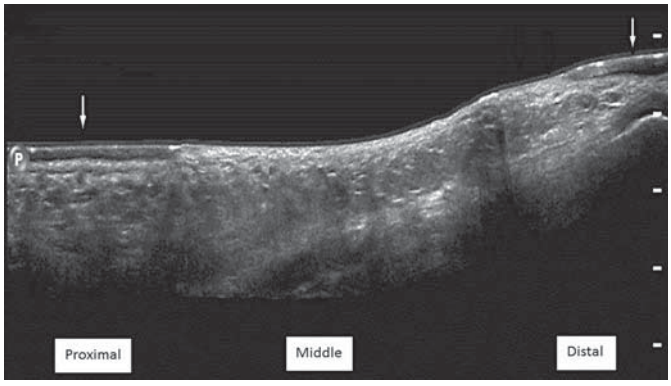

Fig. 4. Panoramic ultrasound view of the whole plantar foot in a PC patient. The differences between the middle plantar and both proximal and distal plantar skin (arrows) are clearly demonstrated.

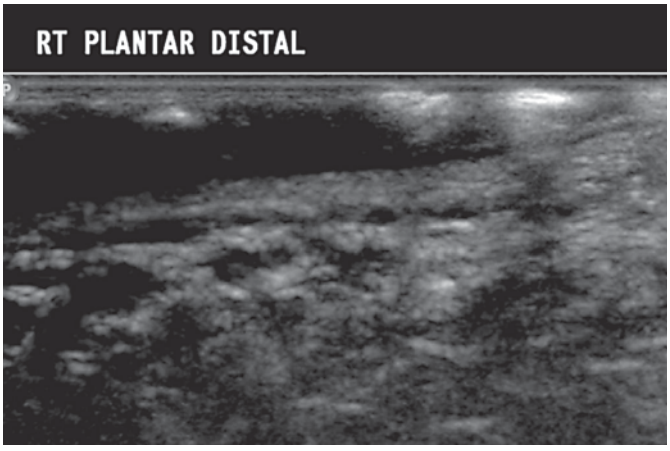

Fig. 5. Ultrasound scan performed over the calluses at the distal plantar foot in a PC patient. Hyperechoic dots and lines at the epidermis, above the blister fluid layer, are seen, reflecting hyperkeratosis.

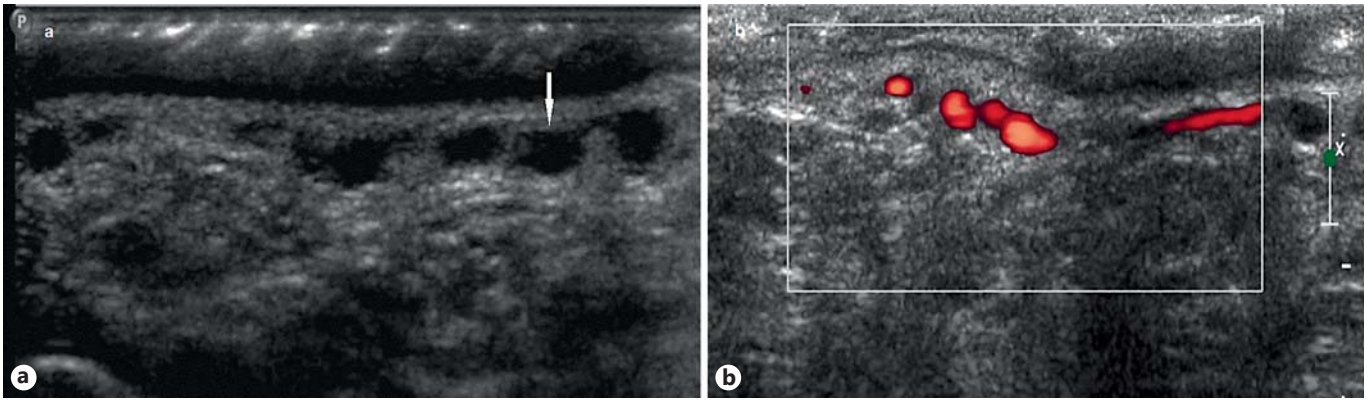

Fig. 6. Ultrasound and color (power) Doppler scans performed over the calluses at the distal plantar foot in a PC patient. Engorged varicose veins are demonstrated in the dermis at the distal plantar foot, on gray scale (arrow) (**a**) and on power Doppler (color box) (**b**).

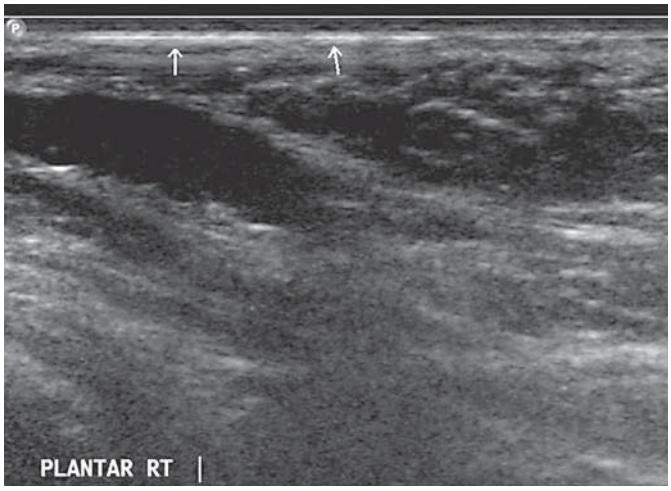

Fig. 7. Ultrasound examination in MDM patients demonstrates a hyperechogenic thickened keratin layer at the epidermis (arrows) but no blisters between the epidermis and the dermis.

and engorged varicose veins in the dermis at the level of the distal plantar foot, which were demonstrated on gray scale (fig. 6a) and on power Doppler in all PC patients (fig. 6b, table 1).

In contrast, ultrasound examination in all MDM and EPPK patients demonstrated a hyperechogenic thickened keratin layer in the epidermis without hypoechogenic subepidermal blisters (fig. 7, table 1). Varices were not found in EPPK patients and were demonstrated in only 1 out of 4 MDM patients (table 1).

Overall, the procedure was well tolerated by all patients regardless of their underlying diagnosis.

As is clear from the data, Fisher's exact test showed a statistically significant difference between the presence of blisters and the diagnosis ($p < 0.0001$) and between varices and the diagnosis ($p < 0.0001$).

Discussion

Palmoplantar keratoderma refers to a highly heterogeneous group of disorders including PC, MDM and EPPK [10]. The diagnosis of these disorders relies upon clinical features (e.g. pseudoainhum in MDM [10], dental problems in Papillon-Lefèvre syndrome [10], hearing loss in Olmsted syndrome [11]) as well as histopathological findings (e.g. epidermolytic changes in EPPK, retained nuclei in the stratum corneum in loricrin keratoderma, keratinocytes disadhesion in keratosis palmoplantaris striata and binuclear granular cells in ichthyosis hystrix) [12–15]. Clinical assessment is thus instrumental in order to direct the subsequent laborious molecular analysis with accuracy. The present data suggest that ultrasound evaluation may be a useful adjunct in the diagnosis of PC-associated palmoplantar keratoderma, especially when additional clinical findings such as nail dystrophy are not present [1].

As opposed to other imaging modalities, ultrasound is readily available, non-invasive, comfortable for the patient, not expensive and yields results in real time. In vivo confocal microscopy has a very low penetration of only 0.5 mm, limiting its usage to lesions of the epidermis and papillary dermis. Other imaging modalities such as positron emission/computed tomography or magnetic resonance imaging require the use of an intravenous contrast medium, are limited to skin lesions >5 mm and are more expensive. Variable-frequency ultrasound scan, on the other hand, is capable of demonstrating lesions in the submillimeter range and examines a depth of 60 mm with a single probe and up to 200 mm with a combination of probes [8]. Wortsman and Wortsman [8] examined the diagnostic accuracy of ultrasound examination in 4,338 various skin lesions as compared to clinical diagnosis. They found skin ultrasound to have 99% sensitivity and 100% specificity.

In the present study, ultrasound detected subcallosal blisters in 100% of the PC cases and in none of the non-PC types of palmoplantar keratoderma assessed. Additional finding in all PC patients included dermal engorged veins, which were found in only one MDM patient.

Plantar keratoderma usually develops in early childhood as the child starts to walk and bear weight [6, 7] and most often manifests as persistent large calluses on weight-bearing surfaces. The keratoderma in PC is usually worse on the soles than on the palms [1, 6, 7]. Plantar pain was found to be the most debilitating feature in a large survey of PC patients and to have the highest influence on patients' quality of life, causing limitations in mobility and leading to the use of a variety of pain killer medications [1, 7]. The pain severity of plantar keratoderma in many cases exceeds the extent and duration of the callus [1, 7]. Presence of fissures and secondary infections may contribute to the pain and require paring of the hyperkeratotic area in order to relieve the pain [7]. The existence of blisters located between the dermis and the hyperkeratotic epidermis, with no possibility to drain, demonstrated in the present study for the first time, may significantly contribute to the sensation of pain experienced by most PC patients.

In conclusion, PC patients, as opposed to a group of patients with MDM and EPPK, display subepidermal blistering beneath their calluses. This finding may help in the diagnosis of PC and explain in part pain, which is a disabling PC symptomatology.

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Disclosure Statement

The authors declare no conflict of interest. There were no funding sources.

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