DOI: 10.1515/sjdv-2017-0012

Pachyonychia Congenita - Can a Specific Phenotype be a Clue to a Genetic Defect? - a Case Report and Literature Review

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UDC 616.596-003.87-056.7

Abstract

Pachyonychia congenita (PC) is a rare inherited disorder of keratinization characterized by hypertrophic nail dystrophy, painful palmoplantar blisters, cysts, follicular hyperkeratosis and oral leukokeratosis. These pathological clinical features are resulting from mutations in keratin proteins including KRT6A, KRT6B, KRT6C, KRT16, and KRT17. We present a 6-year-old girl with hypertrophic nail dystrophy, follicular hyperkeratosis, circumscribed plantar keratoderma and oral leukokeratosis. The features were consistent with the diagnosis of PC. The patient has been registered in the International Pachyonychia Congenita Research Registry (IPCRR) and is waiting for a detailed genetic analysis. The IPCRR has contributed to publication of numerous papers which emphasized the importance of the mutation type affecting various clinical presentations of PC. Based on recent data, a new classification system has been developed for PC, and it is gradually replacing the earlier classifications. It is based almost exclusively on the mutated genes. In this report we have raised the hypothesis that distinctive clinical features may be highly suggestive of a specific keratin mutation.

Key words: Pachyonychia Congenita; Child; Signs and Symptoms; Skin Diseases, Genetic; Mutation; Phenotype; Case Reports

Introduction

Pachyonychia congenita (PC) is a rare genodermatosis transmitted as an autosomal dominant trait, caused by mutations in at least one of 5 keratin genes. PC affects different ectodermal structures to variable extent. Most frequently, it is clinically characterized by nail dystrophy and painful focal plantar keratoderma. Additionally, PC may affect the palms, oral mucosa, tongue and teeth (1). Patients with KRT17 mutations are more likely to have natal teeth and develop steatocystomas, while patients with KRT6A mutations more commonly manifest oral leukokeratosis (2). Historically, based on the clinical features, two subtypes emerged: Jadassohn-Lewandowsky PC type 1, and Jackson-Lawler PC type 2 (3).

Case Report

We present a 6-year-old girl born to non-consanguineous parents, with normal developmental milestones for her age. The family history was unremarkable. On examination, the girl presented with subungual hyperkeratosis resulting in nail abnormalities on all fingers and toes. On the lateral aspects of her upper and lower extremities, as well as on the lower-anterior part of the trunk, she had disseminated follicular hyperkeratosis with a hedgehog-like appearance (Figure 1. A, B, E, F). Circumscribed plantar keratoderma was present on both soles (Figure 1. C). Mucosal examination revealed oral leukokeratosis (Figure 1. D). Due to a mild hoarseness, an ear-nose-throat specialist examined the child, and indirect laryngoscopy showed no signs of laryngeal involvement. Histopathology of the plantar keratoderma showed massive hyperkeratosis with discrete focal parakeratosis, thickening of the granular layer with large keratohyalin granules. Histopathology of the hyperkeratotic papules on the trunk showed mild acanthosis and lamellar hyperkeratosis,

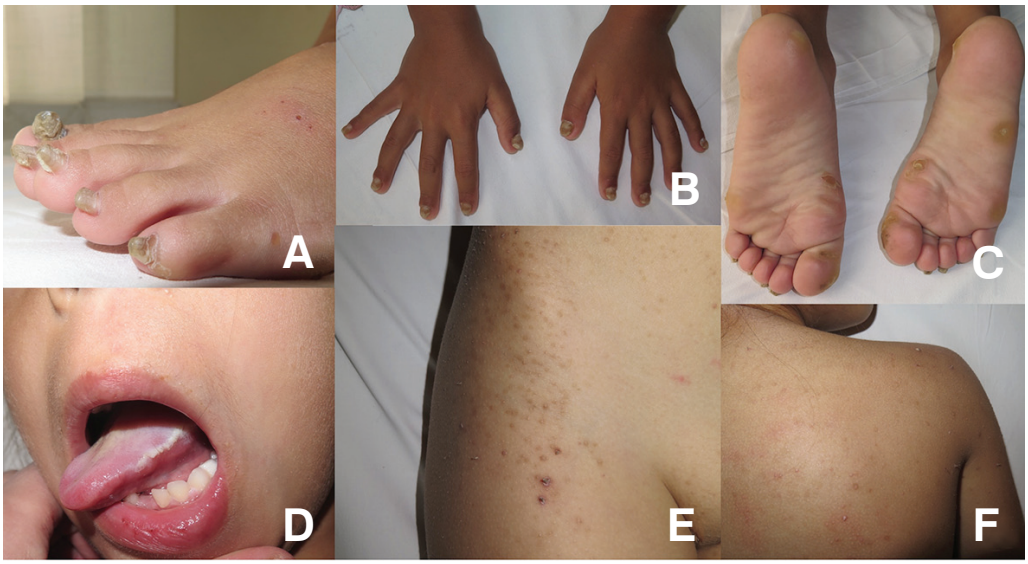

Figure 1. A, B. Subungual hyperkeratosis present on all fingernails and toenails, leading to wedge-shaped nail deformities; **C.** Circumscribed plantar keratoderma; **D.** Oral leukokeratosis, predominantly on the sides of the tongue; **E.** Follicular hyperkeratosis on lateral aspects of the trunk; **F.** Follicular hyperkeratosis with hedgehog spike formations

most intense in the follicular infundibulum (Figure 2).

Routine laboratory test results were normal. Since a large portion of the patient's trunk and extremities was covered with hyperkeratotic papules, oral isotretinoin at 0.6 mg/kg/day was introduced, as well as topical 40% urea ointment for plantar keratoderma. The patient has been registered in the International Pachyonychia Congenita Research Registry (IPCRR) (www.pachyonychia.org) and is waiting for a detailed genetic analysis. Because of frequent nose bleeds, oral isotretinoin had to be discontinued after two weeks, while the topical treatment was regularly applied. On a regular check up, 4 months after the initial admission, the girl showed a mild improvement.

Discussion

Pachyonychia congenita is an autosomal dominant genodermatosis caused by heterozygous mutations in any of the genes encoding the differentiation-specific keratins KRT6A, KRT6B, KRT6C, KRT16, or KRT17 (4). The main clinical features of the condition include painful and highly debilitating plantar keratoderma, hypertrophic nail dystrophy, oral leukokeratosis, and a variety of epidermal cysts (2). Although the condition has previously been subdivided into PC-1 and PC-2 subtypes, the phenotypic characterization of over 700 mutation-verified PC patients enrolled in the IPCRR, shows that there is a considerable overlap between these subtypes (1, 2).

Patients with type 1 PC (Jadassohn-Lewandowsky syndrome) are characterized by nail dystrophy since birth. This may be accompanied by painful paronychia, hyperkeratosis of palms and soles over the pressure sites, oral leukokeratosis, palmoplantar hyperhidrosis and follicular keratotic papules distributed through the body (5). Also, painful blisters can develop over the palms and soles. Additional finding is the presence of verrucous lesions over the elbows and knees, sometimes the gluteal area (2, 6). Furthermore, stridor and hoarseness can develop as severe leukokeratosis may produce laryngeal obstruction (7).

Patients with type 2 PC (Jackson-Lawler syndrome) have natal teeth and hair anomalies (including pili torti, unruly hair and bushy eyebrows). Oral leukokeratosis and palmoplantar keratoderma is milder in comparison to PC-1. Steatocystoma multiplex (epidermal cysts) is the hallmark of PC-2 (8).

The IPCRR was established in 2004 with the aim to collect clinical and molecular data from patients with PC worldwide. The IPCRR has collected data about more than 700 cases with genetically confirmed PC, and more than 100 different dominant mutations have been identified (no cases of confirmed recessive PC). Up to September 2016, 51 cases enrolled in the IPCRR have been identified without mutations in KRT6A, KRT6B, KRT6C, KRT16 or KRT17, but rather with mutations in other genes including GJB6, TRPV3, DSG1, DSP, KRT9, FZD6 or AAGAB. Although these patients do not suffer from PC, their clinical features are similar, even though they have completely distinct genetic mutations (9).

The IPCRR has contributed to the publication of numerous papers that emphasized the importance of the mutation type on various clinical presentations in PC patients (1, 2, 10, 11).

Eliason et al. conducted a large study including 254 PC patients in whom the keratin mutations were associated with their clinical presentations (1). Supported by the results, the authors proposed a new classification for PC based on the specific keratin gene mutation. Three clinical features that were reported in more than 90% of patients across all mutation subtypes were thickened toenails, plantar keratoderma and plantar pain (1). Patients with KRT6A mutations were more than 11-fold more likely to have all 10 toenails affected. Also, patients with these mutations had the earliest average onset of nail dystrophy (about 4 months). In regard to plantar keratoderma, they noted that patients with KRT16 and KRT6A, developed symptoms at a similar age, but significantly earlier than patients with KRT6B and KRT17 mutations. Furthermore, patients with KRT6B mutations appeared to have fewer fingernails affected on average, compared with those with other keratin gene mutations. Concerning mucosal involvement, KRT6A and KRT17 carriers had a significantly increased odds/ratio of earlier onset of oral leukokeratosis compared with KRT6B and KRT16 carriers. Pilosebaceous cysts and natal teeth were a hallmark of the previously described PC type 2, and in this cohort had a much higher likelihood of appearance in patients with KRT17 mutations (1).

Spaunhurst et al., used the IPCRR to describe clinical heterogeneity among patients with PC with genetic mutations in KRT6A and KRT16. They concluded that KRT6A carriers have more extensive nail involvement, which starts at much younger age than those with KRT16. Furthermore, oral leukokeratosis was reported in 94% of patients with KRT6A mutation, in comparison to only 56% of KRT16 carriers. Follicular hyperkeratosis was also more likely to be present in patients with KRT6A mutations than in patients with KRT16 (11).

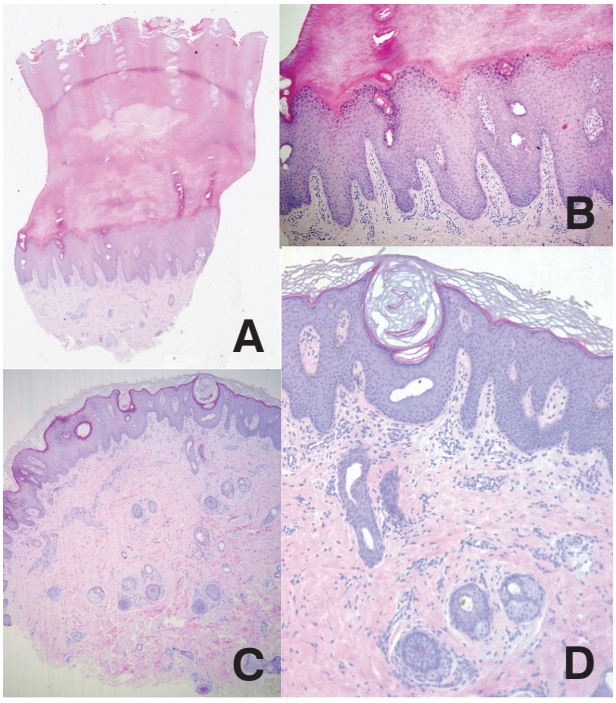

Figure 2. A, B. Severe hyperkeratosis with discrete focal parakeratosis, thickening of the granular layer with large keratohyalin granules; **C, D.** Mild acanthosis and lamellar hyperkeratosis, most intense in the follicular infundibulum

Genetic analysis has been a helpful predictive parameter in determining a potential response to a specific treatment. For example, a study confirmed that carriers of KRT6A and KRT16 mutations are more likely to benefit from keratolytics than carriers of KRT17 mutations (12).

The clinical classification of PC variants was first suggested by Kumer in 1935 (13), and it was intended to assist in the prognosis without genetic testing. After the discovery of the underlying cause of PC, genotype-phenotype analysis initially suggested that mutations in KRT6a/KRT16 and KRT6b/KRT17 were associated with type 1 and type 2 PC, respectively. A large amount of clinical and genetic

information, based on the data collected from the IPCRR, has become available in the last several years. This has provided the basis for a new classification system of PC, gradually replacing earlier classifications, and is based almost exclusively on the mutated genes. The new classification, revealing a broad spectrum of overlapping clinical and pathologic features, has closely correlated phenotype to the specific keratin genotype in PC patients. The new classification is as follows: (a) PC-K6a (caused by mutation of KRT6A); (b) PC-K6b (caused by mutation of KRT6B); (c) PC-K6c (caused by mutation of KRT6C); (d) PC-K16 (caused by mutation of KRT16); and (e) PC-K17 (caused by mutation of KRT17) (1, 2).

Conclusion

Taking into consideration our patient's clinical presentation, early onset of nail dystrophy, presence of follicular hyperkeratosis and plantar keratoderma, we may assume that she is a carrier of a KRT6A mutation. If this is the case, beneficial effects of treatment with keratolytics can be expected. A more promising future for our patient may reside in the genome-based therapy, but before that we are waiting for the findings of her genetic test results.

Abbreviations

PC - Pachyonychia Congenita
IPCRR - International Pachyonychia Congenita Research Registry

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Pachyonychia Congenita – Može li određeni fenotip biti ključ za genetski defekt? Prikaz slučaja i pregled literature

Sažetak

Pachyonychia congenita predstavlja grupu urođenih poremećaja keratinizacije za koju su karakteristične sledeće promene: zadebljale nokatne ploče, bolna palmoplantarna keratodermija, ciste, folikularna hiperkeratoza i oralna leukokeratoza. Ovi patološki nalazi posledica su mutacije na jednom od gena koji kodiraju keratine KRT6A, KRT6B, KRT6C, KRT16 ili KRT17. Prikazujemo devojčicu uzrasta šest godina sa hipertrofičnim nokatnim pločama, folikularnom hiperkeratozom, fokalnom plantarnom keratodemijom i oralnom leukokeratozom. Na osnovu kliničke slike, postavljena je dijagnoza *Pachyonychia congenita*. Pacijent je registrovan u *International Pachyonychia Congenita Research Registry* (IPCRR) i očekujemo nalaze genetskih ispitivanja. Sam IPCRR doprineo je objavljivanju velikog broja radova iz ove oblasti koji naglašavaju značaj tipa mutacije na razvoj specifične kliničke slike. Najnoviji podaci su pružili osnovu za postavljanje novog klasifikacionog sistema koji bi postepeno trebalo da zameni staru klasifikaciju i bazira se skoro u potpunosti na genima koji su mutirani. U ovom prikazu smo postavili hipotezu da određene kliničke karakteristike pacijenata sa dijagnozom *Pachyonychia congenita* mogu da ukažu na određenu mutaciju gena koji kodiraju keratin.

Ključne reči: Pachyonychia congenita; Dete; Znaci i simptomi; Genetske kožne bolesti; Mutacija; Fenotip; Prikazi slučajeva