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A Rare Genetic Disease: Pachyonychia Congenita Type 2

Nadir Bir Genetik Hastalık: Pakionişya Konjenita Tip 2

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ABSTRACT

Pachyonychia congenita (PC) is a rare inherited ectodermal disorder characterized mainly by hypertrophic nail dystrophy and focal palmoplantar keratoderma. Pachyonychia congenita can be divided into two main clinical subtypes, PC-1 and PC-2, which are correlated with mutations in keratins. Although the most prominent clinical feature of both PC subtypes is hypertrophic nail dystrophy, oral leukokeratosis is usually seen in PC-1 while PC-2 generally presents with nail dystrophy, widespread steatocystomas, natal teeth and hair abnormalities. We report a patient with PC type II presenting with the classical features of the disease that had been transmitted for four generations.

Key Words: Child, Keratin, Nail, Pachyonychia congenita, Palmoplantar keratoderma

ÖZET

Pakionişi konjenita (PK), nadir görülen kalıtsal ektodermal hastalık olup temel olarak hipertrofik tırnak distrofisi ve fokal palmoplantar keratoderma ile karakterizedir. Hastalık PK-1 ve PK-2 şeklinde keratin genindeki mutasyonlarla korelasyon gösteren iki klinik alt gruba ayrılmaktadır. Her ne kadar her iki grubun en belirgin klinik özelliği hipertrofik tırnak distrofisi olsa da, oral lökokeratozis genellikle PK-1'de görülürken, PK-2 ise sıklıkla tırnak distrofisi, yaygın steatosistoma, natal diş ve saç anomalileri ile prezente olur. Burada PK-2'nin klasik bulguları ile prezente olmuş ve ailesinde dört kuşağı etkilenmiş olan bir olgu sunulmuştur.

Anahtar Sözcükler: Çocuk, Keratin, Tırnak, Pakionişi konjenita, Palmoplantar keratoderma

INTRODUCTION

Pachyonychia congenita (PC) is a rare inherited ectodermal disorder characterized mainly by hypertrophic nail dystrophy and focal palmoplantar keratoderma (1). It has also been associated with oral leukokeratosis, cyst formation, keratosis pilaris, hyperhydrosis of the hands and feet and hair abnormalities. Pachyonychia congenita can be divided into two main clinical subtypes, PC-1 (Jadassohn-Lewandowski syndrome) and PC-2 (Jackson-Lawler syndrome), which are correlated with mutations in keratins (2). While mutations in keratin 16 or keratin 6a are associated with type 1, mutations in keratin 17 or keratin 6b are associated with type 2 (3). Although sometimes difficult, it is possible to distinguish both subtypes by clinical examination; oral leukokeratosis is usually seen in PC-1, whereas widespread steatocystomas, natal or prenatal teeth and hair abnormalities (pili torti) are common in PC-2. We report a patient with type II PC presenting with the features of the disease that had been transmitted for four generations.

CASE REPORT

A 5-year-old boy was referred to the outpatient clinic for evaluation of nasal symptoms including rhinorrhea, nasal blockage, and snoring. He was born to non-consanguineous parents. He had natal teeth at birth. He had developed thickened and discolored nails on all four extremities in the first year of his life.

His examination revealed thickening and hardening with yellowish-gray discoloration affecting all of the nail plates (Figure 1). There were multiple soft steatocysts over his face and the elbows. Apart from these findings the child did not have oral

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lesions, hair abnormalities, blister formation on feet or palms involvement. He has no itching and increased sweating.

His family history revealed that there were numerous family members who had similar physical findings such as nail dystrophy and cysts for four generations (Figure 2). The 38-year-old father also revealed signs of pachyonychia congenita. He reported nail dystrophy appearing in early childhood and cysts at puberty. He had thick hyperkeratotic toenails and hyperkeratotic plaques on bilateral soles. He had multiple cystic lesions on his forearms and neck.

All hematological and biochemical investigations showed normal results. Direct microscopic examination and cultures showed no fungal elements on repeated occasions. Genetic evaluation was refused by the family. A diagnosis of pachyonychia congenital type-2 was made clinically.

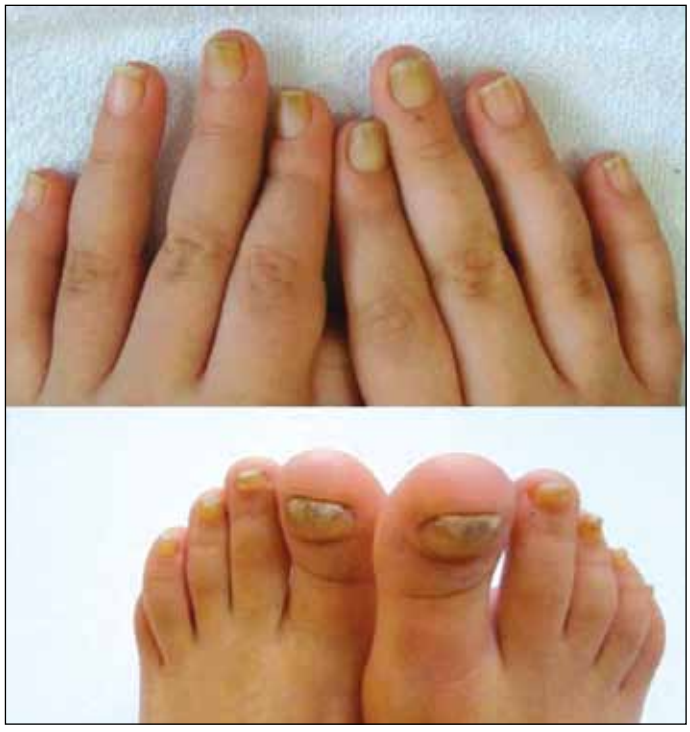

Figure 1: Dystrophy of all nails with subungual hyperkeratosis at toenails.

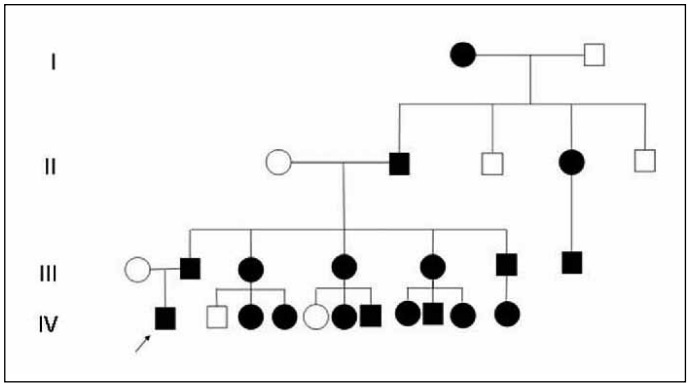

Figure 2: Pedigree of pachyonychia congenita type 2. Squares indicate males and circles females. Blackened symbols are affected individuals. Arrow shows the index case.

DISCUSSION

Pachyonychia congenita is an autosomal dominant keratin disorder first described by Jadassohn and Lewandowsky in 1906 (4). Later Jackson and Lawler described widespread pilosebaceous cysts as a special form of disease (5).

The most prominent clinical feature of both PC subtypes is hypertrophic nail dystrophy which consists of subungual hyperkeratosis; thickening of the nail plate; and distortion or curvature of the nail plate (2,6). PC is classified into two different subtypes according to the clinical findings and the effected keratin gene. Hyperkeratosis of palms, soles, knees and elbows, follicular hyperkeratosis, oral leukokeratosis are common clinical features of PC-1 whereas blister formation, hoarse voice due to laryngeal involvement and hyperhidrosis may also be seen in PC-1. In PC-2 the palmoplantar keratoderma and oral changes are less prominent or absent and also there is a history of natal teeth and the development of epidermal cysts or steatocysts at puberty (7).

Our patient was diagnosed as PC-2 according to the history of neonatal teeth and clinical findings including nail hypertrophy beginning in the first year of his life, multiple steatocysts over his face and the elbows and presence of family members who have similar findings including nail hypertrophy and palmoplantar keratederma.

There is a good correlation between the pattern of PC and the keratin gene mutation (8). Keratins are heterodimeric proteins that constitute the intermediate filament cytoskeleton of epithelial cells. The two keratin genes, KRT6A and KRT16, located on chromosome 12 are known to be associated with PC-1 and two other keratin genes, KRT6B and KRT17, located on chromosome 17 are known to be associated with PC-2 (9). Epithelia in different parts of the body utilize a range of different keratins. Keratins associated with PC-1 are mainly expressed in the nail bed, the palmoplantar epidermis and the oral mucosa, while PC-2 related keratins are mainly expressed in the nail bed, sweat glands, hair follicles, and hair shaft, and to a lesser extent in the palmoplantar epidermis (3,10). Almost all of the reported mutations occur at either the start or the end of the central keratin rod domain that are known as the helix boundary motifs of the keratin polypeptide (8). It has also been detected that there are keratin mutations found outside the helix boundary motif regions of the K16 and K17 proteins, these were related with delayed onset, or tarda subtype of both PC1 and PC-2 (8,11). Keratin gene mutations cause the keratin filaments clump together and that results in prevention of their integration into other cytoskeleton structures. This gives rise to diminished mechanical resistance of the keratinocytes and the epithelial structure (10).

Differential diagnosis of PC includes oral leukokeratosis, onychomycosis, congenital dyskeratosis, pityriasis rubra pilaris, epidermolysis bullosa simplex psoriasis, congenital onychogryphosis, the Clouston syndrome and traumatic thickening of nails (12). There is no curative treatment of PC, and treatment is palliative and frequently disappointing. The only effective treatment for nail lesions is radical excision of the nail, nail bed and nail matrix and skin implantation at the site of the removed nail. Available treatments for skin lesions includes emollients and keratolytic agents, antiseptic dressing, special shoes as well as topical and systemic retinoids; surgical or CO2 laser excision can also be performed for mucosal lesions (12,13). Although there is no curative treatment for PC, there are studies on the use of a K6a mutation-specific siRNA, rapamycin, anti-TNF biologics, and botulism toxin are underway, but have not yet reached the point of being applied generally to treatment of the disorder (14,15). The siRNA trial included treatment of a single K6a mutation carrier in a dose-escalation trial of an siRNA directed against the N171K mutant allele and complete results have not been published. Botulinum toxin has been used in several patients with clinical findings consistent with PC but has not yet been replicated in mutation-tested individuals with PC (16).

CONCLUSION

In summary we reported a case with PC type II with a presenting the features of the disease including nail dystrophy, widespread steatocystomas, natal teeth and hair abnormalities with numerous family members who had similar physical findings for four generations.

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