Use of Articles in the Pachyonychia Congenita Bibliography

The articles in the PC Bibliography may be restricted by copyright laws. These have been made available to you by PC Project for the exclusive use in teaching, scholarship or research regarding Pachyonychia Congenita.

To the best of our understanding, in supplying this material to you we have followed the guidelines of Sec 107 regarding fair use of copyright materials. That section reads as follows:

Sec. 107. - Limitations on exclusive rights: Fair use
Notwithstanding the provisions of sections 106 and 106A, the fair use of a copyrighted work, including such use by reproduction in copies or phonorecords or by any other means specified by that section, for purposes such as criticism, comment, news reporting, teaching (including multiple copies for classroom use), scholarship, or research, is not an infringement of copyright. In determining whether the use made of a work in any particular case is a fair use the factors to be considered shall include - (1) the purpose and character of the use, including whether such use is of a commercial nature or is for nonprofit educational purposes; (2) the nature of the copyrighted work; (3) the amount and substantiality of the portion used in relation to the copyrighted work as a whole; and (4) the effect of the use upon the potential market for or value of the copyrighted work. The fact that a work is unpublished shall not itself bar a finding of fair use if such finding is made upon consideration of all the above factors.

We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
ABSTRACT

Pachyonychia congenita type II is an autosomal dominant inherited rare genodermatosis characterized by dystrophic wedge shaped thickened nails with subungual hyperkeratosis, symmetric palmoplantar keratoderma, steatocystoma multiplex. Here we report a 23-year-old male with characteristic features of dystrophic nails, palmoplantar keratoderma, steatocystoma multiplex, follicular hyperkeratotic papules and history of natal teeth at birth.

KEYWORDS: Dystrophic nails, Palmoplantar keratoderma, Natal teeth, Steatocystoma multiplex

INTRODUCTION

Pachyonychia congenita type II also known as Jackson Sertoli Syndrome/Jackson-Lawler syndrome and Pachyonychia Congenita (Complex) is rare genetic disease, autosomal dominant with a high degree of penetration with mutations in Keratins K6b and K17 and characterized by dystrophic wedge shaped thickened nails with subungual hyperkeratosis, symmetric hyperkeratosis of palms and soles, focal palmoplantar keratoderma, palmoplantar hyperhidrosis, follicular hyperkeratotic papules on body, steatocystoma multiplex, verrucous lesions on the knees, elbows, buttocks, ankles and popliteal regions, natal teeth, multiple epidermal cysts and hair may be unruly, or pili torti and alopecia, bushy eyebrows, oral leukokeratosis and hoarseness.

CASE REPORT

A 23 old male born to consanguineous couple has presented with complaints of bilaterally symmetrical hyperkeratotic lesions over soles since 12 years. It started as multiple painful fluid filled lesions on pressured sites of both soles, ruptured spontaneously within 2–3 days with foul smelling purulent discharge, which formed an ulcer and healed with hyperkeratosis. He had fissure feet since 6 years. Treated locally but lesions recurred. All toenails are discoloured since 10 years, which gradually thickened and grow outwards. All finger nails are discoloured and only thickening of right thumb nail since 3 years is seen. Patient complains of increased sweating all over the body since 7 years, not associated with odor or colour change. H/o fissuring and pain at angles of the mouth since 4 months. His mother gave history of presence of natal teeth, 2 central lower incisors on 3rd day of birth and lost after 3 months and grandmother having similar complaints.

Physical examination showed no signs of icterus, clubbing, cyanosis, pallor, edema, lymphadenopathy. Systemic examination revealed no abnormalities.

Cutaneous examination showed Hyperkeratotic plaques of variable size over the pressure sites on both feet [Figure 1]. Fissures present on heels of both feet.

Multiple smooth, yellow collared compressible cysts of variable size present on neck, axilla, trunk, post auricular area [Figure 2] and inguinal region. On puncturing the cyst with sterile needle a creamy fluid was expressed [Figure 3].
Follicular hyperkeratotic papules [Figure 4] are present on back, extensor aspects of upper and lower limbs which are not associated with itching.

Nail all toe nails are discoloured, lusterless, dystrophic, wedge shaped, thickened with subungual hyperkeratosis [Figure 6].

All fingernails are discoloured, lusterless and right thumbnail is thickened with subungual hyperkeratosis [Figure 7]. Oral-Angular cheilitis, glossitis and high arch palate [Figure 5] are present.

Cyst wall showing intrinsic folding lined by stratified squamous epithelium with hyperkeratosis and flattened sebaceous gland lobules

All routine investigations (CBP, RFT, LFT, RBS, CUE) are within normal limits. Indirect laryngoscopy revealed normal study and fungal culture of nail clippings showed no fungal elements. Ophthalmological assessment was normal. Biopsy of the cyst confirmed steatocystoma multiplex with histopathological features of cyst wall showing intrinsic folding lined by stratified squamous epithelium with hyperkeratosis and sub epithelium showing flattened sebaceous glands lobules separated by fibrous tissue. Genetic evaluation was refused by the patient. Diagnosis of pachyonychia was made clinically and biopsy of the cyst confirmed steatocystoma multiplex [Figure 8]. Patient was treated symptomatically with keratolytics for hyperkeratotic plaques and there was significant clinical improvement.

**DISCUSSION**

Pachyonychia congenita (PC) is a rare genodermatosis. The term pachyonychia congenita (Greek: thick nails from birth) was coined by Jadassohn and Lewandowski in 1906 and this case report is frequently quoted as the original description of the condition (Jadassohn and Lewandowski, 1906). However, based on the descriptions and photographs of cases reported by Muller in 1904 and Wilson in 1905, it is likely that they were also describing PC. Jan Bondeson has performed a comprehensive review of the medical history of PC (Bondeson, 1993). This paper provides compelling evidence that St. George Ash described an Irish case of PC as early as 1685, and that the first reported case of PC-tarda was by the philosopher John Locke in 1695 (Ash, 1685; Locke, 1695). A doctoral dissertation in 1716 by Carl Musaeus on “monstrous nails” was apparently the first to postulate that the constellation of symptoms seen in PC represented a systemic disease called “morbus corneus”. The form of PC with widespread pilosebaceous cysts was first described in the recent literature by Jackson and Lawler (1951). Feinstein et al. (1988) proposed a classification of PC into four overlapping subtypes which are frequently used in case reports. The literature was again reviewed in 1995 (Dahl et al., 1995), and simplified criteria were proposed in which the diagnosis of PC could be made when the characteristic nail changes (major criteria) occurred in association with at least one minor criterion (autosomal dominant inheritance, palmoplantar keratoderma, leukokeratosis oris, follicular keratosis, bullae on palms or soles, or laryngeal leukokeratosis)[1].

Pachyonychia congenita has been classified into four types based on the clinical features found in addition to the nail changes[2].

Patients with type I disease (Jadassohn–Lewandowsky syndrome) have symmetric hyperkeratosis of the palms and soles and follicular keratosis on the body[2]. Type II (Murray–Jackson–Lawler syndrome) has features of type I along with the additional findings of natal teeth and steatocystoma multiplex[2].

Type III (Schafer–Branauer syndrome) includes features of both PC-1 and PC-2 with additional features of angular cheilitis, corneal dyskeratosis and cataract[6].

PC type IV (PC tarda), which has a late onset (in the second or third decade)[2]. PC-4 has features of other three types with additional laryngeal involvement and mental retardation[6].
Fissures present over both heels of feet

Figure 1: Symmetric hyperkeratotic plaques of variable size present over pressure sites on both feet

Yellow coloured cysts on retroauricualr region and chest

Figure 2: Yellow coloured cysts on retroauricualr region and chest

On puncturing these cysts creamy fluid was expressed

Follicular keratotic papules

Figure 4: Follicular keratotic papules

Mutations in the \( KRT6A \), \( KRT6B \), \( KRT16 \), and \( KRT17 \) genes can cause pachyonychia congenita. These genes provide instructions for making tough, fibrous proteins called keratins. These proteins form networks that provide strength and resilience to the tissues that make up the skin, hair, and nails[8].

When pachyonychia congenita is caused by mutations in the \( KRT6A \) gene, it is classified as PC-K6a. Similarly, \( KRT6B \) gene mutations cause PC-K6b, \( KRT16 \) gene mutations cause PC-K16, and \( KRT17 \) gene mutations cause PC-K17. In other cases, the cause of the condition is unknown. These cases are classified as PC-U[8].

Mutations in any of the keratin genes listed above alter the structure of a keratin protein, which prevents keratins from forming strong, stable networks within cells. Without this network, skin cells become fragile and are easily damaged, making the skin less resistant to friction and minor trauma. Even normal activities such as walking can cause skin cells to break down, resulting in the formation of severe, painful blisters and calluses. Defective keratins also disrupt the growth and function of cells in the hair follicles and nails, resulting in the other features of pachyonychia congenita[8].
Pachyonychia Congenita Type II: A Case Report

Histopathology shows gross hyperkeratosis with alternating ortho and parakeratosis. Acanthosis is present with patchy hypergranulosis, in which large keratohyaline granules are present without gross epidermolysis. In PC-2, the cysts may be keratinous epidermoid cysts, eruptive vellus hair cysts or true steatocysts. Different histologies may be seen[9].

PC-1 is the more common variant. It is characterized by hypertrophic nail dystrophy (pachyonychia) which is a characteristic feature in 90–98% cases, present at birth or developing within the first few months of life[9]. Specifically, the nail changes in PC consist of three abnormal findings: hyperkeratosis of the nail bed; thickening of the nail plate; and distortion or curvature of the nail plate[1]. It may be accompanied by painful paronychia with difficulty in fine motor tasks. Nail dystrophy of PC is histologically characterized by changes in the nail bed. A longitudinal lesion, filled with granular tissue, is evident in keratinized substance located between the nail and nail bed[11]. Other features include symmetric focal palmoplantar keratoderma, oral leukokeratosis (not premalignant), palmoplantar hyperhidrosis, follicular keratosis, and laryngeal involvement[9]. PC-1 is also characterized by development of callus over plantar pressure points, blistering on walking and hair abnormalities. The upward angulation of subungual hyperkeratosis is described as ‘door wedge’ distal hyperkeratosis[6].

PC type II is characterized by the presence of additional features, including neonatal teeth, multiple epidermal cysts, steatocystoma multiplex, unruly hair,
and bushy eyebrows[9]. Compared to PC type I, there is a lower frequency of oral leukokeratosis and often milder palmpoplantar keratoderma[9]. It includes numerous steatocystomas, although a variety of cysts, including epidermal inclusion cysts, pilosebaceous cysts and vellus hair cysts[9]. Presence of steatocystoma following puberty is an important factor in PC-2[6]. Nail trimming is impossible because the nails are extremely hard[4].

Steatocystoma multiplex is observed as small, rounded, moderately firm, cystic nodules that are adherent to the overlying skin and usually measure 1–3 cm in diameter[5]. When punctured the cysts discharge an oily or creamy fluid and in some instances small hairs[5]. They are found most commonly in axilla, in sternal region and on arms[5]. Histopathology shows the cysts have walls that are intricately folded with several layers of epithelial cells[5]. Central to these cells there is thick, homogenous, eosinophilic horny layer that forms without an intervening granular layer[5]. It protrudes irregularly into the lumen in a fashion simulating the decapitation secretion of apocrine glands. A characteristic feature is the presence of flattened sebaceous glands lobules either within or close to the cyst wall[5].

Diagnosis of PC is based on clinical examination and is confirmed by molecular genetic testing[7]. PC should be differentiated from other conditions characterized by nail dystrophy (e.g., traumatic thickening of nails, congenital onychographosis, onychomycosis, twenty nail dystrophy), focal PPK associated with oral leukokeratosis, focal non-epidermolytic PPK, striate PPK or other PPKs, psoriasis and pityriasis rubra pilaris[7]. Oral leukokeratosis may be mistaken for Candida albicans (thrush), leukoplakia and white sponge nevus if no other findings of PC are apparent. PC should be also distinguished from curly hair-acral keratoderma-caries syndrome, clouston syndrome and congenital dyskeratosis[7]. Most of these conditions lack the features of PC or have distinctive characteristics, making them easy to recognize, if detailed history and physical examination are performed. However, biopsy, microbiological studies, genetic testing and others may be necessary for a conclusive diagnosis[7]. A range of associated features have been reported, including amyloidosis in one pedigree and a case where PC coincided with tuberous sclerosis[3].

Like most genodermatoses, no specific treatment or cure is known for PC[7]. Therapy is generally directed towards symptomatic improvement of the most troublesome manifestation of the disease[7]. Emollients and keratolytics (e.g., salicylic acid, corn plasters, benzoic acid, propylene glycol) may help mild keratodermas; a comfortable footwear may reduce blistering and callosities[9]. Physical debridement of nails can also be done to reduce the thickness of nails[9]. Mechanical reduction of hyperkeratosis and nails produces symptomatic benefit. Antifungal creams and systemic antifungal agents can be used to provide some relief but may need repeated intermittent courses[9]. Acitretin 25–35 mg/day may be effective but causes increased tenderness in the lesions[9]. A prolonged course of retinoids may produce a degree of flattening of the nails and other complications such as periosteal hyperostosis, increased sensitivity and fragility of the underlying epidermis, and this limits their usefulness[9]. In last instance, surgical avulsion and matrix destruction followed by scarification of the nail bed to prevent re-growth can be performed[7]. Treatment of hyperhidrosis (aluminum chloride lotion, and iontophoresis) may reduce blistering and the use of botulinum toxin under regional analgesia may provide pain relief for several months[9]. When the familial mutation is known, genetic counseling can be done and if required, prenatal diagnosis can be done at early stage of pregnancy by chorionic villi biopsy[10]. Hickerson et al. showed that the macroline sirolimus (rapamycin) selectively blocks K6a expression in human keratinocytes[7]. Other authors found that simvastatin and other statins inhibit K6a promoter activity and K6a protein expression, opening the scene for further clinical trials with statins as a possible therapeutic option[7]. The mechanisms of manipulating gene
expression by small molecules or gene therapy has become possible. Genetic therapies for such diseases must either suppress the production of the toxic proteins or correct the genetic defect in the chromosome[9]. Utilizing the technological by-products of the human genome project, such as RNA interference (RNAi) and quantitative RT-PCR (qRT-PCR), physicians and scientists have collaborated to create a candidate siRNA therapeutic that selectively inhibits a mutant allele of KRT6A, the most commonly affected PC keratin[9]. In vitro investigation of this siRNA demonstrates potent inhibition of the mutant allele and reversal of the cellular aggregation phenotype[9].

CONCLUSION

In summary we report a rare case of PC type II presenting with dystrophic thickened nails, Multiple steatocystomas on neck, axilla, trunk, post auricular area and inguinal region confirmed by biopsy of cyst, presence of natal teeth at the time of birth as informed by mother follicular hyperkeratotic papules on extensor aspects of legs, back and plantar keratoderma.

REFERENCES


