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A REVIEW: "SKIN-RELATED RARE DISEASES: PACHYONYCHIA CONGENITAL"

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ABSTRACT: Keratin is a structural protein from the intermediate filament network, *i.e.*, responsible for maintaining the keratinocyte's structural integrity. Pachyonychia congenita is not a lifetime disease. It is a rare dermatosis disease occurred in the sole's feet and palm's hand. In this review, we have discussed the keratinization that occurs in the stratum corneum that follows mutation in the keratin gene "rare disease" pachyonychia congenital an autosomal dominant disorder or hereditary syndrome by any one of a missense mutation in keratin genes such as KRT6A, KRT6B, KRT16 and KRT17. This disease shows hypertrophic dystrophy in toenails and fingernails, plantar keratoderma, oral leukokeratosis, cysts, and follicular hyperkeratosis in the hair follicles. This review aims to specify the beneficial surgical treatment for the pachyonychia congenita. There is limited treatment for this disease, only for the clinical manifestations. In the future perspective, pachyonychia congenita may be treated with $C_2H_4O_3$ lotions/creams and Keratolytics creams available in the marketed preparation.

INTRODUCTION: A rare autosomal dominant disorder that affects the nails and skin is hypertrophic nail dystrophy, oral leukokeratosis, and palm plantar keratoderma. It generally appears in the adultery stage, and this is not a lifetime disorder, but people may suffer constant pain. In pachyonychia congenital, a mutation occurred in 5 keratin genes, *i.e.*, KRT6A, KRT6B, KRT6C, KRT16, and KRT17 KRT16 is responsible.

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Keratin 16 is a type I intermediate filament protein present on the tongue, hair follicle and a part of glabrous skin [1]. Keratinization or cornification was undergone in developing special cells from the undifferentiated precursor. In this, keratinocytes directly convert into corneocytes, *i.e.*, a non-nucleated cell and move stratum corneum to stratum basal.

Keratinocytes were packed with protein and converted into the hard cell, generating unique keratin structurally and functionally [2, 3]. Cytokeratin and keratin 16 make a protein, *i.e.*, filaggrin (protein maker). Differentiated keratinocytes protein markers are filaggrin, locricrin and involucrin.

The transforming growth factor (TGF-β) was responsible for directing the differentiation process of keratinocytes, which takes about 26–28 days (turnover time) physiologically. Pathological keratinization includes hyperkeratosis, parakeratosis and dyskeratosis [4]. In this disorder, the major protection of the epidermis from UV radiation, mechanical damage and chemically by acidic and alkaline substances that maintain the structure and elasticity of the skin [2, 5].

1. Clinical Manifestations in Pachyonychia Congenital:

1. **Palm Plantar Keratoderma:** It was a group of skin diseases that is distinguished by thickening the skin of the palm's hand and sole's feet [6].

2. **Follicular Hyperkeratosis:** It was shown in the waist, hips, knees, and elbows, with excessive development of keratin in the hair follicle and has shown in that areas where lots of friction occurred [7, 8].

3. **Painful Calluses and Blisters:** These generally occurred in the palms and feet [9].

4. **Oral Leukokeratosis:** Occur inside the oral cavity, and the tongue has been thick and white patches [10].

5. **Hypertrophic Nails Dystrophy:** In this dystrophy, the nail finger and toes were abnormal and thickened in shape[11].

6. **Palmoplantar Hyperhidrosis:** Excessive sweatiness in palm's hand and sole's feet [12].

2. Classification of Pachyonychia Congenital Based on Clinical Manifestation:

2.1 Pachyonychia Congenital –I: Type I pachyonychia congenita or type I keratin (k9-k20) keratin gene with two chromosomal loci that were clustered on 17q12 and q21 chromosomes. They included a KRT16 and KRT17.

2.2 Pachyonychia Congenital –II: Type II pachyonychia congenital or type II keratin (k1-k8) keratin gene with chromosomal loci that were clustered and has been located on 12q11q-14. They included a KRT6A and KRT6B [13].

3. Role of Keratin Genes that are Involved in Pachyonychia Congenital: About 54 members of related protein were present in a keratin family. Keratin is a protein found in nails, hair and skin that forms tough fibers for strength. Keratin genes were located in two clusters normal keratin filament forms a dense structural network that enables cells to withstand pressure and to stretch [14, 15].

Mutation in suprabasal keratin genes that cause epidermolytic hyperkeratosis and palm plantar keratoderma [16].

3.1 KRT6A: Keratin 6A comes under type II cytokeratin, which was located on the long arm (q) of chromosome 12 at position 13 and arranged in pair of heterotypic keratin chains in the tissue of simple and stratified epithelium [17].

3.1.1 A Framework of Keratin 6A: KRT6 gene that instructs the development of keratin 6A. The keratin givens the tough framework to the skin of the nails, palms, feet, and mucous lining inside of the mouth; further, KRT6A teams with KRT16 create a dense network and provide strength to skin and nails. Keratin 6A was also involved in wound healing [18].

3.2 KRT6B: KRT6B also types II cytokeratin that includes a basic and neutral protein that wa located on the long arm (q) of chromosome arranged in pair of heterotypic keratin chains with epithelial tissue. KRT6B joined with keratin 7 to form an intermediate filament and was found in tough fibrous cells that form in the skin, sweat gland, nails, and hair follicle [19].

3.3 KRT16: Keratin 16 type I cytokeratin located on the long arm (q) of chromosome 16 at position 21 found in the esophagus, tongue and hair follicle. KRT16 inhibits the proliferation in keratocytes. It was paired with a heterotypic keratin chain and clustered with chromosome 17q12.q21. It makes tough, strong keratin intermediate filaments [18, 20].

3.4 KRT17: KRT17 gene encodes the type I intermediate filament chain of keratin 17 that locus with chromosome 17q21. Keratin 17 instructs the protein k17 that works with keratin 6 to make the proper structure of keratin that makes tough and found in the nails, sebaceous gland, sweat gland, palms and sole's of feet [21].

4. Pathophysiology of Pachonychia Congenital: A type I keratin protein and a type II keratin protein were created in an alpha-helical heterodimer, which was the starting point for keratin intermediate filament assembly. A tetramer was formed by joining two heterodimers together. The tetramers were assembled to create higher-order polymers, which form a keratin intermediate filament [22]. There were 54 distinct keratin genes that have been discovered. Based on cell function, distinct epithelial cell types express various keratins. The genes encoding keratin 6A (KRT6A), keratin 16 (KRT16), keratin 6B (KRT6B) and keratin 17 (KRT17) were all mutated in pachyonychia congenita. Keratin 6A was forms a complex with keratin 16, while keratin 6B were forms a complex with keratin 1723. A keratin filament's fundamental protein structure was an alpha-helical rod split into four domains (1A, 1B, 2A, 2B) were linked together by non-helical linkers (L1, L12, L2). The majority of mutations in pachyonychia congenital, like most other keratin diseases, occur in the highly conserved helix boundary domains near the rod domain's end. At either end of the alpha-helical rod, a helix initiation motif and a helix termination motif segment may be found, and their sequences were largely conserved among keratins [23, 24].

TABLE 1: GENETIC DISORDER IN LOCI OF KERATIN WHICH HELD IN VARIOUS PARTS

Skin	Mutation
Plamoplantar keratoderma	KRT1, KRT9, KRT16.
Ichthyosis bullosa of simemens	KRT2A
Pachyonychia congenita	KRT16, KRT6B, KRT16, KRT17.
White sponge nerve	KRT17
Epidermolytic hyperkeratosis	KRT1, KRT10.
Steatocystoma multiplex	KRT17.
Hair	
Monilethrix	KRT81, KRT83, KRT86 [25]
Cornea	
Meessman juvenile epithelial corneal dystrophy	KRT3, KRT12 [26]
Liver	
Familial cirrhosis	KRT8, KRT18 [27]

5. Mutation in Keratin Genes with Phenotypic Variation in Pachyonychia Congenital: This gene family's protein products generate α-helical coiled-coil dimers that could quickly be assembled into 10 nm wide filaments without the use of cofactors or related proteins other than intermediate filament proteins. Most intermediate filaments will assemble as homopolymers, but homodimers keratin was exceedingly unstable; thus, heterodimers must be created before filaments may be polymerized. Keratin filaments were always made up of equimolar concentrations of type I and type II proteins [28, 29]. According to the cell's differentiation pathway, keratins were expressed as particular pairings in cells. Single keratins do not form filaments on their own and are swiftly destroyed, which helps to keep the balance between type I and type II keratins in cell [30].

5.1 Mutation in KRT6A: We present the results of a genetic analysis of 90 new PC families in which mutations in KRT6A, KRT6B, KRT16, or KRT17. There were 22 recognized mutations discovered and 21 previously unreported mutations. KRT6A mutations were found in over half of the families (52%), KRT16 mutations in 28%, KRT17 mutations in 17% and KRT6B mutations in 3% of their families. Most missense alterations were heterozygous or minor in-frame mutations in insertion/deletion that occurred inside one of the keratin polypeptide's helix boundary motif areas [31]. In Pachyonychia congenital-I, there were at least 20 mutations. The majority of mutations are only affected by a single AA protein-building component. A few genetic material additions or deletions impair the structure of K6A and prevent the formation of network filament keratin without functional keratin.

Signs and Symptoms:

- Skin, hair, and nails were all readily damaged.
- Nails and skin that were painful or deformed [32].

5.2 Mutation in KRT16: PC-1 was caused by over 13 mutations in KRT16. In most cases, the disease was present at birth or recognized shortly after most mutations occur in the exchange of only one amino acid building block. A few mutations may result in the deletion of a few amino acids, causing the keratin assembly pathways to be disrupted [33].

5.3 Mutation in KRT6B: Over 2 mutations in KRT6B were produced in PC-2, which altered only one amino acid building block and deleted the genetic material; mutations impair keratin 17 function and keratin network formation without correct keratin structure.

Signs and Symptoms:

- ✓ The soles of the feet become exceedingly delicate, blisters form and the nails stop working correctly.
- ✓ Sweat glands are also impacted, resulting in cyst formation [34, 35].

5.4 Mutation in KRT17: PC-2 was caused by 16 mutations in KRT17; the majority of mutations were caused by a single amino acid building block change in the structure of K-17, which has prevented it from functioning efficiently with K-6b and disrupts the filament network, potentially leading to skin cell disintegration. K17 p. Asn 92 Ser was the most frequent mutation discovered.

Signs and Symptoms:

- ✓ Cysts formation occurs.
- ✓ Malfunction of the nails and hair follicles [36].

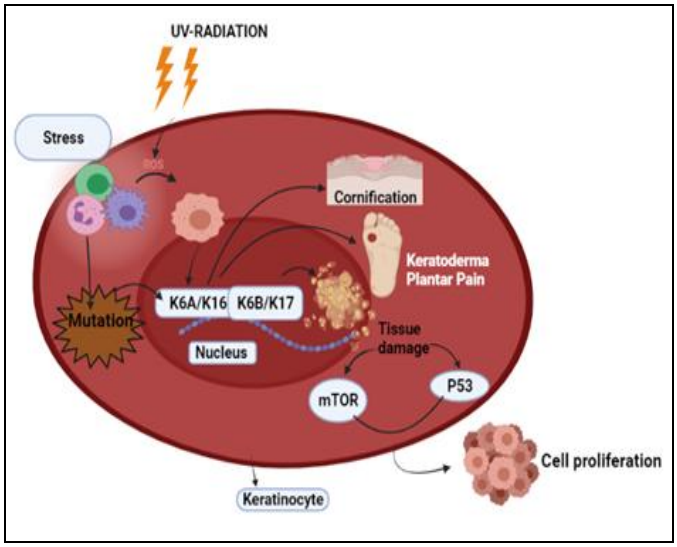

FIG. 1: MUTATION IN KERATINOCYTES BY STRESS, UV- RADIATION THAT MAY LEAD TO TISSUE DAMAGE OR CELL PROLIFERATION

5.5 Expression of Opioid Peptide Receptor that Responsible for Pachyonychia Congenital: In pachyonychia congenita; the mechanism of pain was neuropathic by the recent elucidation of functionally or pathologically. In the model study, the expression nociceptin/ orphanin FQ receptor has shown a wide distribution range and mainly targets the receptor to alleviate neuropathic pain. Nociceptin/ orphanin FQ receptor characterized in a palmoplantar skin of epidermis or dermis and may alter the pain. This receptor belongs to the opioid peptide receptor family and antagonists of the nociceptin/orphanin receptor, *i.e.*, anti-nociceptive and anti-allodynic, were employed to treat the pain model in the experiment. Furthermore, this receptor in epidermal nerve fiber targets epidermal keratosis and keratinocytes for the alleviation of neuropathies have been utilizing a marker called Pain neuronal marker for the unmyelinated fiber [37].

6.0 Epidemiology:

Age: Patients with pachyonychia congenita frequently have hypertrophic toenail dystrophy at birth or shortly after [38].

Sex: Pachyonychia congenita affects both men and women in similar amounts [39].

Frequency: The exact incidence of pachyonychia congenital is undetermined; however, it appears to be infrequent. Globally, an estimated 5,000–10,000 cases have been diagnosed [40].

Surgical Treatment: It is most helpful for treating cysts, with the standard safety measures such as drainage, excision and incision. Treatment for the affected nails has not shown effective because of shown regrowth of nails. Excision and grafting techniques used in the treatment of the plantar skin; reappeared as hyperkeratosis [41, 42].

Medication:

Keratolytics: These chemical agents show the result as a Cornified epithelium swells, softens, macerates, and ultimately desquamates.

Topically used Salicylic Acid: Salicylic acid causes desquamation of the horny layer of skin by dissolving the intercellular cement material while having little effect on the structure of the viable epidermis. Further, Soaked the afflicted region in warm water for 5 minutes before using it to hydrate the skin and improve the medication's effects. Using a brush, washcloth, or emery board, remove any loose tissue and thoroughly dry. In most cases, improvement takes 1-2 weeks [43].

Urea (Ureacin-40): In hyperkeratosis, urea increases hydration and the elimination of extra keratin. Therefore, in the pharmacy urea (40%) and

salicylic acid (20%), rather hydrophilic ointment compound is present [44].

Retinoid: Retinoids belong to the family of vitamin A, and they control epithelial cell differentiation and proliferation and possess anti-tumor activity.

Acitretin (Neotigason, Soriatane): Acitretin and Isotretinoin are the Retinoic Acid Analogue. This is widely used in dermatology and the main metabolic compound is Etretinate [45].

CONCLUSION: Pachyonychia congenita is an autosomal or monogenic skin disorder. These various disorders are related to keratin that affect the skin, oral cavity, and hair follicle. Mutation in KRT6A/KRT16 AND KRT6B/KRT17 belongs to type I and type II phenotypic pachyonychia congenital. Thus a thorough study regarding with diagnosis and treatment of pachyonychia congenita that reduces the cohesivity in the stratum corneum; is beneficial. They reduce the excess friction in the corneum.

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CONFLICT OF INTEREST: NIL

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