Pachyonychia Congenita Project

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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.

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PACHYONYCHIA CONGENITA (MIM:167200, 167210)

Includes Jadassohn-Lewandowsky; Jackson-Lawler; onychogryposis.

Current nosology of pachyonchyia congenita divides this group of disorders into PC-1 (Jadassohn-Lewandowsky type) and PC-2 (Jackson-Lawler). PC-3 is used for the tarda form of the condition(s). Prior to the identification of the underlying mutations, various classification schemes were proposed, and Riehl type (mild with oral leukoplakia), type 3 (Schafer-Brunauer) with corneal dystrophy, and two type 4—one with widespread macular hyperpigmentation of the neck and axillae and the other with mental retardation, alopecia and laryngeal involvement—were delineated.

Overlap within families does occur, and one cannot accurately predict in many families whether an individual at risk for pachyonychia congenita will be spared a specific finding. Leukoplakia is most common in PC-1, but this can also be seen in PC-2. PC-2 is characterized by steatocystoma multiplex, which can also be seen in patients with type 1, and natal teeth, which appear to be specific to type 2, but are not always present. I am also convinced that any inherited disorder with thickened nails in association with a second dermatologic feature has been labeled as pachyonychia congenita in case reports, further muddying the diagnostic waters.

DERMATOLOGIC FEATURES

MAJOR. The fingernails and toenails are thickened, friable, and darkened. The nail beds and

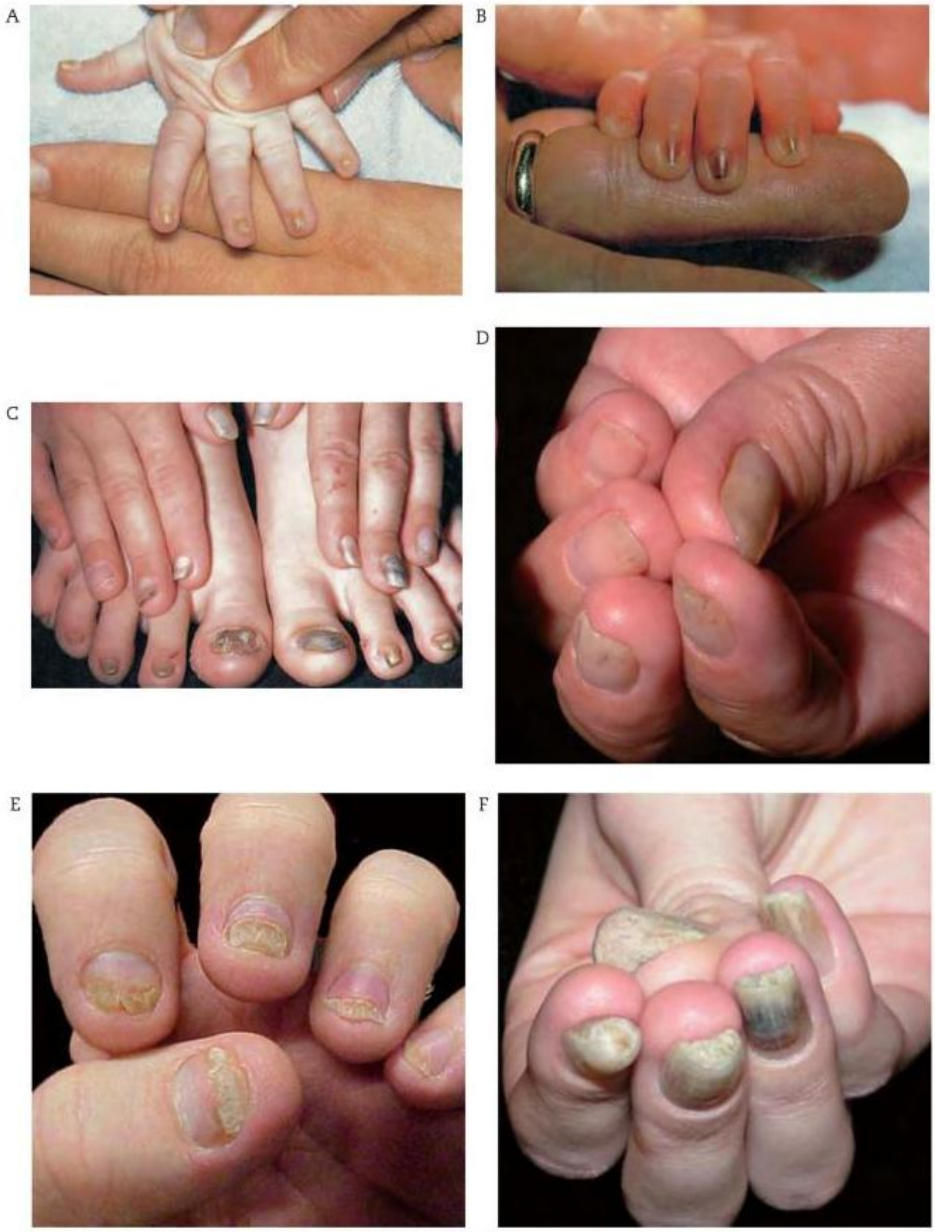

Figure 3.43. (A & B). Nail changes in young children. (C) Finger and toenails in adult with marked difference in severity among nails. (C, Courtesy of Dr. P. Fleckman, Seattle, WA.). (D) Mild, (E) moderate, and (F) severe nail changes. (D, E, & F, Courtesy of Dr. S. Leachman and Ms. M. Schwartz, Pachyonychia Congenita Project, Salt Lake City, UT.)

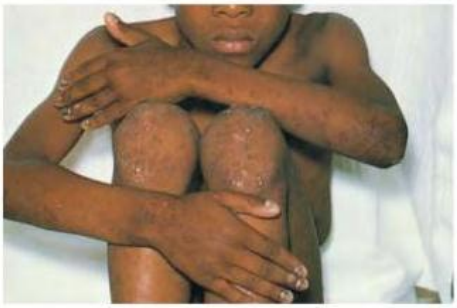

Figure 3.44. Nail changes and typical follicular hyperkeratosis over knees and arms.

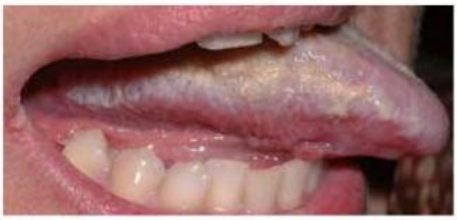

Figure 3.45. Leukokeratosis of tongue, perleche at angle of mouth. (Courtesy of Dr. S. Leachman and Ms. M. Schwartz, Pachyonychia Congenita Project, Salt Lake City, UT.)

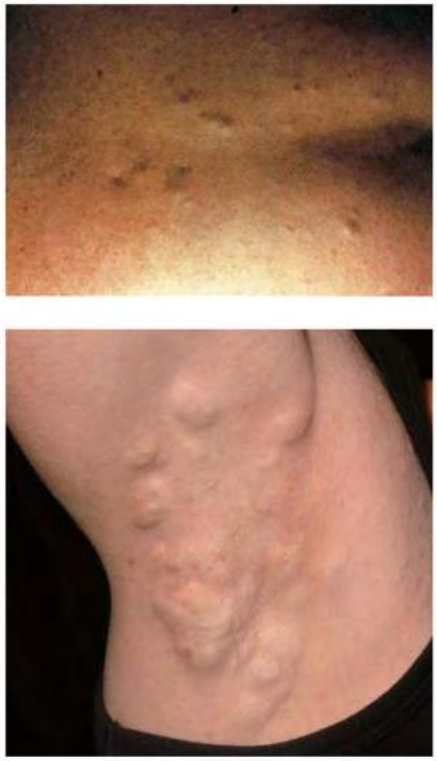

Figure 3.47. (A & B) Inclusion cysts in patients with PC-1 (B, Courtesy of Dr. S. Leachman and Ms. M. Schwartz, Pachyonychia Congenita Project, Salt Lake City, UT.)

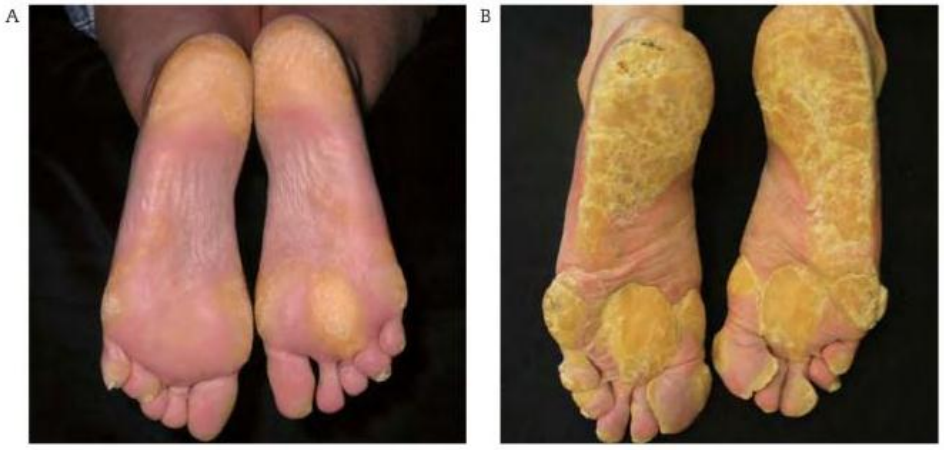

Figure 3.46. (A & B) Variation in hyperkeratosis of soles. (Courtesy of Dr. S. Leachman and Ms. M. Schwartz, Pachyonychia Congenita Project, Salt Lake City, UT.)

nail plates are hypertrophic and thickened and there is distortion or hypercurvature of the nail plate. Distal involvement may be greater than proximal involvement. Conversely, in some, the nail plates may be shortened and thickened. Nail changes can be seen at birth and usually present within the first year of life. Erythema of the nail bed may be the only finding in newborns. Although involvement is often symmetric, not all nails are necessarily involved. The toenails and fingernails of the thumbs and index fingers tend to be more severely involved. The distal nail bed, as well as the nail plate, is also thickened. Nails may be shed; new nails are also dystrophic.

Hyperkeratosis and hyperhidrosis of the palms and soles are common. It may be focal or widespread and may not develop until later in childhood. The hyperkeratosis is often extremely painful in adults and walking maybe compromised.

Follicular hyperkeratosis, primarily of the elbows and knees, develops. More widespread distribution of these skin lesions can also occur.

MINOR. There are occasional reports of blistering of the soles under the calluses.

Epidermal inclusion cysts, steatocystoma multiplex, and cylindromas have been reported. There is some confusion about the histopathology of these lesions in pachyonychia congenita, and there may be overlap. These skin changes occur later in childhood and adult life and are more common in Jackson-Lawler (PC-2).

Alopecia, which may be congenital or occur later, and/or thinning and loss of sheen of the hair are described in some patients, typically in those with Jackson-Lawler (PC-2). Coarseness of eyebrows and body hair, with pili torti of the hair shafts, has also been reported in PC-2.

Reticulated hyperpigmentation of the neck and axillae can occur and may represent a distinct subtype.

Hidradenitis suppurativa was described in one family.

Increased production of earwax has been mentioned.

ASSOCIATED ABNORMALITIES

Oral leukokeratosis of the mucosa of the mouth and on the tongue is histologically similar to white sponge nevus. Malignant degeneration has not been reported. This feature is primarily seen in the Jadassohn-Lewandowsky form (PC-1) and is uncommon in the Jackson-Lawler variant (PC-2). It may present at birth.

Natal teeth are occasionally present, as are malformed teeth, primarily in the Jackson-Lawler variant (PC-2).

The evidence for association with mental retardation in the literature is not compelling, and I suspect that this is not a true feature of pachyonychia congenita.

HISTOPATHOLOGY

LIGHT. None is diagnostic. The nail plate and proximal nail matrix are normal. The nail bed shows marked hyperkeratosis. The distal nail matrix is hypertrophic. There is some disagreement about microscopic features.

ORAL MUCOSA: Acanthosis, parakeratosis, and intracellular vacuolization are seen.

HYPERKERATOSES: Hyperkeratosis, parakeratosis, acanthosis, and a moderate increase in the granular layer with a minimal lymphocytic infiltrate in the upper dermis are reported in some biopsy specimens, orthohyperkeratosis and a decreased granular layer in others. It is unclear if these findings are site or patient specific.

EM. Dense aggregation of tonofilaments at the periphery of the basal keratinocytes and abnormal keratohyalin have been described. These changes are not specific.

BASIC DEFECT

Mutations in *KRT16* or *KRT6a* underlie PC-1. Mutations in *KRT17* or *KRT6b* cause PC-2. The majority of mutations occur in the helix boundary motifs of these keratin genes. Late onset PC (PC tarda) appears to be due to mutations in *KRT16* or *KRT17* that fall outside of the helix boundary motifs. Keratin 6a and keratin 16 are present in the nailbed, palmar and plantar skin and oral mucosa. Keratins 17 and 6b are found in the nailbed , hair follicle, eccrine glands, and palmar and plantar skin.

TREATMENT

Treatment is primarily symptomatic. Emollients and keratolytics (e.g., lactic acid preparations, glycolic acid, salicylic acid) can be used for the palmar–plantar hyperkeratosis. Routine grinding of the nail plates can keep their interference with function at a minimum, but the nails remain cosmetically dystrophic. Use of a 40% urea paste to ease paring of the nails and to reduce the palmar–plantar hyperkeratosis has been reported. Botulinum toxin injections for plantar hyperhidrosis and pain have had anecdotal success. If limitation of hand function becomes unacceptable, ablation of the nail matrix is the only permanent effective therapy for the dystrophic nails. There has been mixed success with treatment with oral retinoids. There is currently an *in vivo* protocol using small interfering RNAs to ablate the abnormal keratin molecule in PC1.

MODE OF INHERITANCE

Autosomal dominant. *KRT16* and *KRT17* are mapped to the type I keratin cluster on 17q. *KRT6a* and *KRT6b* reside at 12q. Phenotype–genotype correlation regarding severity or limited expression is not reliable. Penetrance is complete.

PRENATAL DIAGNOSIS

Possible by mutation or linkage analysis. Approximately half of affected individuals represent new mutations.

DIFFERENTIAL DIAGNOSIS

The involvement of the nails in pachyonychia congenita can often be distal and may be clinically indistinguishable from fungal infection on the basis of nail changes alone. KOH and fungal cultures are always appropriate. The oral leukoplakia may be mistaken for thrush.

The nail changes of dyskeratosis congenita (MIM:305000) are quite different from those of pachyonychia congenita, more similar to those of lichen planus, with hypoplasia and pterygia of the nails rather than thickening.

Individuals with Clouston syndrome (MIM:129500), autosomal dominant hidrotic ectodermal dysplasia, can have similar nail and hair changes and may also have palmar and plantar hyperkeratoses.

Onychogryphosis, the development of claw or talon nails, is usually acquired. One family with claw-like nail changes and plantar hyperkeratoses is described by McKusick (MIM:164680). One individual had dry, coarse hair. Although five generations were involved, no male-to-male transmission occurred.

In EBS-Weber- Cockayne (MIM:131800), nail changes are usually more mild, of later onset, and blistering is more marked.

The molecular differential diagnosis includes focal nonepidermolytic hyperkeratosis (MIM:600962), which can also be due to mutations in *KRT16*, and steatocystoma multiplex (MIM:184500), which is caused by mutations in *KRT17*.

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El-Darouti, M. A., Marzouk, S. A, Nabil, N., Abdel-Halim, M. R., El-Komy, M. H., and Abdel-Latif, M. (2006). Pachyonychia congenita: Treatment of the thickened nails and palmoplantar circumscribed callosities with urea 40% paste. *J. Eur. Acad. Dermatol. Venereol.* **20**, 615–617.

Case report with detailed description of how to formulate and use 40% urea paste. Nice how-to.

Gorlin, R. J., and Chaudhry, A. P. (1958). Oral lesions accompanying pachyonychia

congenita. *Oral Surg. Oral Med. Oral Pathol.* **11,** 541–544.

Authors describe the mucosal changes associated with the disorder as hyperkeratotic, in contrast to the dyskeratosis of true leukoplakia.

Jackson, A. D. M., and Lawler, S. D. (1951). Pachyonychia congenita: A report of six cases in one family. *Ann. Eugen.* **16,** 142–146.

A report of a family with natal teeth, blistering of the soles, multiple skin cysts, follicular hyperkeratoses, and pachyonychia congenita. This family did not have leukoplakia.

Leachman, S. A., Kaspar, R. L., Fleckman, P., Florell, S. R., Smith, F. J., McLean, W. H., et al. (2005). Clinical and pathological features of pachyonychia congenita. *J. Investig. Dermatol. Symp. Proc.* **10,** 3–17.

Review of clinical findings in individuals from two patient registries (for pachyonychia congenita and for ichthyosis) and the literature. Beautiful photographs. This is part of an entire issue devoted to pachyonychia congenita.

McLean, W. H. I., Rugg, E. L., Lunny, D. P., Morley, S. M., Lane, E. B., Swensson, O., et al. (1995). Keratin 16 and keratin 17 mutations cause pachyonychia congenita. *Nat. Genet.* **9,** 273–278.

Presents mutation data and correlates clinical differences between the forms of pachyonychia congenita with specific mutations. KRT16 and KRT17 are acidic keratins that are expressed to different degrees in different tissues. KRT16 alterations might affect oral mucosa more (where it is expressed in greater amounts), whereas KRT17 alterations might be more likely to lead to epidermal cyst formation, as its expression predominates in the infundibulum of sweat glands.

Soderquist, N. A., and Reed, W. B. (1968). Pachyonychia congenita with epidermal cysts and other congenital dyskeratoses. *Arch. Dermatol.* **97,** 31–33.

In this report there was reevaluation of three of the members of the Jackson-Lawler family.

Tidman, J. N. J., Wells, R. S., and MacDonald, D. M. (1987). Pachyonychia congenita with cutaneous amyloidosis and hyperpigmentation—A distinct variant. *J. Am. Acad. Dermatol.* **16,** 935–940.

Better title: Autosomal dominant onychodystrophy with macular amyloidosis. Two pedigrees with onset of nail changes during infancy–early childhood, improving with age. Mild palmoplantar hyperkeratosis, gradual macular hyperpigmentation in axillae, neck, waist, backs of knees, thighs, buttocks, and belly. Amyloid deposition seen. No other features of pachyonychia congenita. Typifies the nonspecific use of the term *pachyonychia congenita*.