

UC Davis

Dermatology Online Journal

Title

Systematized linear epidermolytic hyperkeratosis

Permalink

<https://escholarship.org/uc/item/4km3v0zr>

Journal

Dermatology Online Journal, 20(1)

Authors

Kumar, Piyush
Kumar, Rajesh
Mandal, Rajesh Kumar
et al.

Publication Date

2014

DOI

10.5070/D3201021248

Copyright Information

Copyright 2014 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

Case Presentation

Systematized linear epidermolytic hyperkeratosis

Piyush Kumar¹, Rajesh Kumar², Rajesh Kumar Mandal³, Shahid Hassan¹

Dermatology Online Journal 20 (1): 7

Katihar Medical College, ¹Department of Dermatology, ²Department of Pathology, Katihar, India

³North Bengal Medical College, Department of Dermatology, West Bengal, India

Correspondence:

Piyush Kumar
Katihar Medical College
Katihar, India
docpiyush@gmail.com

Abstract

A 5-year-old boy presented with widespread asymptomatic hyperpigmented verrucous plaques since 3 months of age. The lesions were distributed in a linear manner along Blaschko's lines on trunk and extremities and were accentuated in flexures and around joints. There was no history of blistering or redness and no other family member was affected. Ichthyosis hystrix (of Curth and Macklin) and generalized linear/mosaic epidermolytic hyperkeratosis (EHK) were considered in the differential diagnosis. Biopsy from both trunk lesion and lesion on knee revealed characteristic epidermolytic hyperkeratosis, thereby clinching the diagnosis of systematized linear EHK.

Introduction

Bullous congenital ichthyosiform erythroderma (BCIE) is a rare disorder caused by mutations affecting Keratins 1 or 10 (part of cytoskeleton of suprabasal layers of epidermis) and is clinically characterized by erythroderma and blistering at birth and verrucous plaques on flexures and around joints later on [1]. As the child grows, blistering and erythroderma subsides or even disappears, but the verrucous plaques persist throughout life. The histopathological hallmark of this condition is “epidermolytic hyperkeratosis (EHK)”, though EHK has been described in various congenital and acquired conditions too. In fact, the term EHK is still being used as synonym for BCIE in the medical literature, unless otherwise specified [1, 2]

Apart from the classical presentation, various uncommon presentations are known. Annular and linear BCIE (EHK) are widely recognized clinical variants [3, 4, 5]. Sybert et al have described an unusual “cyclic” variant of BCIE with recurrent explosive erythroderma and migratory erythematous scaling plaques, similar to erythrokeratoderma variabilis, along with palmar and plantar hyperkeratosis and mild ichthyotic changes of the flexures and scalp [6]. Linear BCIE may be unilateral or bilateral, localized or generalized [4, 5]. We here report a case of systematized/ generalized linear BCIE in a 5-year-old boy.

Case synopsis

A 5-year-old boy, born of a non-consanguineous marriage, presented with asymptomatic widespread verrucous, hyperkeratotic plaques in a linear distribution all over the body since 3 months of age. There was no history of widespread erythema or development of bullous lesions at birth or thereafter. The plaques had been increasing in thickness and pigmentation with time. Also, there was a history of summer aggravation. There were no systemic features and no other family members were affected by a similar skin condition. On examination, multiple linear verrucous plaques in a Blaschkoid distribution were noted on the trunk and extremities bilaterally, with accentuation of lesions in the flexures and on the skin around joints. The flexural lesions and lesions around joints were characterized by hyperkeratotic ridges arranged in parallel. Scalp, face, palms, and soles were spared (Figure 1a and 1b).

Samples for histopathology were collected by punch biopsy from two sites, one from the trunk and the other from the knee. The histopathological findings from both these sites were similar and were notable for compact hyperkeratosis, perinuclear vacuolization of keratinocytes of the upper dermis, and coarse keratohyaline granules of different sizes. The dermis was unremarkable (Figures 2a, 2b, 3a and 3b). Histopathological findings were characteristic of epidermolytic hyperkeratosis

(EH). Considering the clinical and histopathological findings, a diagnosis of systematized linear epidermolytic hyperkeratosis was made. Electron microscopy and genetic analysis were not done owing to unavailability in our institute.



Figure 1a. Hyperpigmented verrucous plaques in Blaschkoid distribution on trunk and extremities. Note accentuation of lesions in flexures and around joints. Note sparing of palms.



Figure 1b. Close-up of lesions on knee. Note "corrugated cardboard" appearance.

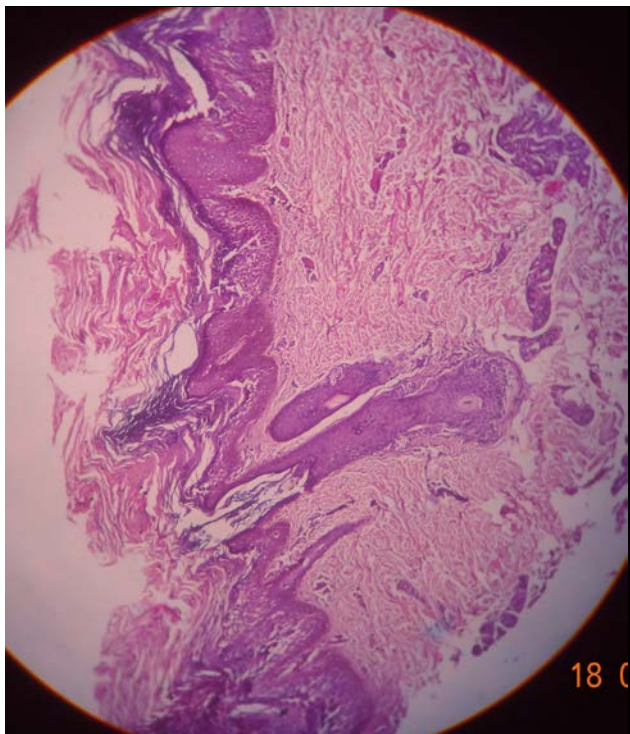


Figure 2a. Histopathology from knee lesion shows compact hyperkeratosis and suprabasal degeneration of epidermis. Note absence of inflammatory cells. (H&E X100).

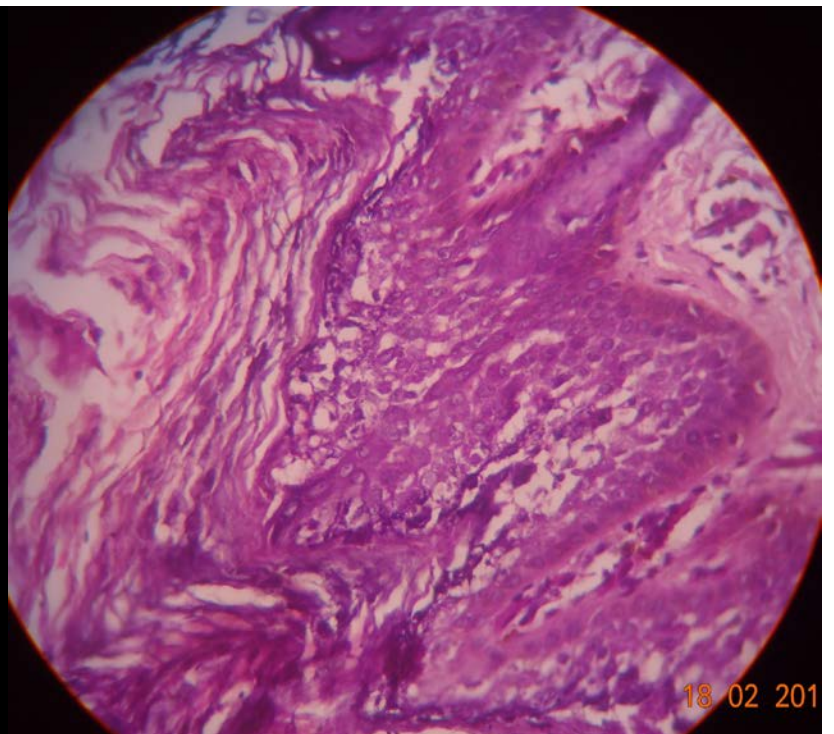


Figure 2b. Epidermolytic hyperkeratosis in sample from knee. (H&E X400).

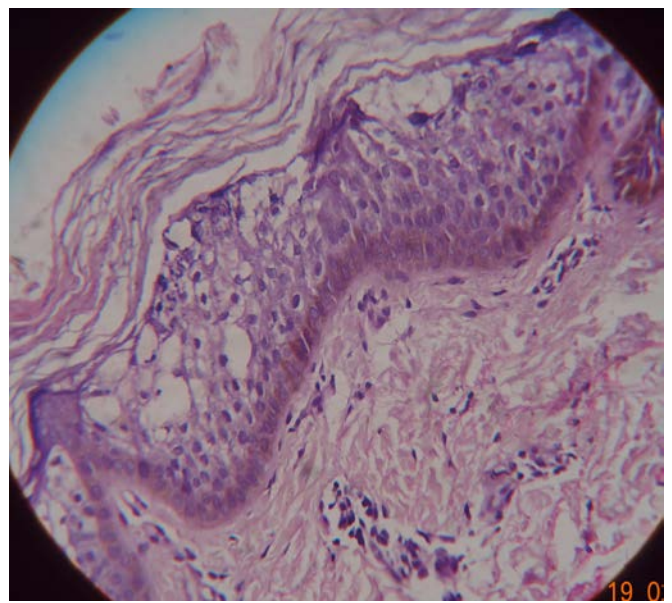
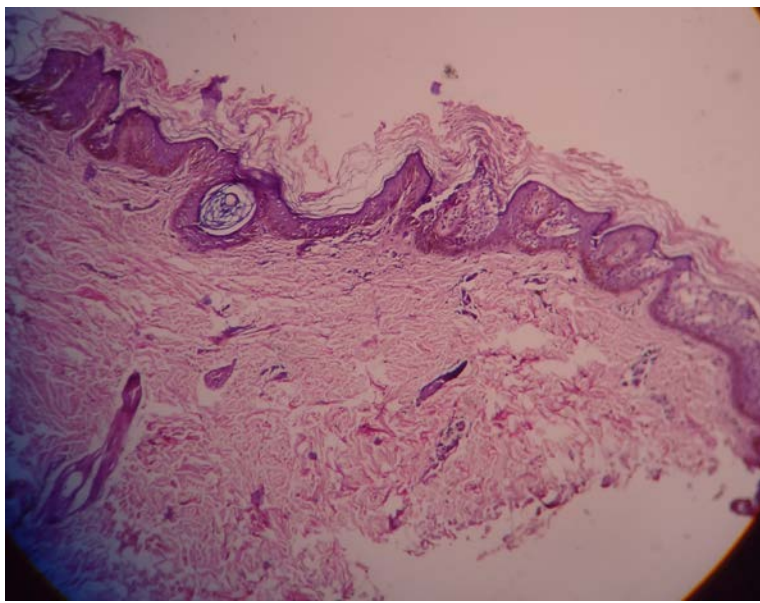


Figure 3a. Histopathology from trunk lesion shows compact hyperkeratosis and suprabasal degeneration of epidermis. (H&E X100)

Figure 3b. Epidermolytic hyperkeratosis in sample from trunk. (H&E X400)

Table 1: Congenital conditions characterized by Epidermolytic hyperkeratosis (EHK)

Features	Bullous Ichthyosiform Erythroderma	Ichthyosis Bullosa of Siemens	Epidermolytic PPK of Vorner
Inheritance	Autosomal dominant (autosomal recessive and sporadic cases too are known)	Autosomal dominant	Autosomal dominant
Gene mutation	Keratin 1 and 10	Keratin 2e	Keratin 9
Clinical presentation	<ul style="list-style-type: none"> Erythroderma and flaccid blisters at birth. Recurrent blistering in childhood- decreases with age. Ridged hyperkeratosis of flexures- increases with age. Palmoplantar involvement-variable. Localized/generalized disease following Blaschko's lines is known. 	<ul style="list-style-type: none"> Erythroderma and superficial blisters at birth. Blistering in response to trauma in infancy. Superficial peeling of skin (Mauserung phenomenon) Hyperkeratosis in flexures 	<ul style="list-style-type: none"> Yellowish thick hyperkeratosis involving palms and soles. Non-transgradient
Histopathology	EH involving all layers of epidermis	EH confined to superficial epidermis with sparing of basal and suprabasal layers	EH involving all layers of epidermis.

Discussion

The term, epidermolytic hyperkeratosis (EH) refers to a distinctive set of histopathologic changes: compact hyperkeratosis, perinuclear vacuolization of keratinocytes of the upper layers of epidermis, and coarse keratohyaline granules (the last two findings together are called granular degeneration). Histopathologically, EH has been noted in a variety of conditions, both acquired and congenital. Among acquired conditions, various *benign* (includes acanthoma, epidermoid cyst, infundibular cyst, epidermal nevus, hidradenoma, nevus comedonicus, seborrheic keratosis, trichilemmal cyst), *pre-malignant* (includes actinic keratosis, leukoplakia, atypical/dysplastic nevus), as well as *malignant* (includes basal cell carcinoma, melanoma, squamous cell carcinoma) conditions have shown findings of EH on histopathology. The exact clinical significance of EH findings in these conditions is largely unknown. EH in these conditions is considered to be incidental and is of no diagnostic value. Of note, such EH findings generally occur in clinically normal skin adjacent to the primary lesion (they can occur in lesional skin too), are restricted to a small area (often one rete ridge is involved), and are associated with prominent solar elastosis. On the other hand, EH in congenital conditions (described later in this review) is considered to be pathognomic and is of diagnostic value. Interestingly, EH in these congenital conditions involves the entire length of the epidermis, but the underlying dermis is usually unremarkable [7, 8].

The congenital conditions, that show EH, include Bullous congenital ichthyosiform erythroderma of Brocq (BCIE), Ichthyosis bullosa of Siemens (IBS), and Epidermolytic palmoplantar keratoderma of Verner [6]. The key features have been summarized in Table 1. IBS shows similar, but milder, clinical and histopathological findings to those in BCIE and hence, has been considered as a milder variant by some authors. However, other authors consider IBS to be a separate entity and distinguish IBS from BCIE by milder clinical manifestations, the absence of erythroderma, the presence of superficial denuded areas over hyperkeratotic skin (the Mauserung phenomenon), and the absence of palmoplantar involvement. Histologically, EH is confined to the granular and upper spinous layers with intracorneal blister formation. Mutations in gene KRT2E, coding Keratin K2e present in the upper spinous and granular layers, are responsible for IBS [9]. Suzuki et al have described an acquired condition “persistent actinic epidermolytic hyperkeratosis, which had light and electron microscopy findings similar to those of the congenital one. Notably, solar elastosis was absent in these cases. Clinically, it was characterized by numerous persistent flat keratotic depigmented papules limited to sun-exposed areas, intermingled with numerous pigmented macules [10].

BCIE is a rare congenital disorder of keratinization with an estimated prevalence of 1:200,000 [11]. It is usually transmitted in an autosomal dominant manner. However, lethal autosomal recessive transmission has been reported [12]. It results from mutations affecting keratin genes KRT1 or KRT10. These mutations cause defective aggregation of keratin, resulting in disruption of the keratin cytoskeleton or abnormal clumping of keratin filaments. Such changes result in less resilient epithelial cells, manifesting as blistering-prone skin even with minor trauma [1, 13].

BCIE typically presents at birth with fragile skin and a mild generalized erythroderma. Skin fragility causes flaccid blisters, peeling, and superficial erosions, even with mild trauma, within the first few hours of birth. Such neonates are at risk of developing sepsis, dehydration, and electrolyte imbalances because of the disruption of the epithelial barrier. As the neonate grows older, the erythroderma and blistering usually improves gradually, although these features can persist throughout life. After a few months, verrucous hyperkeratotic plaques become prominent in the flexures, but can also appear on the scalp, neck and infra-gluteal folds. The surface of lesions is notable for parallel hyperkeratotic ridges, especially in flexures and around joints, mimicking corrugated cardboard [1, 2, 14]. There may be a distinct foul odor owing to secondary bacterial colonization. Di Giovanna and Bale described two main clinical categories of BCIE- one type involves the palms and soles (PS), and the second spares the palms and soles (NPS) [1, 2]. Palm and sole involvement may be noted in about 60% of patients and presents with recurrent painful fissures and contractures. BCIE patients with K1 mutations are more likely to have palm/sole involvement. [1, 2]

Annular epidermolytic ichthyosis (AEI) and linear BCIE are two well-recognized, but uncommon clinical variants [3, 4, 5]. AEI is characterized by recurring, migrating, annular, and polycyclic plaques. Sheth et al have identified a KRT 10 mutation in the annular variant and have reported clinical worsening in pregnancy [3].

Linear BCIE is related to a postzygotic, spontaneous mutation in KRT 1 or KRT 10 keratin genes, thus generating genetic mosaicism. It presents as linear hyperkeratosis distributed in streaks along Blaschko lines and may be unilateral or bilateral, localized or generalized, in distribution [4, 5]. Such linear BCIE cases are notable for the absence of blistering, unlike classical BCIE, as evident in our case. Clinically, it might be indistinguishable from verrucous epidermal nevus, but it shows characteristic histopathological changes of EH. However, the histopathological findings of EH are not as pronounced and widespread as seen in classical BCIE. It is not inherited unless a post-zygotic mutation occurs in the germ line [4, 5].

In the neonatal period, BCIE should be differentiated from epidermolysis bullosa, cutaneous mastocytosis, staphylococcal scalded syndrome, and incontinentia pigmenti with the help of histology and microbiological assessments. In older children, the differential diagnosis may include Ichthyosis bullosa of Siemens and Ichthyosis hystrix of Curth and Macklin. Ichthyosis bullosa of Siemens can be differentiated from BCIE because the epidermal fragility is very superficial and hyperkeratosis and vacuolization are confined to the granular layer in the later. Ichthyosis hystrix of Curth and Macklin presents with extensive and very severe, spiky or verrucous hyperkeratosis without blisters. In addition, the hyperkeratosis is more prominent over the extensor surfaces of the arms and legs [1, 2, 9].

Management is usually for symptomatic relief. In neonates, the goal is to prevent secondary infections, sepsis, dehydration, and electrolyte imbalances. In childhood and adulthood, antibacterial cleansers can control the malodor associated with bacterial overgrowth. Topical emollients such as creams containing glycerine, lactic acid, urea, and α -hydroxy acids have been demonstrated to improve the appearance of hyperkeratotic scaly skin [1, 10, 15]. For more severe cases, oral and topical retinoids have also been shown to improve patients with EHK, although retinoids may promote desquamation and exacerbate blistering. Apparently, individuals with keratin 10 mutations, as opposed to those with keratin 1 mutations, respond better to topical or systemic retinoid therapy [16, 17].

References

1. Lacz NL, Schwartz RA, Kihiczak G. Epidermolytic hyperkeratosis: a keratin 1 or 10 mutational event. *Int J Dermatol.* 2005;44(1):1-6. [PMID: 15663649]
2. Kurosawa M, Takagi A, Tamakoshi A, Kawamura T, Inaba Y, Yokoyama K, Kitajima Y, Aoyama Y, et al. Epidemiology and clinical characteristics of bullous congenital ichthyosiform erythroderma (keratinolytic ichthyosis) in Japan: Results from a nationwide survey. *J Am Acad Dermatol.* 2013;68:278-83. [PMID: 23182068]
3. Sheth N, Greenblatt D, McGrath JA. New KRT10 gene mutation underlying the annular variant of bullous congenital ichthyosiform erythroderma with clinical worsening during pregnancy. *Br J Dermatol.* 2007;157:602-4. [PMID: 17596149]
4. Kocaturk E, Zemheri E, Kavala M, Aktas S, Sarigul S, Sudogan S. Two cases of linear epidermolytic hyperkeratosis: therapeutic challenge with acitretin. *Eur J Dermatol.* 2010;20(3):404-5. [PMID: 20388608]
5. Chassaing N, Kanitakis J, Sportich S, Cordier-Alex MP, Titeux M, Calvas P, Claudy A, Berbis P, Hovnanian A. Generalized epidermolytic hyperkeratosis in two unrelated children from parents with localized linear form, and prenatal diagnosis. *J Invest Dermatol.* 2006;126(12):2715-7. [PMID: 16990804]
6. Sybert VP, Francis JS, Corden LD, Smith LT, Weaver M, Stephens K, McLean WH. Cyclic Ichthyosis with Epidermolytic Hyperkeratosis: A Phenotype Conferred by Mutations in the 2B Domain of Keratin K1. *Am J Hum Genet.* 1999;64:732-8. [PMID: 10053007]
7. Gaertner EM. Incidental Cutaneous Reaction Patterns: Epidermolytic Hyperkeratosis, Acantholytic Dyskeratosis, and Hailey-Hailey-Like Acantholysis: A Potential Marker of Premalignant Skin Change. *J Skin Cancer.* 2011;2011:645743 [PMID: 21773039]
8. Meibodi NT, Nahidi Y, Javidi Z. Epidermolytic hyperkeratosis in inflammatory linear verrucous epidermal nevus. *Indian J Dermatol.* 2011;56(3):309-12. [PMID: 21772595]
9. Akiyama M, Tsuji-Abe Y, Yanagihara M, Nakajima K, Kodama H, Yaosaka M, Abe M, Sawamura D, Shimizu H. Ichthyosisbullosa of Siemens: its correct diagnosis facilitated by molecular genetic testing. *Br J Dermatol.* 2005;152(6):1353-6. [PMID: 15949009]
10. Suzuki H, Takahashi H, Miyashita M, Takemura T. Persistent actinic epidermolytic hyperkeratosis. *J Am Acad Dermatol.* 1995; 32(1):63-6. [PMID: 7822518]
11. Bilgili SG, Karadag AS, Calka O, Bulut G, Cecen I. Widespread hyperpigmented and hyperkeratotic plaques following lines of Blaschko. *Indian J Dermatol Venereol Leprol* 2012;78:403-5 [PMID: 22565454]
12. Covaciu C, Castori M, De Luca N, Ghirri P, Nannipieri A, Ragone G, Zambruno G, Castiglia D. Lethal autosomal recessive epidermolytic ichthyosis due to a novel donor splice-site mutation in KRT10. *Br J Dermatol.* 2010;162(6):1384-7. [PMID: 20302579]
13. Burton JL. Keratin genes and epidermolytic hyperkeratosis. *Lancet.* 1994; 344(8930):1103-4. [PMID: 7523811]
14. Mondal AK, Kumar P, Mondal A. Bullous Congenital Ichthyosiform Erythroderma. *Indian Pediatr* 2011;48: 968 [PMID: 22253153]
15. Kempers S, Katz HI, Wildnauer R, Green B. An evaluation of the effect of an alpha hydroxy acid-blend skin cream in the cosmetic improvement of symptoms of moderate to severe xerosis, epidermolytic hyperkeratosis and ichthyosis. *Cutis* 1998;61:347-50 [PMID: 9640557]
16. Nychay SG, Khorenian SD, Schwartz RA, Janniger CK, Lambert WC, Kihiczak G. Epidermolytic hyperkeratosis treated with etretinate. *Cutis.* 1991;47(4):277-80. [PMID: 2070649]
17. Li H, Törmä H. Retinoids reduce formation of keratin aggregates in heat-stressed immortalized keratinocytes from an epidermolytic ichthyosis patient with a KRT10 mutation. *Acta Derm Venereol.* 2013;93(1):44-9. [PMID: 22504942]