Epidermolytic Hyperkeratosis – Two Autosomal Recessive Cases from Nigeria

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ABSTRACT

Epidermolytic Hyperkeratosis (EHK) is a rare genodermatoses characterized by erythroderma, blistering and erosions at birth and, hyperkeratosis in the subsequent months thereafter. It is a result of mutation in KRT1 or KRT10 genes that encode keratin 1 or keratin 10 respectively.

EHK is transmitted as autosomal dominant trait, with up to 50% spontaneous mutations.A few cases acquired by autosomal recessive inheritance have recently been identified. We present a six- year old boy with EHK NPS1 type. In his family of six, two other siblings were also affected, while his first cousin parents and a sibling were not.

Keywords: Lamellar ichthyosis, ectropion, stigma

INTRODUCTION

Epidermolytic hyperkeratosis (EHK), also known as bullous congenital Ichthyosiform erythroderma (BCIE) to differentiateit from non-bullous ichthyosis, is a very rare cornification disorder with onset right from birth.[1] It is a result of Mutations in KRT1gene and or KRT10 gene that encode keratin 1 and keratin 10 respectively. Keratin 1 and keratin 10 are the intermediate filaments, the major elements of the cytoskeleton of the granular and suprabasal keratinocytes. Mutations in KRT1 and or KRT10 genes disrupt the cytoskeleton and, thus produce abnormal clumping of keratin filaments.[2]These defects manifest clinically as skin fragility and hyperkeratosis with fairly consistent genotype-phenotype correlation. Here we present the cases of asix- year old boy and 2 siblings with recessive EHK,

CASE ONE

A six year old boy presented to our facility with generalized scaly skin. The condition started at birthwith erythroderma, blisters and erosions especially after mild injury. The blisters and erosions improved as he grew. They were replaced by dirty brown thick scales that occasionally produced pungent smell. The face, soles and palms were not involved, so were his nails, teeth and hair. The patient was a product of a full term uneventful pregnancy, born to a consanguineous family of 6, with 2 other affected siblings (both girls).The first cousin parents and a male child were spared.

Physical examination revealed dry dirty brown hyperkeratotic plaques covering the entire body except the face, palms and soles. The plaques over flexures of the elbow and the knees had ridge-like or corrugated appearance. The plaques were brown and warty in appearance over the shins and anterior aspect of the forearms.(fig1&2)

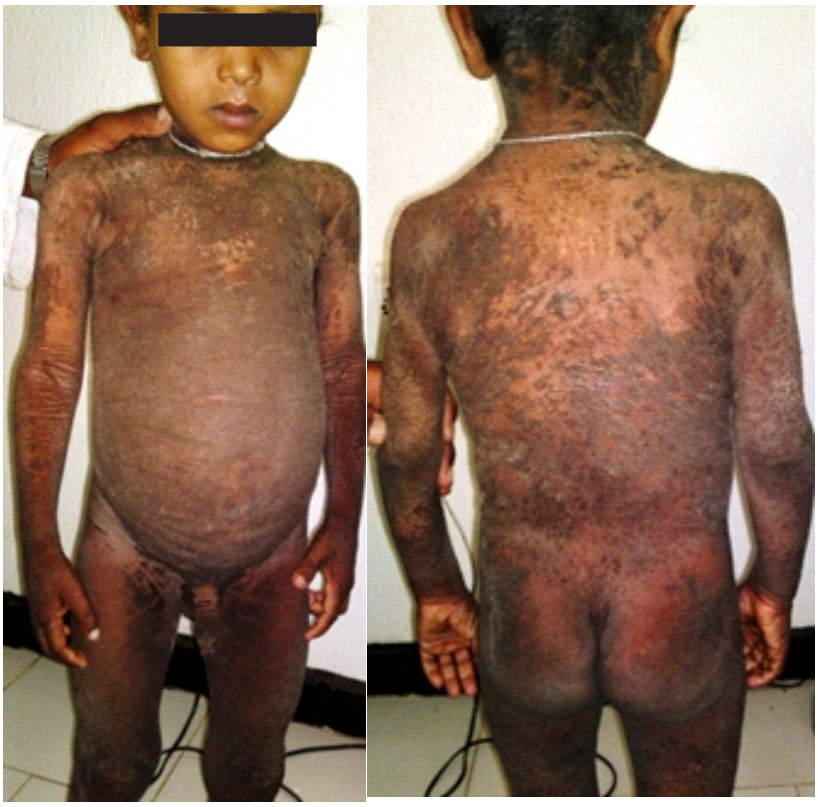

Figure 1 (a & b): Showing extensive dirty brown corrugated wart plaques covering the entire body

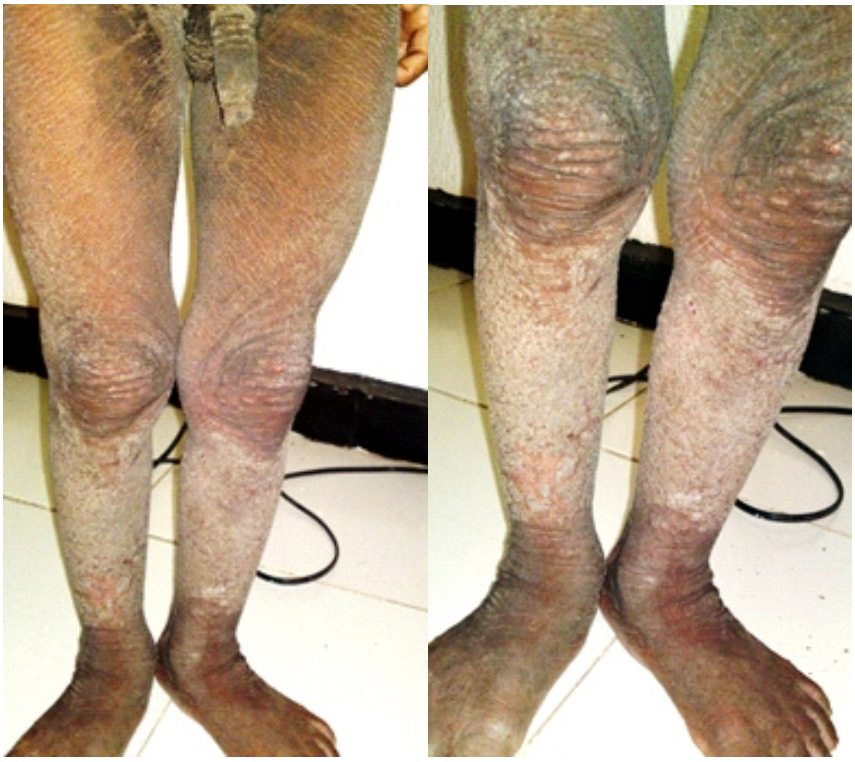

Figure 2 (a & b): Showing dirty brown hyperkeratotic dry plaques covering the lower extremities.

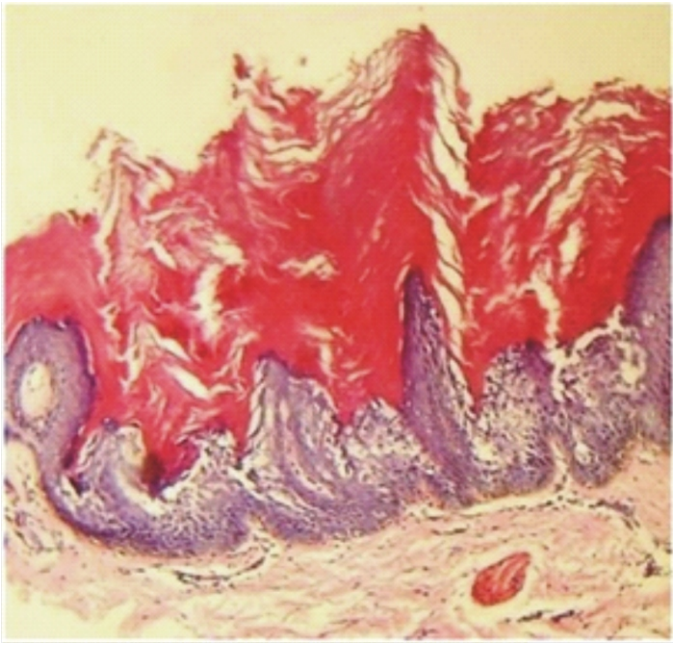

Figure 3: Showing hyperkeratosis,hypergranulosis and vacuolated upper spinous cell (H & E x40)

CASE TWO

A 32-year-old man and his sister aged 29 years old, both products of consanguineous marriage, presented to our dermatology unit with scaly eruptions over the antecubital fossae, the knees and ankles. There was thickening of the palms and soles since early childhood. At birth and during early childhood, their skin looked apparently normal, but easily get bruised after trivial injuries leaving superficial erosions. After the age of seven, the palms and soles started becoming progressively thickened. The skin over the elbows, wrist, knees and the ankles became involved. There was associated occasional pungent body odour.

On examination, thick, waxy, "corrugated cardboard"-like scales were seen over the flexures and overlying elbows, knees and ankles joints (figure 1). There was, however, truncal and facial sparing. Mucosae, teeth and hair were also normal. The palms and soles showed varying degrees of hyperkeratosis (figure 2). The distribution of these skin changes was identical on both siblings. (fig 4)

In both cases, histology showed marked hyperkeratosis, acanthosis and papillomatosis. There was prominent vacuolar degeneration of keratinocyte in the granular and spinous layers of the epidermis. The granular layer also showed marked hypergranulosis with dense enlarged keratohyaline granules. (fig 3,5). None availability of other diagnostic apparatus such as Transmission electron microscopy (EM), Immunofluorescence mapping (IFM) preclude further confirmatory diagnostic investigations. However since the two siblings in case two had characteristic hyperkeratotic ridges in flexural areas, severe palmoplantar hyperkeratosis with apparently normal parents, consanguineous parental marital relationship and the typical histological findings, the diagnosis of recessive PS-1 Bullous congenital Ichthyosiform erythroderma was made and EHK NPS -3 type in the first index case.

Counseling was offered at presentation in both cases, while urea containing emollient (Calmurid®) to alternate with topical retinoid at night were prescribed. In addition systemic retinoid (20mg acitretin) was given to the males. There was remarkable improvement at follow up after 12 weeks in both the cases.

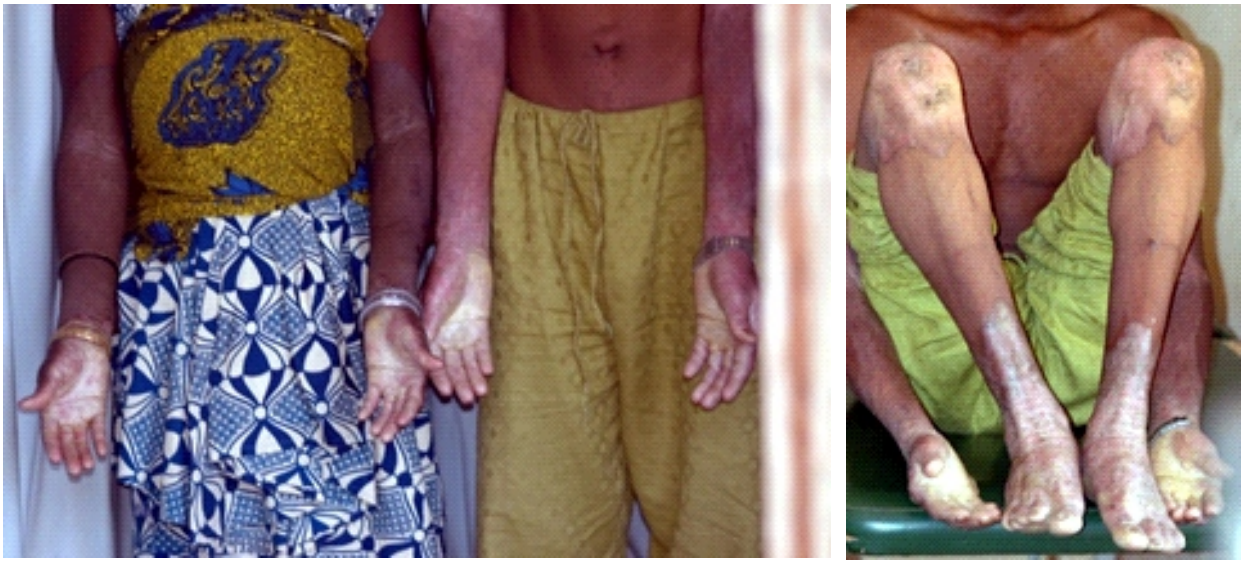

Figure 4: Identically distributed well demarcated erythematous hyperkeratotic corrugated plaques over the joints and flexures with Palmoplantar keratoderma affecting the two siblings.

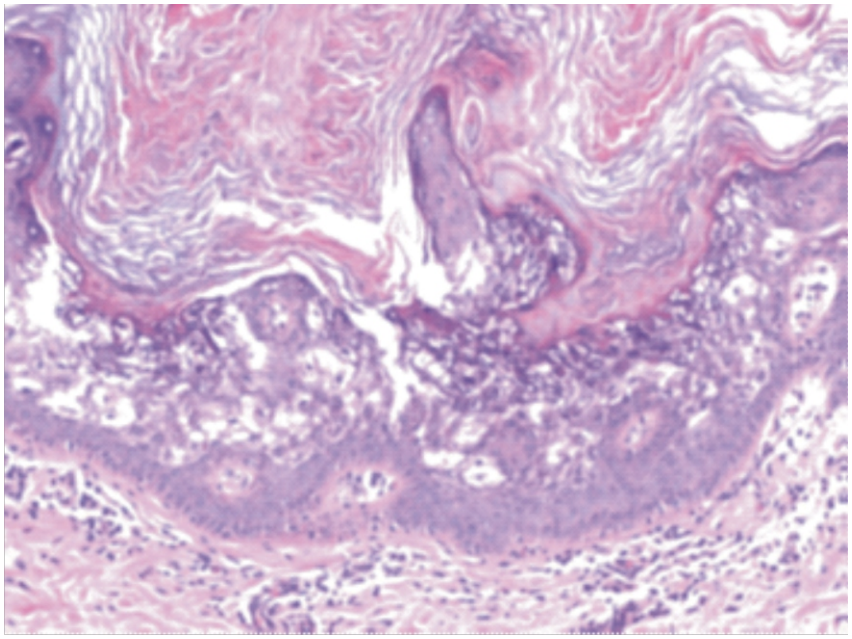

Figure 5: Hyperkeratosis, papillomatosis, acanthosis and vacuolization of the superficial epidermal cells. (Hematoxylin & eosin, x10)

DISCUSSION

EHK was first described and named Bullous Ichthyosiform erythroderma in 1902 by Brocq. It is a rare genodermatosis with a prevalence of 1 in 200,000 to 1 in 300,000 birth.[3]EHK is typically acquired following an autosomal dominant inheritance pattern, albeit 50% of cases arise from spontaneous mutations, however, recently a number of autosomal recessive inheritance has been reported.[4-7] In these cases, parents of the individuals with the autosomal recessive condition, will not exhibit any sign or symptoms of the condition, despite carrying a copy of the mutant gene each.

EHK has a typical onset at birth with generalized erythema, erosion and blistering which is often preceded by trivial injury.[4]As the child grows, blisters and erosions improve, and are replaced by hyperkeratosis. The skin, then develops dirty brown, verrucous, corrugated hyperkeratotic plaques. Macerated scales may exude a distinct foul smell due to bacterial colonization. EHK results from epidermal disruption following skin cell collapse and skin fragility due to abnormal keratin filament clumping. Keratin clumping occurs when there is mutation in keratin 1 (KRT 1) and or keratin 10 (KRT 10) leading to defective formation and

disruption of keratin cytoskeleton. Although both keratin 1 and 10 are co-expressed in the granular layer, Keratin 1 is present in the keratinocyte of the palmar and plantar skin as well as other parts of the body, thus palmoplantar keratoderma (PS-type) hyperkeratosis) is a prominent feature of patients with KRT1 gene mutations. Conversely, mutations in keratin 10 (KRT10) is associated with NPS type hyperkeratosis. Phenotypically, six distinct EHK groups have been identified based on severity and palmo-plantar skin affectation. Those with palmo-plantar involvement (PS-type) are sub-grouped into three (PS1-PS3), similarly those without palmo-plantar affectation (NPS-type) into 3 (NPS1-NPS3). NPS-1 subtype have generalized hyperkeratosis with porcupine-like scale with sparing of palmo-plantar skin akin to what our patient had. The NPS-2 is less severe than NPS 1, it lacks the peculiar porcupine scales. There is relative sparing of the skin between the joints. NPS-3, on the other hand is characterized by exfoliative erythroderma.[4,5]In general, mutations in the highly conserved helix initiative and terminal motifs are associated with more severe presentations, while milder presentation is seen when mutations occur within the non- helical linker region or in the variable N- and C- terminal regions.[6] Thus, the second index case with limited skin but severe palmo-plantar affectation most likely has mutation in the linker domain of KRT 1.

In 2006, Muller et al. reported a recessive case of EHK involving 2 of 4 siblings from a consanguineous family, which was almost identical to our index case.[7]Similarly, in 2009 Terheden et al equally report another recessive EHK in a girl of Sudanese descent from a consanguineous family.All reported mutations in recessive BCIE cited, were located in the 2B domain of K10, thus suggesting a genetic hotspot in recessive BCIE. Additionally, Palmoplantar sites were not affected in all the reported cases, in contrast to what is seen in autosomal dominant BCIE caused by KRT10 mutations. [8]

The histologic features of EHK are not specific, as similar features may be seen in other keratinizing epidermal nevi and keratosis. The typical features include hyperkeratosis, acanthosis, papillomatosis, prominent kerato-hyaline granules, perinuclear globules and bands, and vacuolar degeneration of keratinocytes in the granular and spinous layers of the epidermis.[9] Clumping of filaments are easily demonstrated on electron microscope. The clumps represent keratin intermediate filament that is composed of keratin 1 and keratin 10.[9]

At birth, epidermolysis bullosa simplex, staphylococcal scalded skin syndrome, ichthyosis bullosa of Siemens , ichthyosis hystrix of Curth –Macklin type and Omenn syndrome are the major differential diagnosis. [10,11] The differential diagnoses during neonatal period include other neonatal blistering disorders like toxic epidermal necrolysis, non bullous congenital ichthyosiform erythroderma and incontinentiapigmenti. While the differential diagnoses during childhood and adulthood periods include verrucous epidermal nevus , keratosis palmaris et plantaris and other forms ichthyoses.

The management of EHK, at all stages of the disease, is mainly supportive. In neonates, management is targeted toward symptoms control and reduction of morbidity through control and management of complications of erosions such as dehydration, electrolyte imbalance and sepsis. In childhood and adulthood, hyperkeratotic scaly skin may improve with topical emollient containing keratolytics. Oral and topical retinoid (tretinoin cream) are reserved for severe hyperkeratosis.[12] Topical calcipotriol has been reported to be used successfully in a nine year old boy with BCIE.[13]

Malodor due to bacterial overgrowth may be controlled with antiseptics and antibacterial cleansers. Systemic antibiotics may be used when other measures fail to control infection.[11,14]

CONCLUSION

This is probably the first reported recessive form of this rare genodermatoses from this part of the world. Absence of facilities forgene mutation analysis could not allow further studies on these cases.

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