

## Epidermolytic Hyperkeratosis Type NPS-3: A Case Report

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**SUMMARY** Epidermolytic hyperkeratosis (EHK) or bullous congenital ichthyosiform erythroderma is a rare autosomal dominant disorder characterized by an early onset, with erythroderma and bullous lesions, leading to severe generalized hyperkeratosis in adulthood. Mutations have been found in keratin 1 and keratin 10 genes. The clinical manifestations of EHK present striking heterogeneity and at least six clinical phenotypes have been identified. We report on a case of EHK in a 12-year-old girl with erythroderma, erosions and blisters on the entire body surface at birth and generalized hyperkeratosis but without severe palm and sole involvement in the later stage. On the basis of clinical and histopathologic findings, the diagnosis of EHK type NPS-3 was made.

**KEY WORDS:** epidermolytic hyperkeratosis, type NPS-3

### INTRODUCTION

Epidermolytic hyperkeratosis (EHK, OMIM 113 800), also termed bullous congenital ichthyosiform erythroderma, is a rare genodermatosis with a prevalence of approximately 1 in 200,000-300,000 individuals (1,2). The disorder presents at birth with generalized erythroderma and trauma related blistering. With age, these symptoms resolve and are replaced by hyperkeratosis, which can be associated with a diffuse palmoplantar keratoderma.

Epidermolytic hyperkeratosis is inherited as an autosomal dominant trait, but 50 percent of cases may be sporadic due to spontaneous mutations (3,4). Genetic analysis of mutations in keratins, responsible for this disorder, may elucidate the basis of significant clinical heterogeneity (5,6). The most useful distinguishing feature is the presence or absence of severe palmoplantar hyperkeratosis (7).

While there are differences in clinical appearance, all variants share a similar histological and ultrastructural picture (8).

We report on a case of EHK characterized by an early onset of erythema and blistering of the skin following trauma, and widespread hyperkeratosis but without severe palm and sole involvement in the later stage.

### CASE REPORT

A 12-year-old girl presented with a history of generalized erythema and recurrent multiple bullous lesions from birth. The blisters ruptured after a minor trauma, leaving areas of denuded skin, which healed with hyperpigmentation. No scarring was observed. By age 2, she had developed generalized hyperkeratotic scaling. As hyperkeratosis

became more prominent, the skin developed a foul smelling odor. There was no family history of keratinization disorders.

On examination, generalized yellow-brown hyperkeratotic plaques were seen, predominantly along the joint flexures, scalp, dorsal hands and feet. Areas of moderate erythema were seen mostly on her trunk (Figs. 1 and 2).



**Figure 1.** Generalized hyperkeratotic plaques and moderate erythema.



**Figure 2.** Hyperkeratotic scaling on the scalp and dorsal hands.



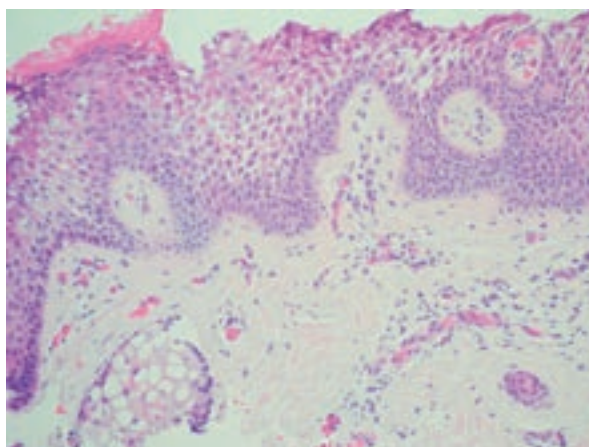
**Figure 3.** Minimal hyperkeratotic scale on the palms and no digital contractures.

Palmoplantar surfaces showed minimal hyperkeratotic scaling and no digital contractures (Fig. 3).

Routine testing of the blood, urine and stool did not reveal any abnormality. Karyotype analysis was normal.

Skin biopsy revealed marked hyperkeratosis, hypergranulosis, acanthosis and vacuolar degeneration involving the upper epidermis. The underlying dermis showed a scanty perivascular lymphoid infiltrate (Fig. 4).

Oral retinoids could not be used because the parents could not afford them.



**Figure 4.** Marked hyperkeratosis, hypergranulosis and vacuolar degeneration within the spinous and granular layers.

## DISCUSSION

The first clinical description of EHK was made by Brocq in 1902 (9). He coined the term "bullous ichthyosiform erythroderma", to distinguish the entity from nonblistering congenital ichthyosiform

erythroderma. The term "epidermolytic hyperkeratosis" refers to the distinctive histopathologic feature of vacuolar degeneration and associated hyperkeratosis of the epidermis (10).

EHK is caused by a mutation in the keratin 1 (K1) and/or keratin 10 (K10) genes linked to chromosomes 12q and 17q (11,12). These mutations cause clumped keratin filaments, keratinocyte fragility and cytolysis resulting in blister formation and hyperkeratosis (13). In addition to scaffold abnormalities, the skin of patients with EHK may demonstrate a defective permeability barrier function or altered stratum corneum lipid composition (14).

EHK presents at birth with a varying degree of erythroderma, blisters and erosions. Precipitating factors for focal blistering include friction, trauma and secondary infection. Because of the widespread areas of denuded skin, neonates with EHK are at a risk of developing recurrent infection, electrolyte imbalance and sepsis. Gradually, the erythroderma and blisters improve and verrucous hyperkeratotic plaques develop, predominantly over large flexural joint areas, but can also appear on the scalp, neck and infraglutal folds (2,15). The scales may become macerated and secondarily infected by bacteria leading to a clinically significant foul odor. The hair and mucous membranes are usually normal, but involvement of the nail matrix may produce abnormal nail plates (16).

EHK shows phenotypic variability. Involvement of the palms and soles occurs in about 60 percent of patients with EHK, resulting in soft-tissue contractures of the hands (17).

DiGiovanna and Bale separated the various clinical presentations of EHK into two primary types, including NPS (those without severe palm/sole hyperkeratosis) and PS (those with severe palm/sole hyperkeratosis) based on the absence or presence of severe palmoplantar hyperkeratosis. Furthermore, three distinct subtypes were identified into each group, depending on different clinical presentation. All of these subtypes present with varying degrees of erythroderma, blistering and hyperkeratosis (7).

So far, there was a correlation between the presence or absence of severe palm/sole hyperkeratosis and the specific keratin involved: keratin 1 mutations were identified in PS types (18) and keratin 10 mutations in NPS types (19).

Our patient fits the criteria of EHK type NPS-3, characterized by generalized distribution, no severe palm and sole involvement, and no digital

contractures similar to NPS-1 and NPS-2 type. In contrast, in NPS-3 type erythroderma is moderate and the palmoplantar surface has minimal scale.

The diagnosis of EHK can be made clinically but laboratory investigation is often required as many of the ichthyoses share clinical similarities. Skin biopsy specimens from involved areas can be submitted to light and electron microscopy as well as immunohistochemistry. Electron microscopy demonstrates clumping of keratin intermediate filaments in the suprabasilar layer. Immunohistochemistry can show a defect in the expression of keratin 1 or 10 (20).

In addition, prenatal diagnosis can be performed by ultrastructural analysis of fetal skin biopsies and amniotic fluid cells, and by direct gene sequencing *via* chorionic villus sampling (21).

As there is no cure for EHK, the management is primarily targeted to symptom reduction. Topical emollients including ointments with glycerin, urea, lactic acid, and  $\alpha$ -hydroxy acid have been shown to reduce the symptoms of dryness and improve the cosmetic appearance (22). Bogenrieder *et al.* report on safe and successful therapy with topical calcipotriol (23). For severe cases, systemic retinoids may be beneficial in reducing hyperkeratosis (24,25), although they may promote desquamation and exacerbate blistering (26).

EHK is a lifelong condition and the most refractory form of ichthyosis. Some patients may experience amelioration of symptoms with age.

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