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Generalized epidermolytic ichthyosis with palmoplantar hyperkeratosis

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Abstract

Epidermolytic ichthyosis (EI, OMIM 113800) is a rare autosomal dominant keratinization disorder that is caused by *keratin 1* or *keratin 10* gene mutation. It can be classified clinically based on the presence of palmoplantar hyperkeratosis involvement and extent of skin involvement. The diagnosis is made by clinical and histopathological examinations that can be confirmed by genetic testing. We present a 2-year-old girl who presented with erythematous and thick scaling skin. Her condition began at birth as multiple flaccid blisters that would easily break into erosions. There was no history of similar condition nor consanguinity within her family. Skin examination revealed diffuse erythematous skin covered with thick scales and erosion, predominantly on her face, extremities, palms, and soles. The skin histopathology examination showed diffuse parakeratosis with vacuolar and granular degeneration within granular and spinous layers along the epidermis. She was diagnosed with generalized EI with palmoplantar hyperkeratosis based on the clinical and histopathological examinations. Clinical improvement was observed after a one-month treatment with mupirocin cream, sodium bicarbonate bath, and moisturizer after bathing.

Keywords: epidermolytic ichthyosis, palmoplantar hyperkeratosis, genodermatosis

Introduction

Epidermolytic ichthyosis (EI, OMIM 113800) is a rare keratinization disorder that is most commonly inherited in an autosomal dominant pattern, although spontaneous mutation represents about half of all cases with no family history [1]. The prevalence of EI is reported to be about 1:100,000-400,000 with mutations located in *keratin* (*KRT*) *1* or *10* genes. The defective *KRT* gene leads to skin fragility and blistering with erythrodermic clinical manifestations at birth. Hyperkeratosis and scaling will form as the severity decreases with age [2].

Epidermolytic ichthyosis can be classified clinically based on the involvement of palmoplantar hyperkeratosis into either palm sole (PS) or no palm sole (NPS) subtypes. Another clinical classification is based on extent of skin involvement which divides EI into localized/linear (nevoid) and generalized forms. The diagnosis is made by clinical and histopathological examinations that can be confirmed by genetic testing [3,4]. Management of EI consists of emollients, hydration, and infection control in addition to keratolytics for hyperkeratotic skin. Family history and consanguinity screening should be done to clarify the diagnosis [2,5]. We present a patient with generalized EI with palmoplantar hyperkeratosis that was suspected clinically and confirmed histopathologically. We did not perform genetic testing. Classic demonstration of EI findings in a young child is the main focus in this case report.

Case Synopsis

A 2-year-old girl presented with erythematous and thick scaling skin that had begun one year prior. According to her parents, the initial lesions, present since birth, were erythematous and multiple flaccid

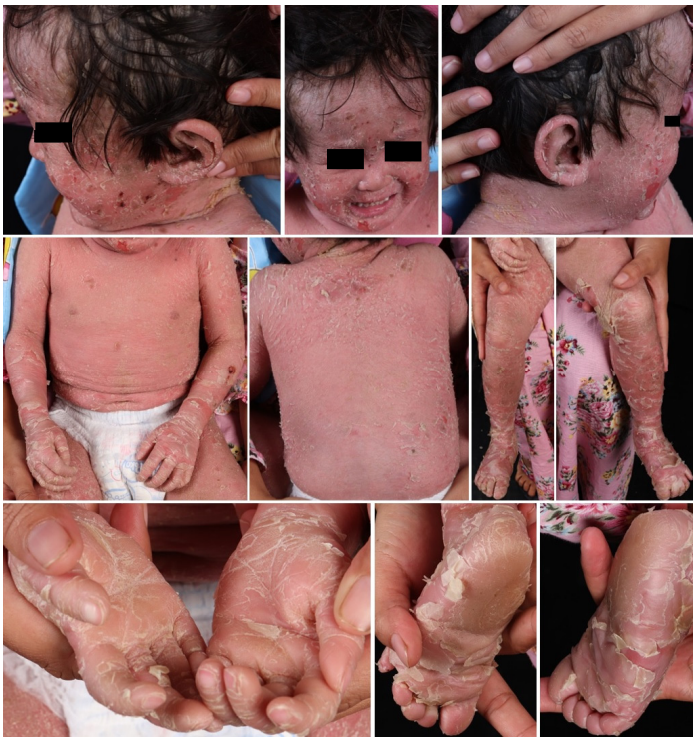

Figure 1. *Diffuse erythematous skin covered with thick scales and erosions, predominantly on the face, extremities, palms and soles.*

blisters all over her body that would easily break into multiple erosions. The blister formation was reduced when she was 6 months old, but her skin became thickened especially on her face, arms, and lower legs. There was no history suggestive of collodion membrane. She had no history of seizures, growth and developmental disorders or sweating abnormality. A history of similar conditions or consanguinity within her family were also denied.

Physical examination showed normal height and weight for her age. Her vital signs were within normal range and no lymphadenopathy was found. Skin examination revealed diffusely erythematous skin that was covered with thick scales and erosion, predominantly on her face, extremities, palms, and soles (**Figure 1**). There were multiple Beau lines and onychodystrophies with opaque changes on her toenails. No abnormalities were found in her hair or mucosal surfaces. The Auspitz sign test was performed on the thick scales and showed negative results. There were no linear epidermal nevi found on her parents by physical examination.

Histopathology examination from a hyperkeratotic lesion on her right arm was performed using hematoxylin and eosin staining. The epidermis showed diffuse parakeratosis with vacuolar and granular degeneration within granular and spinous layers along the epidermis. There were bullae found in the epidermal layer with mild lymphocytic infiltration. Mild patchy lymphocytic infiltrates were also found in the upper dermis (**Figure 2**). From the histopathological findings, the most compatible diagnosis is generalized epidermolytic ichthyosis.

She was diagnosed with generalized EI with palmoplantar hyperkeratosis. Mupirocin cream twice daily on the erosions, sodium bicarbonate bath twice daily, and moisturizer after bathing were administered as the initial treatment. The scaling and erosions improved after only one month of this treatment, but some blisters still appear on her face periodically (**Figure 3**).

Case Discussion

Keratinopathic ichthyoses (KPI) are defined as inherited skin disorders that are caused by mutations

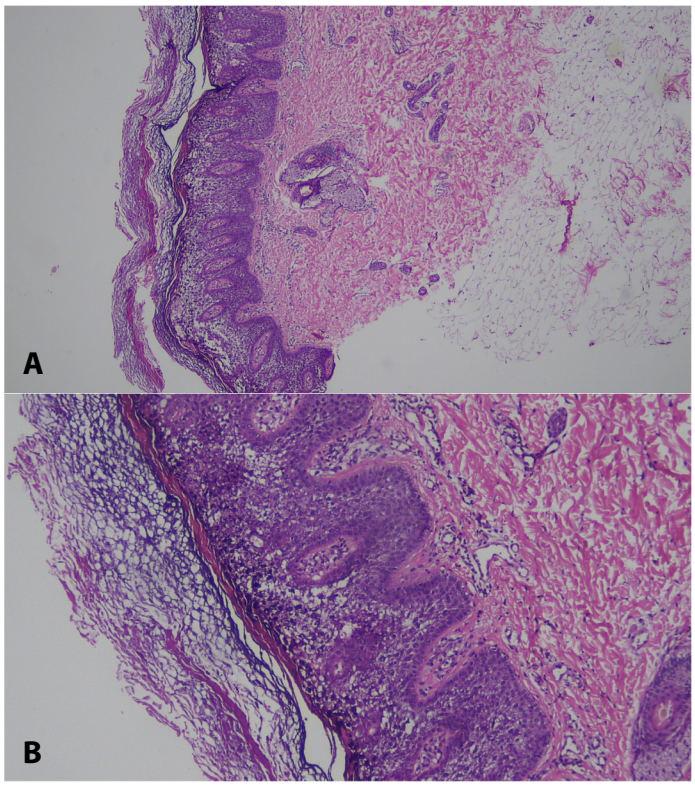

Figure 2. *Diffuse parakeratosis with vacuolar and granular degeneration within granular and spinous layers along the epidermis, and intraepidermal bullae with mild lymphocytic infiltration. Mild patchy lymphocytic infiltrates were also found in the upper dermis. H&E,* ***A)*** *40×,* ***B)*** *100×.*

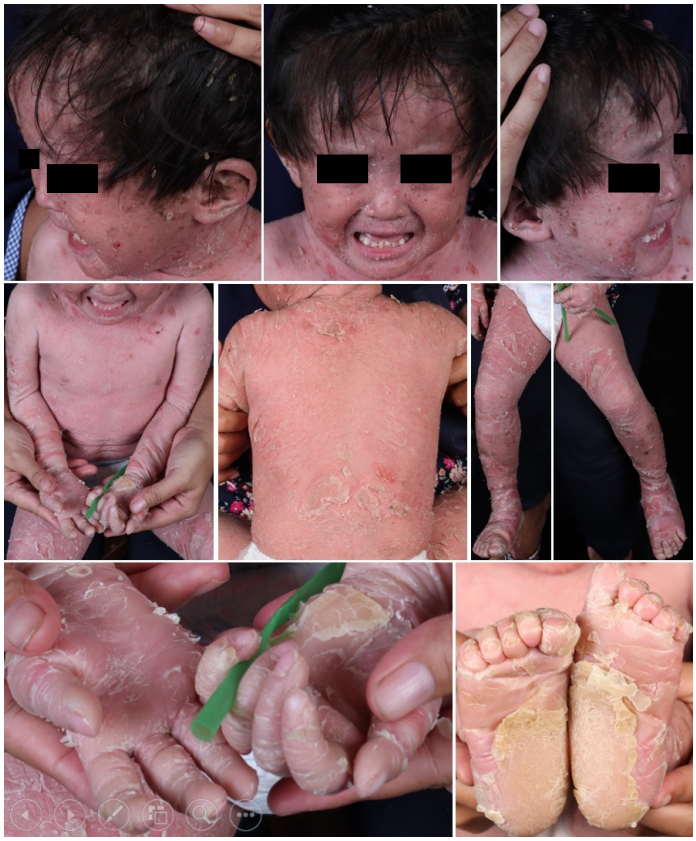

Figure 3. *Clinical improvement after just one-month of topical treatment, although some blisters still appeared on her face.*

in keratin genes expressed by suprabasal keratinocytes. These genes are important for cytoskeleton formation to maintain normal tissue structure and function. Generalized EI and superficial epidermolytic ichthyosis (SEI) are the two major subtypes of KPI [6,7].

Keratins are members of the intermediate filament gene family which are grouped into the acidic type I (KRT9-20) and neutral basic type II (KRT1-8). Keratin intermediate filaments (KIF) are heteropolymer structures formed by type I and II specific partners. The KIF cytoskeleton provides keratinocyte stability under mechanical stress [8]. Keratinocytes at the basal layer express KRT5 and KRT14. However, from the spinous to granular layer at the suprabasal level they switch their expression into KRT1 and KRT10. The KIF of KRT1/10 are thicker than KRT5/14 of the basal layer, so that keratinocytes can survive differentiation phases into keratin and play a protective role [9]. Mutation in KRT1 or 10 can lead to increased skin fragility and cytolysis in EI [8].

Epidermolytic ichthyosis which was formerly known as epidermolytic hyperkeratosis or bullous congenital ichthyosiform erythroderma of Brocq is characterized by diffuse erythroderma and blistering at birth [7]. Progressive hyperkeratosis develops as the age increases, replacing the blistering and erythroderma. Predilection sites of the lesions are on the large flexural joint areas, palms, and soles. The hair, nails, and mucosal surfaces are usually not involved [10]. The palmoplantar involvement in the EI can help to define the keratin gene mutation. Mutation of *KRT1* is associated with palmoplantar hyperkeratosis, whereas the *KRT10* mutation clinically manifested without palmoplantar hyperkeratosis. Based on this clinical manifestation, EI is divided into the PS and NPS subtypes [3]. The clinical manifestations of the patient were compatible for EI manifestation with mild nail involvement and severe palmoplantar hyperkeratosis. Therefore, the PS type of EI with suspected *KRT1* mutation was considered applicable in this case.

The main histopathological findings using H&E staining for EI are vacuolization of keratinocytes in spinous to granular layer and hyperkeratosis. The other typical findings are thick granular layer, coarse keratohyalin granules, and dyskeratosis. The generalized form of EI shows continuous involvement in the entire epidermis with these distinctive findings, whereas the focal involvement and skipped areas of normal epidermis are found in the localized form [10,11]. The typical EI histopathological findings in this case were found in the entire epidermis which are compatible for the generalized EI diagnosis.

Genetic counseling and parental linear epidermal nevus (LEN) screening are important management in EI. Family history of any similar condition and consanguinity identified in genetic counseling are important for mutation or inheritance pattern screening. Autosomal dominance is the main inheritance pattern, whereas spontaneous mutation and autosomal recessive inheritance pattern have also been reported in EI [1,8]. Linear epidermal nevus along the Blaschko lines should be looked for in parents as this can resemble linear epidermolytic

ichthyosis (LEI) variants. The LEI is the nevoid form of EI with LEN clinical appearance and cytoskeletal abnormalities representing somatic mosaicism. Concomitant gonadal mosaicism in LEI will increase the risk of full blown EI in the offspring [3,4]. Based on the history, we suspected a spontaneous mutation pattern because there was no similar condition, consanguinity, nor LEN found within her family.

The topical management of EI consists of emollient, hydration, and infection control in addition to keratolytic for hyperkeratotic skin. Topical emollient and keratolytic are the first line therapy for aiding scale desquamation, hydrating, and enhancing the appearance of the skin. The most common topical agents used are urea, lactic acid, glycolic acid, glycerol, salicylic acid, propylene glycol, and tazarotene [2,9]. Systemic and topical antibiotics with antiseptic washes can be used as needed to control infection [5]. Sodium bicarbonate bath also can help exfoliate scales and reduce malodorous skin [3,12]. Dilute bleach baths may be helpful. We treated the patient using commercial hypoallergenic emollient, topical antibiotic, and sodium bicarbonate bath twice daily. Significant clinical improvement was seen after one month treatment follow-up. Retinoids can be quite irritating in EI due to increased fragility, hence it was not prescribed in our patient.

Conclusion

Epidermolytic ichthyosis is a rare keratinization disorder caused by *KRT1* or *KRT10* gene mutation. Epidermolytic ichthyosis can be diagnosed from physical and histopathological examinations. Genetic counseling and parental linear epidermal nevus screening are important for mutation pattern recognition. Emollients, hydration, infection control, and keratolytics for hyperkeratotic skin are the main topical treatments. Retinoids must be used with extra care and consideration in EI since it can either improve or worsen the clinical condition.

Potential conflicts of interest

The authors declare no conflicts of interest.

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