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Superficial Epidermolytic Ichthyosis: Clinical and Histopathological Features in Two Siblings

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Abstract

Superficial epidermolytic ichthyosis (SEI), a type of keratinopathic ichthyosis (KPI) caused by mutations in the K2e gene, is clinically characterized by superficial blistering, hyperkeratosis predominantly involving flexures and joints, Mauserung phenomenon and epidermolytic hyperkeratosis (EHK) on ultrastructural studies. Though it has been known to mankind for ages, very few families afflicted with this disease are described in the literature and its exact prevalence in the Indian population is yet undetermined. Through this case report, we wanted to highlight its various peculiar manifestations and reiterate the importance of meticulous clinical evaluation and clinicopathological correlation, especially in resource-limited settings, for effective patient management.

Keywords: Corrugated hyperkeratosis; Palmoplantar; Superficial epidermolytic ichthyosis

Introduction

Superficial epidermolytic ichthyosis (SEI; ichthyosis bullosa Siemens) is an exceptionally rare disorder (1 in 500,000) belonging to the group of keratinopathic ichthyosis (KPI) caused by a mutation in the K2e gene resulting in the development of superficial blisters, flexural hyperkeratosis, distinct Mauserung phenomenon (molting) and granular degeneration on histology.[1,2] It may present with varying severity or atypical features and its exact prevalence in the Indian population is yet unascertained. Herein, we report the case of SEI in two siblings in an Indian family.

Case Report

A 4-year-old female and 2-year-old male child born out of consanguineous marriage (third degree) presented with complaints of generalized dryness and scaling of skin over body associated with itching from 3 months of age. Both were born with non-erythematous, non-scaly skin without any history of the restrictive membrane at birth. Both experienced recurrent peeling of skin without underlying erythema and subsequent clearance. Eventually, skin thickened, mainly around joints and flexures, which was more pronounced in the male child. There was no history of blistering, erythroderma, hypertrichosis, hyperhidrosis or pustulation in either child. Parents denied similar complaints in the family, though a history of dry skin was present. Cutaneous examination revealed lichenified plaques (more prominent in the male child) in ripple pattern around the neck, flexural areas and joints and grayish-brown corrugated scales covering the trunk and limbs. Greasy yellow scales covered scalp, ears and face had mild erythema with fine white scaling. Palms, soles showed deep fissures (Figure 1A-1D).

Assessment of nails, teeth, hair, mucosa and systemic examination did not reveal any abnormalities. Skin biopsy from both siblings showed hyperkeratosis, hypergranulosis, perinuclear vacuolization in stratum granulosum and spinosum, acanthosis, papillomatosis and mild inflammatory infiltrate in the dermis (Figure 2A, 2B).

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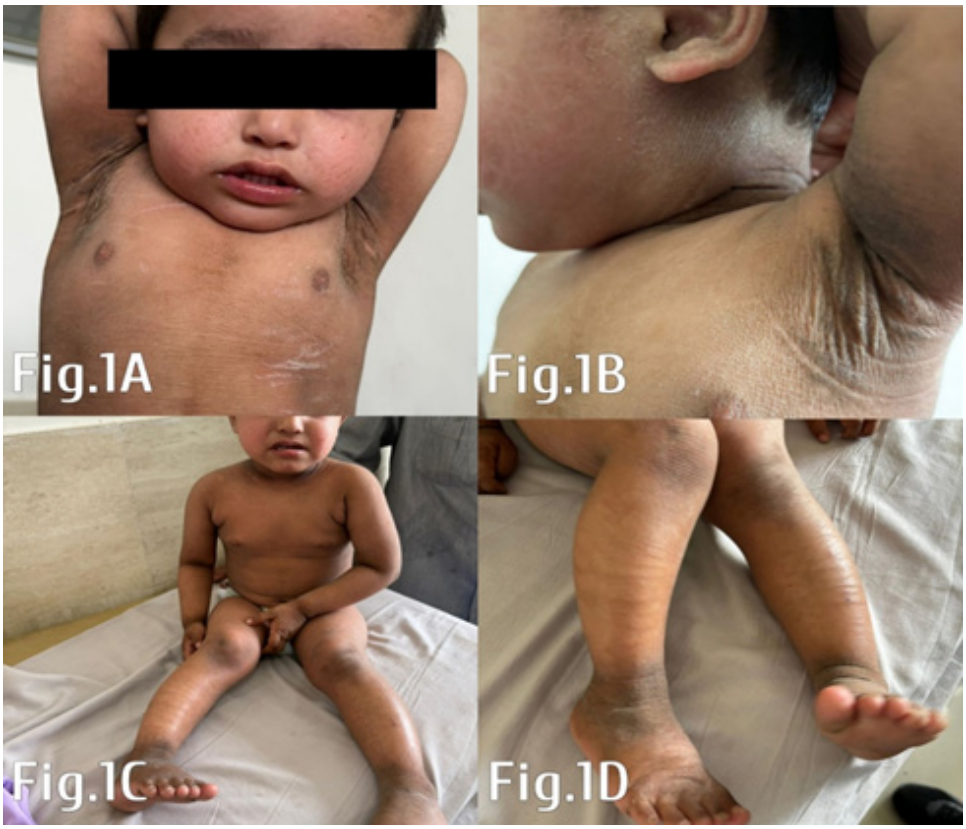

Figure 1: 1A to 1D shows lichenified plaques in a ripple pattern around the neck, flexural areas and joints, grayish-brown corrugated scales over the trunk and limbs, greasy yellow scales over the ears and mild erythema over the face. (Fig.1A, 1B- male; 1C, 1D -female child)

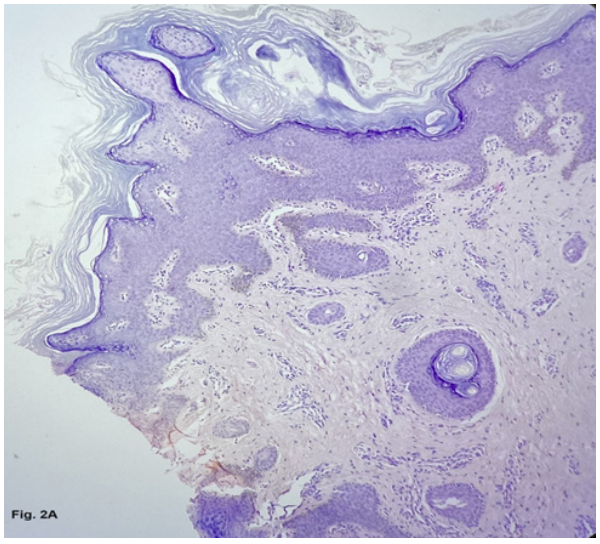

Figure 2A: Histopathology showing hyperkeratosis, hypergranulosis, perinuclear vacuolization in stratum granulosum and spinosum, acanthosis, papillomatosis and mild inflammatory infiltrate in the dermis (Hematoxylin and Eosin stain 10 x).

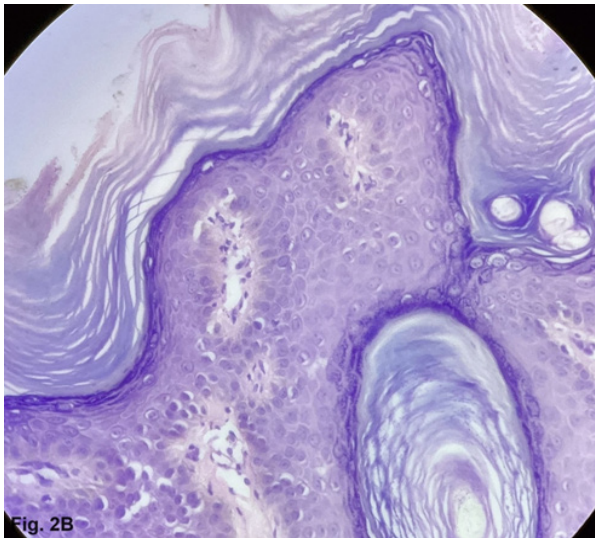

Figure 2B: Histopathology showing hyperkeratosis, hypergranulosis, perinuclear vacuolization in stratum granulosum and spinosum (Hematoxylin and Eosin stain 40 x).

Based on the clinicopathological correlation, they were diagnosed with SEI and treated symptomatically with oral vitamin A (50,000 IU twice a week), antihistamine, emollient and topical keratolytic (urea and glycolic acid combination). Genetic studies could not be performed due to non-availability of resources and financial constraints.

Discussion

Cellular cytoskeleton is constituted by keratin intermediate filaments, amongst which K1 and K10 are present in the suprabasal layer and K2e in the upper spinous and granular layer of the epidermis (prominently in wrists, elbows, thighs, knees, groin and ankles). KPI is an umbrella term for ichthyosis caused by mutations in keratin genes which results in abnormal keratin filament formation leading to an abnormal cytoskeleton along with imperfect desmosomal attachments, resulting in increased mechanical fragility and blister formation, clumping of tonofilaments, intracellular vacuolization ultimately giving rise to epidermolytic hyperkeratosis (EHK) on histology.[1,2]

SEI is an uncommon disorder usually inherited in an autosomal dominant or sporadic manner.

Mutations in the SEI-causing gene, primarily located in the helix initiation and termination motifs of KRT2 disrupt intermediate filament assembly and protein stability. Most patients with diverse demographics have missense mutations at 487th glutamic acid in the helix termination motif of keratin 2, making E493K a known mutational hotspot.[2,3,4]

At birth, the skin may appear normal or show mild erythema with blistering which may worsen with trauma, heat or excessive sweating. Fragility is limited to upper epidermal layers giving rise to superficially denuded areas of skin with collarette-like borders called Mauserung phenomenon/molting. Blistering, peeling usually improve with age while hyperkeratosis and lichenification increase, predominantly over joints, flexures and dorsa of the hands/feet.[5,6]

Rarely palmoplantar blistering (usually spares palms/soles), hyperhidrosis, hypertrichosis and pustulation are recorded.[2]

Other atypical presentations cited in the literature include the presence of erythroderma at birth, a case wherein with advancing age blistering improved but skin peeling worsened and other cases like ours with no history or clinical evidence of blistering at the time of presentation.[2,3,6,7,8]

Another unusual finding in our siblings was the presence of palm/sole involvement and inheritance pattern: maybe sporadic mutation or autosomal recessive (AR). AR seems more likely due to the absence of lesions in parents, consanguinity, both siblings being affected and the possibility of an undiagnosed family member with the disease of variable severity.

Histological hallmark is EHK, characterized by compact hyperkeratosis, hypergranulosis with an increased number of irregularly shaped keratohyalin granules, and perinuclear vacuolization in stratum granulosum and spinosum. Bullae when present are seen intraepidermally due to the separation of edematous keratinocytes, and the upper dermis shows chronic inflammatory infiltrate.[4,9]

SEI may need to be differentiated from epidermolytic ichthyosis (EI), generalized peeling skin syndromes (PSS) and epidermolysis bullosa simplex (EBS).

KRT1/KRT10 mutation causing EI presents with widespread erythema, blistering, erosions or erythroderma at birth, marked palmoplantar involvement, hyperkeratosis, clumping of keratin filaments and epidermolysis also involving deep suprabasal layers.

Generalized PSS is classified into two forms: non-inflammatory (type A, linked to CHST8 mutations) and inflammatory (type B, known as Peeling Skin Disease or PSD, associated with mutations in CDSN/corneodesmosin). PSD presents with congenital ichthyosiform erythroderma, recurrent skin peeling, itching, features of atopic dermatitis and elevated IgE levels. Histologically it shows separation directly above the stratum granulosum or within the stratum corneum, intercellular detachment of corneocytes and no vacuolization of the granular layer.

EBS (mutation in KRT5, KRT14) may have recurrent blistering but the level of blistering is deep (basal epidermolysis), hence it may heal with atrophy and scarring and also shows no hyperkeratosis.[1,2]

EHK is a clinically heterogeneous disorder with varying severity and presentations. Mild EI or severe SEI can be confused clinically or histologically, wherein electron microscopy and immunofluorescence labeling with anti-K2e antibodies can help differentiate them. If needed, molecular analysis is the final recourse.

Though genetic analysis is confirmatory, its use is impeded by its high cost and unavailability thus making clinicopathological correlation a go-to method for diagnosis.

Nonetheless, parents must be offered genetic counseling and if feasible a prenatal diagnosis can be made at 10-11 weeks of gestation using direct gene sequencing of chorionic villus samples and around 19 weeks by light and electron microscopy of fetal skin biopsy.[9] To avert risk in future pregnancies, alternate reproductive options like in vitro fertilization with pre-implantation genetic testing and the use of donor gamete/embryo can be explained.

Owing to no definitive treatment, cases are managed symptomatically with emollients, topical keratolytics and topical or oral retinoids. Although retinoids reduce scaling, they increase skin fragility and may cause blistering. Additionally, systemic therapy is often long-term with a risk of potential toxicities and on treatment cessation, skin reverts to the pre-treatment state, so they should be used judiciously.

Advances in comprehending molecular mechanisms of disease have led to progress in developing pathogenesis-based therapies, like enzyme replacement and gene therapy and repurposed use of biologicals according to the immune profile of ichthyosis patients. This kind of translational science holds the power to change the future for these patients.[10]

The inability to conduct genetic testing due to a lack of institutional facilities and financial constraints can be considered a limitation of this report.

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