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Ichthyosis bullosa of Siemens

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Abstract

Background: Ichthyosis bullosa of Siemens (IBS) is a rare hyperkeratotic blistering condition caused by mutations in keratin 2e gene.

Main observations: This is a case of a 18-year-old female with generalized blisters, erosions and thickened skin since she was 3 months old. As she aged, there was decrease in development of blisters and erosions, with accompanying increase in severity of hyperkeratosis. Skin punch biopsy showed overlying basket weave hyperkeratosis and acanthosis, prominent vacuolization of the granular cell layer, and intraepidermal blisters with the split at the granular layer. The patient was treated with emollients, with marked improvement.

Conclusions: Mutations in the different keratin genes have been shown to underlie a wide range of disorders of keratinization. Epidermolytic hyperkeratosis and ichthyosis bullosa of Siemens are distinct disorders with mutations in different genes. Although molecular genetic testing should ideally be done for confirmation of diagnosis, ichthyosis bullosa of Siemens could be diagnosed in this patients based on key clinical characteristics. (*J Dermatol Case Rep*. 2012; 6(3): 78-81)

Key words:

epidermolytic hyperkeratosis, ichthyosis bullosa of Siemens

Introduction

Epidermolytic hyperkeratosis, also known as bullous congenital ichthyosiform erythroderma (BCIE) was originally described histologically by Nikolski in 1987 and clinically delineated by Brocq in 1902.[1] It is a hyperkeratotic and blistering condition caused by a variety of mutations in the keratin 1 and 10 genes. It is autosomal dominant; however, 50% of cases may be sporadic due to spontaneous mutations.[2] Approximately 1 in 200-300,000 live births will be affected by this disorder.

In 1937, Herman Siemens reported a family with features similar to, but distinct from EHK. This variant has been termed ichthyosis bullosa of Siemens (IBS) and is distinguished clinically from epidermolytic hyperkeratosis by the absence of erythroderma, localization of dark grey hyperkeratosis to the flexural sites, and areas of peeling of the skin known as the "Mauserung phenomenon".[3] It is probably less common than epidermolytic hyperkeratosis.

Case Report

Our patient is a 18-year-old female, who came in with a chief complaint of generalized blisters, erosions and thickened skin since she was 3 months old. Patient was born with normal, non erythematous, non scaly skin, with no history of restrictive membrane at birth. History started when she was 2 months old, when her parents noted blisters forming on her trunk and extremities, which ruptured and became erosions. Lesions occurred recurrently over her whole body, sparing the palms, soles, and face. Blisters and erosions still developed and healed with hyperpigmentation and no scarring. By 1 year of age, patient also developed generalized hyperkeratosis and scaling over her trunk and extremities, especially over flexural areas. The lesions occasionally became pruritic and she would scratch and peel hyperkeratotic skin. When lesions became moist, foul smelling, and painful, she self medicated with Sumapen, which afforded relief. At 6 years of age, consult was done at a local health center

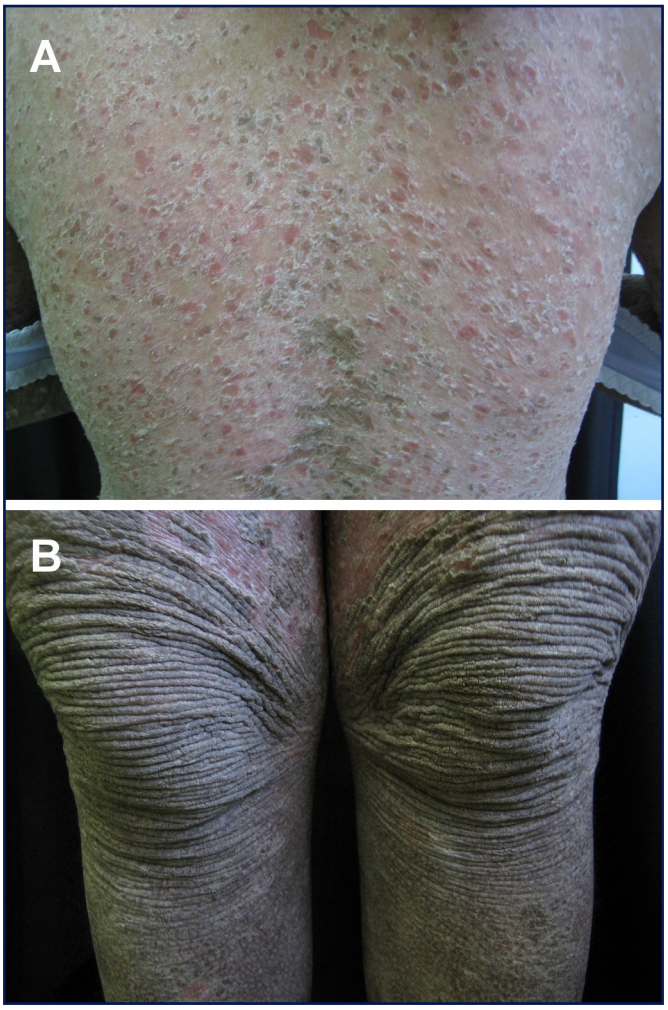

Figure 1

A) Areas of hyperkeratosis, white scales, flaccid blisters, and superficially denuded areas over trunk; B) Severe hyperkeratosis on both knees.

where she was prescribed Celestamine and advised consult with a dermatologist. However, no consult with a specialist was done. She continued to develop blisters and erosions in decreasing severity and frequency, and more prominent generalized hyperkeratosis. Persistence of symptoms prompted consult.

Dermatologic physical examination showed dark grey hyperkeratosis, white scales and erosions over trunk and extremities. Hyperkeratosis was more evident on the flexural areas of extremities and severe on both knees. There were small flaccid blisters over trunk and extremities, sparing of the palms, soles, and face. There was no nail, hair, and teeth involvement.

Skin punch biopsy was done at multiple sites. Biopsy taken from an area of hyperkeratosis on her left arm showed overlying basket weave hyperkeratosis and acanthosis, and vacuolization of the granular cell layer. Biopsy of an erosion from the right arm showed sloughing of the corneal layer. The rest of the epidermal layers were intact. Blister from the left arm showed an intraepidermal subcorneal clefting with neutrophils, plasma cells and basophilic debris. There was overlying basket weave hyperkeratosis, psoriasiform epidermal

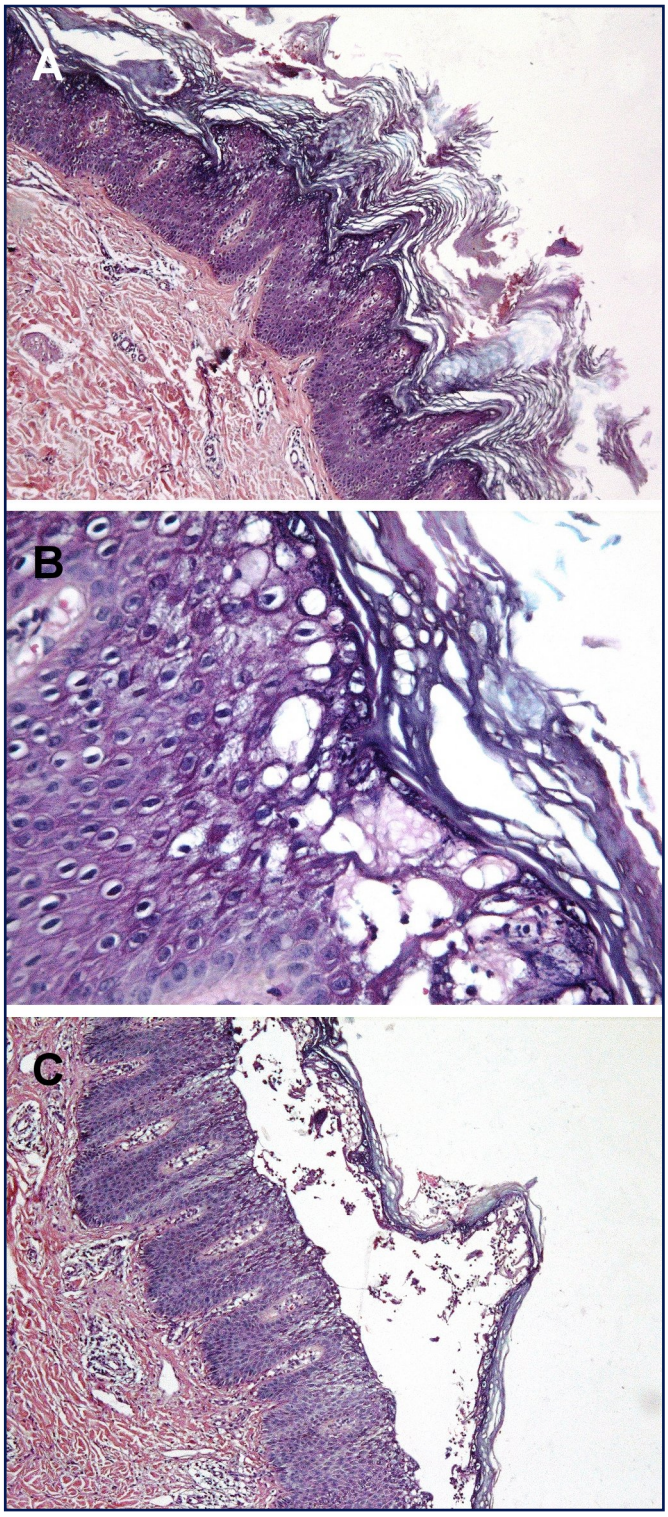

Figure 2

A) Biopsy of area of hyperkeratosis on her left arm revealed overlying basket weave hyperkeratosis and acanthosis; B) prominent vacuolization of the granular layer; C) Biopsy from blister from the left arm shows an intraepidermal clefting with neutrophils, plasma cells and basophilic debris (Hematoxylin-eosin stain).

hyperplasia, superficial neutrophilic and eosinophilic perivascular infiltrate. At closer view, the intraepidermal blister was characterized by separation of the granular layer from

the overlying squamous layer. There was note of necrosis of keratinocytes within the blister, spongiosis of the epidermis with eosinophils, and acanthotic epidermis. Direct immunofluorescence was negative with note of vacuolization and cleft formation at the stratum granulosum layer.

The patient was given petrolatum, which she religiously applied several times a day. Patient counseling was done. Follow up after 1 month showed resolution of the blister formation and marked improvement in the hyperkeratotic plaques.

Discussion

Keratins are structural proteins that belong to the superfamily of intermediate filament proteins. Human keratins are expressed in pairs of type 1 (acidic) and type 2 (basic) polypeptides in a tissue and differentiation-specific manner.[4] Mutations in keratin genes have been shown to underlie a wide range of disorders of keratinization. Most pathogenic keratin mutations are dominant mutations caused by missense mutations that alter amino acids in the helix initiation or termination motifs.[5]

K1 and K10 are present in the suprabasal cells; and K2e is normally expressed in the upper spinous cells.[6] The interaction of keratin 1 and 10 proteins results in a secure epithelial cell cytoskeleton.[7] A defect in any component of the matrix may destabilize the keratin network, and compromise mechanical strength. These eventually result in blistering and perturbed epithelial differentiation, such as in this case.

Epidermolytic hyperkeratosis manifests at birth with erythema, blisters, and superficial ulcerations, especially involving the flexural regions initially. Areas of denuded skin, as well as fissures, may be present. Blistering improves with age and, after the first few months of life, is replaced by thickening and scaling of the epidermis. The color of the scales may vary from dark brown to gray or white. The hair, nails, and mucosal surfaces are usually not involved.[1]

Ichthyosis Bullosa of Siemens is milder than epidermolytic hyperkeratosis, often with no abnormalities at birth. Blistering in response to trauma develops in infancy. Hyperkeratosis with dark brown skin, but little true scale, develops mainly on the flexural areas of extremities. Superficial peeling of the skin ("Mauserung" phenomenon) is typical.[8]

Patients with IBS who had severe skin phenotypes have previously been misdiagnosed with BCIE from their clinicopathological findings.[9] Conversely, mild BCIE can show clinical and histological features similar to IBS.[4] Due to this, laboratory investigation is often needed to arrive at a correct diagnosis as the two share clinical similarities. Skin biopsy specimens from involved areas can be prepared for light and electron microscopy. Direct immunofluorescence and labelling can also be performed. The definitive diagnosis in many cases of BCIE and IBS is made by performing molecular studies.[9]

Typical pathological findings are compact hyperkeratosis, pronounced vacuolar degeneration in the upper stratum spinosum and stratum granulosum, filament clumping, a thickened granular layer with irregularly shaped keratohyaline granules, and acantholysis.[1] Electron microscopy reveals a disrupted keratin filament network and clumped keratin filaments in the granular and in the spinous cells.[1] Immunofluorescence labelling with specific anti-keratin antibodies shows the keratin expressed in different epidermal layers. By using molecular techniques, the exact gene defect can be identified, providing an unequivocal diagnosis. Analysis at the molecular level is by DNA sequencing of candidate genes.[4]

There is no cure for epidermolytic hyperkeratosis and management involves symptom reduction.[10] Daily bathing and application of moisturizers twice each day may keep the skin supple. Alpha hydroxy acids, glycerin, urea and lactic acid can also reduce the symptoms of xerosis by normalizing the keratinization process and improve the cosmetic appearance with continued use.

Conclusion

Mutations in the different keratin genes have been shown to underlie a wide range of disorders of keratinization. Epidermolytic hyperkeratosis and Ichthyosis Bullosa of Siemens are distinct disorders with mutations in two different genes. Although molecular genetic testing should ideally be done for confirmation of diagnosis, identifying key clinical characteristics are important to help differentiate the two closely related conditions.

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