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Histopathologic Characterization of Epidermolytic Hyperkeratosis: A Systematic Review of Histology from the National Registry for Ichthyosis and Related Skin Disorders

Rustin Ross, M.D.¹, John J. DiGiovanna, M.D.¹, Laura Capaldi, M.D.², Zsolt Argenyi, M.D.^{3,4}, Philip Fleckman, M.D.⁴, and Leslie Robinson-Bostom, M.D.^{1,5}

¹ Department of Dermatology, The Warren Alpert Medical School of Brown University, Providence, RI

² Division of Dermatology, University of Massachusetts, Worcester, MA

³ Department of Pathology, University of Washington, Seattle, WA

⁴ Department of Medicine (Dermatology), University of Washington, Seattle, WA

⁵ Department of Pathology, Rhode Island Hospital, Providence, RI

Abstract

Background—The clinical condition generalized epidermolytic hyperkeratosis, also known as bullous congenital ichthyosiform erythroderma, is an autosomal dominant disorder and presents as a bullous disease of the newborn followed by an ichthyotic skin disorder throughout life. Clinical epidermolytic hyperkeratosis (cEHK) has characteristic histopathologic findings. Mosaic cEHK, which occurs without a family history, is a sporadic condition that clinically resembles epidermal nevi but demonstrates histopathologic findings similar to the generalized disorder; when a post zygotic mutation involves the germ line, the disease can occur in subsequent generations as generalized cEHK. Ichthyosis Bullosa of Siemens (IBS) is similar histopathologically, but clinically distinct from generalized cEHK, presenting with more superficial bullae.

Objectives—It is well established that the clinical diagnoses generalized cEHK, mosaic cEHK, and IBS have similar histopathologic findings of epidermolysis with hyperkeratosis. We sought to characterize a) the spectrum of histopathologic features and b) to assess whether there were histopathologic differences between these clinically distinct disorders.

Methods—One hundred seventeen skin biopsy slides from the National Registry for Ichthyosis and Related Skin Disorders were reviewed blinded to clinical information. All slides were systematically evaluated for a variety of features including differences in the pattern of the epidermolysis and hyperkeratosis. Clinical predictions of whether the biopsy was obtained from patients with

Correspondence to: Leslie Robinson-Bostom M.D., Department of Dermatology, The Warren Alpert Medical School of Brown University, and Department of Pathology, Rhode Island Hospital, 593 Eddy St., APC-10, Providence, RI 02903, Telephone: (401) 444-7139, Fax: (401) 444-7105, Email: Lrobinson-bostom@Lifespan.org.

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generalized cEHK, mosaic cEHK, or IBS were made based on the histologic pattern of the epidermolysis and hyperkeratosis.

Results—Eighteen of the one hundred seventeen slides revealed features sufficient to make a histologic diagnosis of epidermolytic hyperkeratosis (hEHK). One additional slide, for which a definitive histologic diagnosis was not possible, had features of both hEHK and acantholytic dyskeratosis. Two distinct patterns of the histopathologic changes were observed within the eighteen slides diagnostic of hEHK, a) continuous involvement of the entire horizontal epidermis and b) focal involvement revealing skip areas of normal appearing epidermis along the horizontal epidermis. Upon clinical correlation, all twelve of the slides with continuous involvement were from patients with generalized cEHK. One slide was from acral skin and had continuous involvement. This was from a patient with Vörner's palmoplantar keratoderma. Of the remaining five slides with focal involvement, two patterns were observed; focal involvement of both the granular and spinous layers and focal involvement of only the granular layer. The three slides with focal involvement of the granular and spinous layer were from patients with mosaic cEHK. Of the two slides with focal involvement confined to the granular layer, one was from a patient with IBS and the other from a patient with generalized cEHK.

Limitation—The sample pool is biased by who was enrolled in the registry and therefore may not represent the full spectrum of the disease.

Conclusion—The pattern of histologic involvement may be a useful predictor of the clinical phenotype of cEHK.

INTRODUCTION

The clinical condition generalized epidermolytic hyperkeratosis, or bullous congenital ichthyosiform erythroderma, is characterized at birth and in the neonatal period by erythroderma, widespread bullae, and desquamation resulting in denuded skin. Focal hyperkeratosis may accompany these clinical findings. In infancy and into adulthood, the erythema and bullae are replaced with widespread hyperkeratosis, most prominent over joints, leading to a characteristic cobblestone appearance. Generalized cEHK is an autosomal dominant condition with one hundred percent penetrance, although approximately 50% of all cases represent new spontaneous mutations. Mutations in the genes encoding keratin 1 and keratin 10 have been found in patients with generalized cEHK, however, the phenotype can vary significantly between different affected families. This difference in clinical presentation among different affected individuals has led to the description of six distinct phenotypes that are subdivided based on the presence or absence of involvement of the palms and soles.¹

Vörner's palmoplantar keratoderma is an autosomal dominant condition caused by a mutation in keratin 9. This presents shortly after birth as symmetric bilateral thick hyperkeratosis of the palms and soles which can result in significant discomfort. This disorder is differentiated from other palmoplantar keratodermas by lack of other cutaneous findings and by the presence of histologic features of epidermolytic hyperkeratosis (hEHK).

Ichthyosis Bullosa of Siemens (IBS) is clinically distinct from generalized cEHK. Its presentation typically lacks the erythema seen in generalized cEHK. Additionally, the blistering is much milder and tends to be trauma induced on the extremities. The blistering is superficial, and has been called molting (Mauserung). IBS is an autosomal dominant condition resulting from mutations in the gene that encodes keratin 2.

Mosaic cEHK presents as hyperkeratosis that follows Blaschko's lines. The clinical appearance may resemble that of an epidermal nevus. This phenotype represents a somatic mutation during embryogenesis resulting in abnormal keratin 1 or keratin 10 in the areas of hyperkeratosis.

Patients with mosaic cEHK have been reported to have children with generalized cEHK if the mosaic mutation involves the germ line.²

Confusion can result because the term epidermolytic hyperkeratosis is used to describe both the clinical disease and the characteristic histopathologic features of hyperkeratosis with epidermolysis. Histologically, epidermolysis is seen as various sized clear spaces around keratinocyte nuclei with indistinct cell boundaries in the upper spinous and granular layers. Keratohyalin granules appear basophilic and clumped. Eosinophilic granules are seen in the spinous layers. The histology of EHK is seen in a spectrum of clinical conditions including generalized cEHK, mosaic cEHK, and IBS.

The National Registry for Ichthyosis and Related Disorders (the Registry) was funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases to improve understanding of the diagnosis, pathophysiology, and treatment of affected individuals. The Registry contains a large collection of histopathologic material from clinically well characterized subjects. We studied this collection in an effort to characterize the histopathologic features observed across the spectrum of generalized cEHK, IBS and mosaic cEHK.

METHODS

This study was approved by the institutional review board for human subjects research. Six hundred and ten individuals have been enrolled in the Registry and have been well characterized by clinical, histologic, biochemical and molecular means. One hundred and twelve (18%) of the 610 cases had histologic material submitted for review. This consisted of 117 slides plus digital images from one additional biopsy. We evaluated all 117 biopsy slides from the Registry blinded to clinical information. For each slide a series of features was critically evaluated using a standardized score sheet (fig 1). Features related to hEHK included evaluation of individual epidermal layers. In the stratum corneum, the degree of hyperkeratosis was quantified; the type of hyperkeratosis, ie basket weave or compact, was evaluated; and the presence of parakeratosis was noted. The granular layer was evaluated for perinuclear vacuolar changes, cytolysis, and the appearance of the keratohyalin granules, findings consistent with hEHK. The spinous layer was evaluated for extension of these features. In both the granular and spinous layer these changes were characterized as either continuous or focal. Focal was defined as involvement horizontally alternating with uninvolved areas, whereas, continuous involved the entire horizontal epidermis. Additionally, the degree of acanthosis and papillomatosis were quantified and the basal layer was evaluated.

RESULTS

Eighteen of the one hundred seventeen slides revealed features sufficient to make the histologic diagnosis of EHK. One additional slide, for which a definitive histologic diagnosis was not possible, had features of both hEHK and acantholytic dyskeratosis. Focal involvement, defined as involved areas with skip areas of normal appearing epidermis (fig 2), was seen in 5 of the 18 slides evaluated. The remaining 13 slides showed continuous involvement of the entire horizontal epidermis (fig 3). Two of the 5 had focal involvement of the granular layer but not the spinous layer (fig 4). These 2 were predicted to be from patients who had IBS. We predicted the remaining 3, with focal areas of involvement within both the granular and spinous layers to be from patients with mosaic cEHK. After blinded review of the histology slides, all subjects who were enrolled in the Registry with a clinical diagnosis of generalized cEHK, mosaic cEHK, or IBS and who submitted biopsies were identified.

Clinical information about the patients was correlated with the predictions made on the basis of histologic features. The clinical information revealed that the 3 slides with focal involvement

came from patients with mosaic cEHK. Of the 2 slides predicted to be IBS, one was from an enrollee with IBS, the other, generalized cEHK. Twelve of the 13 slides with continuous involvement were predicted to be from patients with generalized cEHK. Subsequently, clinical data revealed all 12 to be from patients with generalized cEHK. One slide with continuous involvement showed prominent hyperkeratosis and prominent acanthosis, features that led us to predict that the biopsy came from acral skin. It was predicted this biopsy was from either Vorner's palmoplantar keratoderma or from acral skin of a patient with generalized cEHK. Clinical correlation showed that this biopsy was from a patient with Vorner's palmoplantar keratoderma. The slide with features of both hEHK and acantholytic dyskeratosis was from a patient who did not have blisters at birth but who within the first few days of life developed thickening and flaking of the skin in a generalized distribution including volar skin. Because volar skin was involved a keratin 1 mutation was suspected, however molecular testing for the common mutations was negative and a definitive clinical diagnosis was not reached.

After clinical data were retrieved, additional histopathologic data analysis was performed to evaluate for additional differentiating features. The only additional differentiating feature was focal parakeratosis which was found in 8 of the 13 slides with a clinical diagnosis of generalized cEHK. No parakeratosis was found in the 3 mosaic cEHK patients, nor was parakeratosis found in the one patient with IBS. Stratum corneum changes of degree of hyperkeratosis or type of hyperkeratosis, ie basket weave or compact, had no differentiating patterns among the three entities. Additionally, all of the slides had some degree of acanthosis but the extent of acanthosis did not differ among the different entities. Papillomatosis was also not significantly different and there were no significant basal layer abnormalities.

DISCUSSION

In this paper we identify histopathologic features that may help differentiate patients with generalized cEHK from mosaic cEHK, and possibly from IBS. Twelve of the 13 slides reviewed (blinded to clinical information) that showed continuous involvement corresponded to generalized cEHK. The only slide with acral skin with continuous involvement was from a patient with a clinical diagnosis of Vorner's palmoplantar keratoderma. The 3 cases of mosaic cEHK had histopathologic features of focal involvement in both the granular and spinous layers. The one clinical case of IBS had focal involvement in the granular layer only. However, one additional case with focal involvement limited to the granular layer corresponded to generalized cEHK. Therefore, finding the involvement confined to the granular layer only may not be a consistent differentiating feature between patients with generalized cEHK and IBS. Focal parakeratosis was seen only in generalized cEHK.

The histopathologic features of epidermolytic hyperkeratosis are hyperkeratosis, hypergranulosis, and epidermolysis. Within areas of epidermolysis are characteristic epidermal cells with perinuclear vacuolization with indistinct peripheral boundaries. By light microscopy the boundaries appear to be formed by eosinophilic and basophilic granules. These histologic features are characteristic for patients with generalized cEHK, IBS, and mosaic cEHK. It should be noted that these same histopathologic features of hEHK are seen in a variety of other conditions including epidermolytic acanthoma and nevoid follicular epidermolytic hyperkeratosis.^{3,4} EHK histology has been reported as an incidental finding in a large variety of conditions including melanocytic nevus, solar keratosis, squamous cell carcinoma, basal cell carcinoma, pilar cyst, seborrheic keratosis, cutaneous horn, skin tag, both oral and genital mucosal leukoplakia, nevus comedonicus, and progressive systemic sclerosis.⁵⁻¹⁴ It has also been seen incidentally in normal skin and in normal oral mucosa.¹⁵

In summary, the characteristic EHK histologic features of hyperkeratosis with vacuolar degeneration when seen in a continuous pattern involving the granular and spinous layers with

focal parakeratosis should favor a clinical diagnosis of generalized EHK. Focal involvement within the granular and spinous layers suggests a clinical diagnosis of mosaic EHK. These histopathologic hints may help in the differentiation of these clinical conditions.

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Abbreviation and acronym list

EHK

Epidermolytic hyperkeratosis

IBS

Ichthyosis Bullosa of Siemens

The Registry

The National Registry for Ichthyosis and Related Disorders

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Date: Registry ID number:	Slide Number: 0 - none Site of Biopsy: 1 - mild Age/DOB: 2 - moderate 3 - severe
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Stratum corneum

- ♦ Normal orthokeratosis
- ♦ Hyperkeratosis 0 - 1 - 2 - 3
 - Basket-weave
 - Compact
 - Verrucous
 - Church spire
 - Focal-vs.-Continuous
- ♦ Parakeratosis 0 - 1 - 2 - 3
 - Focal-vs.-Continuous
 - Mounds
 - Confluent
 - Verrucous
 - Church spires
 - Grains

Dermis

- ♦ Normal
- ♦ Papillomatosis 0 - 1 - 2 - 3
- ♦ Infiltrate
 - Location
 - superficial perivascular
 - superficial and deep perivascular
 - interstitial
 - nodular and diffuse
 - vasculitis
 - Composition
 - Lymphohistiocytes
 - Eosinophils
 - Plasma cells
 - Granulomas

Granular layer

- ♦ Normal
- ♦ Absent-vs.-Atrophic-vs.-Thickened
- ♦ Number of layers _____
- ♦ Vacuolar degeneration 0 - 1 - 2 - 3
- ♦ Cytolysis 0 - 1 - 2 - 3
- ♦ Dyskeratosis 0 - 1 - 2 - 3
- ♦ Epidermolysis 0 - 1 - 2 - 3
- ♦ Vacuolated
- ♦ Keratohyalin Granules
 - Normal
 - Crumbly
 - Spongy
 - Coarse
 - Basophilic-vs.-Eosinophilic
- ♦ Corp ronds
- ♦ Perinuclear halos

Sebaceous and sweat glands/ducts

- ♦ Normal
- ♦ Size
 - Small
 - Normal
 - Large
- ♦ Number
 - Decreased
 - Normal
 - Increased
- ♦ Plugging 0 - 1 - 2 - 3
- ♦ Hyperkeratosis 0 - 1 - 2 - 3
- ♦ Vacuolated 0 - 1 - 2 - 3

Spinous layer

- ♦ Normal
- ♦ Acanthosis 0 - 1 - 2 - 3
- ♦ Spongiosis 0 - 1 - 2 - 3
- ♦ Vacuolated 0 - 1 - 2 - 3
- ♦ Dyskeratosis 0 - 1 - 2 - 3
- ♦ Epidermolysis 0 - 1 - 2 - 3
- ♦ Suprabasal clefting 0 - 1 - 2 - 3
- ♦ Acantholysis 0 - 1 - 2 - 3
- ♦ Psoriasiform hyperplasia 0 - 1 - 2 - 3
- ♦ "Trichohyalin-like granules" 0 - 1 - 2 - 3

Follicles

- ♦ Normal
- ♦ Absent
- ♦ Plugging 0 - 1 - 2 - 3
- ♦ Hyperkeratosis 0 - 1 - 2 - 3
- ♦ Dyskeratosis 0 - 1 - 2 - 3
- ♦ Parakeratosis 0 - 1 - 2 - 3
 - Shoulder
 - Confluent
- ♦ Dilatation 0 - 1 - 2 - 3

Basal cell layer

- ♦ Normal
- ♦ Vacuolated 0 - 1 - 2 - 3
- ♦ Vacuolar degeneration 0 - 1 - 2 - 3
- ♦ Dyskeratosis 0 - 1 - 2 - 3

Blood vessels

- ♦ Normal
- ♦ Dilated 0 - 1 - 2 - 3
- ♦ Tortuous 0 - 1 - 2 - 3

General

- ♦ Mitoses 0 - 1 - 2 - 3
- ♦ Papillomatosis 0 - 1 - 2 - 3
- ♦ Rete ridge pattern: Normal - Blunted - Accentuated
- ♦ Dermal epidermal junction _____

Figure 1.
Standardized score sheet used to grade specific histologic features of each slide

Figure 2.

Focal epidermolytic hyperkeratosis with epidermolytic hyperkeratosis horizontally alternating with areas without epidermolytic hyperkeratosis in mosaic epidermolytic hyperkeratosis. (H&E stain, original magnification 100×)

Figure 3. Continuous epidermolytic hyperkeratosis throughout the entire horizontal epidermis in generalized epidermolytic hyperkeratosis. (H&E stain, original magnification 100×)

Figure 4.
Focal epidermolytic hyperkeratosis of the granular layer without extension into the spinous layer in Ichthyosis Bullosa of Siemens (H&E stain, original magnification 100×)