Epidermolytic ichthyosis complicated by staphylococcal scalded skin syndrome in the newborn

Gabrielle M Peck[1] BA, Kelsey Flood[2] MD, Kalyani Marathe[3] MD

Affiliations: [1]College of Medicine, University of Cincinnati, Cincinnati, Ohio, USA, [2]Department of Dermatology, University of Cincinnati, Cincinnati, Ohio, USA, [3]Department of Dermatology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

Corresponding Author: Kalyani Marathe MD, 3333 Burnet Avenue, Cincinnati, Ohio 45229, Email: Kalyani.Marathe@cchmc.org

Abstract

Epidermolytic ichthyosis is characterized by erythema and blistering at birth. We present a neonate with epidermolytic ichthyosis who had a subtle change in clinical findings while hospitalized, including increased fussiness, erythema, and a change in her skin odor, which represented superimposed staphylococcal scalded skin syndrome. This case highlights the unique challenge of recognizing cutaneous infections in neonates with blistering skin disorders and emphasizes the importance of having a high suspicion for superinfection in this population.

Keywords: blister, epidermolytic hyperkeratosis, infant, keratin 1, newborn, scalded skin syndrome, staphylococcal

Introduction

Epidermolytic ichthyosis (EI), also known as epidermolytic hyperkeratosis or bullous congenital ichthyosiform erythroderma, is a keratinopathic ichthyosis, conditions associated with genetic mutations in keratin intermediate filaments. Specifically, EI is caused by mutations in the keratin 1 (*KRT1*) gene or keratin 10 (*KRT10*) gene which causes failed keratinocyte migration from the proliferating stratum basale to the stratum corneum [1-3]. At birth, a vesicular eruption and diffuse erythema is observed. Due to a compromised skin barrier, infants with this condition are at an increased risk of infections [4].

Case Synopsis

A female infant (gestational age 37 weeks, three days) with no known family history of dermatologic disease was noted to have erosions and vesicles at birth. Differential diagnosis included infection, epidermolysis bullosa (EB), and epidermolytic ichthyosis (EI). Empiric treatment with vancomycin, cefepime, and acyclovir was initiated. Workup including blood cultures and herpes simplex virus PCR were negative. The patient was transferred to College of Medicine, University of Cincinnati (CCHMC) given concern for EB as our institution has an EB center.

On presentation on day of life 1, physical examination was notable for hyperkeratotic palms and soles and diffuse erythema with variable desquamating erosions and plaques, accentuated at sites of pressure, and scattered, few-millimeter focal vesicles (**Figure 1**). Notably, features of EB including nail changes, excessive granulation tissue, and oral changes were absent. Skin snip biopsy on day 1 of life demonstrated a sloughed corneal layer with necrosis of the superficial epidermis suggesting a superficial intraepidermal level of splitting (**Figure 2**. Genetic testing revealed a pathogenic spontaneous heterozygous mutation in *KRT1*, c559C>T.

Rigorous wound care was initiated as follows: petrolatum gauze was used to wrap the arms, legs, and trunk, then wrapped with Flexicon bandages and secured with Tubifast. Mineral oil on a cotton pad was used to clean the perineum and buttocks with diaper changes. On day 9 of life, the patient

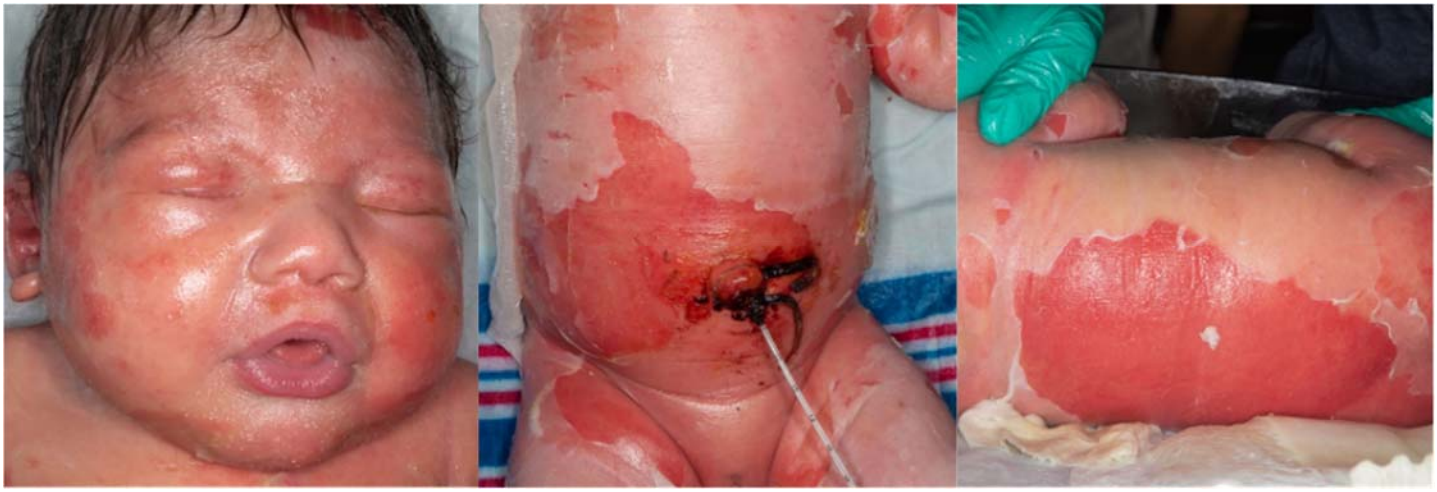

Figure 1. *Day of life 1. Diffuse erythema with variable desquamating erosions and plaques, accentuated at sites of pressure.*

suddenly developed fussiness, a change in odor, and increased skin erythema with variable desquamating erosions and plaques, accentuated at sites of pressure (**Figure 3**). Repeat perianal cultures at CCHMC grew out *Staphylococcus aureus* confirming the diagnosis of staphylococcal scalded skin syndrome (SSSS). Blood cultures were negative. Treatment with clindamycin and topical mupirocin was initiated with improvement in her symptoms and examination notable for scattered erythema with plaques and scattered, few-millimeter focal vesicles on day of life 14 (**Figure 4**). The patient was discharged on day of life 19 with instructions to apply emollients during daily dressing changes, perform bleach baths two-to-three times weekly, and complete the course of antibiotics. She continues to follow at our dermatology clinic and has required no further admissions.

Case Discussion

In neonates presenting with a vesiculobullous skin eruption, the priority is to empirically cover for infectious etiologies, especially Group B streptococcal and staphylococcal infections, until these are ruled out. Other infectious etiologies such as herpes simplex or congenital syphilis should be considered. After infection is excluded, EB is a common concern. Epidermolytic ichthyosis may overlap clinically with EB in the neonatal period. The main feature that suggested EI over EB in this patient was palmoplantar hyperkeratosis. The absence of oral and nail changes may suggest EI over EB [5].

Genetic testing is the gold standard for diagnosis of EI [3]. Sporadic mutations account for 50% of cases of EI, as in this patient [4]. Our patient's specific mutation, *KRT1*, c559C>T, was previously identified

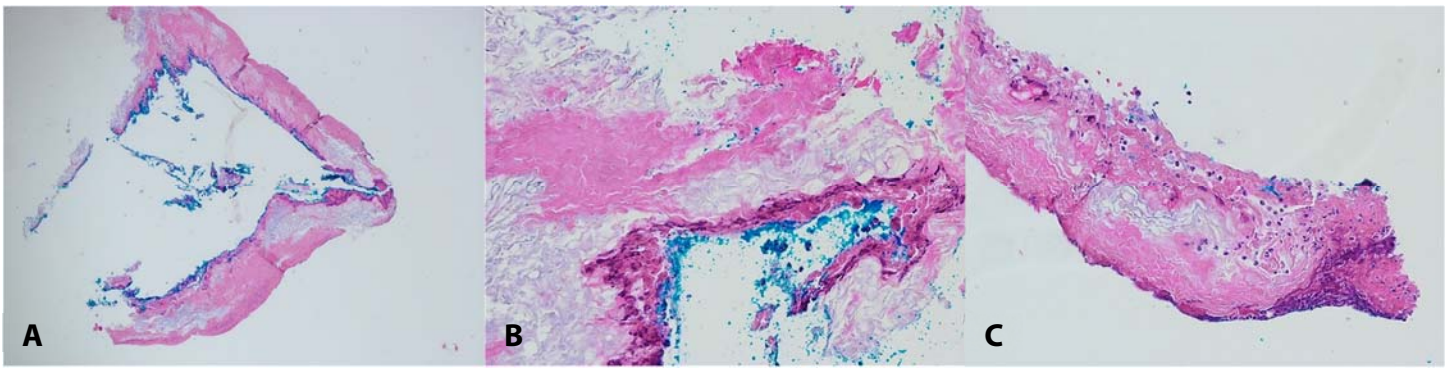

Figure 2. *H&E skin histopathology on day of life 1.* ***A)*** *Fragments of keratin (stratum corneum) with small amounts of necrotic and degenerating superficial epidermis along the deep blue inked aspects, 40×.* ***B)*** *Higher power magnification shows degenerating superficial epidermis along blue inked deep aspect, suggesting split is within the superficial epidermis, 200×.* ***C)*** *Neutrophils within the stratum corneum are present, 200×.*

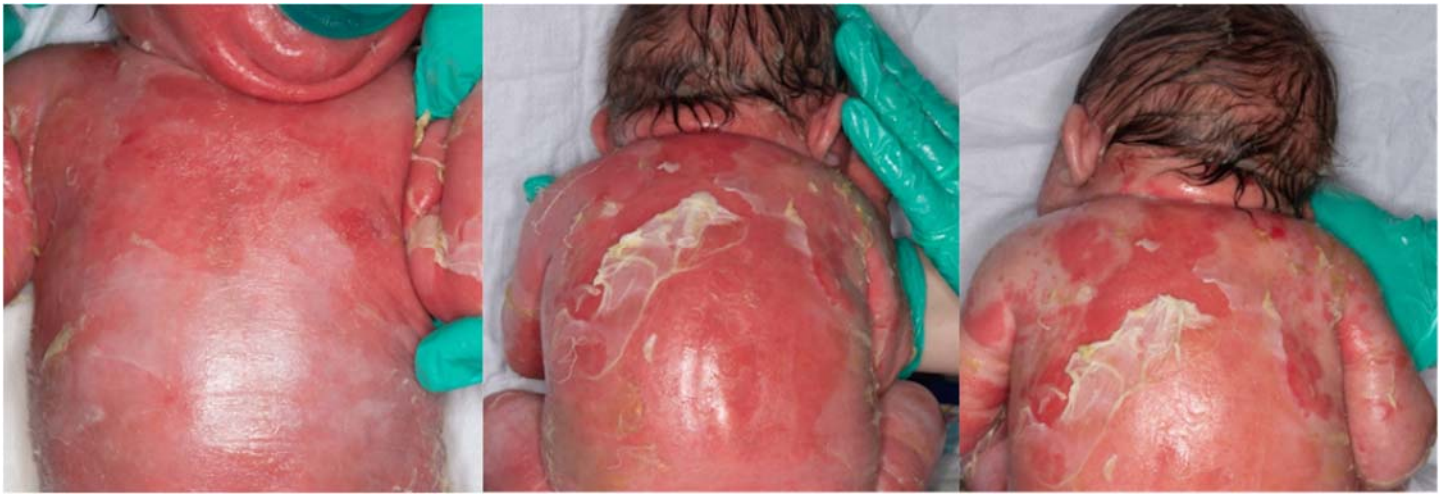

Figure 3. *Day of life 9. Diffuse erythema with variable desquamating erosions and plaques, accentuated at sites of pressure. This change in physical examination prompted skin cultures and subsequent diagnosis of staphylococcal scalded skin syndrome.*

as a de novo mutation in patients with EI and epidermolytic hyperkeratosis with palmoplantar involvement [6,7]. The variant is reported in the ClinVar database (Variation ID: 66648), but is absent from the genomAD population database and is thus assumed to be rare [8]. This substitution occurs within the helix initiation motif, a known mutational hotspot region. Mutations affecting the helix initiation, central rod domains, and termination motifs disrupt keratin intermediate filament assembly and function leading to hyperkeratosis and skin fragility [8,9]. One case report documenting the same mutation as observed in our patient detailed a sporadic case of EI that presented with blisters, erosion, and erythroderma on the entire body surface area at birth and hyperkeratosis in the palmoplantar and flexural areas in the months following initial presentation [7]. Another report with our patient's mutation described a patient who presented with generalized hyperkeratosis involving the palms and soles [6]. Both reports described de novo mutations [6,7].

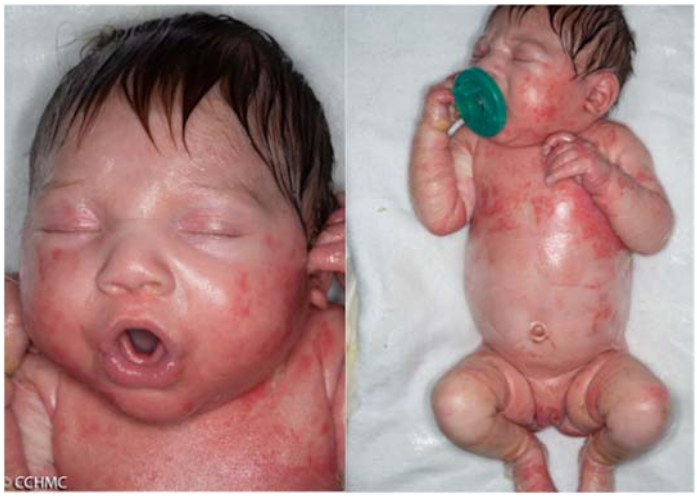

Figure 4. *Day of life 14. Scattered erythema with plaques and scattered, few-millimeter focal vesicles consistent with staphylococcal scalded skin syndrome.*

Neonates with blistering skin diseases have compromised skin integrity and must be carefully monitored for dehydration, electrolyte imbalances, and infection [3]. Patients should be placed in an Isolette to maintain body temperature and decrease infection risk. Bullae may occur at sites of friction. Therefore, neonates should be carefully handled to minimize shearing forces [4]. In all EI phenotypes, therapeutic strategies include use of hydrating emollients to promote re-epithelization and accelerate desquamation [2,10]. Dilute bleach baths are recommended to regulate the local microbiome and decrease risk of infection.

We conducted a literature review on PubMed using the search terms 'epidermolytic ichthyosis,' 'epidermolytic hyperkeratosis,' 'bullous congenital ichthyosiform erythroderma,' and 'staphylococcal scalded skin syndrome.' We identified one case report describing a neonate diagnosed with EI without palmoplantar involvement who developed SSSS at two months of age [11]. There were no other case reports in the literature documenting SSSS in a patient with EI.

Typically, SSSS presents with irritability, fever, fatigue, and a tender rash that develops 24 to 48 hours after initial symptoms. The eruption is characterized by erythema and fissures on the face and flexor surfaces which later evolves into localized or diffuse flaccid bullae. Patients may appear well or may be quite ill with sepsis, hypotension, and/or shock [12]. Cultures should be obtained from the nares, buttocks, and umbilicus in addition to any areas which appear superinfected. Interpretation of culture results may be difficult in these patients as they are often colonized with bacteria at baseline [13,14]. Clinical correlation is therefore important, as in our case.

Management of SSSS includes antibiotics covering staphylococcus such as cefazolin or nafcillin or vancomycin if methicillin-resistant *Staphylococcus aureus* is suspected. Non-adherent dressings and emollients should be applied for wound care. Supportive care measures include temperature regulation, management of dehydration, proper hand hygiene, and nutritional supplementation. Given the potentially severe consequences of SSSS superimposed on EI, such as pain, electrolyte imbalances, or sepsis, appropriate antibiotics and treatment for SSSS should be initiated promptly [12,15].

Identification of infections, especially SSSS, can prove difficult in neonates who at baseline have an atypical skin examination. It is difficult to distinguish the erythema present on baseline examination in patients with EI from the macular erythema found on examination in patients with SSSS [2,12]. Although SSSS infrequently complicates EI, it is a common condition in the differential diagnosis for neonates with vesicles, pustules, and/or blistering. Infections in EI are a feared complication discussed in the literature, but the true incidence of infection in this population is unknown [2]. This is likely because of the low prevalence of EI amongst the general population and subsequent small collection of literature on EI.

Infections in patients with blistering skin diseases are better characterized in EB patients. Since there is currently no cure available for EB, management of patients with this condition centers on appropriate wound management. Wound care management in EB requires an individualized management plan due to clinical variability amongst patients and a wide spectrum of wound care products available. Although sepsis was previously a major cause of mortality in this population, improvements in wound care have led to improved patient outcomes and quality of life. Nevertheless, patients with more severe EB subtypes remain prone to infection [2].

Differentiating between superficial critical colonization and deep or surrounding skin infection is important in determining appropriate wound care for patients with EB [2]. The mnemonics NERDS and STONEES help differentiate superficial critical colonization from deeper/surrounding skin infection in the setting of chronic wounds. The NERDS criteria (nonhealing, increased exudate, red, friable tissue, debris, dead slough, smell) indicate superficial critical colonization when three or more are present, which warrants treatment with a topical antimicrobial. To prevent resistance, antimicrobials should be prescribed for short durations and rotated every two to 6 weeks [2]. Alternatives to topical antimicrobials include silver, honey, iodine, polyhexamethylene biguanide, diluted bleach baths, compresses, and sprays with diluted vinegar. Three or more of the STONEES criteria [16], (increased size, os (the latin word for bone) referring to exposed bone or ability to probe to bone, new areas of breakdown, erythema/edema of surrounding skin, increased exudate, and smell) indicates deeper/surrounding skin infection which necessitates systemic antimicrobial therapy [2]. Although wound care for treatment of infections in patients with EI is not well documented in the literature, principles for treatment of infections in other blistering skin conditions, such as EB, can be applied [2].

Conclusion

Owing to a compromised skin barrier, infants with EI are at increased risk of infection. However, identification of infections, especially SSSS, can prove difficult in neonates, who at baseline have an atypical examination. By promptly recognizing and treating infection in patients with EI, morbidity and mortality can be reduced for these patient populations.

Potential conflicts of interest

Gabrielle Peck and Dr. Kalyani Marathe declare no conflicts of interest. Dr. Kelsey Flood previously received fellowship funding paid directly to her institution from the National Psoriasis Foundation, Abbvie, and Janssen.

References

1. Oji V, Tadini G, Akiyama M, et al. Revised nomenclature and classification of inherited ichthyoses: Results of the First Ichthyosis Consensus Conference in Sorze 2009. *J Am Acad Dermatol*. 2010;63:607–41. [PMID: 20643494].
2. Rout DP, Nair A, Gupta A, Kumar P. Epidermolytic hyperkeratosis: Clinical update. *Clin Cosmet Investig Dermatol*. 2019;12:333–44. [PMID: 31190940].
3. Rice AS, Crane JS. Epidermolytic Hyperkeratosis. *StatPearls*. 2020. [PMID: 31335043].
4. Cheng S, Moss C, Upton CJ, Levell NJ. Bullous congenital ichthyosiform erythroderma clinically resembling neonatal staphylococcal scalded skin syndrome. *Clin Exp Dermatol*. 2009;34:747–8. [PMID: 19635120].
5. Remais J V, Zeng G, Li G, Tian L, Engelgau MM. Convergence of non-communicable and infectious diseases in low-and middle-income countries. *Int J Epidemiol*. 2013;42:221–7. [PMID: 23064501].
6. Math A, Frank J, Handisurya A, et al. Identification of a de novo keratin one mutation in epidermolytic hyperkeratosis with palmoplantar involvement. *Eur J Dermatology*. 2006;16:507–10. [PMID: 17101470].
7. Uezato H, Yamamoto YI, Kuwae C, et al. A case of bullous congenital ichthyosiform erythroderma (BCIE) caused by a mutation in the 1A helix initiation motif of keratin 1. *J Dermatol*. 2005;32:801–8. [PMID: 16361731].
8. NM_006121.4(KRT1):c.559C>T. *ClinVar Database*. https://www.ncbi.nlm.nih.gov/clinvar/variation/66648/. Accessed on December 27, 2020.
9. Chamcheu JC, Siddiqui IA, Syed DN, et al. Keratin gene mutations in disorders of human skin and its appendages. *Arch Biochem Biophys*. 2011;508:123–37. [PMID: 21176769].
10. Vahlquist A, Fischer J, Törmä H. Inherited Nonsyndromic Ichthyoses: An Update on Pathophysiology, Diagnosis and Treatment. *Am J Clin Dermatol*. 2018;19:51–66. [PMID: 28815464].
11. Betlloch I, Lucas Costa A, Mataix J, Perez-Cresto M, Ballester I. Bullous Congenital Ichthyosiform Erythroderma: A Sporadic Case Produced by a New KRT10 Gene Mutation. *Pediatr Dermatol*. 2009;26:489–91. [PMID: 19689541].
12. Ruocco E, Baroni A, Russo T, Moscarella E, Piccolo V. Staphylococcal scalded skin syndrome. In: Emerg. Dermatology, Second Ed. CRC Press; 2017. p. 108–13.
13. Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: A randomised placebo-controlled trial. *Lancet*. 2002;360:7–22. [PMID: 12114036].
14. Mellerio JE. Infection and colonization in epidermolysis bullosa. *Dermatol Clin*. 2010;28:267–9. [PMID: 20447490].
15. Staiman A, Hsu DY, Silverberg JI. Epidemiology of staphylococcal scalded skin syndrome in U.S. children. *Br J Dermatol*. 2018;178:704–8. [PMID: 29077993].
16. Gary Sibbald R, Ovington LG, Ayello EA, Goodman L, Elliott JA. Wound bed preparation 2014 update: Management of critical colonization with a gentian violet and methylene blue absorbent antibacterial dressing and elevated levels of matrix metalloproteases with an ovine collagen extracellular matrix dressing. *Adv Ski Wound Care*. 2014;27:1–6. [PMID: 24521847].