Assessing the use of dupilumab in a pediatric patient with bullous congenital ichthyosiform erythroderma

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INTRODUCTION

Bullous congenital ichthyosiform erythroderma (BCIE), formerly known as epidermolytic hyperkeratosis, is a rare, autosomal dominant, keratinization disorder. BCIE is characterized by erythroderma, epidermal blistering, and erosions at birth, followed by chronic hyperkeratosis. It is believed to be caused by point or missense mutations in the genes encoding keratin-1 (KRT1) and keratin-10 (KRT10). The literature suggests that sporadic mutations may cause up to 50% of cases. *KRT10* mutations typically lack the palmoplantar keratoderma phenotype that is classically present in patients with *KRT1* mutations.[1]

BCIE has an estimated prevalence of 1:100,000 to 1:300,000 infants, with no gender predilection. Because of the presence of denuded epithelium and consequent increase in transepidermal water loss, infants with BCIE are at an increased risk of dehydration, electrolyte imbalances, and secondary infection. Although skin fragility and blistering may improve with age, these findings may lead to fatal complications in the neonatal period. The exact mortality rate, however, is currently unknown.[1]

It presents as a treatment challenge because there is no treatment currently available that has been approved by the Food and Drug Administration (FDA) for patients with BCIE.

Abbreviations used:

BCIE:	bullous congenital ichthyosiform erythroderma
FDA:	Food and Drug Administration
NRS:	Numerical Rating Scale

CASE REPORT

A 22-month-old girl presented to our dermatology clinic with a history of a generalized, scaly, pruritic eruption with diffuse erythema and crusted erosions. Her background medical history was notable for spontaneous vaginal delivery at full term to nonconsanguineous parents. Her history was also notable for a 2-week stay in the neonatal intensive care unit for erythroderma with diffuse erosions. She had no known drug allergies and had no other medical or relevant family history. She was initially managed as a case of presumed congenital ichthyosis while genetic testing was pending. She received oral antihistamines, wound care, topical emollients, corticosteroids, and a trial of urea cream 10% with 5% lactic acid, which was discontinued because of irritation.

Genetic testing confirmed a heterozygous mutation of the *KRT10* gene on chromosome 17q21.2, thus confirming the diagnosis of BCIE. The parents declined parental segregation analysis and genetic counseling. Her topical regimen barely improved her condition by follow-up, and her mother continued to endorse pruritus.

At 3 years of age, the patient was started on off-label dupilumab at 300 mg/mo for her uncontrolled pruritus. Systemic retinoids were considered;

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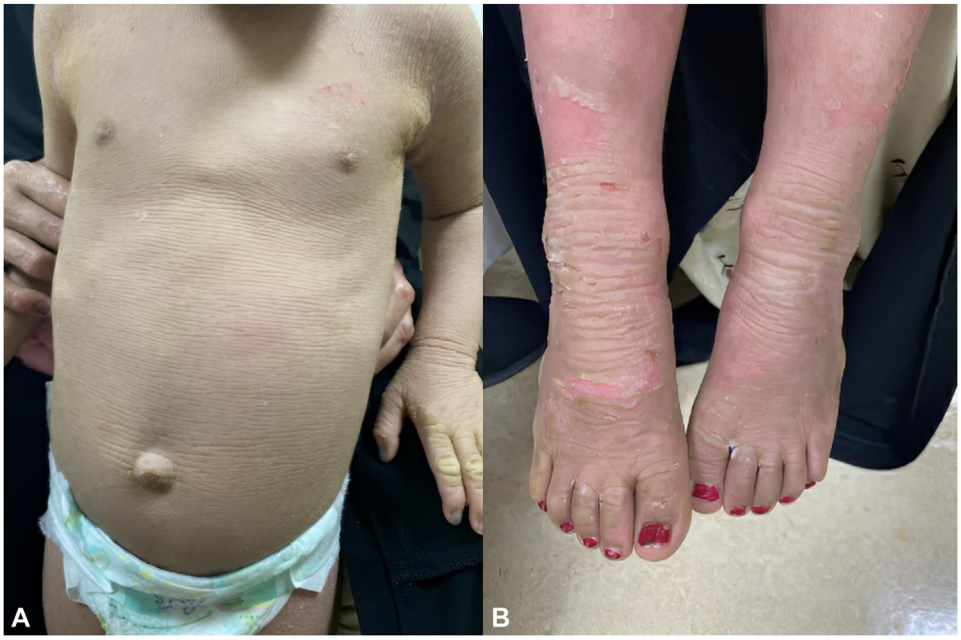

Fig 1. Scattered erosions and yellow-brown hyperkeratotic plaques, with scaling and desquamation on a background of faint erythema on (**A**) the anterior aspect of the trunk and left upper extremity, (**B**) with a more diffusely erythematous background noted on the bilateral aspect of the lower portion of the legs.

however, because of the risk of skin fragility, we elected to postpone treatment until a later stage.

Pretreatment assessment revealed a height of 0.92 m, weight of 14.1 kg, and stable vitals. Skin examination showed scattered, hyperkeratotic, scaly, "cobblestone-like" plaques, with crusted erosions and desquamation on a background of erythema throughout her skin (Fig 1). She had an affected body surface area of >90%, with an Ichthyosis Scoring System score of 4.885 and parent-proxy Peak Pruritus Numerical Rating Scale score (NRS) of 10.[2,3] There were no eclabium, ectropion, palmoplantar keratoderma, joint contractures, epidermal nevi, gait, or postural abnormalities noted on examination.

The mother reported a reduction in the patient's pruritus within the first few weeks of treatment. By the 7-month follow-up, the father reported a 70% reduction in the patient's pruritus, with a parent-proxy NRS score of 3.[3] There was no improvement in her hyperkeratotic plaques or erythema noted, with an Ichthyosis Scoring System score of 5.127.[2] Reduction in her erosions was also noted on examination (Fig 2). Posttreatment laboratory results were within normal limits.

She continues to take dupilumab monthly, with continued improvement of her pruritus, and has regular follow-ups with dermatology. Written informed consent was obtained from the patient and her parents.

DISCUSSION

The treatment of BCIE in the pediatric population is challenging given its rarity and lack of treatment approved by the FDA. Treatments are usually based on symptomatic management with the goal of controlling hyperkeratosis.[1] Treatment regimens typically consist of wound care for erosions; topical emollients, such as glycerin, and keratolytics, such as lactic acid; and α-hydroxy acid, urea, or topical retinoids for hyperkeratotic plaques. However, some patients may not be able to tolerate the stinging or irritation associated with keratolytics. In addition, systemic retinoids have been reported to provide some improvement; however, they may cause increased skin fragility and blistering, necessitating a cautious, gradual approach.[1]

Promising developments for various ichthyoses are on the horizon in pathogenesis-based therapies, such as enzyme replacement therapy and gene therapy, with clinical trials currently underway to assess the safety and efficacy of these modalities.[4] Furthermore, recent findings concerning the immune profile of patients with ichthyosis have given new ground for repurposing biologics. Biologics such as secukinumab, ustekinumab, and dupilumab have shown promising results in the treatment of other ichthyotic entities, namely Netherton syndrome, and autosomal recessive congenital ichthyosis (including lamellar ichthyosis and harlequin ichthyosis).[4-6]

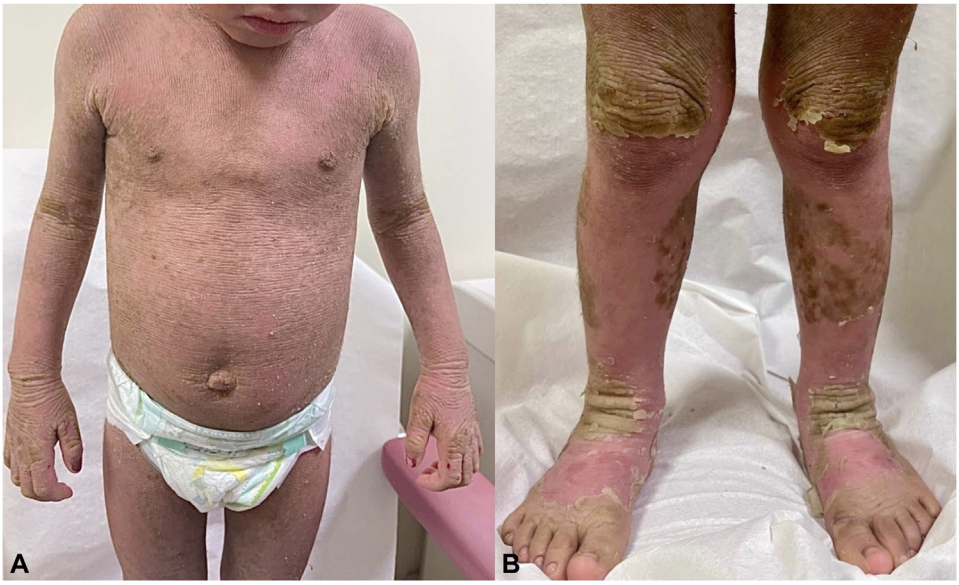

Fig 2. Scattered, desquamating, yellow-brown hyperkeratotic plaques on a background of diffuse erythema, with scaling on the anterior aspect of the trunk. **A,** Bilateral aspect of upper extremities and (**B**) bilateral aspect of lower extremities. No erosions are noted.

Dupilumab is a human, monoclonal, IgG4 antibody that inhibits signaling between interleukin-4 and interleukin-13 by binding to interleukin-4 receptor-α. This ultimately leads to inhibition of proinflammatory cytokines, chemokines, and IgE. We postulate that this cascade of events may lead to reduction in inflammation and pruritus in patients with BCIE. Additionally, dupilumab may help normalize keratinocyte differentiation and proliferation. As a result, this could theoretically help improve skin barrier function and reduce blistering.[7-9] However, the exact underlying mechanism of action of dupilumab in patients with BCIE is currently unknown.

Dupilumab is FDA approved for the treatment of atopic dermatitis and prurigo nodularis. Furthermore, dupilumab has also been identified as a viable therapy option for several pruritic entities, including bullous pemphigoid, pemphigus vulgaris, and Netherton syndrome.[6-8,10]

Our patient had a 70% reduction in her pruritus and parent-proxy NRS score with dupilumab.[3] To our knowledge, this is the first reported case of successful treatment of pruritus with dupilumab in a pediatric patient with BCIE. Although our patient also had a reduction in the number of erosions (Figs 1 and 2), there was no improvement observed in her hyperkeratosis despite treatment. This may have been due, in part, to the natural course of her disease because skin fragility tends to improve with age, whereas hyperkeratosis worsens.

In conclusion, our case report suggests that dupilumab helps improve pruritus in pediatric patients with BCIE. However, additional research on the clinical efficacy of dupilumab in the treatment of BCIE in pediatric patients is required.

Conflicts of interest

None disclosed.

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