A case report of fatal harlequin ichthyosis: Insights into infectious and respiratory complications

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INTRODUCTION

Harlequin ichthyosis (HI) is a rare autosomal recessive congenital ichthyosis associated with mutations in the keratinocyte lipid transporter adenosine triphosphate binding cassette A12 (*ABCA12*),[1] leading to disruption in lipid and protease transport into lamellar granules in the granular layer of the epidermis. Subsequent defective desquamation with compensatory hyperkeratinization follows.[2] Historically, there has been a high early mortality rate in infants with HI; however, improved neonatal management and the early introduction of systemic retinoids may contribute to improved prognosis. Death in these patients is most commonly caused by sepsis, respiratory failure, or electrolyte imbalances.

We report a case of a neonate with HI treated in the first few days of life with acitretin. The patient initially improved but eventually died of pseudomonas sepsis at 6 weeks of age.

REPORT OF A CASE

The dermatology department was consulted for a male infant born at 33 weeks of gestation to consanguineous parents of Pakistani origin. Physical examination found generalized thick yellow hyperkeratotic scale with fissuring, bilateral ectropion and eclabium, and thick encasement and contractures of all extremities (Fig 1).

Family history was significant for an 8-year-old sibling with HI caused by a homozygous mutation (W1294X) in the *ABCA12* gene confirmed by DNA sequence analysis. The family received preconception genetic counseling and was offered chorionic villus sampling, which the mother declined. No anomalies on ultrasound scan were reported during pregnancy.

Abbreviations used:

ABCA12:	adenosine triphosphate binding cassette A12
HI:	harlequin ichthyosis
NICU:	neonatal intensive care unit

Initial neonatal intensive care unit (NICU) management included broad-spectrum antibiotics, intravenous fluids, liberal emollients, complete blood count, and electrolyte monitoring. On day 3 of life, 1 mg/kg/d of acitretin was administered. The infant was also evaluated by the orthopedic surgery department, and fasciotomies of all 4 extremities were performed. Postfasciotomy, the patient had a decrease in leukocyte count and was placed on an additional course of vancomycin and piperacillin/tazobactam, which was discontinued after 7 days because of negative cultures and clinical improvement.

Clinical improvement in the infant's condition was seen over the subsequent weeks (Fig 2). On day 44 of life, the patient spiked a fever to 100.4°F and was again started on intravenous vancomycin and piperacillin/tazobactam, which were discontinued after 2 days of treatment because of negative blood

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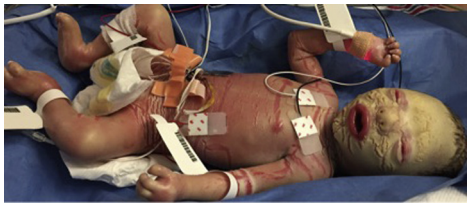

Fig 1. A neonate with harlequin ichthyosis on day 1 of life.

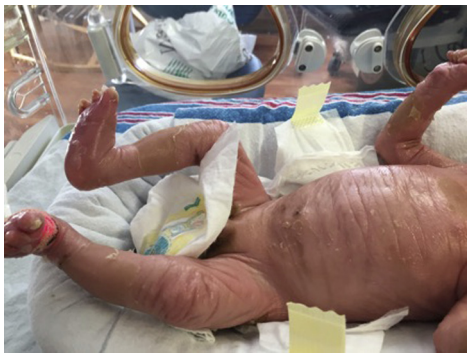

Fig 2. The neonate on day 21 of life after 3 weeks of treatment with acitretin at 1 mg/kg/d. Note the significant improvement in hypekeratosis and fissuring.

and urine cultures. Two days after discontinuation of antibiotics, the patient had an abrupt bradycardic event requiring cardiopulmonary resuscitation and intubation. The family elected to withdraw supportive care, and the patient died soon after. Blood cultures from the time of the bradycardic event were positive for *Pseudomonas aeruginosa* that was not detected in the initial blood culture several days prior.

DISCUSSION

HI is characterized by abnormal hyperkeratinization and desquamation of the epidermis secondary to a mutation in the *ABCA12* gene, resulting in faulty intercellular and intracellular lipid transport into the lamellar granule from the Golgi apparatus of keratinocytes in the upper granular layer.[2] Clinically, this manifests as thick, platelike scaling and fissuring, which may act as a nidus for infection. As the neonate adapts to a drier environment, there is shedding of the encased stratum corneum, leaving diffuse erythema and fine scale. This later phenotype is relatively more protective because of decreased transepidermal water loss and risk of contractures and increased ease of respiration.[3]

Systemic retinoids can be used early in life to hasten this shift in clinical presentation and may lead to a decrease in mortality, as they encourage keratinolysis, keratinocyte differentiation, and shedding of the thick hyperkeratotic encasing. They may also have an anti-inflammatory effect related to the drugs' ability to modulate neutrophil activation and function.[4]

Additionally, the dysfunction of lamellar granule transport in patients with HI may lead to compromised innate immunity, as these are known to play a role in the transport and secretion of various antimicrobial peptides, including LL37, the terminal end of cathelicidin, human beta defensin 2 (HBD2), and kallikrein-related peptidase 7. A study in patients with HI found significantly reduced immunostaining for antimicrobial peptides LL37, human beta defensin 2, and kallikrein-related peptidase 7 in the stratum corneum when compared with controls. This resulting dysfunction in innate immunity may contribute to increased risk of skin and possibly lung infections in HI patients.[5]

Pseudomonas aeruginosa is an opportunistic gram-negative bacterium commonly found in soil and water; infections primarily occur in open wounds and the urinary tract and cause chronic lung infections in cystic fibrosis patients.[6] Pseudomonas is also an important cause of fatal nosocomial infections particularly in NICUs, likely owing to the underdeveloped immune systems of neonates.[7] A review of pseudomonas outbreaks in the NICU setting found sources of pseudomonas to include a milk pasteurizer, a water bath used for thawing fresh-frozen plasma, a blood-gas analyzer, hands and fingernails of health care workers, and mineral water bottles.[6] There are limited studies on the benefits of antibiotic or fungal prophylaxis in patients with HI, and there are cases of HI patients who died of pseudomonas sepsis despite broad-spectrum antibiotic coverage.[8]

Other causes of mortality in HI include respiratory distress related to underventilation and decreased chest expansion secondary to painful fissures and thickened keratinized skin.[3] Respiratory difficulties in patients with HI may be associated with dysfunction of the *ABCA12* transporter in the lung; however, there is one report conflicting this observation.[9,10]

The pathogenesis and presentation of harlequin ichthyosis may be more complex than solely a disorder of keratinization. Studies found that *ABCA12* may have more widespread function than previously recognized, including a role in immune regulation, secretion of antimicrobial peptides, and respiratory homeostasis. Neonates with HI are more susceptible to respiratory dysfunction and infections especially from pseudomonas aeruginosa. Although we do not suggest routine antibiotic prophylaxis in HI, we do recommend enhanced surveillance for infection with reduced threshold for intubation[11] and antibiotic coverage with treatment length similar to that of an immunocompromised patient.

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