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Case Report

A fatal case of Harlequin ichthyosis: Experience from low-resource setting

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Abstract

Harlequin ichthyosis is a severe and fatal presentation of ichthyosis with an autosomal recessive inheritance. Infants with Harlequin ichthyosis have a high mortality rate, and a dismal prognosis; therefore the majority of neonates die shortly after birth from infection, heat loss, dehydration, electrolytic imbalances, or respiratory distress. The aim of this case report was to present a fatal case of Harlequin ichthyosis with no family history of any inherited skin disorder. A 3-day-old baby was presented to the emergency room with congenital abnormalities at birth, fissured hyperkeratotic skin, and thick yellow plates of scales. The parents had no history of consanguineous marriage, no relevant past medical history, and no family history of the same condition. The patient was unwell, pulse 162 times/minute, respiratory rate 48 times/minute, and axillary temperature 36.9°C. APGAR score was 8 in the 1st minute and 9 in the 5th minute. Based on the typical clinical appearance, the patient was diagnosed with Harlequin ichthyosis. Due to a lack of facility, a mutation analysis was not carried out. The patient was then transferred to the neonatal intensive care unit (NICU) and treated in a humidified incubator and medicated with intravenous antibiotics (ampicillin sulbactam 125 mg/12 hour and gentamicin 13 mg/24 hour), topically fusidic acid and mild emollients. A central venous catheter was used for intravenous access. The poor prognosis resulted in the patient dying at the age of 5-day-old. This case highlights that prenatal diagnosis is critical for early detection and disease prevention. Mutation screening for the *ABCA12* gene is suggested for consanguinity marriages and with a history of ichthyosis.

Keywords: Harlequin ichthyosis, ichthyosis, hyperkeratotic, scales, *ABCA12*

Introduction

Harlequin ichthyosis (HI) is a severe and rare form of congenital ichthyosis [1]. This rare condition is autosomal recessive and has been observed in patients from a wide range of ethnic origins [2]. HI is caused by biallelic loss-of-function mutations in the adenosine-triphosphate-binding cassette (ABC) transporter gene (*ABCA12*) which is responsible for transferring ceramides and other lipids into lamellar bodies [2]. Infants with HI have a high mortality rate, and a dismal prognosis making the majority of neonates die shortly after birth from infection, heat loss, dehydration, electrolytic imbalances, or respiratory distress [3].

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HI affects one in every 300,000 newborns and approximately 100 cases have been documented worldwide [4]. This most extreme and distinct form of ichthyosis was described as early as 1750 by the Reverend Oliver Hart [2]. In 1900, Riecke recognized the histopathologic features of dramatic thickening of the stratum corneum and follicular hyperkeratosis and distinguished this disorder from other types of congenital ichthyosis [2]. HI has distinctive characteristics, including thickening of the stratum corneum in the form of hyperkeratosis scales separated by fissures and therefore the baby looks as it is wrapped in a thick membrane. Other abnormalities can also be found on the face such as eclabium, ectropion, flat nose, hypoplasia of the fingers and ears [1].

Some infants experience restricted respiration, require tube feeding, failure to thrive, and neonatal sepsis, which often leads to neonatal death [5]. Prenatal diagnosis is crucial for effective perinatal and postnatal care, as well as preparing parents for future pregnancies. Ultrasonography (USG), amniotic fluid, and umbilical cord blood molecular detection are the mainstays of prenatal diagnosis [3]. In children and adults, topical and systemic retinoids can be helpful in the management of ectropion and hyperkeratosis [5]. There's no cure for HI, so prenatal diagnosis becomes crucial to prevent the disease [6]. Herein, we present a fatal case of Harlequin ichthyosis in low-resouce setting with no family history of any inherited skin disorder.

Case

A 3-day-old boy baby was presented to the emergency room of Dr. Zainoel Abidin Hospital located in Banda Aceh, the western most Indonesian archipelago, with fissured hyperkeratotic skin, thick yellow plates of scales, and face and finger abnormalities. The patient was referred from the previous hospital due to congenital abnormalities at birth and requiring neonatal intensive care. The patient was the third child of three siblings, born at 40 weeks of gestation from a 34-year-old mother by section cesarean due to oligohydramnios. After delivery, the patient immediately cried with active movements (APGAR score of 8/9) and the birth weight was 2,500 grams. The patient was born with clear amniotic fluid, no history of fever and no history of dyspnea. The mother had done antenatal care with the midwife and obstetrician. USG examination was only performed twice during pregnancy, at 8th week and 20th week of pregnancy, and found no abnormalities. There was no history of fever, hypertension, or diabetes during pregnancy. In previous pregnancies, the mother had two other healthy normal children. The parents had no history of consanguineous marriage, no relevant past medical history, no family history of the condition, and denied any history of allergies and skin disorders.

The general condition of the patient was weak. Physical examination showed normocephalic, eversion of the eyelids (ectropion), eversion of the lips (eclabium), flattened nose, and hypoplasia of the ears. The facial skin was thick and flaky with a yellowish crust (**Figure 1A**). Extremities showed a bluish color in both hands and flexion of fingers (**Figure 1B**). Dermatological status reported fissured hyperkeratotic skin and thick yellow plates of scales. The skin was peeling off the whole body leaving erythematous fissures and a thickening skin covering that appeared partially cracked across the body. Deep reddish fissures were found all over the body with bleeding from the fissures (**Figure 1C**).

The pulse was pulse 162 times/minute, respiratory rate 48 times/minute, and axillary temperature 36.9^{o}C. Immediately after born, the patient was referred to the neonatal intensive care unit (NICU). Blood tests on admission showed hemoglobin 18.3 mmHg, platelets 194,000/mm^3, leukocytes 24.360/mm^3, hematocrit 48.7% and blood glucose 54 mg/dl. Based on the typical clinical appearance, the patient was diagnosed with HI and neonatal sepsis. Due to a lack of facilities, mutation analysis was not carried out.

The patient was given supportive therapy with an incubator in the NICU and fluid balance was monitored by calculating the fluid input and output. The patient was given formula milk for 10cc/3 hour via nasogastric tube feeding. The diaper was changed 3–4 times per day and was always full. The patient was treated by interdisciplinary team from neonatology, dermatology, ophthalmology, otorhinolaryngology, orthopedic, pediatric surgery, and plastic surgery departments.

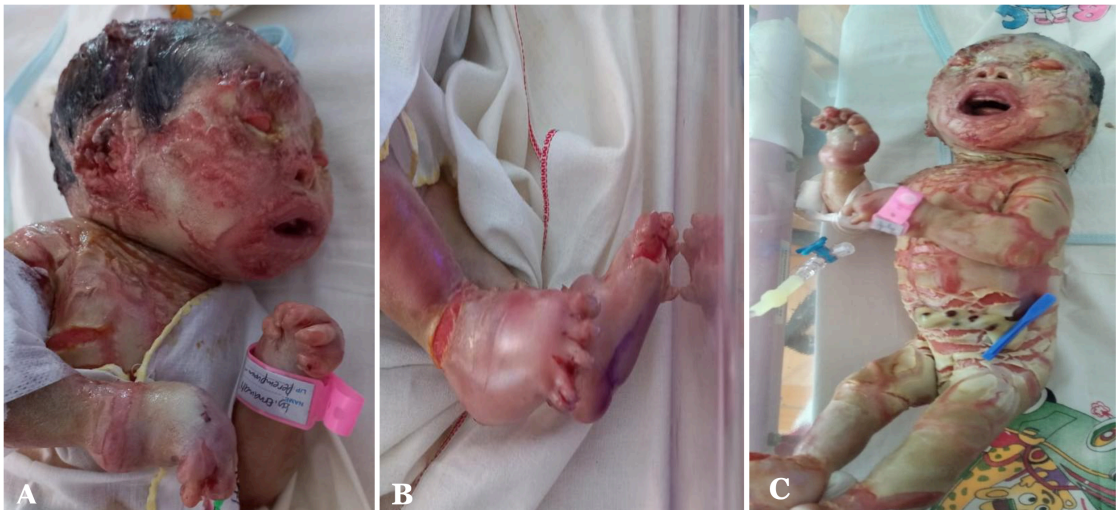

Figure 1. Clinical presentation of the patient. (A) Ectropion, eclabium, flattened nose, and hypoplasia ear. (B) Flexion of fingers. (C) Hyperkeratotic skin and deep reddish fissures all over the body.

A central venous catheter was used for intravenous access and intravenous fluids. Intravenous antibiotics were given (ampicillin sulbactam 125 mg/12 hour and gentamicin 13 mg/24 hour). The patient's whole body was compressed with normal saline twice a day for 30 minutes and white petrolatum emollient was applied four times a day immediately after wet wrap removal. The patient was also given topical fusidic acid in the fissures. Chloramphenicol eye ointment and artificial tears were given three times daily to treat ectropion, as recommended by the ophthalmology department. The patient unfortunately died at the age of 5 days mostly due to respiratory failure, fluid loss, and septicemia.

Discussion

HI is a rare and most severe form of ichthyosis and it is more common in consanguineous marriages, premature birth, and young pregnancies [7]. Vaginal delivery is possible, but in cases of high-risk pregnancies, cesarean section can be performed [8,9]. In this case, the mother of the patient underwent a cesarean section due to oligohydramnios, a condition where the volume of amniotic fluid is less than the minimum amount expected for gestational age. HI is anticipated to reoccur in 25% of subsequent pregnancies [10]. As a result, it is important to inform the parents about the genetic condition and the likelihood of their next conception.

There is a wide range of HI-related symptoms and some of the most noticeable and apparent symptoms are brown or white skin, grooved or cracked (fissures), eclabium, ectropion, nasal hypoplasia, lack of external ears, scant scalp hair, short limbs, hypoplastic fingers, and complete absence of eyebrows and eyelashes [1]. These deep and vividly red fissures enhanced the transcutaneous loss of water and heat, resulting in dehydration, electrolyte imbalances, and temperature instability [3]. Furthermore, newborns suffer from hypoglycemia, infections, sepsis, insufficient feeding habits, renal failure, and, more frequently, respiratory difficulties as a result of limited chest expansion and skeletal abnormalities, which can lead to death in the first few days of life [11,12]. All of these clinical symptoms were presented in the patient suggested the presence of HI.

Studies have found that polymorphism in the *ABCA12* gene that codes for a protein involved in lipid transport in the skin, is involved in the disease's pathogenesis [13,14]. The *ABCA12* gene on chromosome 2 encodes a protein involved in keratinocyte lipid transport across the skin's epidermis, which aids in skin formation and controls the development of desquamation. The inability of ABCA12 to transfer lipids from the cytosol to the lamellar granules leads to impaired skin permeability and scale formation [13,14].

The first step toward early disease detection would be prenatal diagnosis. As a result, establishing the family history, consanguinity between the parents, and the existence of other skin diseases in offspring would be extremely beneficial for early disease detection. A microscopic

study of amniotic fluid cells and USG for fetal mouth shape assessment at 17 weeks of pregnancy may be effective for early detection [7]. Prenatal diagnosis via skin biopsy at 24 weeks of pregnancy is also possible, especially in families with a history of HI. Although USG can be useful in some circumstances, it may not be appropriate due to delayed phenotypic expression and the disease's rarity [13,15]. Furthermore, for patients with HI history, *ABCA12* sequence analysis should be performed first and many cases are missed by those without a family history [3]. In our case there was no abnormalities observed on USG examination at 8 and 20 weeks of pregnancy. Hence, the fetus's external appearance is frequently insufficient for diagnosis.

The first step in treatment is to stabilize the patient's airway, breathing, and circulation. Effective management necessitates aggressive and supportive care from an interdisciplinary team [1]. Infants should be monitored in the NICU, kept in humidified incubators, and treated topically with light emollients. To avoid subsequent bacterial infection, broad-spectrum antibiotics should be administered [1,2]. More HI patients have experienced prolonged survival during the past two decades due to better postnatal care and oral retinoid therapy. Early administration of systemic retinoids, in particular acitretin, usually is given with an initial dose of 1 mg/kg/day [2]. Treatment with systemic retinoids during the newborn period can facilitate desquamation of the membrane and is associated with improved outcomes [5]. A study found that early oral retinoids aided in the shedding of hyperkeratotic scales in a comprehensive case series of 45 patients, with an overall survival rate of more than 50% [16]. However, they are only used in severe cases due to their known toxicity and side effects [6]. Since systemic retinoids were not available at Dr. Zainoel Abidin Hospital, supportive therapies such as liquid, intravenous and topical antibiotics, emollient, and ophthalmologic care were given to control the disease. The patient died at the age of 5 days, probably because of neonatal complications such as respiratory failure, fluid loss, and septicemia.

Conclusion

HI is a rare genetic skin disorder with a poor prognosis that causes a high mortality rate. Prenatal diagnosis of HI, mostly by sonographic techniques, is critical for early detection and disease prevention. We suggest that mutation screening for the *ABCA12* gene and genetic counselling for families, particularly those with consanguinity marriages, would be beneficial.

Ethics approval

The father of the patient provided written informed consent to be published as a case report.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

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