Congenital harlequin ichthyosis: A rare case report and literature review

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ABSTRACT

Harlequin ichthyosis is an extremely rare congenital genetic disorder. One of the most prominent features is the severe thickening and scales of newborn skin covering the whole body surface. Here, we report the case of a 31-year-old woman admitted to the maternity emergency unit due to labor pains, with no remarkable history or previous ultrasound examination. A baby boy was born with typical findings of harlequin ichthyosis and clinical diagnosis was made. Despite treatment, the newborn died on the third day. The purpose of this report is to share our experience in managing this rare case and to increase awareness of the severity of the disease.

Keywords: *Congenital, Harlequin ichthyosis, Ichthyosiform erythroderma, Lamellar.*

Harlequin ichthyosis (HI) is a rare genetic skin disorder that is the most severe of all congenital ichthyosis [1]. The word ichthyosis itself is derived from the Greek word "ichthys" which means fish, referring to the skin with fish-scale-like appearance [2]. The reported incidence is relatively low, occurring 1 in 300,000 live births [1]. However, it poses a high rate of natal mortality [3]. Its mode of inheritance is autosomal recessive with a 25% chance of recurring in subsequent pregnancies [4].

There are still few reports on this case with most affected neonates not being able to survive beyond the first few days of life. To date, there is no definite cure but merely supportive treatment in order to prolong a newborn's life [1,2]. The rationale of this case report is to share our experience and comprehensively review the proper management of this rare case. Through increased awareness, hopefully, better treatment can be provided in other health facilities.

CASE REPORT

A 31-year-old woman, 35 weeks gestation with gravida 1, para 0, live 0, came with labor pains to maternity emergency unit at our primary facility hospital. The pregnancy was not due to a consanguinous relationship, with no history of previous miscarriage. The mother is healthy with no previous history of illness or intake of drugs and noted no relevant issues during pregnancy. The father is a healthy 35-year-old man with no previous history of illness as well. There is no known history of genetic anomalies, skin disorders, or any genetic conditions inherited in both the paternal and maternal side. Due to low socioeconomic status and low education background, she had only undergone antenatal check-up once during the beginning of pregnancy with a local midwife. She never had any previous ultrasound examination performed.

A caesarean section was done and a baby boy weighing 2600 grams was delivered. The infant had APGAR scores of 9 at 1 minute and 9 at 5 minutes. At birth, he was covered with thick vernix which on removal revealed layers of widespread yellowish scales. Between these scales was fissured skin which was more prominent in flexures. Scalp hair was evident; however, the eyes, eyebrow, and eyelashes were undeveloped and ectropion was present. The infant's mouth was persistently open with the traction of the lips causing eclabium. The nose and ears were hypoplastic with undeveloped orifices. Limited body movements were present, as all extremities were semi-flexed in a rigid manner (Fig. 1).

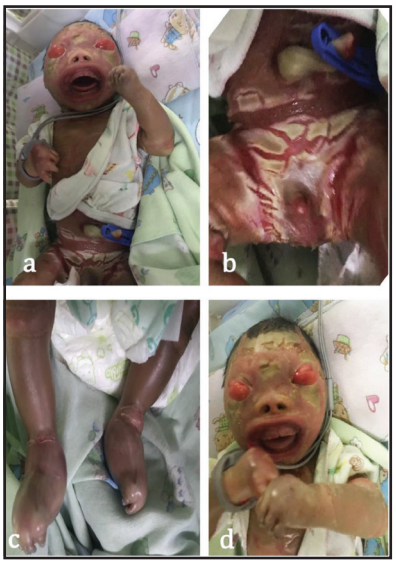

Figure 1: Showing features of (a) thick white scale and fissure with flexion deformity of the hands (b) patent orifice (c) undeveloped extremity (d) ectropion and eclabium of the mouth.

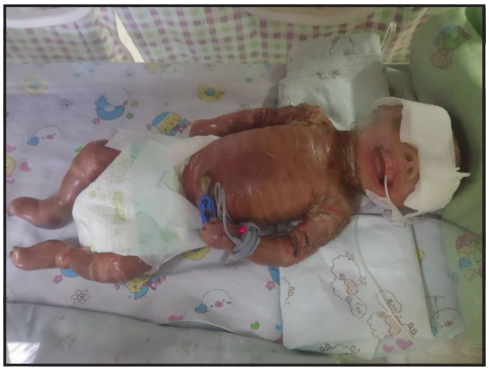

Figure 2: Presentation at day 2 with shredding of the skin.

Based on typical findings of the patient's impaired skin barrier function as prominently shown by the hyperkeratoses and scales over the whole body surface area, a clinical diagnosis of Harlequin ichthyosis was made by a pediatrician. While waiting for referral hospital availability, the baby was kept in an incubator at the neonatal intensive care unit (NICU). Vital signs were normal with vesicular breathing.

Supportive management was given. The patient was started on intravenous fluids and antibiotics, nasogastric feeding, as well as continuous positive airway pressure (CPAP). The patient was given cefotaxime 150 mg IV twice daily and gentamycin 15 mg IV once daily. The skin surface was cleansed with clean gauze pads and applied with topical gentamycin cream and vaseline petroleum gel every two to three hours. Treatment continued for two days with a slight improvement seen where the thick scales and creases have slowly shredded (Fig. 2). However, despite our efforts, the baby died on the third day of life from respiratory distress. The parents were counseled about the condition and advised to undergo genetic counseling for future pregnancies.

DISCUSSION

The first reported case of harlequin ichthyosis was discovered on 1750 by Reverend Oliver Hart [4]. The term "harlequin" refers to the character named Harlequin from an Italian theater, which depicts a person with a chequered costume [2]. Harlequin ichthyosis itself is among one of the three subtypes of autosomal recessive congenital ichthyoses [5]. The two other types, namely congenital ichthyosiform erythroderma and lamellar ichthyosis, were less severe than HI [5]. The mortality rate of HI is high and approaching 50% [5]. Age of infant's death may range from day one up to day 52 [6].

It has been found that HI is caused by an autosomal recessive mutation in the ABCA12 gene [2]. Due to the rare nature of this disease, no data is available regarding the predilection of HI on race and gender. However, a study reported that higher numbers are found in cultures with the practice of parental consanguinity [2,5]. This is evident by the high incidence in Pakistani and Arab population with parents who were first cousins [5]. Further analyses found that genetic mutation on the ABCA12 allele was higher in those groups [5].

A proposed etiology in HI is due to the altered lipid transport coming from mutation of the ABCA12 gene on chromosome 2 [4,7]. This gene plays a critical role in the coding of membrane-based lipid transporter protein, the lamellar granules [8]. In individuals with normal ABCA12, lipids are transported into the lamellar granules which will then be secreted into the intercellular space to form the lipid layers of epidermal barrier [9]. A disruption in this process causes no lipids to be transported and secreted, leading to a collapsed epidermal barrier [9]. The deformed lipid layers will consequently alter the normal lipid composition, leading to impaired differentiation of keratinocytes or hyperkeratosis [7]. Disrupted epidermal barrier function will also compensate itself by hyperkeratosis, thus making up the features of the HI phenotype [9]. With the loss of protective epidermal barrier, deposition of scales or dead skin is impaired, making it more hyperkeratotic and susceptible to infection [4].

There are very typical clinical features of this disorder. Neonates born with HI present with profound hyperkeratotic appearance as evident in the thick white scales and deep erythematous diamond-shaped scales [4]. The facial region may mimic a clown-like appearance with large open mouth, eclabium, flattened nose, rigid flexion deformity in the hands and feet, and bilateral ectropion [2,10]. Due to the hyperkeratotic skin, the nares seem anteverted and ears are lacking retroaural folds [5]. Moreover, the hyperkeratotic skin forms a constriction band which hinders the chest movement and leads to respiratory failure [3], a common cause of death as evident in our case. A study also reported that generalized lack of hair growth is present in 64% of cases [5]. Although the patient in our case had scalp hair, in other cases this was often only limited to occipital region subsequent with declining hair margins [8].

Besides the orofacial manifestations, neonates with HI also present with ophthalmological, gastrointestinal, and neurological problems, amongst others [6]. Due to the prominent ectropion, exposure keratitis and further corneal scarring may develop [9]. Regarding the nutrition intake, newborns who were able to survive longer were found to be more likely to have chronic constipation, gastroesophageal reflux, and growth deficiency [5]. This also impairs neurological development, as evident in survivors who show significantly delayed developmental milestones [5].

Prenatal diagnosis particularly 3-dimension ultrasonography is the first step for early diagnosis in the absence of previous history [4]. Most of the cases can be diagnosed as early as the 17th week of gestation or immediately after birth [8]. Findings on ultrasound may reveal typical HI features with an absence of ear, abnormal facial dysmorphism, thick skin and limited fetal movement with stiff extremities [8]. Other associated findings are intrauterine growth restriction, polyhydramnios, and increased echogenicity of the amniotic fluid [11]. However, a late phenotypic expression may pose a challenge for early diagnosis through ultrasound [11]. DNA testing for mutation in ABCA12 gene provides a more conclusive aid in diagnosis [8]. Other useful modalities include fetal skin biopsy at the 18th week of gestation to look for

abnormal lamellar granules, as well as chorionic villous sampling and amniocentesis [1,8].

The principles of treatment involve supportive and multidisciplinary management. Newborns are placed in a humidified incubator to minimize transcutaneous water loss, appropriate infection control with intravenous antibiotics and maintenance of intake [12]. The skin surface must be cared for with hourly emollient application andtwo hourly eye lubrication [13]. In cases where ischemia develops due to constriction bands, a definitive surgical escharotomy must be performed to release [3]. A study recommended this intervention to avoid the complication of ischemic autoamputation [3]. Another case series of 45 patients showed that acitretin, an oral retinoid, is proven efficient to shed the hyperkeratosis and increase survival [1,5]. However, acitretin may not be widely available particularly in developing countries.

This severe chronic disease poses a high risk of patients developing dehydration, supervening infection as well as respiratory failure [2]. Although the prognosis is very poor and most affected neonates do not survive more than one week, however, survival rate may still depend on the severity of the condition [5,12]. It is very crucial for parents to be well informed that there is a 25% risk of recurrence in the next offspring, and that genetic counseling and prenatal diagnosis are truly necessary [8].

CONCLUSION

There is no definite cure from this congenital disease, but early prenatal diagnosis can be made, complications can be prevented and managed comprehensively, although certain therapy may be limited in developing countries. Harlequin ichthyosis has high morbidity and mortality soon after birth. It is important to know that even surviving newborns may still develop severe complications in the long-term, as well as other delayed developmental milestones.

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