Open Access

OBM Genetics

Case Report

A Case of Harlequin Ichthyosis: Improvement Survival Rate with Early Isotretinoin Therapy

Hanny Tanasal [1, *], Iline Michaela [1], Retno Danarti [2]

1. Dr. M. Haulussy Hospital, Ambon, Indonesia; E-Mails: handew70@yahoo.com; ilinemichaela@yahoo.com
2. Department of Dermatology and Venereology, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia; E-Mail: danarti@ugm.ac.id

* **Correspondence:** Hanny Tanasal; E-Mail: handew70@yahoo.com

Academic Editor: Fabrizio Stasolla

Collection: Rare Genetic Syndromes: From Diagnosis to Treatment

OBM Genetics
2025, volume 9, issue 1
doi:10.21926/obm.genet.2501281

Received: October 28, 2024
Accepted: December 20, 2024
Published: January 08, 2025

Abstract

Harlequin ichthyosis (HI) is among the most severe hereditary skin conditions of autosomal recessive congenital ichthyosis (ARCI) in newborns, associated with a mutation of the *ABCA12* gene. Patients have a typical clinical appearance at birth. A thick layer of armor-like scales covers the entire body. Affected newborns have abnormal facial features, such as ectropion, eclabium, and ears and nose flattening. Although HI was formerly assumed to be fatal, more intensive neonatal care and early retinoid therapy may improve the patients' survival rates. This case report aims to present a case of a 5-year-old boy born with HI who survived with isotretinoin treatment since day 5 of life. Despite advances in medical care, HI remains a challenging condition with an abnormality that lasts a lifetime and can lead to a variety of medical difficulties following birth.

Keywords

Harlequin ichthyosis; isotretinoin; quality of life

1. Introduction

Harlequin ichthyosis (HI) is the most severe form of congenital ichthyosiform erythroderma, a group of disorders marked by widespread erythema and scaling. Hyperkeratosis and aberrant skin desquamation are the hallmarks of this potentially fatal dermatologic disease. The condition is linked to a mutation in the *ABCA12* gene located on chromosome 2q35, essential for lipid transport and skin barrier function [1]. It appears at birth as coarse, massive plate-like scales with deep fissures, severe ectropion, eclabium, and joint contractures, causing significant impairment in critical processes such as breathing, feeding, and thermoregulation [1]. These deep, red cracks accelerated transcutaneous fluid and heat loss, causing dehydration, electrolyte imbalance, and temperature instability [2]. There has been a high early mortality rate in newborns with HI. They may suffer from hypoglycemia, infection, sepsis, improper feeding habits, renal failure, and often respiratory distress due to restricted chest expansion and skeletal abnormalities, which can lead to death within the first few days of life [2-5]. The most prevalent causes of death for these patients are sepsis, respiratory failure, and electrolyte problems. They need critical care treatment to increase their chances of survival [6]. Improved newborn care and early administration of systemic retinoids may lead to a better outcome [5, 7].

Patients who survive the neonatal period will have chronic ichthyosiform erythroderma for the remainder of their life. We present the case of a 5-year-old boy with the condition who has been treated with isotretinoin since day five of life.

2. Case Report

A male neonate was delivered at 36 weeks of pregnancy with an unusual and distinctive appearance. The patient is the third child with no family history of the same condition. The parents had no history of consanguineous marriage and no significant medical history. During her past pregnancies, the mother had two other children who were both healthy and normal.

Physical examination showed thick, hyperkeratotic scales resembling plates on his body, extremities, head, deep cracks, significant eclabium, and bilateral ectropion. Furthermore, his ears and nose were poorly formed and flattened. The fingers and toes are fused and wrapped in skin (Figure 1). A diagnosis of harlequin ichthyosis was clinically determined, and supportive treatment was promptly initiated.

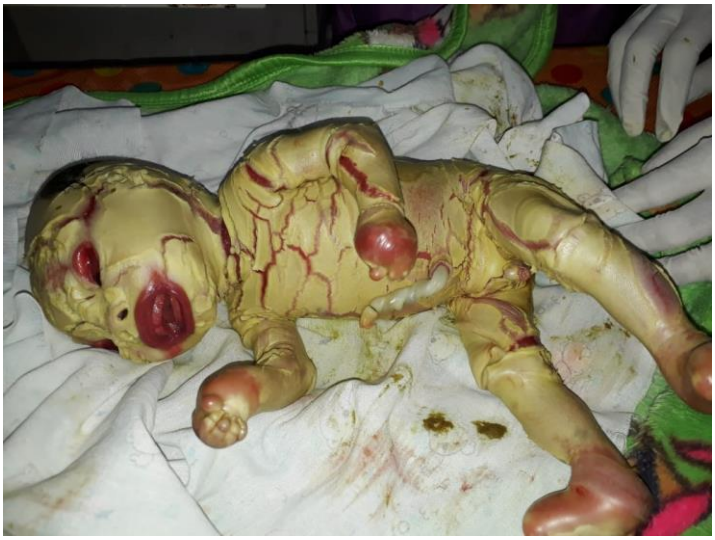

Figure 1 On day one of birth, the patient's trunk, extremities, and head were covered with thick, hyperkeratotic plate-like scales with deep fissures, significant eclabium, and bilateral ectropion. He had poorly developed and flattened ears and nose. The fingers and toes are fused and covered in skin.

The pediatric team evaluated and transferred him to the neonatal intensive care unit (NICU). The patient was given comprehensive, intensive care, placed in an incubator to prevent hypothermia, and treated with topical moisturizer. An ophthalmologist was asked for advice and prescribed eye lubricant ointment every three hours. He initially received total parenteral nutrition but was later transitioned to oral tube feeding using breast milk.

Administration of systemic retinoid (Isotretinoin) (1 mg/kg/day in two doses) began within the first five days after birth, followed by a reduced dose of 0.5 mg/kg/day and a one-month break from isotretinoin. The same dose was then adjusted to three times per week and maintained at that level. The patient temporarily discontinued isotretinoin for one month at the age of 4 due to financial constraints but later resumed treatment at the minimal dose. He tolerated the medication well. Liver function tests were supervised and showed a typical progression. In the subsequent assessment, there was an improvement in eclabium and significant improvement in skin findings, but unfortunately, ectropion remains persistent. Following a three-month treatment, he was released from the hospital and received care from his family while still attending follow-up appointments at the hospital. No issues were noted during the patient follow-up.

The patient is five years old, with a current weight of 12 kilograms, height of 96 cm, and head circumference of 50.5 cm; the patient’s psychomotor development is age-appropriate, with no observed delays or abnormalities, and he will enter a public school. His skin is reddish with generalized scaling or ichthyosiform erythroderma, he has bilateral ectropion, eyebrow and eyelash alopecia, and hypoplastic ears (Figure 2). However, despite his hypoplastic pinnae, his hearing is normal. Due to the known risks of ectropion and other ocular complications associated with harlequin ichthyosis, an ophthalmologist regularly monitors the patient. Preventative measures, such as lubricating eye drops, have been implemented to maintain corneal health. His fingers remained bent, and a finger was missing. Because it doesn't produce sweat, the scalp often can't stand the heat. The dermatological regimen is ongoing and provides the patient with a quality of

life far exceeding that expected at birth. There are concerns regarding the long-term risks of ongoing isotretinoin treatment, but the treatment was well tolerated in this case.

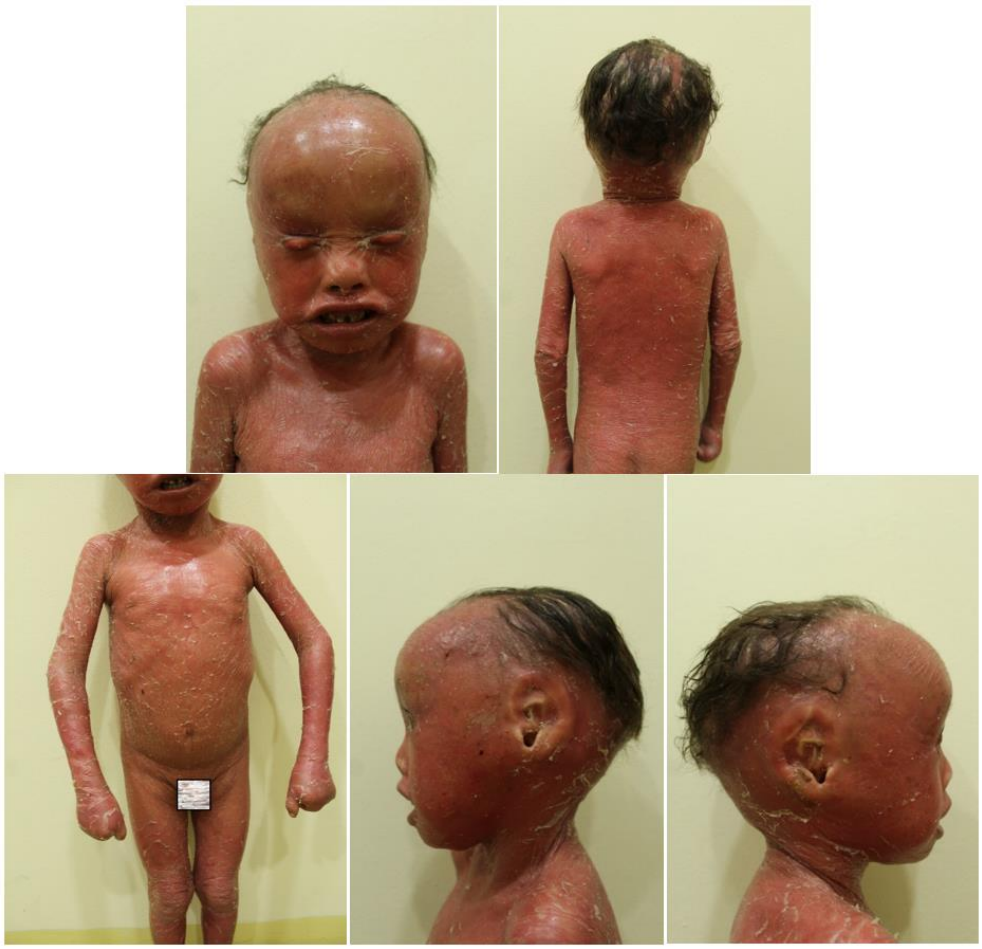

Figure 2 At 4-year and 9-month, the patient has a persistent ichthyosis with fine scale and erythroderma with ectropion and eclabium.

3. Discussion

Harlequin ichthyosis (HI) is the most serious type of autosomal recessive congenital ichthyosis, resulting from mutations in the *ABCA12* gene, which creates the adenosine triphosphate-binding cassette (ABC) transporter responsible for the skin conditions. We did not perform a genetic investigation to confirm ABCA12 mutations, as this test is unavailable in our region. However, the clinical presentation strongly supports a diagnosis of harlequin ichthyosis. While genetic testing would have provided additional confirmation, the diagnosis and treatment were based on the clinical phenotype and established guidelines for managing this condition.

At birth, it presents with severe ectropion, eclabium, flattened ears, and large, thick, plate-like scales on the entire body [1]. The ATP-binding cassette gene plays a role in lipid transport within and between skin keratinocytes, and when missing or not working correctly, it leads to a compromised epidermal barrier. This results in impaired lipid transport, intracellular accumulation of glucosylceramide, epidermal hyperplasia, abnormal desquamation, and secondary inflammation seen in harlequin ichthyosis [1].

The disease affects nearly 1 in 300,000 live births, with around 100 cases have been documented worldwide [8]. Infants suffering from this condition have impaired protective function and are at higher risk of infection. Most of the newborns pass away shortly after birth due to disease, heat loss, dehydration, electrolyte imbalance, or respiratory distress [2]. However, more HI patients have had extended lifespans over the last twenty years due to improved postnatal treatment and oral retinoid therapy. There is a report of a survivor now age 12 years in the United Kingdom who has been treated with long-term oral retinoids, and it is accepted that though they carry a risk of skeletal toxicity and teratogenicity, the risks are outweighed by the significant benefits in terms of improved survival and quality of life [9]. Systemic retinoids can be utilized early in life to speed up this change in clinical symptoms. They could reduce mortality as they promote keratinocytes, keratinocyte differentiation, and sloughing off the thick hyperkeratotic layer. These drugs may also possess a property that reduces inflammations by interacting with neutrophils to regulate their activation and function [10].

Our patient displayed typical signs of HI, including thick, hyperkeratotic plate-like scales on his body, extremities, and head, deep fissures, marked eclabium, and bilateral ectropion. The initial administration of systemic retinoids has been crucial for saving his life, and he responded well to isotretinoin. Isotretinoin was chosen over acitretin primarily due to the unavailability of acitretin in our region. Systemic retinoids are proven to aid in shedding hyperkeratotic plaques and can enhance digital and thoracic restrictions, resulting in better breathing and movement capabilities [11].

It is advised to use the lowest effective dose of oral retinoid (usually 1 mg/kg/day or less) due to its potential side effects on the skin and other body parts [12]. While numerous patients have been prescribed systemic retinoids for many years, there have not been any extended prospective studies to explain the proper dosage for long-term treatment. The long-term use of retinoids can impact other organ systems, potentially leading to increased bone abnormalities such as osteoporosis and osteophyte formation and the risk of early closure of growth plates in children. The impact of these bone effects seems to rely on the amount and length of time [13]. Apart from the negative implications for bones, there doesn't seem to be any link between toxicity and how long the medication is used [12]. Our patient responded more positively to a combination of emollients and supportive measures. The main benefits of emollients include their effectiveness in enhancing epidermal structure and barrier function. Unfortunately, the illness may persist throughout life.

4. Conclusion

While previously seen as incurable, HI can now be treated more successfully in newborns with aggressive treatment and early retinoid therapy, leading to enhanced survival rates and improved quality of life for survivors. Limitations include long-term use of retinoids, which could cause potential harm to internal organs. Nevertheless, further research is needed to offer safer treatment alternatives.

Prompt diagnosis is crucial for the patient and their family. Implementing the team of Doctors' management plan, including pediatrics, dermatologist, and ophthalmologist, is crucial for enhancing the survival and quality of life of HI patients. Positive outcomes are achieved through active family participation and meticulous management, as significant recovery requires a long period of time.

Providing counseling to parents is crucial in preventing children from rejecting or bullying others at school, taking into account the child's age.

Author Contributions

Hanny Tanasal collected patient data, prepared the case report manuscript, assisted with clinical data interpretation, critically revised the manuscript for intellectual content, and reviewed and approved the final version for publication. Iline Michaela contributed to the interpretation of clinical data, assisted in drafting the manuscript, critically revised the manuscript for intellectual content, finalised and approved the final version for publication; Retno Danarti was responsible for providing oversight and guidance in case report preparation, assisting in interpreting clinical data, critically revising the manuscript for intellectual content, finalising and approving the manuscript for submission.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Tsivilika M, Kavvadas D, Karachrysafi S, Sioga A, Papamitsou T. Management of harlequin ichthyosis: A brief review of the recent literature. Children. 2022; 9: 893.
2. Zhou Y, Li L, Wang L, Zhang C. Prenatal diagnosis of a rare variant of harlequin ichthyosis with literature review. BMC Med Imaging. 2021; 21: 56.
3. Tahir A, Tariq SM, Haider SA, Hasan M. Ichthyosis congenita, harlequin type: A fatal case report. Cureus. 2018; 10: e3524.
4. Shahada O, Kurdi A. Harlequin ichthyosis: A fatal case report in Al-Medina, Saudi Arabia. Cureus. 2022; 14: e23533.
5. Vella V, Maulida M, Earlia N, Hidayati A, Handriani R, Gondokaryono SP, et al. A fatal case of harlequin ichthyosis: Experience from low-resource setting. Narra J. 2023; 3: e302.
6. Glick JB, Craiglow BG, Choate KA, Kato H, Fleming RE, Siegfried E, et al. Improved management of harlequin ichthyosis with advances in neonatal intensive care. Pediatrics. 2017; 139: e20161003.
7. Rajpopat S, Moss C, Mellerio J, Vahlquist A, Gånemo A, Hellstrom-Pigg M, et al. Harlequin ichthyosis: A review of clinical and molecular findings in 45 cases. AMA Arch Derm. 2011; 147: 681-686.
8. Shrestha AB, Biswas P, Shrestha S, Riyaz R, Nawaz MH, Shrestha S, et al. Harlequin ichthyosis: A case report and literature review. Clin Case Rep. 2022; 10: e6709.
9. Heap J, Judge M, Padmakumar B. Harlequin ichthyosis from birth to 12 years. BMJ Case Rep. 2020; 13: e235225.
10. Nelson AM, Zhao W, Gilliland KL, Zaenglein AL, Liu W, Thiboutot DM. Neutrophil gelatinase-associated lipocalin mediates 13-cis retinoic acid-induced apoptosis of human sebaceous gland cells. J Clin Invest. 2008; 118: 1468-1478.
11. Elkhatib AM, Omar M. Ichthyosis fetalis. StatPearls. Treasure Island, FL: StatPearls Publishing; 2024.

12. Zaenglein AL, Levy ML, Stefanko NS, Benjamin LT, Bruckner AL, Choate K, et al. Consensus recommendations for the use of retinoids in ichthyosis and other disorders of cornification in children and adolescents. Pediatr Dermatol. 2021; 38: 164-180.
13. Zaenglein AL, Levy ML, Stefanko NS, Benjamin LT, Bruckner AL, Choate K, et al. Executive summary: Consensus recommendations for the use of retinoids in ichthyosis and other disorders of cornification in children and adolescents. J Am Acad Dermatol. 2022; 86: 158-161.