Clinical and Experimental Dermatology and Therapies

OPEN ACCESS

Akasaka E, et al. Clin Exp Dermatol Ther 8: 205.

www.doi.org/10.29011/2575-8268.100205

www.gavinpublishers.com

GAVIN PUBLISHERS

Case Report

A Case of Epidermolytic Ichthyosis with Massive Hyperkeratosis Successfully Treated with Systemic Etretinate

Eijiro Akasaka[1*], Toshihide Akasaka[2], Michiyo Nakagawa[2], Hajime Nakano[1], Daisuke Sawamura[1]

[1]Department of Dermatology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

[2]Department of Dermatology, Iwate Medical University, Morioka, Japan

[*]**Corresponding author:** Eijiro Akasaka, Department of Dermatology, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki 036-5268, Japan

Citation: Akasaka E, Akasaka T, Nakagawa M, Nakano H, Sawamura D (2023) A Case of Epidermolytic Ichthyosis with Massive Hyperkeratosis Successfully Treated with Systemic Etretinate. Clin Exp Dermatol Ther 8: 205. DOI:10.29011/2575-8268.100205

Received Date: 06 March 2023; **Accepted Date:** 15 March 2023; **Published Date:** 20 March 2023

Abstract

A 2-day-old female infant was referred to our department because of diffuse erythema, blistering, and denuded skin over the body. Her skin had decreased blistering, however, diffuse erythema with scaling became more prominent with age. Histopathology showed marked orthohyperkeratosis and acanthosis accompanied by granular degeneration. Mutational analysis for KRT10 revealed a previously reported variant, c.467G>A (p.Arg156His) in the heterozygous state. Taken together, the diagnosis of Epidermolytic Ichthyosis (EI) caused by a KRT10 variant was confirmed. Oral retinoids dramatically decreased the hyperkeratosis. Among reported cases of EI caused by mutations in KRT10, the most frequent mutation is Arg156His. Most patients with EI reported in the literature with mutations at Arg156 have a severe phenotype. This arginine residue and the surrounding residues are conserved in all type I keratins throughout evolution. These findings suggest that the arginine residue is structurally critical to the formation of the keratin filament network. In patients with EI, epidermal barrier function is decreased, indicating that the phenotype of EI can result from not only aberrant keratinization but also mutational skin barrier defects. Etretinate is a retinoid that encourages desquamation and can induce prompt keratinization. It has been reported that retinoid therapy is much more effective in patients with KRT10 mutations compared to those with KRT1 mutations. In addition, EI patients with more extensive involvement benefit more from retinoids than those with mild or limited involvement. Therefore, retinoid should be considered as the first therapeutic option for severe EI and EI caused by KRT10 mutations.

Keywords: Ichthyosis; Epidermolytic Ichthyosis; Keratin 10; Etretinate

Introduction

Epidermolytic Ichthyosis (EI) is the most prevalent keratinopathic ichthyosis caused by mutations in KRT1 or KRT10 in an autosomal dominant manner [1]. Patients with EI show blisters and erythema at birth, which alleviates with age, and generalized epidermolytic hyperkeratosis in adulthood with the distinctive histopathology of intracellular vacuolization, clumping of tonofilaments, and formation of small intraepidermal blisters. Epidermolytic palmoplantar keratoderma is observed mainly in patients with mutations in KRT1. Although treatment options for EI are limited, systemic retinoid is widely used for the treatment of inherited ichthyosis including EI. However, the efficacy and the possible working mechanisms in EI are not fully elucidated. Here, we report a case of a patient of EI with KRT10 mutation, who was successfully treated with systemic etretinate and discussed the underlying pathomechanisms and other possible treatment options in this manuscript.

Case Report

A 2-day-old female infant presented to the department of dermatology at Iwate Medical University with diffuse erythema over the entire body. She was born at term after an uneventful pregnancy as the first daughter of healthy non-consanguineous parents. There was no known family history of skin disease. She presented with diffuse erythema, blistering, and denuded skin over the body without palmoplantar involvement. At 3 months of age, her skin had decreased blistering. However, diffuse mild erythema with massive scaling and hyperkeratosis became more prominent and some areas of denuded skin were still observed (Figure 1a and 1b). Histopathology of a specimen obtained from the skin of the left leg showed marked orthohyperkeratosis and acanthosis accompanied by granular degeneration of the cells in the spinous and granular layers (Figure 1c). After obtaining written informed consent, mutational analysis for KRT10 was performed. The genetic test was approved by the ethics committee of the Hirosaki University Graduate School of Medicine (approval number, 2020-16-6). It revealed a previously reported variant, a G to A transition at nucleotide position 467 (c.467G>A) in the heterozygous state, which was predicted to result in an arginine to histidine substitution at amino acid 156, designated as p.Arg156His (Figure 1d). Taken together, the diagnosis of Epidermolytic Ichthyosis (EI) caused by a KRT10 variant was confirmed.

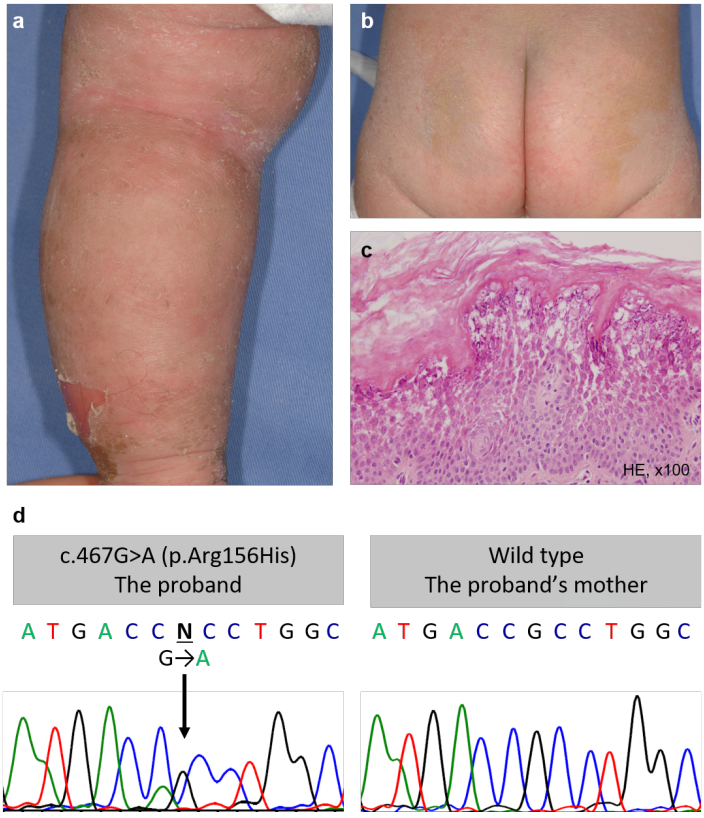

Figure 1: Clinical manifestation in the flexure crease of the (a) left lower leg and (b) buttocks at 3 months of age. Mild erythema with massive scaling and hyperkeratosis were prominent. (c) Histopathology of the skin. Marked hyperkeratosis and acanthosis accompanied by granular degeneration. (Hematoxylin-eosin (HE) stain; original magnification: ×100). (d) Mutational analysis for *KRT10*. A variant c.467G>A (p.Arg156His) was detected in the heterozygous state in the proband. Left, Proband; Left, Healthy control (Proband's mother).

She was treated with topical keratolytic agents such as salicylic acid ointment. However, hyperkeratosis and scaling gradually worsened, resulting in a typical corrugated cardboard-like appearance, especially on the anterior neck, dorsum of the hands and feet, knees, elbows, and abdomen (Figure 2a and 2b). At the age of 12 years, she began treatment with oral retinoids (etretinate 1.0 mg/kg/day), which dramatically decreased the hyperkeratosis associated with minor cutaneous adverse effects such as desquamation of palms and lips (Figure 2c and 2d).

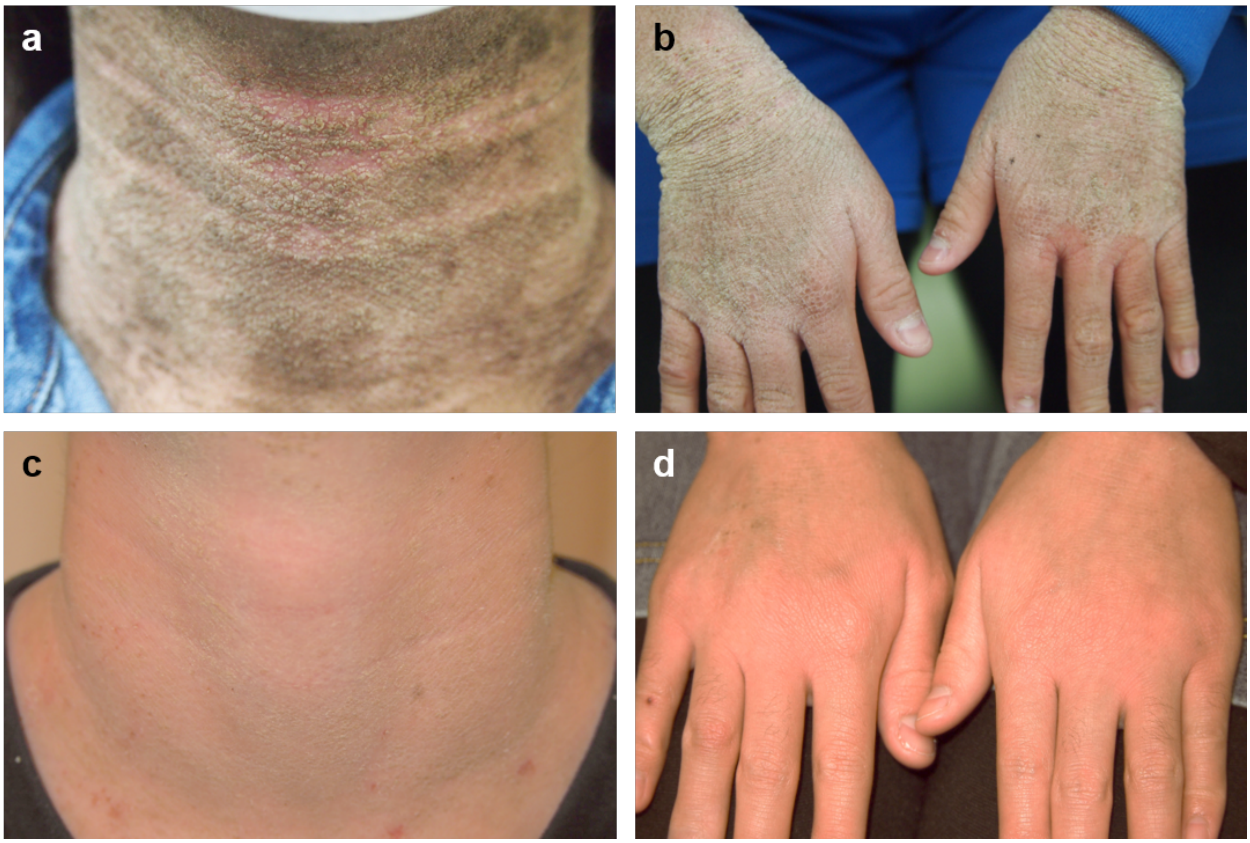

Figure 2: (a), (b) Clinical manifestations in the anterior neck and the dorsum of the hands at 12 years of age. There was hyperkeratosis with a corrugated cardboard-like or cobblestone-like appearance. (c), (d) Oral etretinate dramatically decreased the hyperkeratosis.

Discussion

In EI, genotype-phenotype relationships largely depend on the location of the mutation. In severe cases, mutations in KRT1 or KRT10 are located in the highly conserved helix initiation and termination peptides or the nonhelical H1 domain [1]. Among 121 reported cases of EI caused by mutations in KRT10, the most frequent mutation is Arg156His (35/121, 29%) (Human Intermediate Filament Database, http://www.interfil.org). Arg156 is a "hot spot" in KRT10; mutations at this location account for 47% (57/121) of all reported mutations, including the replacement of arginine by histidine as well as cysteine, proline, serine, leucine, or glycine. Most patients with EI reported in the literature with Arg156 mutations have a severe phenotype, regardless of the substituted amino acid (Human Intermediate Filament Database, http://www.interfil.org). In addition, Arg156 is conserved in all type I keratins. For example, patients with epidermolysis bullosa simplex with Arg125His in KRT14, analogous to Arg156His in KRT10, reportedly have severe phenotypes [2]. Furthermore, Arg156 and surrounding residues are also conserved throughout evolution. These findings suggest that the arginine residue is structurally critical to the formation of the keratin filament network.

In patients with EI, normal keratinization is perturbed. Thus, epidermal barrier function is decreased, indicating that the phenotype of EI can result from not only aberrant keratinization but also skin barrier defects. Etretinate is a retinoid that has a keratolytic effect; it encourages desquamation and can induce prompt keratinization. In the present patient, oral etretinate dramatically decreased the devastating hyperkeratosis. It has been reported that retinoid therapy is much more effective in patients with KRT10 mutations compared to those with KRT1 mutations, possibly because the former are less vulnerable to retinoid-induced downregulation of keratin 2e [3]. In addition, it has been reported that EI patients with more extensive involvement benefit more from retinoid than those with mild or limited involvement [4]. Therefore, retinoids should be considered as the first therapeutic option for severe EI and EI caused by KRT10 mutations. Regarding skin barrier defects, patients with EI have been reported to have interleukin (IL)-17 dominant immune profiles [5], indicating that

inflammatory responses to barrier dysfunction in the *stratum corneum* can be a secondary contributing factor to the development of the EI phenotype. To date, therapies for EI have aimed at reducing hyperkeratosis with topical emollients and keratolytic agents, systemic retinoids, or both. However, immune responses to the IL-17 or IL-23 pathway with mutation-derived barrier dysfunction might be a novel therapeutic target for ichthyosis [5]. Indeed, a case report demonstrated ustekinumab, an anti–IL-12/23 p40 monoclonal antibody, is efficacious for severe EI [6]. In contrast, a double-blind, randomized, placebo-controlled trial of secukinumab, an anti–IL-17A monoclonal antibody, revealed that IL-17A inhibition is not effective for ichthyoses, including EI [7]. Therefore, accumulation of cases and further investigation are needed to evaluate the efficacy of biologics targeting the IL-17/IL-23 pathway. Oral etretinate remains an effective treatment option for EI caused by KRT10 mutations.

Acknowledgment

The authors are grateful to Y. Toyomaki and Y. Kanda, technicians in the Department of Dermatology, Hirosaki University Graduate School of Medicine, for their technical assistance in the genetic analysis.

Statement of Ethics

Written informed consent was obtained from the patient and the parents for the genetic test. The genetic test was reviewed and approved by the ethics committee of the Hirosaki University Graduate School of Medicine, approval number 2020-16-6. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient and the parents for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors are not being funded.

Author Contributions

1. EA, TA, HN, and DS substantially contributed to the conception or design of the work. EA, TA, MN, and HN substantially contributed to the acquisition, analysis, or interpretation of data for the work. TA and MN are involved in direct management of the patient.
2. EA wrote the majority of the original draft of the manuscript. TA, MN, HN, and DS substantially contributed to revising it critically for important intellectual content.
3. EA, TA, MN, HN, and DS have approved the final version of the work.
4. EA, TA, MN, HN, and DS have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1. Takeichi T, Akiyama M (2016) Inherited ichthyosis: Non-syndromic forms. J Dermatol 43: 242-251.
2. Wertheim-Tysarowska K, Ołdak M, Giza A, Kutkowska-Kaźmierczak A, Sota J, et al. (2016) Novel sporadic and recurrent mutations in KRT5 and KRT14 genes in Polish epidermolysis bullosa simplex patients: further insights into epidemiology and genotype-phenotype correlation. J Appl Genet 57: 175-181.
3. Virtanen M, Gedde-Dahl T, Mörk NJ, Leigh I, Bowden PE, et al. (2001) Phenotypic/genotypic correlations in patients with epidermolytic hyperkeratosis and the effects of retinoid therapy on keratin expression. Acta Derm Venereol 81: 163-170.
4. Digiovanna JJ, Mauro T, Milstone LM, Schmuth M, Toro J (2013) Systemic retinoids in the management of ichthyoses and related skin types. Dermatol Ther 26: 26-38.
5. Akiyama M (2022) Understanding immune profiles in ichthyosis may lead to novel therapeutic targets. J Allergy Clin Immunol 149: 1210-1212.
6. Foster ML, Jones JM, Schadt CR (2021) Epidermolytic Hyperkeratosis. JAMA Dermatol 157: 1114.
7. Lefferdink R, Rangel SM, Chima M, Ibler E, Pavel AB, et al. (2022) Secukinumab responses vary across the spectrum of congenital ichthyosis in adults. Arch Dermatol Res 315: 305-315.