

Epidermolytic Ichthyosis without Keratin 1 or 10 Mutations: A Case Report

Ali A. Al Raddadi, Taha H. Habibullah, Ahmed M. Abdelaal¹, Angie M. Felimban, Hosam A. Al Raddadi, Mohamed B. Satti¹

Department of Medicine, Section of Dermatology, King Abdulaziz Medical City, King Saud bin Abdulaziz University for Health Sciences, ¹Department of Pathology, King Abdulaziz Medical City, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Kingdom of Saudi Arabia

Abstract

In this paper, the authors report a case of an 11-year-old boy with epidermolytic ichthyosis who presented with multiple scattered erosions and typical hyperkeratotic plaques over the face, upper and lower extremities, the trunk, palms and soles. Family history revealed an affected older male sibling and an affected first-degree female relative. In addition, there was a positive history of generations of consanguinity in the patient's family pedigree, increasing the probability of an autosomal recessive inheritance. The clinical diagnosis was confirmed by histopathology; however, mutations in the keratin 1 and 10 genes were absent. This case report addresses the importance of establishing correct diagnosis and mode of inheritance, with literature review of genetic mutations, possible differential diagnosis and the most common and successful treatment modalities for epidermolytic ichthyosis.

Key words: Epidermolytic, hyperkeratosis, ichthyosis, keratin, superficial epidermolytic ichthyosis

Address for correspondence: Dr. Ahmed M. Abdelaal, Department of Pathology and Laboratory Medicine, King Abdulaziz Medical City, King Khalid National Guard Hospital, PO Box 9515, Jeddah 21423, Kingdom of Saudi Arabia. E-mail: ahmed3bdelaal@gmail.com

INTRODUCTION

Epidermolytic ichthyosis (EI) is a rare ailment that is most commonly inherited in an autosomal dominant pattern with a prevalence of 1:100,000–400,000.^[1,2] EI is caused by mutations in keratin (KRT) 1 or 10 genes.^[3,4] Up to 50% of EI cases are due to spontaneous mutations in these genes.^[5] Disease manifestations begin at or shortly after birth, with multiple erosions and blisters that decrease in occurrence and severity with age to give way to scaling and hyperkeratosis.^[1,6] Here, the authors report a case of EI of possible autosomal recessive inheritance not due to KRT1 or KRT10 mutations that were suspected clinically and confirmed pathologically and review the literature of such cases.

CASE REPORT

An 11-year-old Saudi male born to consanguineous parents following an unremarkable pregnancy presented to the emergency department of our hospital with a 5-day history of fever and generalized body erythema. Apart from being diagnosed with EI in another hospital from a young age, the patient had no other medical illness. At admission, he was only using emollients and was not taking medications for any other condition. He had no prior surgeries or known allergies.

Family history revealed an older male sibling and a first-degree female relative with EI. His older brother was taken to another hospital with clinical sepsis 1 week before

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Al Raddadi AA, Habibullah TH, Abdelaal AM, Felimban AM, Al Raddadi HA, Satti MB. Epidermolytic ichthyosis without keratin 1 or 10 mutations: A case report. Saudi J Med Med Sci 2018;6:36-9.

Access this article online	
Quick Response Code:	Website: www.sjmms.net
	DOI: 10.4103/1658-631X.220800

our patient's presentation and was later transferred to our hospital, where he passed away. His other siblings include three healthy sisters. His parents are consanguineous with generations of consanguinity reported in their respective families [Figure 1].

On examination, a strong and unpleasant odor was immediately noted; dermatological examination revealed marked erythema with scattered erosions and scales over the face. Soles and palms showed hyperkeratotic plaques [Figure 2]. The upper and lower extremities had thick scales with ridging, especially over the flexors [Figures 3 and 4]. The trunk was also affected with scattered thick scales [Figure 5].

Pathology reports from our patient's skin biopsies showed prominent hyperkeratosis with irregular acanthosis and vacuolar degeneration of the granular and spinous layers. In addition, there were occasional keratohyalin bodies and minimal blistering with an overlying mild perivascular chronic inflammatory infiltrate [Figure 6].

The diagnosis was made based on the clinical picture and histopathology findings. For genetic testing, the patient's blood samples were collected in an ethylenediaminetetraacetic acid tube and sent to a referral laboratory in the United States. Testing for KRT1 and KRT10 mutations was negative. Subsequently, an ichthyosis panel was performed, the results of which were inconclusive. A diagnosis of EI due to probable autosomal recessive mutations in other genes was suspected.

Our patient was started on topical treatment in the form of emollients: 1% hydrocortisone for the face and 5% salicylic acid for the palms and soles. He also received oral acitretin 10 mg once daily and was given appropriate antibiotic treatment for his presenting complaints and for suppression therapy. When discharged, he was in a stable condition and was given an appointment to be seen at the outpatient clinic after 1 week and again after 2 weeks. On follow-up, he showed a good response to treatment, with an almost complete remission of all skin manifestations.

DISCUSSION

EI is a disorder of keratinization with prevalence rates varying between 1:100,000 and 1:400,000.^[1,2] It is a known consequence of mutations most commonly inherited in an autosomal dominant pattern in either or both of the KRT1 or KRT10 genes.^[3,4] Exceptional cases of autosomal recessive EI have been reported, representing a rare form of EI inheritance.^[1-3,5]

KRT1 and KRT10 proteins are central to the cytoskeleton constituents and are expressed in the suprabasal layers of keratinized stratified epithelial tissue. In their absence, the keratinocytes of the superficial epidermis are more fragile and break easily. At birth, the dominant manifestations are erythroderma, desquamation and superficial fragile blisters. KRT1 and KRT10 proteins also play a role in inhibiting cell proliferation; therefore, the ensuing hyperkeratosis that becomes the prominent feature in the latter stages of EI is likely due to a lack of inhibition.^[7]

When considering the differential diagnosis of EI, other forms of ichthyosis such as superficial epidermolytic ichthyosis (SEI), which is due to mutations in KRT2, can be considered.^[3,8] In a study where 26 families with keratinopathic ichthyosis and their genetic mutations were studied, difficulty in clinically differentiating between EI and SEI was encountered. Some patients who were initially suspected to have EI and mutations in KRT1 or KRT10 were found to carry mutations in KRT2 and suffer from SEI, whereas others suspected to have SEI exhibited a milder phenotype of EI and carried mutations in KRT1 or KRT10.^[9] Consequently, patients suspected to have either EI or SEI with no mutations identified in their corresponding genes may benefit from testing for mutations in other KRT genes.^[3,9]

The diagnosis of EI can be made clinically in correlation with other findings such as pathology or molecular biology. Histopathology may reveal reticulated appearance of the epidermis, perinuclear vacuolization of keratinocytes of the stratum granulosum and corneum, increase in basophilic bodies and eosinophilic bodies with keratohyalin appearance, and compact hyperkeratosis of the stratum corneum with a trichohyalin appearance.^[2,4]

EI and other forms of ichthyosis are treated with emollients, topical retinoids, keratolytic agents and topical analogs of vitamin D.^[10,11] The drug most commonly used in the treatment of generalized cases is acitretin.^[6]

The importance of establishing accurate diagnosis of EI such as in our case is that once discovered, parents of affected individuals within this family and cases with similar backgrounds can receive necessary genetic testing and counseling. The possibility of pregestational diagnosis may also be discussed and offered for future pregnancies. In addition, the exclusion of more severe forms of inherited EI can also be achieved with accurate diagnosis.

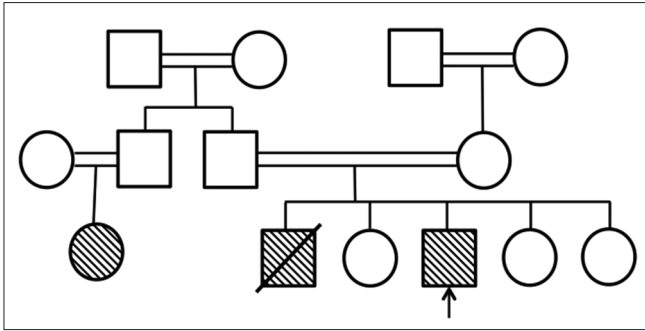


Figure 1: Family pedigree demonstrating affected individuals and consanguinity, favoring autosomal recessive inheritance



Figure 2: Compact hyperkeratotic plaques and thick scales affecting the soles



Figure 3: Scattered thick scales with ridging over the palms and flexor aspect of the upper limb



Figure 4: Scattered thick scales with ridging over the dorsal aspect of the feet and lower extremities

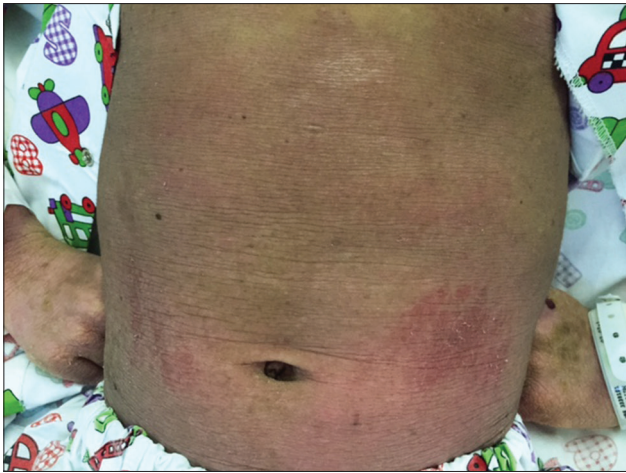


Figure 5: Erythematous patches and scattered scales over the trunk

In a region where consanguinity is more common than others, shedding light on the autosomal recessive form of EI can impact how we prevent, counsel and educate the Saudi population, motivating us to seek publication of this case. This case report stresses on the importance of establishing diagnosis and the correct mode of inheritance.

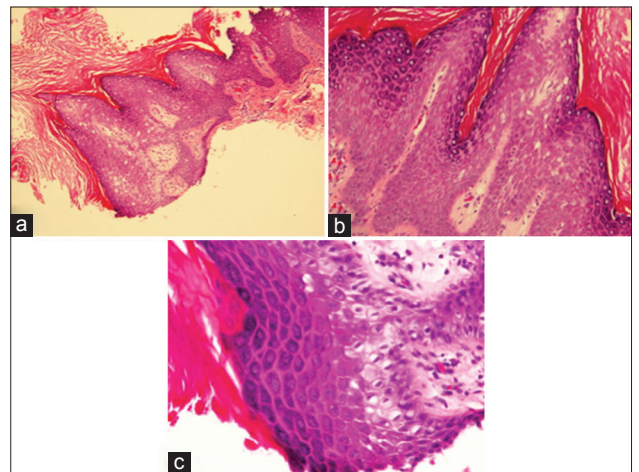


Figure 6: Prominent hyperkeratosis with irregular acanthosis and vacuolar degeneration of the granular and spinous layers (a and b); occasional keratohyalin bodies with minimal blistering overlying chronic inflammatory infiltrate (c); hematoxylin and eosin stain, original magnification (a and b) $\times 10$; (c) $\times 40$

It also addresses the genetic mutations, possible differential diagnosis and the most common and successful treatment modalities for EI.

CONCLUSION

EI is a rare dermatological ailment most commonly caused by autosomal dominant mutations in KRT1 and KRT10. However, other patterns of inheritance and mutations in other KRT genes have been reported. Genetic mutations should be identified when resources are available to complete the diagnostic picture and provide adequate counseling to patients and their families.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's father has given his consent for his child's images and other clinical information to be reported in the journal. The patient's father understands that his child's name and initials will not be published and due efforts will be made to conceal the child's identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Oji V, Tadini G, Akiyama M, Blanchet Bardon C, Bodemer C,

- Bourrat E, *et al.* Revised nomenclature and classification of inherited ichthyoses: Results of the First Ichthyosis Consensus Conference in Sorèze 2009. *J Am Acad Dermatol* 2010;63:607-41.
2. Lacz NL, Schwartz RA, Kihiczak G. Epidermolytic hyperkeratosis: A keratin 1 or 10 mutational event. *Int J Dermatol* 2005;44:1-6.
3. Mendes MS, Kouzak SS, Aquino TA, Takano GH, Lima Ade P. Mosaic epidermolytic ichthyosis – Case report. *An Bras Dermatol* 2013;88 6 Suppl 1:116-9.
4. Ross R, DiGiovanna JJ, Capaldi L, Argenyi Z, Fleckman P, Robinson-Bostom L. Histopathologic characterization of epidermolytic hyperkeratosis: A systematic review of histology from the National Registry for Ichthyosis and Related Skin Disorders. *J Am Acad Dermatol* 2008;59:86-90.
5. Terheyden P, Grimberg G, Hausser I, Rose C, Korge BP, Krieg T, *et al.* Recessive epidermolytic hyperkeratosis caused by a previously unreported termination codon mutation in the keratin 10 gene. *J Invest Dermatol* 2009;129:2721-3.
6. Nassif PW, Nakandakari S, Fogagnolo L, Contin LA, Alves CJ. Epidermolytic hyperkeratosis: A follow-up of 23 years of use of systemic retinoids. *An Bras Dermatol* 2011;86 4 Suppl 1:S72-5.
7. Chamcheu JC, Siddiqui IA, Syed DN, Adhami VM, Liovic M, Mukhtar H. Keratin gene mutations in disorders of human skin and its appendages. *Arch Biochem Biophys* 2011;508:123-37.
8. Arin MJ, Oji V, Emmert S, Hausser I, Traupe H, Krieg T, *et al.* Expanding the keratin mutation database: Novel and recurrent mutations and genotype-phenotype correlations in 28 patients with epidermolytic ichthyosis. *Br J Dermatol* 2011;164:442-7.
9. Hotz A, Oji V, Bourrat E, Jonca N, Mazereeuw-Hautier J, Betz RC, *et al.* Expanding the clinical and genetic spectrum of KRT1, KRT2 and KRT10 mutations in keratinopathic ichthyosis. *Acta Derm Venereol* 2016;96:473-8.
10. Umekoji A, Fukai K, Ishii M. A case of mosaic-type bullous congenital ichthyosiform erythroderma successfully treated with topical maxacalcitol, a Vitamin D3 analogue. *Clin Exp Dermatol* 2008;33:501-2.
11. Morais P, Mota A, Baudrier T, Lopes JM, Cerqueira R, Tavares P, *et al.* Epidermolytic hyperkeratosis with palmoplantar keratoderma in a patient with KRT10 mutation. *Eur J Dermatol* 2009;19:333-6.