

Received: 2021.11.07

Accepted: 2022.01.12

Available online: 2022.01.18

Published: 2022.02.24

Annular Epidermolytic Ichthyosis Mimicking Greither Disease: A Case Report and Literature Review

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

DEF 1,2 **Fatimah J. Almuqarrab**
ABDEFG 1 **Omar Mohammed Alakloby**
ABFG 1 **Jamal Mohammed Alqahtani**
DEFG 3 **Hans Christian Hennies**

1 Department of Dermatology, College of Medicine, Imam Abdulrahman Bin Faisal University (formerly University of Dammam), Dammam, Saudi Arabia

2 Saudi Board of Dermatology, Arab Board of Dermatology and Venereology (ABDV), King Fahd Hospital, Hofuf, Saudi Arabia

3 Department of Biological and Geographical Sciences, University of Huddersfield, Huddersfield, UK

Corresponding Author: Fatimah J. Almuqarrab, e-mail: fatimah.muq12@gmail.com

Financial support: None declared

Conflict of interest: None declared

Patient: Female, 3-year-old
Final Diagnosis: Annulare epidermolytic ichthyosis
Symptoms: Hyperhidrosis • itch • malodorous sweating
Medication: —
Clinical Procedure: —
Specialty: Dermatology

Objective: Congenital defects/diseases

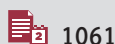
Background: Annular epidermolytic ichthyosis is a rare form of epidermolytic ichthyosis caused by specific pathogenic variants of KRT1 and KRT10. Classically, it manifests at birth with variable degrees of erythroderma and superficial erosions, which subsequently improve with time. Later, it is characterized by a cyclic history of annular hyperkeratotic erythematous plaques over the trunk and proximal extremities, with or without palmoplantar keratoderma. Greither syndrome, another autosomal dominant disorder of KRT1 mutation, is demonstrated by the diffuse, thick, scaly yellow PPK with transgrediens and erythematous border extending up to the Achilles' tendon, patchy hyperkeratotic plaques over the knees, shins, thighs, elbows, knuckles, and axillary folds. We describe a patient with clinical findings consistent with annular epidermolytic ichthyosis mimicking Greither disease with a likely associated pathogenic variant of KRT1.

Case Report: A 3-year-old Saudi girl presented with a diffuse palmoplantar keratoderma (PPK) extending to the dorsal aspects of the hands and feet up to the Achilles' tendon, first noticed at the age of 3 months, with a history of recurrent coin-shaped erythematous crusted erosions over the trunk, which were spontaneously healed over time, and an associated history of hyperhidrosis. Patchy hyperkeratotic plaques were noticed upon further examination over the bilateral elbows, axillary folds, and oral commissures.

Conclusions: The phenotype of our patient is consistent with the clinical features described for AEI, making the new K1 variant a likely pathogenic variant. When K1 mutation is the causative variant of the disease expression, phenotypically, it can present with Greither-like PPK.

Keywords: Hyperkeratosis, Epidermolytic • Ichthyosis • Ichthyosis, Cyclic, with Epidermolytic Hyperkeratosis

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/935393>



1061



4



13



13



Background

Annular epidermolytic ichthyosis (cyclic ichthyosis with epidermolytic hyperkeratosis [EHK] OMIM 607602) is a rare form of epidermolytic ichthyosis that can be caused by heterozygous pathogenic variants in KRT1 and KRT10 [1], with only 11 families reported [2]. Classically, it manifests at birth with variable degrees of erythroderma and superficial erosions, which subsequently improve with time. Later, it is characterized by a cyclic history of annular hyperkeratotic erythematous plaques over the trunk and proximal extremities. Additionally, variable clinical findings have been reported in several cases, including hyperkeratotic plaques over the flexures, corrugated plaques around the mouth, and PPK [1-3]. The diversity of clinical findings may be related to the causative variant, as with the previously noticed association between the KRT1 mutation and the presence of PPK. Most of the reported cases, as in our patient, had a heterozygous mutation in the 2B segment of the KRT1 gene [4]. Histopathological findings of the AEI reveal hyperkeratosis, acanthosis, and a thickened vacuolated granular layer [2].

Case Report

A 3-year-old Saudi girl presented to the dermatology clinic with a diffuse palmoplantar keratoderma (PPK) extending to

the dorsal aspects of the hands and feet (**Figure 1**) up to the Achilles' tendon (**Figure 2A**), first seen at the age of 3 months, with a history of recurrent coin-shaped erythematous crusted erosions over the trunk, which spontaneously healed over time (**Figure 2B**), and history of hyperhidrosis. The patient was a product of consanguineous marriage, with full-term, normal spontaneous vaginal delivery with no perinatal complications. Her skin was normal at birth. There were no other affected family members. Patchy hyperkeratotic plaques were noticed upon further examination over the bilateral elbows, axillary folds, and oral commissures (**Figure 3A, 3B**). The oral examination also revealed excessive dental caries of the incisors (**Figure 4**), which was noted by her mother to be unusual compared to her siblings.

A swab was taken from the pyoderma lesions and revealed β hemolytic streptococcal infection, which was successfully treated with a topical antibiotic. A skin punch biopsy was taken for Hematoxylin and Eosin (H & E) staining, showing compact hyperkeratosis, granular and vacuolar degeneration of the spinous layer, and large irregular keratohyalin granules (**Figure 4**). Genomic DNA analysis was performed for the candidate genes CTSC, SERPINB7, TRPV3, and SMARCAD1 using enrichment with specific capture probes and high-throughput sequencing on the Illumina platform (Centogene, Rostock, Germany). A coverage of $\geq 20\times$ was achieved for more than 98% of the

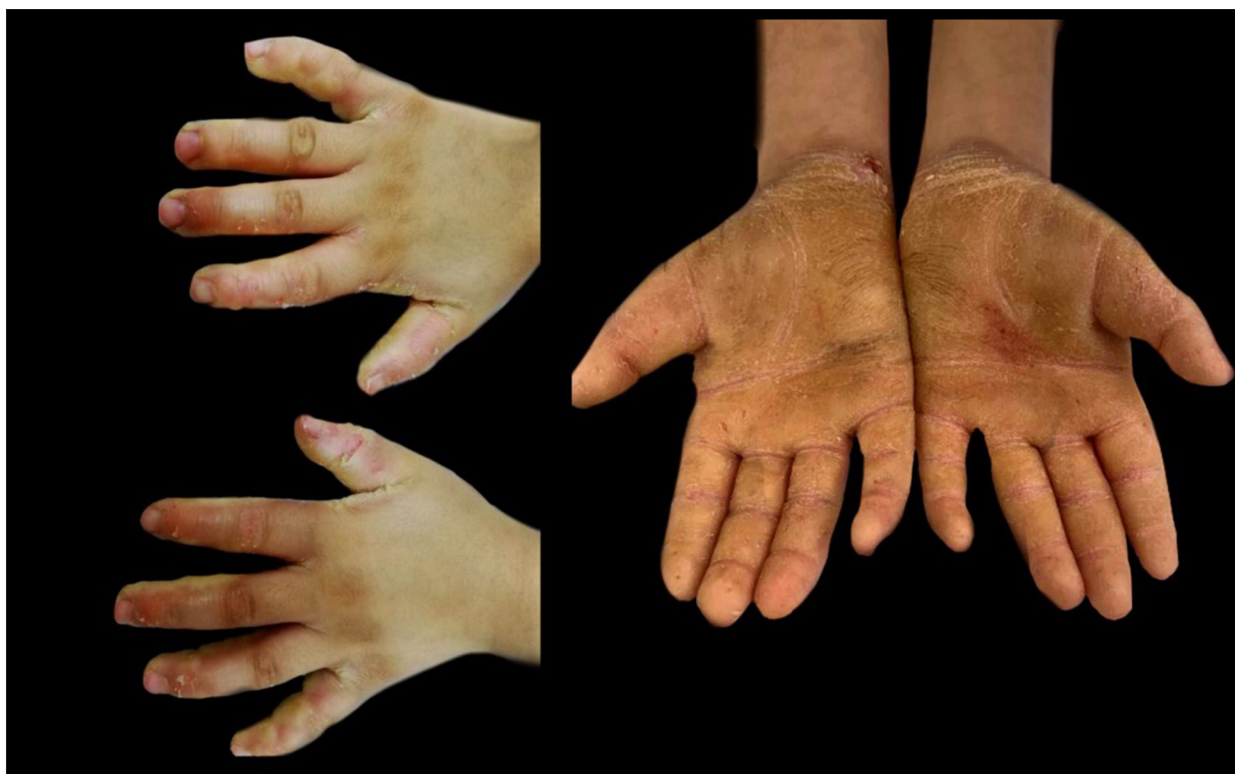


Figure 1. Palmer Keratoderma: diffuse palmer keratoderma extending to the dorsal hands, mild sclerodermatous changed of the dorsal fingers along with pseudoainhum formation over the 5th fingers. Localized area of erosion is noticed over the right wrist.



Figure 2. (A) Planter Keratoderma: the diffuse keratoderma is extending to the Achilles' tendon mimicking the clinical picture of Greither syndrome. (B) Trunk Epidermolytic Plaques: coin-shaped superficial crusted erosions, with several annular polycyclic scaly plaques over the upper left quadrant of the back.



Figure 3. (A) Keratotic Joints' Plaques: keratotic papillomatous plaques over the elbows. (B) Keratotic Flexural Plaques: keratotic corrugated plaques over the axilla.

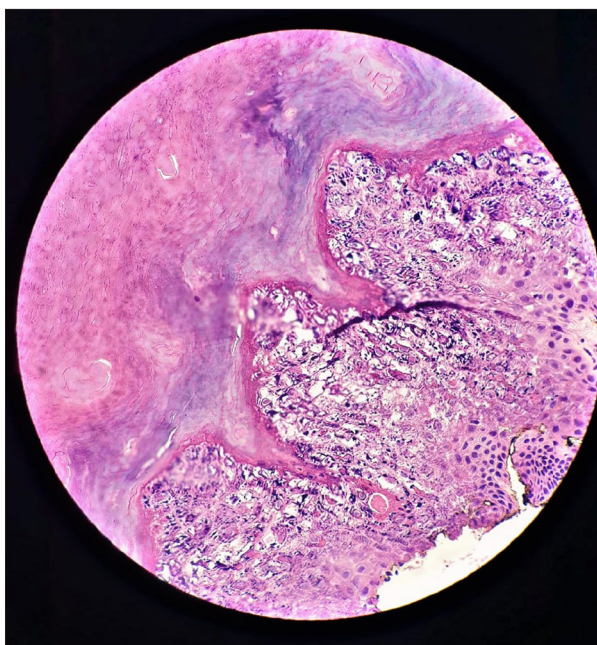


Figure 4. Hematoxylin and Eosin (H&E) staining, 40 high-power field: shows compact hyperkeratosis, granular and vacuolar degeneration of the spinous layer, and large irregular keratohyaline granules.

coding sequence. In addition, SLURP1 (NM_020427.3), KRT1 (NM_006121.3), and KRT9 (NM_000226.3) were analyzed by Sanger sequencing of both DNA strands of the entire coding region and the highly conserved exon-intron splice junctions (Centogene, Rostock, Germany). The genetic analysis revealed a heterozygous KRT1 missense variant c.1349C>A and a heterozygous variant in SLURP1, c.*68T>C. Both variants were not identified in the Genome Aggregation Database (gnomAD; gnomad.broadinstitute.org) and were initially classified as variants of uncertain significance. The KRT1 variant is predicted to produce a missense mutation, p.(Ala450Asp), located in the 2B segment of the keratin 1 rod domain. Prediction of pathogenicity pointed to a disease-causing variant, as determined using PolyPhen (genetics.bwh.harvard.edu/pph2), Align-GVGD (agvgd.hci.utah.edu), SIFT (provean.jcvi.org), and MutationTaster (mutationtaster.org). No other variants were identified in the candidate genes analyzed. Based on the genetic analysis and the medical history, the patient was diagnosed with annular epidermolytic ichthyosis associated with a likely pathogenic variant in KRT1.

A trial of topical treatments, including salicylic acid 3%/beta-methasone 0.5% ointment, urea 20% cream, and topical tretinoin 0.05% cream, shows modest efficacy. She is planned to start systemic retinoid treatment.

Discussion

The KRT1 variant c.1349C>A in our patient caused an amino acid change from alanine to aspartate at position 450. It affects the keratin 1 2B domain, which is part of the central rod domain. The variant p.(478Ile>Thr) was described before in a case with a similar phenotype [5]. The milder appearance of our patient and the more prominent PPK phenotype might be because our patient's KRT1 variant affects a residue located closer to the 5' and outside the terminal part of the 2B domain, which is critical for intermediate filament assembly. The rod domain's initial and terminal parts are highly conserved among keratins, and variants of these segments are thought to lead to rather severe phenotypes involving epidermolytic hyperkeratosis.

Transgrediens et progrediens palmoplantar keratoderma (Greither syndrome) was initially described by Greither in 1952, is another autosomal dominant inherited entity of the gene encoding keratin one filaments [6]. Clinically, our patient presented with the classic disease as demonstrated by diffuse, thick, scaly yellow PPK with transgrediens and erythematous border extending up to the Achilles' tendon, as well as patchy hyperkeratotic plaques over the knees, shins, thighs, elbows, knuckles, and axillary folds [6,7]. Hyperhidrosis is a common feature of the syndrome as well. Greither PPK tends to develop after 2 years of life and involutes after the 5th decade; however, earlier age of onset has been described. Severe cases may be complicated with spontaneous autoamputation of the digits. Greither syndrome has been described in association with incontinentia pigmenti, acrocyanosis, and erythrokeratoderma variabilis [6,8]. Additionally, 1 case of melanoma has been reported over the keratotic plaque of Greither PPK [9].

Mal de Meleda is an autosomal recessive disorder caused by a homozygous mutation in the SLURP-1 gene, the main differential of Greither syndrome [8,10,11]. On the other hand, it is characterized by transgrediens PPK and perioral keratotic plaques, with a more severe mutilating course and earlier age of onset [10].

Treatment of AEI is mainly based on case reports. Several measures have been tried, including topical medications such as retinoids, calcipotriene, steroids, emollients, humectants, and keratolytic agents, with modest to good responses. Several other reports show a good response to low doses of systemic vitamin A derivatives, with a good tolerability profile. However, the response to retinoids differs among patients depending on their genotype/phenotype variations. Notably, the patients with keratin 10 pathogenic variants have a favorable outcome when treated with retinoids [2,12,13].

Conclusions

In conclusion, the phenotype of our patient is consistent with the clinical features described for AEI, making the new K1 variant a likely pathogenic variant. When K1 mutation is the causative variant of the disease expression, phenotypically, it can present with Greither-like PPK.

References:

1. Chamcheu JC, Siddiqui IA, Syed DN, et al. Keratin gene mutations in disorders of human skin and its appendages. *Arch Biochem Biophys*. 2011;508(2):123-37
2. Mikilita ES, Hernandez IP, Boff AL, et al. AE. Annular epidermolytic ichthyosis: A case report and literature review. *An Bras Dermatol*. 2020;95(4):484-89
3. Ramesh V, Singh A, Jha A, et al. Annular epidermolytic ichthyosis: A rare phenotypic variant of bullous congenital ichthyosiform erythroderma. *Indian J Dermatol Venereol Leprol*. 2015;81(2):194
4. Sybert VP, Francis JS, Corden LD, et al. Cyclic ichthyosis with epidermolytic hyperkeratosis: A phenotype conferred by mutations in the 2B domain of keratin K1. *Am J Hum Genet*. 1999;64(3):732-38
5. Zaki TD, Yoo K, Kassardjian M, et al. A p.478IT KRT1 mutation in a case of annular epidermolytic ichthyosis. *Pediatr Dermatol*. 2018;35(6):e414-15
6. Gach JE, Munro CS, Lane EB, et al. Two families with Greither's syndrome caused by a keratin 1 mutation. *J Am Acad Dermatol*. 2005;53(5):S225-30
7. Athanikar SB, Inamadar AC, Palit A, et al. Greither's disease. *Indian J Dermatol Venereol Leprol*. 2003;69:292-93
8. Bernice RK, Tay Y. What syndrome is this? Greither syndrome. *Pediatr Dermatol*. 2003;20(3):272-75
9. Seike T, Nakanishi H, Urano Y, et al. Malignant melanoma developing in an area of palmoplantar keratoderma (Greither's disease). *J Dermatol*. 1995;22(1):55-61
10. Fitzpatrick TB, Kang S. *Fitzpatrick's dermatology* (9th ed., Vol. 1). New York: McGraw Hill Education. 2019;823-24
11. Tjiu J, Lin P, Wu W, et al. SLURP1 mutation-impaired T-cell activation in a family with mal de Meleda. *Br J Dermatol*. 2010;164(1):47-53
12. Virtanen M, Gedde-Dahl T, Mörk JN, et al. Phenotypic/genotypic correlations in patients with epidermolytic hyperkeratosis and the effects of retinoid therapy on keratin expression. *Acta Derm Venereol*. 2001;81:163-70
13. Reolid A, Carrasco L, Noguera-Morel L, et al. Annular epidermolytic ichthyosis: An exceptional mild subtype of epidermolytic ichthyosis without genotype and phenotype correlation. *JAAD Case Rep*. 2019;6(1):46-50

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.