Progressive symmetrical erythrokeratoderma manifesting as harlequin-like ichthyosis with severe thrombocytopenia secondary to a homozygous 3-ketodihydrosphingosine reductase mutation

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Key words: EKVP4; genodermatosis; harlequin; ichthyoses; 3-ketodihydrosphingosine reductase; KDSR; Progressive symmetrical erythrokeratoderma; PSEK.

Progressive symmetrical erythrokeratoderma (PSEK), also known as Gottron syndrome, is a rare type of erythrokeratoderma. PSEK classically manifests as fixed, symmetric, well-demarcated hyperkeratotic plaques with peripheral erythema with a predilection toward extensor surfaces and occasional involvement of the face and trunk. A harlequin phenotype is typically due to ABCA12 gene mutations causing harlequin ichthyosis (HI). Although HI neonates rarely survive, those who do usually evolve into generalized erythroderma with small scales. We present a case of an infant with a harlequin-like presentation of PSEK with amegakaryocytic thrombocytopenia secondary to a rare homozygous variant in the gene encoding 3-ketodihydrosphingosine reductase (KDSR) based on whole-genome sequencing.

CASE REPORT

This case involves a 4-year-old Saudi boy who was the fourth child (one deceased sister and 2 other siblings) of consanguineous parents. The sister died at 2 years of age with severe HI. The patient was electively born by cesarean section at 38 weeks of gestation due to prior cesarean section. At birth, he was covered in thick, platelike hyperkeratotic scales and marked ectropion and eclabium, and he was considered to have HI. He was admitted to the neonatal intensive care unit before transport to our tertiary center at the age of 2 months for further treatment.

The boy spent an additional 2 months in our neonatal intensive care unit, requiring multiple transfusions for severe anemia and thrombocytopenia, intravenous antibiotics for recurrent sepsis, and skin care. The thick scales gradually desquamated, resulting in well-demarcated, symmetric, erythematous thick hyperkeratotic plaques involving the face, neck, trunk, axillae, groin, buttocks, medial aspect of the extremities, and dorsal and volar aspects of the hands and feet. Additionally, fixed flexion deformity of the elbows, hands, and feet along with mitten hand deformity was noted. Furthermore, a sharply demarcated erythematous scaly plaque confined to the upper half of his face was observed (Fig 1, A and B). Because HI was initially considered, whole-exome sequencing...
was performed to confirm the diagnosis. However, because the results were not conclusive, whole-genome sequencing was requested and revealed a novel homozygous missense variant in KDSR (NM_002035.4:c.434A>G [p. Asn145Ser]), which was compatible with the phenotype. This variant was not found in gnomAD or in our local database. In addition, the mutation was predicted to be pathogenic by all in silico tools queried (CADD 27.5, DANN 0.999, PolyPhen 0.999, SIFT 0.007, and GERP 5.9499).

Additional tests, including skeletal surveys, showed no evidence of dysplasia. A bone marrow biopsy result was consistent with congenital megakaryocytic aplasia or thrombocytopenia. Skin biopsy revealed nonspecific hyperkeratosis, acanthosis, and papillary dermis fibrosis (Fig 2).

After his discharge in a stable condition, the patient was admitted several times for sepsis, epistaxis, and a mild subdural hematoma not warranting evacuation. Because of frequent platelet counts dropping below $20 \times 10^9/L$, the patient was placed on twice-weekly platelet transfusions, monthly intravenous immunoglobulin, and packed red blood cells when hemoglobin levels dropped below 8 g/dL. Acitretin 1 mg/kg/day was started at the age of 5 months, with a remarkable response (Fig 3). Because of a lack of availability, acitretin was replaced by isotretinoin 1 mg/kg/day with slow tapering to 0.5 mg/kg/day, which resulted in good control of his skin condition apart from flareups during febrile episodes.

**DISCUSSION**

Erythrokeratodermas comprise a group of both autosomal dominant and recessive rare genetic skin disorders characterized by well-demarcated, symmetric thick plaques distributed over the body. The severity can vary even among family members. The 2 main types of erythrokeratoderma are PSEK and erythrokeratoderma variabilis (the latter is characterized by transient migratory erythematous patches). To date, only 12 cases of erythrokeratoderma...
secondary to autosomal recessive KDSR variants have been reported. First described by Boyden et al, cases have shown variable clinical pictures presenting either at birth or shortly thereafter, with displaying focal red hyperkeratotic plaques limited to the buttocks, genitals, and face with palmoplantar scaling; 1 born with a collodion membrane died after only 9 days of life. Takeichi et al reported an additional 4 cases, 2 of whom had an HI-like picture along with thrombocytopenia. In contrast, our patient’s thick, platelike scales did not evolve into erythroderma with fine scales. Interestingly, Bariana et al reported a case of limited and self-resolving skin involvement with progressive myelofibrosis, highlighting the clinical variability. In their report, thrombocytopenia and anemia spontaneously resolved within the first decade of life.

Of note, all previously reported KDSR variants were compound heterozygous mutations, except for one that was homozygous, and the associated phenotype involved thick plates that resolved spontaneously at 1 month of age, with persistent severe thrombocytopenia and hepatic hemangioendothelioma.

The gene KDSR encodes an early, essential enzyme, 3-keto-dihydrosphingosine reductase, in the de novo synthesis pathway of sphingolipids. Perturbation of this pathway due to pathogenic KDSR mutation is thought to be responsible for both skin and platelet manifestations.

In general, near-complete resolution with retinoic acid derivatives might be explained by the ability of these derivatives to increase sphingosine acylation and up-regulate sphingomyelinase in pathways independent of the de novo pathway.

KDSR mutations are associated with a broad spectrum of clinical manifestations ranging from HI-like features to localized keratodermas, with the presence or absence of severe self-resolving or persistent hematological manifestations. In view of the novel nature of the variant we describe here and the very limited number of reported cases to date, it is difficult to predict long-term sequelae, prognosis, or survival; accordingly, the child in this case will be closely monitored.

In conclusion, we report a child with HI-like features gradually evolving into PSEK with congenital amegakaryocytic thrombocytopenia secondary to a homozygous variant in the KDSR gene. We believe this case will add to our understanding of this very rare clinical entity. We suggest consideration of PSEK in the differential diagnosis and encourage future exploration of the role of KDSR mutation, if any, in the pathogenesis of non-ABCA12 HI.

Conflicts of interest
None disclosed.

REFERENCES
1. Guaraldi Bde M, Jaime TJ, Guaraldi Rde M, Melo DF, Nogueira OM, Rodrigues N. Eritroqueratodermia simétrica progressiva—Relato de caso. An Bras Dermatol. 2013;88(1):109-112.
2. Prabhu S, Shenoi S, Pai S, Handattu S, Bhattachan B. Progressive and symmetric erythrokeratoderma of adult onset: a rare case. Indian Dermatol Online J. 2010;1(1):43-45.
3. Rajpoot S, Moss C, Mellerio J, et al. Harlequin ichthyosis: a review of clinical and molecular findings in 45 cases. Arch Dermatol. 2011;147(6):681-686.
4. Boyden LM, Vincent NG, Zhou J, et al. Mutations in KDSR cause progressive symmetric erythrokeratoderma. Am J Hum Genet. 2017;100(6):978-984.
5. Liu C, Chen XY, Wu WQ, Zhu XF. A homozygotic mutation in KDSR may cause keratinization disorders and thrombocytopenia: a case report. Chin Med Sci J. 2020;35(3):278-282.
6. Bursztejn AC, Happle R, Charbit L, et al. The PERIOPTER syndrome (periorificial and ptychotropic erythrokeratoderma): a new Mendelian disorder of cornification. J Eur Acad Dermatol Venereol. 2019;33(1):e1-63.
7. Takeichi T, Torrelo A, Lee JYW, et al. Biallelic mutations in KDSR disrupt ceramide synthesis and result in a spectrum of
keratinization disorders associated with thrombocytopenia. *J Invest Dermatol.* 2017;137(11):2344-2353.

8. Bariana TK, Labarque V, Heremans J, et al. Sphingolipid dysregulation due to lack of functional KDSR impairs proplatelet formation causing thrombocytopenia. *Haematologica.* 2019;104(5):1036-1045.

9. Kihara A, Igarashi Y. FVT-1 is a mammalian 3-ketodihydrosphingosine reductase with an active site that faces the cytosolic side of the endoplasmic reticulum membrane. *J Biol Chem.* 2004;279(47):49243-49250.

10. Uchida Y. Ceramide signaling in mammalian epidermis. *Biochim Biophys Acta—Mol Cell Biol Lipids.* 2014;1841(3):453-462.