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.[1,2] 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.[1] 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.[3] 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.

Abbreviations used:

HI:	harlequin ichthyosis
KDSR:	3-ketodihydrosphingosine reductase
PSEK:	progressive symmetrical erythrokeratoderma

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

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Funding sources: None.
IRB approval status: Not applicable.

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JAAD Case Reports 2021;14:55-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.06.006

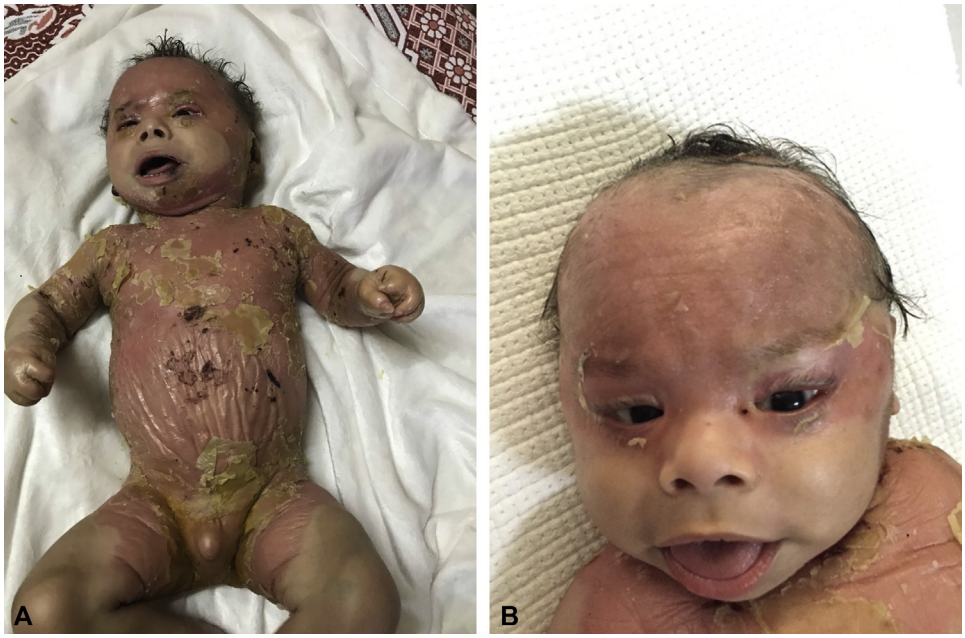

Fig 1. A, Diffuse, thick, sheetlike hyperkeratotic plaques on an erythematous base over the anterior aspect of the trunk, with prominent extension to the face, neck, proximal thighs, genitals, and upper portion of the limbs. **B**, Sharply demarcated erythematous hyperkeratotic plaques over the nasal bridge and periorbital areas extending to the forehead and scalp, with evident ectropion. Similar findings can be seen over the anterior aspect of the trunk.

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 20×10^9/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.

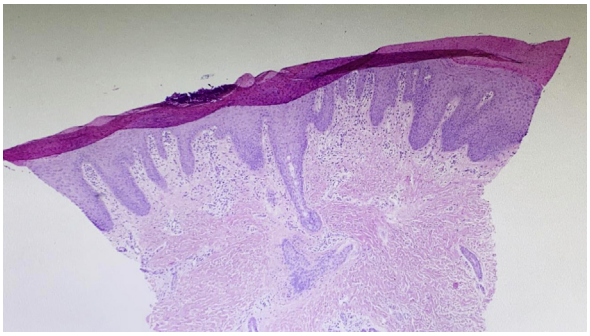

Fig 2. Skin biopsy photograph shows hyperkeratosis, acanthosis, and papillary dermis fibrosis. (Hematoxylin-eosin stain; original magnification: ×100.)

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).[4] To date, only 12 cases of erythrokeratoderma

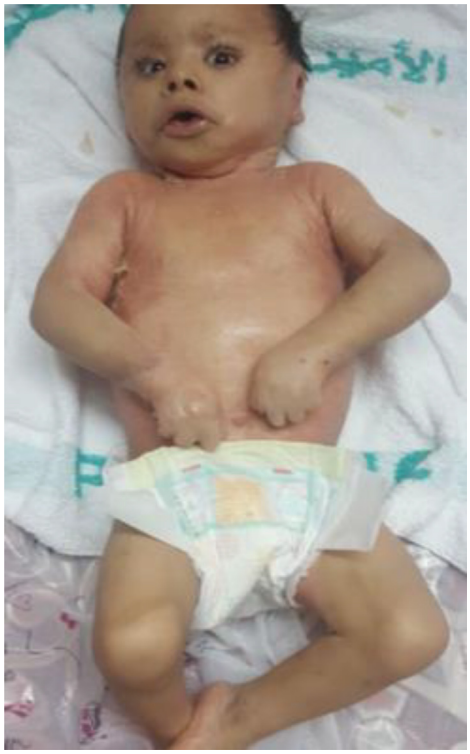

Fig 3. Evident improvement in scales and erythema following treatment with acitretin 1 mg/kg/day at approximately 1.5 years of age.

secondary to autosomal recessive *KDSR* variants have been reported.[5,6] First described by Boyden et al,[4] 4 cases have shown variable clinical pictures presenting either at birth or shortly thereafter, with 3 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[7] 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[8] 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.[5]

The gene *KDSR* encodes an early, essential enzyme, 3-keto-dihydrosphingosine reductase, in the de novo synthesis pathway of sphingolipids.[9] This pathway is important for megakaryopoiesis, cytoplasmic organization, and proplatelet formation, as well as for maintaining skin integrity and regulating cutaneous proliferation and differentiation.[8,10] Perturbation of this pathway due to pathogenic *KDSR* mutation is thought to be responsible for both skin and platelet manifestations.[7]

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.[4]

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.

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