CASE REPORT

A Homozygotic Mutation in *KDSR* may Cause Keratinization Disorders and Thrombocytopenia: A Case Report

Chao Liu, Xiaoyan Chen, Wenqi Wu, Xiaofan Zhu*

State Key Laboratory of Experimental Hematology, National Clinical Research
Center for Blood Diseases, Institute of Hematology and Blood Diseases
Hospital, Chinese Academy of Medical Sciences & Peking
Union Medical College, 300020 Tianjin, China

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Abstract Pathogenic mutations in 3-keto-dihydrosphingosine reductase (*KDSR*) gene are associated with keratinization disorders and impaired platelet function. However, no case with both homozygotic mutation of *KDSR* and hepatic hemangioendothelioma has ever been reported due to its low prevalence. Here we report a seven months old Chinese boy with a homozygotic missense mutation in *KDSR* and both of his parents carry a same heterozygous mutation. He was born with thick plate-like scales overlying erythrodermic skin, but the skin symptoms were resolved spontaneously over the first month of his birth. He was also diagnosed with hepatic hemangioendothelioma at birth and accepted a resection surgery at 2 months old. At birth, his platelet count was severely low ($10\text{-}20 \times 10^9/\text{L}$) with recurrent skin and gingival bleeding. Meanwhile, he suffered a mild normocytic, normochromic anemia with normal iron and hematinic levels. The anemia spontaneously recovered over the first 6 months, while the platelet count kepted at a low level ($4\text{-}20 \times 10^9/\text{L}$). Treatment with corticosteroids, immunoglobulin or thrombopoietin was all suboptimal.

KDSR, which encodes 3-keto-dihydrosphingosine reductase, is a fundamental enzyme for de novo sphingolipid synthesis.^[1, 2] Sphingolipids are essential to membrane trafficking, apoptosis and cell differentiation and proliferation.^[3, 4] Recent discoveries showed that pathogenic mutations in *KDSR* can result in mild to severe skin disorder, mostly severe thrombocytopenia and self-re-

covery anemia.^[5-7] Up to now, all of ten reported cases carry compound heterozygous mutations in *KDSR* and are born to unrelated parents.^[5-7] Besides, to our knowledge hepatic hemangioendothelioma has never been reported in these patients. Here we review a case with thrombocytopenia, anemia, minimal skin involvement and hepatic hemangioendothelioma, which may be associated with a homozygotic mutation in *KDSR*.

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*Corresponding author Tel/Fax: 86-22-23909001, E-mail: xfzhu@ihcams.ac.cn

CASE DESCRIPTION

A seven-month boy is the only child of related

healthy parents and the only affected individual among his relatives. His mother's and father's grandmothers are cousins. He was delivered vaginally following spontaneous onset of labor at 38+2 weeks with a birth weight of 3.35 kg.

He was born with a thick covering of plate-like scales overlying erythrodermic skin, but eclabium and ectropion were not observed. Histopathological examination of the affected skin was not tested because of his parents' refusal. The skin symptoms were resolved spontaneously over the first month of his life only with intermittent use of urea and vitamin E cream.

At birth, his platelet count was severely low (10×10^9 - 20×10^9 /L) accompanied by recurrent skin and gingival bleeding. He also had mild normocytic, normochromic anemia with normal iron and hematinic levels. But the white blood cell count and the mean volume of platelets were normal. The bone marrow morphology test showed increased number of primitive and naive lymphocytes (6.6%). The total number of megakaryocyte was 25 and no apparent morphology dysplasia was found. The bone marrow biopsy and immunohistochemistry were not performed in view of his age. Serum immunoglobulins and peripheral T-lymphocyte subsets were both normal. The whole exome sequencing showed a novel homozygotic missense mutation in *KDSR* and both of his parents have a same heterozygous mutation [NM-002035.4: exon9: c.869G>A (p.Gly290Glu)]. The mutation was not included in Exome Sequencing Project, 1000 Genomes Project and Exome Aggregation Consortium. However, it was predicted by multiple computer simulations to be probably damaging. According to the American College of Medical Genetics and Genomics (ACMG) guidelines, the clinical significance of this mutation is still unclear.

The anemia had a spontaneous recovery over the first 6 months, while the platelet count keeps low (4 - 20×10^9 /L). He was once treated with corticosteroids, immunoglobulin and thrombopoietin, but none of them made a significant improvement of platelet count.

The abdominal ultrasound at birth suggested a heterogeneous mass in the right lobe of his liver, whose maximum diameter was 5.3 mm. His liver function tests showed elevated levels of both alanine aminotransferase (112.2 U/L) and aspartate aminotransferase (227.5 U/L). Coagulation test showed a significant decrease in fibrinogen (0.88 g/L) and prolonged thrombin time (21 s). Besides, alpha-fetoprotein was 16 038.0 ng/ml, which was significantly higher

than normal. Then abdominal plain scan and enhanced CT were carried out to determine the nature of the mass and infantile hemangioendothelioma was suggested. After transfusion of platelets, his platelet count rose up to 200×10^9 /L and then he accepted a resection surgery successfully at 2 months old.

The patient is currently one year old and has no abnormalities other than thrombocytopenia. He has not received any treatment since he was 2 months old. The platelet count keeps low (4×10^9 - 20×10^9 /L) with recurrent skin and gingival bleeding.

DISCUSSION

KDSR is one of the most essential enzymes in the pathway of de novo sphingolipid synthesis.^[1, 2] It catalyzes the conversion of 3-keto-dihydrosphingosine to dihydrosphingosine on the cytosolic leaflet of the endoplasmic reticulum. Sphingolipids are essential to apoptosis, cell differentiation, proliferation and membrane trafficking.^[3, 4] Boyden *et al.*^[5] reported compound heterozygous damaging mutations in *KDSR* of four unrelated probands in 2017 (**Table 1**). All of them exhibited recessive progressive symmetric erythrokeratoderma, a skin disorder with symmetric scaling, erythema, and palmoplantar keratoderma. In the report, both of probands who received systemic isotretinoin therapy have achieved nearly complete resolution and it is consistent with the effects of retinoic acid on alternative pathways for ceramide generation. But later studies showed that mutations in *KDSR* may not cause progressive symmetric erythrokeratoderma.^[6, 7] Takeichi *et al.*^[6] reported four cases in June 2017 (**Table 1**): Patient 1 and 2 developed diffuse hyperkeratosis and had anogenital hyperkeratosis and erythema. Light microscopy of the affected skin showed psoriasiform acanthosis, parakeratosis, and focal hypergranulosis but no epidermolytic changes. Patient 3 and 4 were both covered in thick plate-like scales at birth and had severe ectropion and eclabium. Skin biopsy of Patient 4 showed marked hyperkeratosis with parakeratosis, which was consistent with Harlequin ichthyosis. However, the thick scales desquamated gradually over the first 2 months of his life without any special treatment and resulted in generalized erythroderma and small scaling. Three of the four patients once received oral acitretin, two of them had no improvement in skin, one showed some reduction in adherent scaling. In the report of Bariana *et al.* (**Table 1**),^[7] one patient's

Table 1. Summary of clinical and mutation details of all ten reported individuals

Patient	Country of origin	Age of onset	Gender	Dermatologic phenotype	Platelet count (10 ⁹ /L)	Hemoglobin (g/dl)	DNA change	Protein change	Inheritance
1 ^[5]	-	At birth or perinatal period		Recessive progressive symmetric erythrodermatoderma	-	-	g.63,361,789_63,707,612inv c.879G>A	Expression lost p. Gln293Gln, p.Gln260_Gln293del	Maternal Paternal
2 ^[5]	-	At birth or perinatal period		Recessive progressive symmetric erythrodermatoderma	-	-	c.164_166delAAG c.879G>A	p. Gln55_Gly56 delinsArg p. Gln293Gln, p.Gln260_Gln293del	Paternal Maternal
3 ^[5]	-	At birth or perinatal period		Recessive progressive symmetric erythrodermatoderma	-	-	c.256-2A>C c.879G>A	p. Val86_Gln107del p. Gln293Gln, p.Gln260_Gln293del	Maternal Paternal
4 ^[5]	-	At birth or perinatal period		Recessive progressive symmetric erythrodermatoderma	-	-	g.63,361,789_63,707,612inv c.557A>T	Expression lost p. Tyr186Phe	Paternal Maternal
5 ^[6]	Spain	12 months		Palmoplantar and perianal keratoderma	<40	-	c.413T>G c.417t3A>C	p. Phe138Cys -	- -
6 ^[6]	Spain	15 months		Palmoplantar and perianal keratoderma	<20	-	c.413T>G c.417+3A>C	p. Phe138Cys -	- -
7 ^[6]	United Kingdom	At birth	Male	Harlequin ichthyosis	20-30	-	c.812G>A c.879G>A	p. Gly271Glu p. Gln293Gln, p.Gln260_Gln293del	- -
8 ^[6]	Japan	At birth	Male	Harlequin ichthyosis	4-11	-	c.223_224delGA c.544G>A	p. Glu75Asnfs*2 p. Gly182Ser	- -
9 ^[7]	Europe	4 months	Male	A slow-to-heal perianal wound following rectal manometry.	9-152	9.1-13.4	c.706C>T c.460C>T	p. Arg236* p. Arg154Trp	Maternal Paternal
10 ^[7]	Europe	At birth	Female	Mild ichthyosis in her left axilla	24-148	6.3-19.1	c.706C>T c.460C>T	p. Arg236* p. Arg154Trp	Maternal Paternal

"-": unknown.

possible skin involvement was a slow-to-heal perianal wound following rectal manometry, the other had mild ichthyosis in her left axilla, but the skin symptoms resolved spontaneously over her first month. Our patient was born with thick plate-like scales overlying erythrodermic skin, but eclabium and ectropion were not observed. The skin symptoms were resolved spontaneously over the first month of his life without any special treatment.

Boyden *et al.*^[5] did not mention the decrease of platelet count, but further studies showed that mutations in *KDSR* are implicated in an extended spectrum of disorders, not only including keratinization disorders but also impaired platelet function. In the report of Takeichi *et al.*,^[6] all of four patients had a severe isolated thrombocytopenia and the platelet counts were mostly less than $30 \times 10^9/L$. One of the four patients accepted oral corticosteroids and splenectomy, both of the treatments were suboptimal. Bone marrow studies of one patient showed normal hematologic morphology. Detailed analysis of platelets performed in two patients revealed no morphologic abnormalities except for slightly increased platelet volume. The adhesive surface glycoproteins levels of the two patients were both normal, but in terms of basal annexin V binding positive percentages, the level of phosphatidylserine exposure was low and thromboplastin expression in unstimulated washed platelets was reduced. Besides, the platelet function of granule release and the conformational change of $\alpha IIb\beta 3$ integrin with different platelet agonists were also impaired. Bariana *et al.*^[7] later reported two related patients and both of them had thrombocytopenia and normocytic, normochromic anemia. The mean volumes of the platelets are both within the normal ranges, which is contrary to the report of Takeichi *et al.*^[6] The hemoglobin level of the elder patient was spontaneously improved in the absence of identifiable environmental, therapeutic, or dietary interventions. His bone marrow examinations showed increased numbers of dysplastic megakaryocyte and progressive severe myelofibrosis. Megakaryocyte obtained by differentiation of patients' hematopoietic stem cells or programming of induced pluripotent stem cells derived from their fibroblasts was abnormal in size and proplatelet formation. They found that downstream metabolites in the sphingolipid pathway were not reduced in plasma. This suggests that hypofunction of *KDSR* in de novo sphingolipid synthesis is compensated by an alternative pathway and the way

may be recycling of relatively abundant sphingomyelins. They also knocked down *KDSR* in a zebrafish model and found that it is associated with impaired thrombocyte formation.

Our patient had a homozygotic missense mutation in *KDSR*. Though the mutation was not included in Exome Sequencing Project, 1000 Genomes Project and Exome Aggregation Consortium, it was predicted by multiple computer simulations to be probably damaging. The patient not only had keratinization disorders, but also had severe thrombocytopenia and transient anemia. All together we consider the mutation probably is the pathogenic cause of the patient. Since it has not ever been reported, further studies of more cases are essential to determine whether pathogenic mutations in *KDSR* is the cause of infantile hepatic hemangioendothelioma. But a recent study showed that *KDSR* dysfunction can induce hepatic injury phenotype in both homozygous *KDSR* mutant larvae and heterozygous *KDSR* mutant adult zebrafish.^[8] The researchers suggest that genetic mutations causing decrease of *KDSR* activity could be an underlying risk factor for development of liver disease and patients who carry these mutations might be highly susceptible to liver diseases such as steatohepatitis, fibrosis or hepatocellular carcinoma.

In conclusion, our data add a pathogenic mutation in *KDSR*, which associated with skin disorder, mostly severe thrombocytopenia and self-recovery anemia. Besides, it is probably responsible for infantile hepatic hemangioendothelioma. Further studies of more individuals affected by pathogenic *KDSR* variants are essential to determine whether systemic retinoid or sphingosine-1-phosphate receptor-targeting drugs are effective or not. Because two patients had spontaneous improvement of platelet count and anemia,^[7] a careful watch-and-wait approach may be more appropriate than early intervention for patients without severe clinical bleeding symptoms.

Conflict of Interests Statement

The authors declare no conflict of interests.

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