Hemoglobin Kansas as a Rare Cause of Cyanosis: A Case Report and Review of the Literature

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Abstract

Hemoglobin (Hb) Kansas is an inherited Hb variant with a low oxygen affinity that is associated with low oxygen saturation on pulse oximetry (SpO₂). It leads to asymptomatic cyanosis. Patients with Hb Kansas do not require any specific treatment and the prognosis is good. In patients with unexplained cyanosis, we should thus consider Hb variants, including Hb Kansas and avoid unnecessary investigations and managements. We herein report the case of 65-year-old woman with Hb Kansas and review five other cases (three lineages) that have been reported in Japan.

Key words: hemoglobin Kansas, hemoglobin variants, oxygen affinity, cyanosis

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Introduction

More than 1,000 Hb variants have been identified (1). Abnormal oxygen saturation is not detected by pulse oximetry (SpO₂) in the majority of Hb variants. However, some patients inherit an Hb variant with a low oxygen affinity that displays low SpO₂ and arterial oxygen saturation (SaO₂) (2). Hb Kansas was first reported in 1961 as an Hb variant that displays a very low oxygen affinity (3). The Hb molecule consists of two β -globin subunits and two α -globin subunits, which maintain the equilibrium between the relaxed state (R), with a high oxygen affinity and the tense state (T), with a low oxygen affinity. Hb Kansas has an AAC to ACC mutation at codon 102 of the β -globin gene, which results in an asparagine (Asn) to threonine (Thr) substitution.

The binding between β 102 Asn and α 94 Asp (aspartic acid) is imperative for the stabilization of R; however, it is impossible for β 102 Thr to bind to α 94 Asp. The substitution pushes the equilibrium toward T (4, 5). Thus, patients with Hb Kansas present cyanosis; however, they are otherwise asymptomatic and do not require any specific treatment.

Case Report

A 65-year-old woman was referred to our hospital for renal dysfunction. She had a history of hypertension and hypercholesterolemia. Seven days prior to her admission she had been diagnosed with a facial herpes zoster infection, which was treated with valaciclovir and non-steroidal anti-inflammatory drugs. She subsequently experienced a loss of appetite. There were no remarkable symptoms with the exception of cyanosis of the face, lips and nail beds. Her SpO₂ was 70% on room air, despite the SpO₂ being tested using different oximeter probes on different fingers. Her complete blood counts were normal (hemoglobin (Hb), 13.9 g/dL; hematocrit, 41.6%; mean corpuscular volume, 89.5 fL; reticulocyte count, 1.1%; white blood cell count, 5,160/ μ L and platelet count 23.3×10^4 / μ L). There was no evidence of hemolysis. An arterial blood gas analysis (room air) showed that the arterial partial pressure of oxygen (PaO₂) was 88.7 mmHg, with an SaO₂ value of 58.1%. Her carboxyhemoglobin and methemoglobin levels were both negligible. A urinalysis showed a pH of 5.0, a specific gravity of 1.013, ($\pm$) protein and ($\pm$) blood (by dipstick), and negligible casts. The urine sodium and creatinine concentrations were 21 mEq/L and 221 mg/dL, respectively. Moreover, the following values were observed: albumin, 4.4 g/dL; aspartate

Table 1. Hemoglobin Screening Tests Results of the Present Patient.

	the present patient	normal range
HbF (%)	0.5	<1.0
HbA ₂ (%)	2.5	2~3.5
Isopropanol test	(±)	(-)
glycerol lysis time (sec)	32	22~55
Inclusion body	(-)	(-)
Isoelectric focusing	Abnormal band (+)	(-)

aminotransferase, 17 U/L; lactate dehydrogenase, 259 U/L; blood urea nitrogen, 39 mg/dL; creatinine, 3.0 mg/dL; uric acid, 8.6 mg/dL; creatine kinase, 137 U/L; sodium, 140 mEq/L; potassium, 4.3 mEq/L; glucose, 128 mg/dL and C-reactive protein, 0.5 mg/dL. Computed tomography revealed normal kidney conformation, no pneumonia and no pulmonary edema. Sufficient fluid replacement rapidly improved her renal function, with her serum creatinine level reaching 0.74 mg/dL; after which the patient recovered. Her renal dysfunction was mainly caused by pre-renal factors.

However, her SpO₂ value remained low. We investigated the cause of the unexpectedly low SpO₂. Ultrasound cardiography showed almost normal findings and no shunt flow. A respiratory functional test was also normal. We examined whether her SpO₂ value improved when oxygen was administered in abundance. However, her SpO₂ value remained at 78% under both 5 and 10 L oxygen by mask. On the other hand, under 5 L oxygen, her PaO₂ and SaO₂ values were 230 mmHg and 77.4%, respectively. Thus, we suspected that the patient's condition involved an Hb variant with low oxygen affinity. In fact, the patient had looked pale since adolescence; however, she had no critical symptoms. In addition, the patient's mother also had asymptomatic cyanosis, but she had already died. The patient's son did not have cyanosis. The Hb screening test results were as follows (Table 1): both the percentage of HbF and HbA₂ were normal; an isopropanol test, which shows the presence of unstable Hb, was within the normal range; the glycerol lysis time was normal and an HbH inclusion body test was negative (ruling out thalassemia); Hb electrophoresis (isoelectric focusing) revealed an abnormal band, at the approximate position of HbA (Figure A). Finally, a DNA sequence analysis of the α - and β -globin genes revealed an AAC to ACC mutation at codon 102 of the β -globin gene, resulting in asparagine to threonine substitution (Hb Kansas) (Figure B).

Discussion

Generally, patients with low SpO₂ and cyanosis may suffer from some cardiopulmonary problems. However, Hb variants with a low oxygen affinity should be considered in patients with unexplained cyanosis, if there is dissociation between PaO₂ and SaO₂ (or SpO₂). These Hb variants, in which the alteration of the globin structure due to a genetic mutation causes the low oxygen affinity of Hb, are very rare. An increase in the ratio of deoxidized Hb to oxidized

Figure. A: Hb electrophoresis (isoelectric focusing) of the patient and a control. An abnormal band around the position of HbA was observed in the patient (arrow). **B:** The direct DNA sequence analysis of the patient's β -globin gene. An AAC to ACC mutation was observed at codon 102 of the β -globin gene. This resulted in an asparagine to threonine substitution.

Hb can lead to cyanosis. Such patients are otherwise asymptomatic and display slightly decreased Hb levels. The oxygen dissociation curve of these patients is shifted markedly to the right in comparison to healthy controls. The delivery of oxygen to peripheral tissues may be enhanced, resulting in the reduction of erythropoietin-mediated erythropoiesis. In addition to Hb Kansas, Hb Beth Israel (6) and Hb Saint Mande (7) are typical Hb variants which display a reduced oxygen affinity, and which lead to cyanosis.

Since Ishiguro et al. reported the first case of Hb Kansas in a Japanese family (8), six cases (four lineages), including the case of the present patient, have been reported in Japan (8-10) (Table 2). Case nos. 1-2 and 3-5 (Table 2) were reported from Toyama (mid-west Japan) and Hokkaido (north of Japan) prefecture, respectively. Our patient was from Hokkaido; thus, there were three lineages of Hb Kansas in Hokkaido. However, the relationships among the families were unclear. The patients were diagnosed at various ages (9 to 65 years of age). All of the patients were diagnosed with Hb Kansas based on investigations for asymptomatic cyanosis and family examinations. Hb Kansas patients do not require any specific treatments and their prognosis is good; however patient No. 3 (Table 2) who had polycythemia and diabetes mellitus died due to a cerebral infarction.

The awareness of Hb variants will help ensure a timely diagnosis and avoid unnecessary investigations and management.

Table 2. Clinical Data of Hb Kansas Patients Reported in Japan.

Patient No.	Ref.	Sex	Age (year)	Hb (g/dL)	MCV (fL)	Reticulocyte (%)	SpO ₂ (%)	SaO ₂ (%)	PaO ₂ (mmHg)	comorbidity
1	8	F	9	12.4	80	2.1	ND	69	101.3	none
2	8	M	40	14.9	94	2.1	ND	ND	87	none
(father of 1)										
3	9	F	62	17.7	92	ND	ND	57.2	96.8	Polycythemia, DM
4	9	F	ND	12.5	92	ND	ND	60.8	100	ND
(daughter of 3)										
5	10	F	57	13.7	96	ND	ND	57.3	84.6	DM
6	Present	F	65	13.9	90	1.1	70	58.1	88.7	Dyslipidemia, HT

MCV: mean corpuscular volume, SpO₂: oxygen saturation by pulse oximetry, SaO₂: arterial oxygen saturation, PaO₂: arterial partial pressure of oxygen, ND: not described, DM: diabetes mellitus, HT: hypertension

Note: SpO₂, SaO₂, and PaO₂ were all measured under room air

The authors state that they have no Conflict of Interest (COI).

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