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

Yoshikuni Nagayama, Minoru Yoshida, Tadashi Kohyama and Katsuyuki Matsui

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 β102 Asn and α94 Asp (aspartic acid) is imperative for the stabilization of R; however, it is impossible for β102 Thr to bind to α94 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/μL and platelet count 23.3×10^4/μL). 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, (±) protein and (±) 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.

<table>
<thead>
<tr>
<th>Test</th>
<th>Present Patient</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hbf (%)</td>
<td>0.5</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Hba2 (%)</td>
<td>2.5</td>
<td>2–3.5</td>
</tr>
<tr>
<td>Isopropanol test (+/-)</td>
<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>Glycerol lysis time (sec)</td>
<td>32</td>
<td>22–55</td>
</tr>
<tr>
<td>Inclusion body (+/-)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Isoelectric focusing</td>
<td>Abnormal band (+)</td>
<td>(-)</td>
</tr>
</tbody>
</table>

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 remained at 230 mmHg and 77.4%, respectively. Thus, we suspected that the patient’s condition involved an Hb variant. 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.

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 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 a 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.

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

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Ref.</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Hb (g/dL)</th>
<th>MCV (fL)</th>
<th>Reticulocyte (%)</th>
<th>SpO2 (%)</th>
<th>SaO2 (%)</th>
<th>PaO2 (mmHg)</th>
<th>comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>F</td>
<td>9</td>
<td>12.4</td>
<td>80</td>
<td>2.1</td>
<td>ND</td>
<td>69</td>
<td>101.3</td>
<td>none</td>
</tr>
<tr>
<td>(father of 1)</td>
<td>8</td>
<td>M</td>
<td>40</td>
<td>14.9</td>
<td>94</td>
<td>2.1</td>
<td>ND</td>
<td>ND</td>
<td>87</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>F</td>
<td>62</td>
<td>17.7</td>
<td>92</td>
<td>ND</td>
<td>ND</td>
<td>57.2</td>
<td>96.8</td>
<td>Polycythemia, DM</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>F</td>
<td>ND</td>
<td>12.5</td>
<td>92</td>
<td>ND</td>
<td>ND</td>
<td>60.8</td>
<td>100</td>
<td>ND</td>
</tr>
<tr>
<td>(daughter of 3)</td>
<td>10</td>
<td>F</td>
<td>57</td>
<td>13.7</td>
<td>96</td>
<td>ND</td>
<td>ND</td>
<td>57.3</td>
<td>84.6</td>
<td>DM</td>
</tr>
<tr>
<td>5</td>
<td>Present</td>
<td>F</td>
<td>65</td>
<td>13.9</td>
<td>90</td>
<td>1.1</td>
<td>70</td>
<td>58.1</td>
<td>88.7</td>
<td>Dyslipidemia, HT</td>
</tr>
</tbody>
</table>

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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References

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