A 37-Year-Old Man With Bronchial Asthma and Unexplained Hypoxemia

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CASE PRESENTATION: A 37-year-old man presented with breathlessness and wheeze of 3 weeks’ duration. There was no chest pain, cough, palpitation, pedal edema, or fever. For the past 12 years, he had been experiencing episodic breathlessness and wheeze, which improved with inhaled salbutamol. He also had symptoms of nasal obstruction, nasal discharge, and sneezing. There was no history of smoking, substance abuse, or the use of any over-the-counter medication. The current episode of bronchial asthma exacerbation was managed with bronchodilators and systemic glucocorticoids. Despite symptomatic relief and clinical improvement, his oxygen saturation remained at 75% to 80%, and he was referred to our facility for further evaluation.

Physical Examination
On examination, the patient was comfortable with a resting pulse oximetric saturation of 75% on room air. The heart rate was 84 beats/minute, respiratory rate 18 breaths/minute, and BP was 110/70 mm Hg. Jugular venous pressure was not elevated. There was no cyanosis, pedal edema, or wheeze. The rest of the physical examination was unremarkable.

Diagnostic Studies
Results of the chest radiograph, spirometry, and ECG were normal. Complete blood count showed a hemoglobin of 11.8 g/dL, and peripheral blood film was normocytic and normochromic with occasional microcytes. Serum bilirubin, liver, and renal functions were normal. High-resolution CT of the chest and CT pulmonary angiography were normal. Echocardiography was normal, and a bubble contrast echocardiography failed to indicate any abnormality. Arterial blood gas analysis showed normal PaO₂ (94.2 mm Hg), and oxygen saturation (SaO₂, 97.5%) while breathing ambient air. The saturation gap was 20. On co-oximetry, the fraction of oxygenated hemoglobin, carboxyhemoglobin, methemoglobin, and deoxygenated hemoglobin were 90%, 0.4%, 0.9%, and 8.7%, respectively. The methemoglobin level estimated by Evelyn-Malloy method was 2.8%. On high-performance liquid chromatography (HPLC), the HbA2 and fetal hemoglobin were normal (2.26% and <1.00%, respectively). Although the adult hemoglobin (HbA) was also normal (84.9%), its peak showed a very subtle shift to the left, with a shallower ascending limb than the normal chromatogram (Fig 1). In addition, a small C-window peak was noted. Cellulose acetate electrophoresis at alkaline pH was normal. Sanger sequencing of the hemoglobin subunit beta gene (HBB) showed a heterozygous missense mutation in codon 45 of exon 2, resulting in a thymidine to cytosine substitution in the codon 45 of exon 2 (HBB:c.137T>C, Fig 2). A heat instability test was positive.
Figure 1 – Hemoglobin high-performance liquid chromatography (BioRad Variant II analyzer Beta Thal Short program) showing a flat ascending slope of the HbA0 peak (blue arrows) in the index patient (A) as compared with the more vertical slope in the normal (B). Additionally, a tiny C-window peak was seen in the patient (A) at just after 5 minutes (orange arrow), which is absent in the normal chromatogram (B).
What is the diagnosis?

Sanger sequencing of the beta-globin gene revealed a heterozygous mutation with a thymidine to cytosine substitution in the codon 45 of exon 2.
Diagnosis: Hemoglobin Cheverly (low-oxygen affinity variant Hb) causing saturation gap and spurious hypoxemia

Discussion
Hypoxemia in a patient with asthma indicates severe acute asthma, which requires aggressive management. Occasionally intracardiac shunt could be unmasked after evaluation for persistent hypoxemia in patients recovering from severe acute asthma.

Pulse oximetry is commonly used for assessing oxygenation status because of its noninvasiveness and widespread availability. The finger pulse oximeter works on the principle of differential absorption of two different wavelengths of light by oxygenated (approximately 940 nm; oxyHb) and deoxygenated hemoglobin (approximately 660 nm; deoxyHb) in the blood. A standard pulse oximeter uses two wavelengths and can usually identify only two species of hemoglobins. Co-oximeter can measure various absorption spectra, because it uses light of multiple wavelengths (at least four) and can identify multiple hemoglobin fractions, including abnormal hemoglobins. Peripheral arterial oxygen saturation measured by the pulse oximeter (SpO2) is generally a surrogate for direct arterial oxygen saturation (SaO2) and tissue oxygenation. The arterial blood gas analysis provides a functional SaO2, which is calculated as oxyHb/(oxyHb + deoxyHb). On the contrary, co-oximetry can measure multiple hemoglobin fractions and provide a fractional SaO2 (oxyHb/[oxyHb + deoxyHb + metHb + carboxyHb]). In physiological conditions, both fractional and functional SaO2 are similar. The knowledge of functional and fractional SaO2 is essential when encountering discrepancies between finger pulse oximetry and arterial blood gas analysis (Table 1).

Although the pulse oximeter is an indispensable tool for measuring oxygen, several factors can affect the measurements, including inadequate tissue perfusion, movement artifacts, and the use of nail color. Falsely normal values may be seen in the presence of carboxyhemoglobin (carboxyHb, which absorbs light at 940 nm and mimics oxyHb). A falsely low SpO2 reading is noted in the presence of methemoglobin (metHb), which absorbs light at both 660 nm and 940 nm. In the presence of abnormal hemoglobins, the pulse oximeter may thus provide erroneous values, and an abnormal "saturation gap" (SaO2 – SpO2 > 5) may be noted. Abnormal

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hemoglobins presenting as saturation gap are most often caused by acquired causes such as methemoglobinemia. Rarely, one may encounter variant hemoglobins with altered oxygen affinity. The variant hemoglobins can have low SpO₂ or normal SpO₂ depending on their light absorption properties. For instance, Hb Cheverly has an increased absorption between 600 to 660 nm (near the absorption spectrum of deoxyHb), leading to a low SpO₂ on pulse oximetry (Table 1). Because the absorption spectrum of Hb Cheverly is akin to deoxyHb, co-oximetry also may be normal.

More than 1,000 inherited variant hemoglobins are known, many of which are clinically insignificant (particularly in the heterozygous state) and often remain undetected. Other hemoglobinopathies can cause significant morbidity because of anemia, hemolysis, sickling, instability, or abnormal oxygen affinity. Rarely, the hemoglobinopathies are severe enough to be compatible with postnatal life (Hb Bart’s hydrops fetalis). A few of the variant hemoglobins, including Hb Cheverly, can be asymptomatic. Of the eight cases of Hb Cheverly reported thus far, most were incidentally detected when the patients were evaluated for an elevated saturation gap or unexplained mild anemia. The youngest patient was 10 days old, and the oldest was 67 years old. Only one of the previously reported patients of Hb Cheverly presented with clinical cyanosis, attributable to the co-existing methemoglobinemia and increased tendency for auto-oxidation with Hb Cheverly.

Hb Cheverly has an amino acid substitution of phenylalanine to serine at position 45 (CD4) in the β chain. Being a mildly unstable variant, Hb Cheverly does not show typical evidence of hemolysis or reticulocytosis. A heat instability test offers an initial clue. Further evaluation requires the performance of HPLC. The HPLC abnormality observed in Hb Cheverly can be subtle, causing difficulty in its identification. Thus, when an unstable hemoglobin variant is suspected, a close inspection of the chromatogram is warranted. Also, if the clinical suspicion is strong, early recourse to genetic testing is judicious. The underrecognition or underreporting of Hb Cheverly is not only because of its rarity and difficulty in diagnosis but also the lack of symptoms related to anemia or hemolysis, common with other abnormal variant hemoglobins.

Clinical Course
In the index case, we excluded severe acute asthma as a cause of persistent low oxygen saturation because of the absence of tachypnea, clinical improvement with treatment, and normal spirometry. We also excluded an intracardiac shunt and other potential causes of hypoxemia by performing relevant investigations. The index case had a saturation gap of >20 and normal co-oximetry, suggesting the presence of spurious hypoxemia and abnormal hemoglobin. The HPLC findings hinted of a variant hemoglobin co-eluting with HbA and was subsequently diagnosed as Hb Cheverly.

We started him on appropriate therapy for his bronchial asthma and allergic rhinosinusitis. Because Hb Cheverly does not cause symptoms, we reassured the patient. None of his family members reported any illness. His parents were deceased, and both of his asymptomatic siblings were found to have a saturation of gap >10, and Sanger sequencing showed Hb Cheverly in both. We counseled the family regarding the benign nature of the hemoglobinopathy and its mode of inheritance. Additionally, we provided emergency cards to the patient and his family indicating their abnormality, to avoid unnecessary diagnostic or therapeutic procedures in the future.

Clinical Pearls
1. Pulse oximetric measurement of oxygen saturation is unreliable in the presence of abnormal hemoglobins. A saturation gap (Sao₂-SpO₂) of >5 is abnormal and is most commonly caused by acquired causes of abnormal hemoglobins (methemoglobin, sulfhemoglobin, and others)
2. Inherited variant hemoglobins presenting as isolated spurious hypoxemia are rare, because most of them are associated with co-existing anemia or hemolysis.
3. Congenital variant hemoglobin causing falsely low SpO₂ should be suspected in patients without any ascribable cardiopulmonary symptoms and normal methemoglobin levels. Confirmation of the diagnosis requires high-performance liquid chromatography, hemoglobin electrophoresis, and gene sequencing.

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Suggested Reading


