Respiratory Medicine Case Reports 21 (2017) 21–24

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

A case of sulfhemoglobinemia in a child with chronic constipation

Ashish George [a, *], Danielle Goetz [a, b]

[a] Department of Pediatrics, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, United States
[b] Women and Children's Hospital of Buffalo, United States

ARTICLE INFO

Article history:
Received 14 February 2017
Received in revised form
9 March 2017
Accepted 11 March 2017

Keywords:
Sulfhemoglobinemia
Sulfhemoglobin
Constipation
Hypoxemia
Cyanosis
Dyshemoglobinemia
Pulmonary arteriovenous malformation (AVM)

ABSTRACT

Sulfhemoglobinemia is a rare condition in which a sulfur atom oxidizes the heme moiety in hemoglobin, making the hemoglobin incapable of carrying oxygen and leading to hypoxia and cyanosis.

This condition has been described in patients taking sulfur medications or who have cultured hydrogen sulfide producing intestinal bacteria such as *Morganella morganii*. This case describes a pediatric patient who was found to have cyanosis on two occasions of urinary tract infection in the setting of chronic constipation, with confirmed sulfhemoglobinemia during the second admission. Sulfhemoglobinemia due to increases in sulfur producing intestinal bacteria led to cyanosis and low oxygen saturations. The patient had an incidental finding of a pulmonary arteriovenous malformation (AVM) but had a normal PAO2 so was not hypoxemic though she was cyanotic. Low oxygen saturations by pulse oximetry may be explained by dyshemoglobinemia as opposed to true arterial hypoxemia; the importance of measuring an arterial blood gas in cases of cyanosis is paramount.

1. Introduction

Sulfhemoglobinemia is a hemoglobinopathy caused by the oxidation of hemoglobin with compounds containing a sulfur atom [1,2]. It involves the incorporation of a sulfur atom into the porphyrin ring of hemoglobin; the heme moiety is oxidized from the normal divalent to a trivalent state, resulting in reduced oxygen affinity and cyanosis. Normally, sulfhemoglobin is not present in the blood (levels <2%), and levels of greater than 60% can lead to death due to tissue hypoxia. Unlike methemoglobinemia and carboxyhemoglobinemia, there is no antidote for sulfhemoglobinemia [3]. Resolution of the sulfhemoglobin occurs with the end of the red blood cell life-cycle. Sulfhemoglobinemia has most often been associated with the use of drugs such as phenacetin, metoclopramide, dapsone, phenzopyridine, and trimethoprim-sulfamethoxazole [2]. Other causes of sulfhemoglobinemia include hydrogen-sulfide-producing intestinal bacteria, such as *Morganella morganii* [4]. Sulfhemoglobinemia is a recognized cause of cyanosis in patients without respiratory symptoms. This case report describes a pediatric patient with sulfhemoglobinemia associated with urinary tract infection and chronic constipation, and an incidental finding of pulmonary AVM.

2. Case

The patient was a seven-year-old female with chronic constipation and history of hemorrhagic cystitis associated with urinary tract infection (UTI). She presented with dysuria without fever. She complained of mild rhinorrhea, but no cough, wheeze or chest pain. The patient took only polyethylene glycol for chronic constipation; there were no accidental or intentional ingestions of chemicals or medications. She had one prior hospitalization for UTI three months prior with hemorrhagic cystitis, during which time she was also noted to have low oxygen saturation for three days while hospitalized. She did not have other respiratory symptoms or exam findings at that time; chest radiograph was normal. She was treated with supplemental oxygen and ceftriaxone while hospitalized and sent home to complete eight days of cefdinir. The patient lived in a rural setting near dairy farms, and had outdoor exposure to cigarette smoke. The patient did not have any known family history of cardiopulmonary diseases, and immunizations were up-to-date.

In the patient's community emergency department, her oxygen saturation by pulse oximetry was 82% on room air. Pulse was 130 beats per minute and respirations 24 per minute. Patient was not in respiratory distress and cardiopulmonary exam was benign.

* Corresponding author.
E-mail address: ashishge@buffalo.edu (A. George).

http://dx.doi.org/10.1016/j.rmcr.2017.03.009

Complete blood count (CBC) showed a hemoglobin and hematocrit of 12.7 g/dL and 37.6% respectively. Urinalysis demonstrated hemoglobin 3+, with >100 red blood cells (RBCs), moderate leukocyte esterase but negative nitrites. Chest radiograph was normal. Ceftriaxone was given for treatment of UTI. During transfer to the Women and Children's Hospital of Buffalo oxygen saturation was 93% on 3L/min via nasal cannula (NC), pulse was 110 beats per minute, and respiratory rate 18 per minute. She was pale with perioral cyanosis. Chest exam was clear. Electrocardiogram was within normal limits. Capillary blood gas while on 3L NC oxygen showed pH 7.44, pCO2 32 mmHg and pO2 170 mmHg. CBC showed hemoglobin and hematocrit at 9.9g/dL and 30.4% respectively, with normal mean corpuscular volume and reticulocyte count. Methemoglobin levels were indeterminate on co-oximetry due to interference from sulfhemoglobin. Per the manufacturer's reference manual, the levels of sulfhemoglobin had to be between 2 and 10% since sulfhemoglobin was detected but able to be corrected. A venous blood gas the day after admission showed pH 7.35/CO2 47/HCO3 24 and continued elevation of sulfhemoglobin. Hemoglobin electrophoresis was normal; blood and urine cultures showed no growth. A CT angiogram of the chest revealed a tiny (<3mm) right lower lobe AVM, thought to be clinically insignificant (Fig. 1). MRI with and without contrast of the brain was negative for any AVMs. A 2D echocardiogram did not reveal any anatomical or physiological abnormalities.

The patient continued with paleness and perioral cyanosis. Arterial blood gas showed pH 7.42, PCO2 38 mmHg, PAO2 104 mmHg, HCO3 25 mEq/L, base excess 0.2. Carboxyhemoglobin levels were within normal limits. Given the normal PAO2 and the presence of an unknown level of sulfhemoglobin on the co-oximeter, a sulfhemoglobin level was sent to an outside laboratory four days after admission. The result was at 3.4% (normal levels less than 2.0%). Stool cultures showed normal intestinal flora.

The patient's oxygen saturations and dysuria improved; she was discharged on amoxicillin for her UTI. The patient saw hematology nine days later; she had no respiratory distress or cyanosis and pulse oximetry was 98% on room air. Repeat sulfhemoglobin level was normal (<2%).

3. Discussion

This case illustrates sulfhemoglobinemia as a cause of cyanosis in a child with UTI in the setting of chronic constipation. Sulfhemoglobin is a stable green-pigmented molecule that lasts the lifespan of an erythrocyte (approximately 120 days) [1]. The presence of this molecule is rare, and has been associated with the use of drugs such as phenacetin, dapsone, metoclopramide, nitrates, and acetanilide [1,2], none of which our patient ingested. In this case, since there were no exogenous causes identified, we postulate that the sulfhemoglobinemia was most likely due to the transmigration of intestinal bacteria during acute illness of UTI with underlying constipation, leading to hydrogen sulfide production. Constipation has been reported in the literature with cases of sulfhemoglobinemia as early as 1948 [3]. Cases of neonatal sulfhemoglobinemia have been caused by intestinal *Morganella morganii* [4]. In our patient, stool cultures showed normal intestinal growth; blood and urine cultures were negative. However, since the patient has had recurrent UTIs, likely secondary to the constipation, and has been treated with multiple courses of antibiotics, it is likely that the intestinal flora had undergone transformation and could

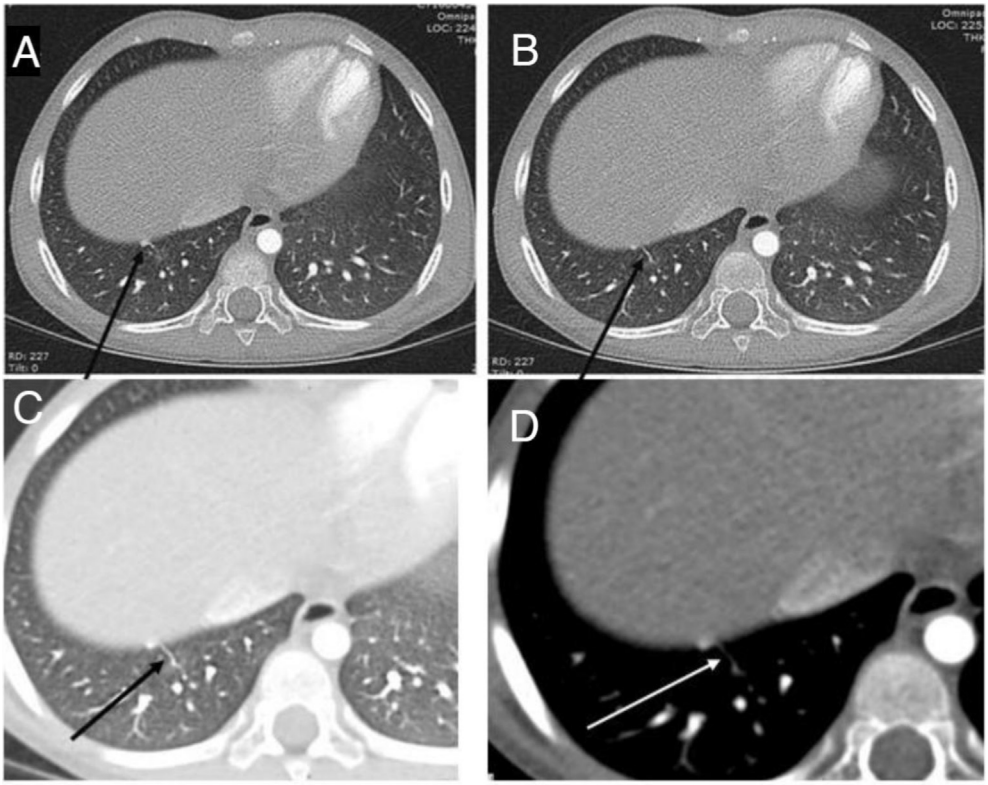

Fig. 1. Right lower lobe arteriovenous malformation.

have produced hydrogen sulfide leading to the sulfhemoglobinemia. In constipated patients there is a dysbiosis of intestinal flora with a 10–100-fold increase in sulfate-reducing bacteria leading to an increase in hydrogen sulfide [5]. Further, the increased colonic transit in constipated individuals leads to increased bacterial breakdown of amino acids that leads to release of hydrogen sulfide [6]. These changes were likely present from the first presentation with sulfhemoglobin levels slowly decreasing to normal levels during the three-month interval between admissions.

The patient had an *Escherichia coli* UTI with hemorrhagic cystitis three months prior to admission treated inpatient with ceftriaxone and outpatient with cefdinir. It is reasonable to postulate that the cephalosporins could have been the cause of the sulfhemoglobinemia. Cephalosporins have a sulfur atom in their core structure that under the right circumstances has the potential to oxidize hemoglobin. Cephalosporins in the presence of certain bacteria can be oxidized to cephalosporin sulfoxides [7]. The patient did have low pulse oximetry noted during the prior hospitalization while on the cephalosporins, but this resolved prior to discharge. In the second UTI, the patient's symptoms preceded her being given the cephalosporins, making this drug a less likely cause of the sulfhemoglobinemia. Within one week after discharge, the patient's sulfhemoglobin levels were undetectable. The patient was on cephalosporins while inpatient, but was discharged on amoxicillin. Nitrofurantoin and trimethoprim-sulfamethoxazole were avoided due to possible contribution to the production of sulfhemoglobin.

On presentation to the ED, the patient was placed on supplementary oxygen due to cyanosis and low pulse oximetry. Pulse oximetry works on two light wavelengths (660 and 940 nm) to determine the ratio of pulse-added absorbencies, which is associated with SpO2 by comparing values to a table of healthy volunteers [1]. Interference with these wavelengths leading to low pulse oximetry readings has been documented with dyshemoglobinemia, such as carboxyhemoglobin, methemoglobin and sulfhemoglobin, intravenous dyes, anemia, and low perfusion states [8]. Sulfhemoglobin has a peak spectral absorbance at 620nm; in order to distinguish from methemoglobin, multiple different wavelengths of light may be used with co-oximetry or more advanced techniques [9–11]. The patient was found to have sulfhemoglobinemia, as determined by the blood gas analyzer reading “unable to measure methemoglobin due to the presence of sulfhemoglobin”, which per manufacturer indicates a level above between 2 and 10%; a level of more than 10% could not be corrected on the co-oximeter. The effects of increasing concentrations of sulfhemoglobin on the pulse oximetry is unknown; studies were performed in dogs with methemoglobin but not with sulfhemoglobin [1]. Sulfhemoglobin is not capable of carrying oxygen; when it binds to the heme tetramers it only binds to 1 or 2 of the subunits, and reduces the affinity of the remaining heme moieties [1,9]. This results in the release of oxygen at the tissues, which can facilitate tissue oxygenation until very high concentrations of sulfhemoglobin are reached. This relationship is demonstrated by the oxyhemoglobin dissociation curve, showing the relationship between oxyhemoglobin % saturation and arterial partial pressure of oxygen (PAO2). Sulfhemoglobin shifts the curve to the right, which means that the PAO2 at which 50% of the oxyhemoglobin units are bound (P50) is higher than regular hemoglobin. Methemoglobin, in contrast, shifts the oxyhemoglobin curve to the left, meaning that oxygen is held more tightly to the molecule, resulting in decreased tissue oxygenation at the same oxyhemoglobin % saturation [9]. In addition, early research has determined that less sulfhemoglobin (0.5g/dL) is needed to cause cyanosis as compared to methemoglobin (1.5g/dL) and deoxygenated hemoglobin (5g/dL) [3].

An important teaching point from this case is the inability of a capillary blood gas (CBG) or venous blood gas (VBG) to determine the actual arterial oxygen saturation, although they may be less painful for the patient. In the context of cyanosis and low oxygen saturation by pulse oximetry, the next step should have been an arterial blood gas (ABG), since this is the only type of blood gas that demonstrates the arterial partial pressure of oxygen, which should be 100 mmHg in a normal individual in room air. An ABG done on room air demonstrated a normal PAO2, which helped confirm the diagnosis of a dyshemoglobinemia causing cyanosis as opposed to actual hypoxemia.

Before the ABG was performed, several investigations were done to look at reasons for hypoxemia. The five physiological reasons for hypoxemia include: high altitude (low partial pressure of oxygen in the air), ventilation-perfusion (VQ) mismatch, hypoventilation, diffusion block and shunting. The patient lived in Western New York and was hospitalized in Buffalo, New York and therefore not at high altitude. In terms of reasons for VQ mismatch, history, exam and chest radiograph findings did not reveal pneumothorax, pneumonia or asthma. Hypoventilation was ruled out with the normal PCO2 on the capillary and arterial blood gases. Diffusion block was unlikely based on normal chest radiograph. Diagnostic evaluations for intracardiac shunting included 2D echocardiogram, which was unremarkable. In terms of intrapulmonary shunting, a CTA of the chest revealed a small pulmonary AVM less than 3 mm. A single AVM less than 2 cm is unlikely to cause significant shunting to cause hypoxemia [12]. The severity of symptoms associated with AVMs has been correlated with both the size and number of AVMs present. Pulmonary AVMs are rarely diagnosed in children and only 10% of cases of pulmonary AVMs are identified in infancy or childhood, with an incidence of 2–3 per 1,000,000 with a female predominance [13]. The presence of an AVM can many times be an incidental finding However, AVMs can be associated with Hereditary Hemorrhagic Telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome [12]. HHT is a genetic disorder that is accentuated by numerous vascular abnormalities, such as AVMs, that present in multiple organ systems, including but not limited to the skin, lungs, and brain [14]. One of the most important consequences to recognize is the risk of rupture of AVMs that might be present in the brain or the risk of embolization of clots formed in pulmonary AVMs leading to brain infarction. This risk of brain infarction had mainly been associated with patients with pulmonary AVMs with feeding arteries greater than 3mm in diameter. However, there have been reports of brain infarctions in adults with pulmonary AVMs with feeding arteries as small as 1.8mm. Of note, these patients did have a history of deep vein thrombosis [15]. Fortunately, in this case an MRI of the brain with and without contrast ruled-out any AVM. Our patient should be monitored for possible increase in the size of the pulmonary AVM with time.

4. Conclusion

Sulfhemoglobinemia is a rare hematologic condition associated with central cyanosis and low pulse oximetry. This case demonstrates the rare entity of sulfhemoglobinemia in a pediatric patient with chronic constipation and acute UTI, likely caused by the dysbiosis of her intestinal flora leading to an increase in sulfate-reducing bacteria. Low pulse oximetry may not always be due to hypoxemia, and may be due to dyshemoglobinemia. Sulfhemoglobinemia should be considered in the differential diagnosis of patients with central cyanosis in the absence of hypoxemia, and an arterial blood gas analysis is an essential part of the evaluation.

Acknowledgments

We wish to thank Dr. Michael Bye for proofreading our

manuscript.

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