A 5-year Old Male with Cyanosis: A Case Report of a Diagnostic Dilemma During the COVID-19 Pandemic

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BACKGROUND

Methemoglobinemia occurs when ferrous iron is oxidized to ferric iron in the hemoglobin molecule, forming methemoglobin [1-3]. It is characterized by profound cyanosis, headaches, dizziness, confusion, and can progress to coma and death. Symptoms worsen as the level of methemoglobin in the body increases. The percentage of methemoglobin relative to the amount of total hemoglobin is a better predictor of symptomatology rather than the actual methemoglobin level [2]. The arterial blood gas will show normal $Po2$ levels despite cyanosis and a normal calculated oxygen saturation. The co-oximetry is used to measure direct levels of methemoglobin [1-3]. Glucose 6-phosphate dehydrogenase (G6PD) deficiency causes increased risk of hemolysis and methemoglobinemia due to lack of nicotinamide adenine dinucleotide phosphate in the reduced form (NADPH) [1,2]. There have been few case reports in adults and one child with methemoglobinemia associated with acute SARS-CoV-2 infection but there has not been any association with presence of SARS-CoV-2 antibodies [4-6]. We report the case of a 5-year-old male with methemoglobinemia, refractory to methylene blue, who was positive for SARS-CoV-2 antibodies but PCR negative for active infection, all prior to vaccine availability to children.

CASE REPORT

A 5-year-old boy of East Asian descent presented to the emergency department for lethargy and vomiting. He has developmental delay of unknown etiology and is exclusively g-tube dependent, but has no other known medical issues. He lives with family and attends school during the day. He was born and has received all of his healthcare in the United States. Family denies any medications, herbal supplements, or well-water usage.

Family reported vomiting for 2 days, lethargy for 1 day, and pallor for 1 day prior to admission. They denied fever, upper respiratory infection symptoms, or known SARS-CoV-2 exposure. His initial vitals were remarkable for tachycardia of 188 beats per minute,

respiratory rate of 42 breaths per minute, oxygen saturation of 55% on room air, and his blood pressure was normal for age. On exam, he was pale, had cracked, dry lips, and would only moan to painful stimulation. His lung sounds were clear and he did not have retractions or nasal flaring. He was placed on heated flow nasal cannula at 10 liters per minute, 100% FiO2 with no improvement in his hypoxia or tachypnea. The emergency department providers were concerned about the accuracy of the pulse oximetry reading and briefly trialed continuous positive airway pressure at 100% FiO2, again with no change in his hypoxia or tachypnea. Initial laboratory analysis revealed anemia with a hemoglobin of 7.9 g/dl, an elevated white blood cell count of 16.58 g/dl, normal chemistries except for elevated total bilirubin of 2.9 mg/dl, C-reactive protein of 15.2 mg/L, and a procalcitonin of 1.52 ng/ml. Blood and urine cultures were obtained along with an arterial blood gas, which had a normal pH and PO2 of >417 mmHg. Due to his symptomatic anemia, a 20 ml/kg packed red blood cell transfusion was started. Empiric antibiotics added due to elevated white blood cell count and C-reactive protein with an equivocal procalcitonin.

He was transferred to the pediatric intensive care unit (PICU) at a tertiary care center, where a co-oximetry was performed, which revealed a methemoglobin level of 15%. Hypoxia unresponsive to 100% oxygen along with a normal-high Po2 and elevated methemoglobin level led to the diagnosis of methemoglobinemia with an unidentifiable etiology.

He was given 2mg/kg of intravenous methylene blue without improvement in his oxygen saturations. Repeat co-oximetry approximately 2 hours after the dose showed a methemoglobin level of 13.6%. A second 2mg/kg dose of methylene blue was administered again with no observable improvement. Repeat complete blood count revealed a hemoglobin of 8.1 g/dl despite receiving a blood transfusion, which raised suspicion for a hemolytic process. Pediatric hematology-oncology was consulted and recommended high dose ascorbic acid due to hemolysis with methylene blue, which can be seen in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. He was started on high dose oral ascorbic acid every 6 hours. Within 12 hours, his oxygen saturations normalized and he was taken off supplemental oxygen. 24 hours after PICU admission, his qualitative SARS-CoV-2 Spike Protein IgG/IgM Antibody test returned positive. No quantitative antibody measure was performed. Blood and urine cultures were negative, so antibiotics were discontinued after 48 hours. He was discharged home on hospital day 4 on oral ascorbic acid, requiring no supplemental oxygen and had returned to his neurologic baseline. Upon outpatient follow-up, he was found to have G6PD deficiency.

DISCUSSION

Methemoglobinemia is a rare condition that results in tissue hypoxia secondary to disruption in the ability of the red blood cell to transport both oxygen and carbon dioxide [1,2]. Methylene blue is the treatment of choice for severe methemoglobinemia with an initial dose of 1-2mg/kg intravenous over 5 minutes [1-3,7]. It is a co-factor that increases the reduction of methemoglobin to oxyhemoglobin in the presence of NADPH, but requires G6PD to function [8]. If a patient has a deficiency of G6PD, administration of methylene blue can cause hemolysis and paradoxical methemoglobinemia [2,8,9]. Our patient had worsening hemolysis after administration of methylene blue and his methemoglobin levels were not improving. This led us to treatment with ascorbic acid, which reduces methemoglobin in vitro and is the treatment of choice for severe methemoglobinemia in patients with G6PD deficiency or in which methylene blue is unavailable [10]. The initial dose of ascorbic acid is 1-2g intravenously administered over 10 minutes followed by daily oral dosing [10]. Our patient did not have known G6PD deficiency, but was diagnosed during outpatient hematology follow-up.

Methemoglobinemia can be congenital or acquired. Acquired cases are usually secondary to exposure to toxic agents, such as nitrates or chlorates. Medications such as dapsone or benzocaine have also been implicated as inciters of methemoglobinemia. Multiple cases have been reported of patients with SARS-CoV-2 who were also treated with hydroxychloroquine [4-6]. Other potential causes of methemoglobinemia in our patient that were explored include medications, toxins, or genetics. Family repeatedly denied the use of any herbs, oral non-prescribed medications, or supplements. They also denied any known toxin exposure. Finally, although genetic studies had been obtained, it is unlikely for congenital methemoglobinemia to present at this age.

The presence of SARS-CoV-2 antibodies and the ambiguity of the COVID-19 pandemic at the time of this case presented a clinical conundrum in our patient. The final diagnosis of methemoglobinemia was not clear initially and was likely clouded due to SARS-CoV-2 antibody positivity. The family was not aware of any SARS-CoV-2 exposures and did not endorse any acute illness consistent with acute SAR-CoV-2 infection. Our patient was positive for SARS-CoV-2 antibodies, but negative PCR, suggesting previous exposure

to the virus, but not acute infection. There have been few case reports in the published literature noting unexplained methemoglobinemia in the setting of acute SARS-CoV-2 infection [4-6]. The patients were mostly adults who required hospitalization for acute hypoxic respiratory failure and had received hydroxychloroquine at some point during their hospitalizations. There have also been reports of elevated methemoglobin levels in patients with acute SARS-CoV-2 infections compared to healthy patients [4]. There has been a pediatric report of a patient with Kawasaki-like shock syndrome who presented twenty-two days after SARS-CoV-2 diagnosis. She had multiple methemoglobin measurements, with the highest being 1.9%. This patient was not diagnosed with Multisystem Inflammatory Syndrome in Children clinically, but she was found to have G6PD post-mortem [4]. Finally, there have been reports that patients with G6PD deficiency are potentially more vulnerable to SARS-CoV-2 infection [11,12]. Our patient did not have any clinical symptoms of active COVID-19 infection and also had complicating factors, including gastrointestinal symptoms that may have precipitated the hemolysis and methemoglobinemia, but the COVID-19 pandemic likely played a role in the initial diagnostic dilemma that was faced in this case.

Methemoglobinemia is an important diagnosis to consider in patients with refractory hypoxemia, even without any risk factors. It is especially essential to consider the diagnosis when the hypoxemia is out of proportion to the patient's respiratory exam. SARS-CoV-2 may play a role in the pathogenesis of hemolysis related to methemoglobinemia, especially in patients with G6PD deficiency, but again, further investigation is necessary [4, 11-12].

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