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Case report

Methemoglobinemia and hemolytic anemia after COVID-19 infection without identifiable eliciting drug: A case-report

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ABSTRACT

We report a second case of methemoglobinemia and non-autoimmune hemolytic anemia after contracting the SARS-CoV-2 infection in the absence of an identifiable eliciting drug. A 35-year old male without previous known comorbidities was admitted after he was diagnosed with the COVID-19 infection and had large pulmonary involvement. Seven days later, he desaturated but was without any signs of respiratory distress. A check of arterial blood gas revealed normal partial pressure of oxygen and follow-up tests confirmed a methemoglobinemia diagnosis. Over the next few days, hemolysis was established after decreased levels of hemoglobin and increased levels of indirect bilirubin and lactate dehydrogenase. A hemolytic anemia investigation panel came back normal, including G6PD. A second G6PD test was ordered at the 5-month follow-up appointment and revealed decreased levels. Clinicians should thus be aware of possible false negative tests when testing for G6PD during hemolytic crisis. In addition, whether the COVID-19 infection alone would be responsible for this chain of events remains a challenging question.

Introduction

COVID-19 is an emerging infectious disease caused by the SARS-CoV-2 virus that has infected more than 50 million people worldwide [1]. Although most patients will have mild limited symptoms, 5 % of them will develop severe acute distress syndrome and need advanced care [2]. In addition to respiratory involvement, thrombotic complications are well described after infection [3]. A possible explanation include the activation of cytokines, ultimately leading to vascular damage and activation of the coagulation cascade [4].

Conversely, there are few cases of hemolysis described in the medical literature. A seven patient case-series reported both warm and cold anti-erythrocyte antibodies mediated hemolysis in COVID-19 infected patients [5]. Methemoglobinemia, also uncommon, has been described mostly after hydroxychloroquine administration [6]. Only one case-report has shown both hemolysis and methemoglobinemia without any known eliciting drug in a COVID-19 infected patient with a G6PD deficiency [7]. Here we report a second case of both concurrent conditions following infection.

Case report

A 35-year old man presented to the emergency department with a 5 day history of abdominal pain and nausea, and a 2 day history of subjective fevers and diarrhea. He denied any upper or lower respiratory symptoms. His initial vital signs included a blood pressure of 110/90 mmHg, heart rate of 78, temperature of 36 degrees Celsius and respiratory rate of 20. His peripheral oximetry showed a 93 % saturation on room air. Physical exam was unremarkable, white any signs of respiratory distress. Initial laboratory exams showed a slight elevation in hepatic transaminases, lymphopenia and altered c-reactive protein (Table 1). A chest x-ray revealed bilateral infiltrates and chest tomography demonstrated multiple ground glass opacities involving 50 % of lung fields. Although the patient denied any suspicious COVID-19 contact, a rt-PCR from nasopharyngeal swab was ordered and confirmed the infection. He was then sent to the inpatient unit and started on antibiotics according to hospital protocol (seven and five-day administration of ceftriaxone and azithromycin respectively).

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Table 1
Admission and Follow-up Laboratory Exams.

	Reference Range	Admission	Days After Admission						
			7D	8D	12D	20D	33D*	62D*	131D*
Hemoglobin (g/dL)	13.5–17.5	13.3	8.3	7.7	6.9	7.6	10.5	11.9	14.3
Hematocrit (%)	39–50	39	26.8	23.9	20.3	22.5	31.9	36.5	42.3
MV (fl)	81–95	87.1	96.4	90.5	89	87.2	90.4	88.4	85.8
MCHC (g/dL)	31–36	34.1	31	32.2	34	33.8	32.9	28.8	33.8
RDW (%)	11.5–16.5	12.3	13.6	15.4	19.4	16.1	14.1	13.5	13
Reticulocyte Count (%)	0,6–1,8			5.6		1.8			
Schistocyte (%)	Up to 0.5				0.4				
White Blood Count (unit/L)	3500–10500	3630	13120	19720	10880	4900	5090	5790	6090
ANC (unit/L)	1700–8000	2360	11414	16368	8563	3082	2901	3277	3721
ALC (unit/L)	900–2900	726	918	2366	1055	1171	1410	1581	1577
Platelet count (unit /μl)	150–450	125	301	389	288	216	232	188	201000
Billirubin, Total (mg/dL)	Up to 1.2			2.23	1.06	0.36			0.73
Billirubin, Indirect (mg/dL)	0.1–0.9			1.86	0.75	0.12			0.49
Haptoglobin (mg/dL)	40–280			1					
LDH (unit/L)	135–225			2882		705			247
PCR (mg/L)	Up to 5	58.64	13.34			19.5			
Creatinine (mg/dL)	0.7–1.2	1.2	1.8	1.8	6.8	3.9	1.5	1.4	1.3
Urea (mg/dL)	16.6–48.5	27.4	33.5	36.3	72.5	41.4	43.6	49.4	31.5
AST (IU/L)	Up to 40	180.2		135.1		26.5			
ALT (IU/L)	18,537	62.2		80		31.1			
Direct Antiglobulin Test	Negative				Negative				
G6PD (U/g)	6.97–20.5			7.7		8.2			3.78
Methemoglobin (%)	0–3			10.5					

MCV = Mean corpuscular volume; **MCHC** = Mean Corpuscular Hemoglobin Concentration; **RDW** = Red Cell Distribution Width; **WBC** = White Blood Cell; **ANC** = Absolute Neutrophil Count; **ALC** = Absolute Lymphocytes Count; **LDH** = Lactate Dehydrogenase; **CRP** = C-Reactive Protein; **AST** = Aspartate Aminotransferase ; **ALT** = Alanine Aminotransferase; **G6PD** = Glucose-6-phosphate Dehydrogenase.
* Follow up after hospital discharge.

Seven days later, the patient desaturated to 78 % on room air, still without any signs of respiratory distress or dyspnea complaints. He was pale (2+/4+), icteric (+/4+) and with brown-colored urine at physical examination. He was then placed on a non-rebreather mask (7 L/minute) but remained hypoxemic – 82 %. An arterial blood gas (ABG) while in oxygen therapy showed pH of 7.42, pCO2 of 46 mmHg, pO2 of 167 mmHg and oxygen saturation of 100 %. Methemoglobin ordered the next day was found to be at 10.5 %. In addition, blood count revealed new anemia with 8.3 g/dL hemoglobin, 26.8 hematocrit levels and 301.000 u/L platelets count. Further investigation identified increased indirect bilirubin (1.86 mg/dL) and lactic dehydrogenase (2882 U/L, reference range 135–225 U/L), decreased haptoglobin (1 mg/dL) and increased reticulocytosis (147,840 or 5.6 %). A concurrent risen of creatinine levels was also observed, from 1.2 to 2.0 mg/dL. He had no coagulation abnormalities except for an elevated d-dimer (>7650 ng/mL). Patient was then transferred to the intensive care unit (ICU) and initiated on ascorbic acid 5 mg/day. Anemia investigation panel showed increased ferritin, lower folic acid levels, normal serum vitamin B12 and negative direct coombs test. In addition, within the reference range results were found for the following exams: G6PD (8,27 U/g/Hb), hemoglobin electrophoresis, serum porphobilinogen, osmotic fragility test, cryoglobulinemia levels and schistocytes. Rheumatological panel indicated only a cytoplasmic 1/160 antinuclear antibody without any complement consumption. A careful review of inpatient prescription records showed no suspicious medications until that date (ceftriaxone, azithromycin, oseltamivir, scopolamine, methimazole, omeprazole, enoxaparin, ondasentron, 0.9 % saline and ringer lactate solution).

The patient progressed with worsening anemia and renal dysfunction in the following days but without need for renal replacement therapy. He had a minimum hemoglobin of 5 g/dL and a maximum creatinine of 6.8 g/dL during hospitalization. His peripheral oxygen saturation continued to be lower than observed at the ABG over the next 3 days. He received two packed red blood cells while in UCI. After three days, laboratory evidence of hemolysis diminished and the patient clinically improved. He is sent back to the inpatient unit on the 14th day of hospitalization and is discharged home 7 days later. His pre-discharge medical exams showed a hemoglobin of 7.6 g/dL and creatinine of 3.9 g/dL. At the 2 month follow-up in the outpatient clinic, he did not have any complaints and his laboratory panel revealed hemoglobin of 10.5 g/dL and improved renal function with a creatinine of 1.5 g/dL. A new G6PD dosage ordered after 5 months revealed decreased levels (3.78 U/g/Hb) and therefore confirmed the diagnosis of G6PD deficiency.

Discussion

Methemoglobinemia is an uncommon condition characterized by tissue hypoxia with normal partial pressure of oxygen in the blood [8]. Patients typically present with cyanosis and dyspnea that, in rare cases, progress to coma, shock or severe respiratory failure due to hypoxia [9]. This is caused by the oxidation of hemoglobin's iron to its ferric state, which leads to a failure of oxygen carriage by the hemoglobin. In its acquired form, toxins and medications are the major triggers of the oxidation burst. Because of its pathophysiology, patients with anti-oxidation genetic defects are more prone to this condition [8].

The concurrence of methemoglobinemia and non-immune hemolytic anemia has been well-documented in patients with an inherited G6PD defect and/or the overdose of a known oxidative medication. The proposed mechanism involves the production of excess reactive oxygen species (ROS) leading to both iron oxidation and hemolysis. If G6PD is low, reduced glutathione is rapidly depleted, and even small oxidative insults can cause irreversible damage [10]. Conversely, when G6PD levels are normal, the insult must be high enough to saturate cell oxidation reduction capacity and damage red blood cells. This is commonly observed after an overdose of highly oxidative medications such as dapsone [11].

Oxidative stress damage plays also an important role in infections. For instance, influenza perhaps promotes most lung

cell injury through excessive production of ROS derivatives [12]. However, whether infection-related ROS insults are enough to promote both methemoglobin and hemolysis is still unknown. Researchers reported the above co-occurrence after campylobacter enteritis [13] and hepatitis E virus infection [14]. With respect to COVID-19, there is increasing evidence that oxidative stress worsens lung injury during infection: an imbalance of high ROS production and weak anti-oxidation system is thought to explain disease progression and severity in preclinical studies [15].

A recent report described the concurrence of hemolysis and methemoglobinemia in a COVID-19 infected patient with a G6PD deficiency [7]. Here we report a second case of both conditions in a patient with the same inherited defect. Interestingly, G6PD was within normal ranges in the first dosage. A plausible explanation is the effect of reticulocytosis on plasma levels [16]. Importantly, in both reports, no medication trigger was found. Whether the COVID-19 infection alone is responsible for this chain of events remains a challenging question. Our case expands on this topic by presenting the second case of hemolysis and methemoglobinemia co-occurrence in a patient with G6PD deficiency without previous use of a clear eliciting drug.

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Authors statements

DVL collected the data. DVL, LCM and FLN wrote the manuscript with the supervision of RBOL and AAGSB. All authors helped shape the manuscript. All authors provided critical feedback and helped shape the research, interpretation and manuscript.

Publication consentiment

The patient consented with the publication of this manuscript.

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