Methemoglobinemia and acute hemolysis induced by high intravenous doses of vitamin C in a COVID-19 patient with unrecognized glucose-6-phosphate-dehydrogenase deficiency

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Abstract

In glucose-6-phosphate-dehydrogenase deficiency (favism), exposure to oxidant agents can trigger hemolytic crises. The intravenous administration of very high doses of vitamin C was proposed as a treatment for severe coronavirus disease 2019 (COVID-19) pneumonia. Unlike low vitamin C doses, very high doses (>6 gr daily) can promote H_2O_2 formation, oxidation of hemoglobin to methemoglobin and, eventually, hemolytic anemia in patients with favism. We here describe the case of a 77-year old man hospitalized for severe COVID-19 pneumonia and treated with a mean daily dose of 9.5 gr of intravenous vitamin C during the first 6 days. He developed methemoglobinemia and hemolytic anemia, which improved after interruption of vitamin C treatment. Previously unrecognized glucose-6-phophate-dehydrogenase deficiency was diagnosed. This first case of vitamin C-induced hemolytic anemia in a COVID-19 patient indicates the need of a screening for glucose-6-phosphate-dehydrogenase deficiency before treatment with very high vitamin C doses or for long period.

Introduction

Coronavirus disease 2019 (COVID-19) is a global health issue and can be life threatening in geriatric patients.[1] In about 30% of cases, COVID-19 can be a highly severe illness, owing to a potent inflammatory response to the infectious viral insult, the so-called cytokine storm, leading to extensive lung involvement, multiple organ failure and death.[1] There is no resolutive treatment of severe COVID-19, even though some drugs (such as corticosteroids, tocilizumab, baricitinib, and anakinra) may help counteracting the cytokine storm of hospitalized COVID-19 patients with critical illness.[2] Very high (>10 gr per day) intravenous doses of ascorbic acid (vitamin C) have been found to improve the outcome of non-COVID-19 patients with severe sepsis, a benefit due to the recognized anti-inflammatory and antioxidant properties of vitamin C.[3,4] Very high intravenous doses of vitamin C are currently studied also in critically ill COVID-19 patients and are often used in clinical practice.[4,5] In a small randomized controlled trial, vitamin C proved effective in ameliorating arterial oxygenation in critical COVID-19 patients.[6] We applied a therapeutic protocol based on the off-label intravenous administration of very-high doses of vitamin C (starting from 6 gr per day) in patients admitted for COVID-19 pneumonia to our COVID Unit of Geriatrics of the *Azienda Ospedaliera di Cosenza*, Italy.

Case Report

A 77-year old man presented to the emergency department (ED) of our hospital for dyspnea and was admitted to our ward on the 4th of April 2021. Medical history included only arterial hypertension treated with bisoprolol and telmisartan/hydrochlorothiazide. Activity of daily living (ADL) score before the onset of the acute illness was 6/6. In ED, a positive molecular testing on nasopharyngeal swab was positive for severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection and computed tomography (CT) imaging confirmed the diagnosis of COVID-19 bilateral pneumonia involving 80% of lung parenchyma. On admission to our ward (day 0) peripheral oxygen saturation measured by pulse oximetry (SpO_2) was 96% with 85% of fraction of inspired oxygen (FiO_2) delivered through high flow nasal cannula (HFNC) at 60 L/min. Intravenous dexamethasone (6 mg per day) and piperacillin/tazobactam (2.25 gr three times daily), oral calcitriol and n-acetylcysteine, and subcutaneous enoxaparin were started. At the time of patient's admission (April 2021), remdesivir was not approved for hospitalized COVID-19 patients requiring HFNC,[2] and immunomodulatory drugs such as tocilizumab, baricitinib or anakinra were not considered due to the normal interleukin 6 blood levels at admission,[7] the decreasing trend of C-reactive protein values (Table 1), the absence of rapidly increasing oxygen need, and because the clinical picture was soon complicated by severe hemolytic anemia (see below).

After having obtained written consent, an intravenous loading dose of 3 gr of vitamin C was administered on day 0, followed by a mean daily dose of 9.5 gr by continuous intravenous infusion for the subsequent 6 days. From day 4, however, we observed worsening anemia, dark urine, sub-jaundice and asthenia, together with dissociation between low SpO_2 (about 88%) *versus* high partial pressure of O_2 (pO_2 125 mmHg) and SO_2 (99%) at arterial blood gases analysis performed during HFNC oxygen therapy at a

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Informed consent: This is a description of a case from Unit records; no ethical approval was necessary and informed. Consent was obtained by the patient for data publishing.

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FiO_2 of 80%. Laboratory parameters suggested the diagnosis of methemoglobinemia and intravascular hemolysis (Table 1). In the subsequent days, our patient underwent 4 erythrocytes transfusions and intravenous vitamin C therapy was stopped on day 6. Glucose-6-phosphate-dehydrogenase (G6PD) activity was 20% on day 12 and 5% on day 29, confirming previously unrecognized G6PD deficiency. His clinical conditions progressively improved and HFNC was switched to conventional oxygen therapy on day 12. He was discharged on day 29 with oxygen therapy at 4 L/min, repeatedly negative SARS-CoV-2 testing on nasopharyngeal swabs and improved CT lung imaging.

Discussion

G6PD protects erythrocytes from oxidative damage by maintaining adequate intracellular level of reduced glutathione, a free radical scavenger.[8] G6PD catalyzes the reduction of nicotinamide adenine dinucleotide phosphate (NADP) to nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), which, in turn, allows the erythrocytes to maintain glutathione in its reduced form.[8] In general, NADPH is central in all enzymatic processes of defense against oxidative challenges, mostly against hydrogen peroxide (H_2O_2), a strong oxidizing agent.[8] G6PD deficiency (a genetic disorder caused by inherited chromosome X defect) limits such processes making erythrocytes vulnerable to the development of methemoglobinemia (the accumulation of the oxidized form of hemoglobin) and hemolytic anemia, triggered by oxidant agents such as drugs, infections and fava beans ingestion[8]. Nearly all persons affected by G6PD have no manifestation of disease until exposure to the oxidant agent, that will determine a severe, and frequently life-threatening, hemolytic anemia.[8] A treatment of moderate vitamin C doses (on average 6 gr per day) has been proposed as an antioxidant intervention to counteract methemoglobinemia if methylene blue is contraindicated, like in G6PD deficiency (the reduction of methemoglobinemia by methylene blue is dependent on NADPH, insufficient in G6PD deficiency).[9] However, the real effect, if any, of moderate doses of vitamin C in reducing methemoglobin (Fe^{+++}) to hemoglobin (Fe^{++}) is difficult to estimate, since vitamin C requires 12-24 hours to exert its hypothesized action (unlike methylene blue, that reduces methemoglobin to hemoglobin within minutes), while in the meantime methemoglobinemia is probably corrected by the immediate transfusion of packed red cells.[9] Indeed, repeated case reports have documented that very high daily (>6 gr per day) and cumulative vitamin C doses can cause oxidation, methemoglobinemia and severe acute hemolytic anemia in patients with G6PD deficiency.[10] Vitamin C elicits hemolysis *in vitro* by promoting the formation of H_2O_2;[11] in G6PD deficiency, blood H_2O_2 is not destroyed by glutathione peroxidase, causing lipid peroxidation and change of heme iron from ferrous (Fe^{++}) to oxidized ferric (Fe^{+++}, *i.e.*, methemoglobin), and eventually intravascular haemolysis.[12]

Our patient received about 60 gr of vitamin C in the first 6 days, methemoglobin increased on day 3, anemia occurred on day 4, hemolysis improved after discontinuing only vitamin C (Table 1), and his treatment did not include other drugs known to precipitate hemolytic crises. It should be mentioned that in G6PD deficient patients, hemolytic anemia can be triggered also by acute infections *per se*, mainly severe bacterial infections.[8] SARS-CoV-2 has infected so far over 250 million persons and G6PD deficiency affects 500 million people worldwide.[8] Nonetheless, only 2 case reports have been published of patients with both G6PD deficiency and COVID-19 in which SARS-CoV-2 infection *per se* - without the role of any possible eliciting drug - may have precipitated methemoglobinemia and hemolytic anemia,[13] while other sporadic cases of hemolysis in G6PD deficient patients have been attributed to the administration of hydroxychloroquine for COVID-19.[14] Considering that the potential of causing hemolysis is far more documented for very high doses of vitamin C than for COVID-19, in this patient vitamin C was the '*probable*' responsible for hemolysis according to the Naranjo Adverse Drug Reaction Probability Scale, with a score ranging from 7 (no alternative causes) to 5 (not known if there are alternative causes).[15]

Conclusions

This is the first reported case of vitamin C-induced methemoglobinemia and hemolytic anemia in a COVID-19 patient with unrecognized G6PD deficiency.[10] Considering the possible therapeutic use of vitamin C in COVID-19,[2,4-6] clinicians should be alert to this possible complication. A screening for G6PD deficiency appears advisable before treatment with very high vitamin C doses (>6 gr daily) or for long period.

Table 1. Trajectories of laboratory values.

	Day number of stay in the ward											
	1	3	4	5	6*	7	8	9	11	13	20	29
Hemoglobin, g/dL	12.7	12	9.5	8.9	6.8	6.9	7	9	9.2	9.8	9.8	12
Reticulocytes, %				6.9	8.1	6	5.5					
Total bilirubin, mg/dL	0.73				4.7	4.21	4.43	1.91	1.14			
Indirect bilirubin, mg/dL					3.66	3.49	3.78	1.47	0.87			
Lactate dehydrogenase, U/L	413				1627	1552						
Haptoglobin, mg/dL					6							
Methemoglobin, %	0.6	2.3	4.3	5.1								0.5
G6PD activity, %										20°		5
Serum creatinine, mg/dL	2.57			1.2		1.48		1.21	1		0.78	
White blood cells × microliter	13.500										7.300	
C-reactive protein, mg/L	80.5				14.5						0.5	
Interleukin 6, pg/mL#	3.2										3.9	

Day zero is the day of admission to the ward. *Vitamin C therapy was discontinued on day 6; °reasonable overestimation related to recent transfusions of normal erythrocytes (reference 8); #normal values of interleukin 6 range from 0 to 43 pg/mL (reference 7). G6PD, glucose-6-phosphate-dehydrogenase.

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