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The emergence of methemoglobinemia amidst the COVID-19 pandemic

To the Editor:

Coronavirus disease 2019 (COVID-19) has been associated with a range of hematologic findings and complications [1]. We have encountered three cases of significant methemoglobinemia, and five cases of relatively mild methemoglobinemia, among patients being treated for COVID-19 in our health system during a 4 week period in April 2020. For comparison, there was only one case of mild acquired methemoglobinemia of any cause documented in our health system during the preceding year. Below we describe the three cases of significant methemoglobinemia, including their presentations, treatments, and outcomes.

Case 1: A 50 year-old man with no medical history presented with acute hypoxic respiratory failure (AHRF) due to COVID-19. He received hydroxychloroquine on hospital day (HD) 1, and continued through HD5. He also received brief courses of azithromycin and ceftriaxone. He deteriorated quickly, requiring intubation and mechanical ventilation on HD2, initiation of vasopressors on HD3, and renal replacement therapy on HD4. Persistently low oxygen saturation on pulse oximetry, despite mechanical ventilation with 100% FIO_2, prompted blood co-oximetry. This demonstrated steadily increasing levels of methemoglobin (Met-Hb) which peaked at 10.6% on HD6. He received 1mg/kg of methylene blue, however demonstrated minimal response with respect to oxygenation and Met-Hb level, and therefore received another 1 mg/kg on HD7, and 2 mg/kg on HD8. The Met-Hb levels began to decrease gradually thereafter although did not normalize, and the patient was treated with ascorbic acid 500 mg thrice daily on HD8 – HD10, with normalization of Met-Hb level by HD11. The patient's clinical status improved thereafter, and although he no longer requires mechanical ventilation or dialysis, he remains hospitalized.

Case 2: A 52 year-old man with history of morbid obesity and uncomplicated diabetes mellitus was admitted for AHRF in the setting of COVID-19 infection. He required initiation of mechanical ventilation and vasopressors on HD2, and renal replacement therapy on HD7. He received a 5 day course of hydroxychloroquine on HD2-6. Other medications received included azithromycin, cefepime, vancomycin, and apixaban. On HD6, persistently low oxygen saturation on pulse oximetry despite mechanical ventilation with 100% FIO_2 prompted blood co-oximetry, which demonstrated a Met-Hb level of 22%. The patient received methylene blue 1 mg/kg and then 2 mg/kg as well as concurrent ascorbic acid, however his Met-Hb level increased to > 30%. He therefore received red cell exchange on HD9 with prompt improvement in his Met-Hb level (to 2.9%) and his oxygenation. He was continued on ascorbic acid for several days thereafter until complete normalization of his Met-Hb level. The patient remains critically ill and although he is no longer requiring vasopressors, he remains intubated and dialysis dependent.

Case 3: A 54 year-old man with a history of uncomplicated diabetes mellitus was admitted for AHRF due to COVID-19 infection. He was started on azithromycin on HD1 and hydroxychloroquine on HD2. He required intubation for worsening respiratory failure on HD4, however demonstrated persistent hypoxia despite mechanical ventilation with FIO_2 of 100%. This prompted blood co-oximetery which demonstrated a Met-Hb level of 13.7%. Concurrently, he was noted to have evidence of Coombs-negative hemolysis. He received 1.8 mg/kg of methylene blue however his Met-Hb increased further to 18.8%, and laboratory studies indicated worsening hemolysis as well as a new diagnosis of G6PD deficiency. The patient passed away shortly thereafter.

Methemoglobinemia occurs when iron in the porphyrin group of heme is oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) form [2]. Ferric heme binds oxygen irreversibly resulting in a left shift of the oxygen-hemoglobin dissociation curve. Methemoglobinemia is most often acquired, predominantly due to oxidizing medications. Antimalarial agents including chloroquine have been associated with methemoglobinemia, albeit rarely [3]. Although seemingly of less oxidizing potential than chloroquine, it is possible that the dramatic increase in use of hydroxychloroquine amidst the COVID-19 pandemic is now making this complication more common. This is likely exacerbated by the degree of critical illness among many COVID-19 patients, which puts them under greater oxidative stress, leaving them more susceptible to medication-induced methemoglobinemia. All three patients with significant methemoglobinemia discussed above received hydroxychloroquine, as did all five patients with relatively mild Met-Hb elevations (3% - 7%) encountered during this time period. The only other drug frequently used among this patient cohort was azithromycin, which is not known to be an oxidizing agent. Additionally, all patients in this series (including the three with significant Met-Hb elevation presented above, and the five with milder elevations) were already severely ill prior to initiation of hydroxychloroquine, and thus likely under oxidative stress even before the initiation of any medications. It is unclear if any additional properties of COVID-19, besides inducing oxidative stress during severe illness, might predispose to

methemoglobinemia. Given the many atypical properties of this pandemic this is certainly worth consideration, however, rigorous evidence linking the two remains lacking.

The diagnosis of methemoglobinemia is seldom thought of given its rarity, and thus may remain underdiagnosed during the COVID-19 pandemic. The typical presentation consists of abrupt symptoms of tissue hypoxia following exposure to an oxidizing substance. Notably, as this is a condition of increased heme-oxygen avidity rather than hypoxemia, dissolved oxygen levels on blood gas may be normal in spite of clinical evidence of hypoxia and decreased readings on pulse oximetry. A high index of suspicion is thus required and diagnosis is most often made on co-oximetry or specific blood Met-Hb assay. The severity of symptoms usually correlates with Met-Hb level, although patients with concurrent respiratory compromise (as those in this series) may become symptomatic at lower levels [4]. Treatment consists of discontinuation of the offending drug, and use of reduction agents such as methylene blue and/or ascorbic acid [2]. Refractory instances of methemoglobinemia may benefit from red-cell exchange (as demonstrated in case 2).

Importantly, methylene blue is to be avoided among patients with G6PD deficiency, as demonstrated in case 3 wherein it worsened Coombs negative hemolysis in a G6PD deficient patient. Notably, this patient had some evidence of hemolysis even before receiving methylene blue, and it is unclear whether this may have been related to hydroxychloroquine (as he was on no other potentially oxidizing medications) or COVID-19 itself (although such a complication has not been well-described to date). The other patients in this series were not G6PD deficient (both were tested).

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The first case of acquired hemophilia A associated with SARS-CoV-2 infection

To the Editor:

Acquired hemophilia A (AHA) is a rare bleeding disorder caused by circulating autoantibodies directed against clotting factor VIII (FVIII).[1,2] It involves more frequently elderly people with no previous personal or family history of bleeding. Approximately half of patients with AHA do not have underlying or predisposing disorders (idiopathic cases), with the remaining cases being associated with a wide array of conditions or diseases (ie, post-partum, autoimmune and dermatologic disorders, malignancies, infections and drugs).[3] In more than 80% of cases AHA is characterized by hemorrhage into the skin, muscles, soft tissues and mucous membranes (eg, epistaxis, gastrointestinal and urological bleeds, retroperitoneal hematomas).[3] We present here the case of a 66-year-old man, who in November 2011 presented to the emergency room of the Mantua city hospital with spontaneous severe cutaneous and muscle bleeding. He had no history of bleeding. Blood tests revealed normocytic anemia (hemoglobin 9 g/dL) with normal white cell and platelet count and a prolonged activated partial-thromboplastin time (aPTT) (ratio 2.97, normal range 0.82-1.18) with normal prothrombin time. A mixing study resulted in failure of aPTT correction, suggesting the presence of an inhibitor that was successively identified as directed against FVIII (FVIII activity <1%, inhibitor titer 25 Bethesda units [BU]). The diagnosis of idiopathic AHA was made. The patient was successfully treated with intravenous recombinant activated factor VII (90 μg/kg every 3 hours until bleeding stopped) and oral prednisone and cyclophosphamide (1 mg/kg/day for 4 weeks, then gradually tapered) with a complete remission (CR) achieved on day +21. Following a 9-year period of well-being with normal coagulation checks performed every 6 months, the patient was re-admitted to the Mantua city Hospital on March 2020 because of fever (38.7°C), cough, asthenia and difficulty breathing for 3 days. The diagnosis of Coronavirus Disease 2019 (COVID-19) was confirmed by RT-PCR in nasal swab. A chest CT scan showed a bilateral interstitial pneumonia. Due to the concomitant presence of an extensive hematoma in the trunk, an aPTT was performed and resulted prolonged (ratio 2.87). The diagnosis of AHA was