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

again formulated (FVIII <1%, inhibitor titer 19 BU) and the patient was treated with the same anti-hemorrhagic and immunosuppressive treatment, reaching CR on day +20. In addition, the patient received anti-viral drugs (lopinavir-ritonavir 400 mg/twice daily) and non-invasive mechanical ventilation with oxygen as treatment for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, leading to the resolution of the disease on day +14.

In this case, the first reported in literature, the re-appearance of AHA was triggered by acute SARS-Cov-2 infection. This finding is particularly interesting considering the close interaction between SARS-Cov-2 and the hemostatic system.[4] The AHA cases associated with other viral infections, including hepatitis B and C viruses, have also been described.[3] The recent association between immune thrombocytopenic purpura and COVID-19 further strengthens the virus-induced immune dysregulation,[5] which could have played a key role in the pathogenesis of AHA. We therefore recommend a daily coagulation monitoring (APTT) in patients admitted with acute COVID-19 infection and the inhibitor search (through a mixing test) in those cases with otherwise unexplained onset or worsening of the hemorrhagic picture and/or aPTT prolongation.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

M.F., F.S. and M.P. designed and performed research; I.T., C.G. and B.C. analyzed data; M.F., C.D.F., C.P., G.D.D. and S.C. wrote the paper together; and all authors approved the final manuscript.

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SARS-CoV-2 infection in beta thalassemia: Preliminary data from the Italian experience

To the Editor:

Patients with pre-existent chronic morbidities are likely to be more severely affected by SARS-Cov2 infection, but no data are available regarding Thalassemic Syndromes (TS). Note, TS and hemoglobin variants represent, according to WHO, one of the most frequent causes of anemia, affecting more than 7% of the world population.[1] Thalassemic Syndromes are classified in either transfusion-dependent thalassemia (TDT) or non-transfusion-dependent thalassemia (NTDT). Infectious complications, mainly from bacteria, constitute a common cause of mortality and morbidity in TS. Stress erythropoiesis, iron overload, splenectomy and adrenal insufficiency among others may contribute to increase susceptibility to infection.[2]

To verify the impact of SARS-CoV-2 infection on TS, we set-up a specific survey by electronic Case Report Form (eCRF).[3] Inclusion criteria require at least 15 days of follow-up from either the onset of symptoms or SARS-CoV2 positivity. The survey was approved by Ethics Committee and eCRF was shared with the Centers of Italian Hemoglobinopathies Network. The "Società Italiana Talassemie ed Emoglobinopatie" (SITE), has estimated the presence in Italy of approximately 5000 TDT and 1900 NTDT patients.[3]

As of 10 April 2020, 11 cases of TS and COVID-19 have been collected (see supplementary information). All the reported patients are in Northern Italy, where the rate of infection is higher, reflecting the national epidemiology.

The mean age is 44 ± 11 years (range 31-61 years) and 55% (6/11) are females. Ten patients are TDT, and one is NTDT. All the patients have thalassemia associated comorbidities, eight are splenectomized, and one patient (#9 in the supplementary table) has pulmonary hypertension treated with sildenafil. The likely source of