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LETTER TO THE EDITOR

Severe bleeding in a patient with factor XIII deficiency and COVID-19

To the Editor

Since the outbreak in last December of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in Wuhan, China, scientific literature is providing essential contributions to elucidate the pathophysiological and clinical features of the coronavirus disease 2019 (COVID-19).[1] Consistent evidence shows that COVID-19 is associated with significant changes in coagulation laboratory testing, mainly prolonged prothrombin time and elevated D-dimer.[2] These abnormalities reflect the activation of coagulation system and hyperfibrinolysis, induced by the acute lung injury, hypoxia and the consequent inflammatory responses, which in turn amplify in a vicious cycle. This results in a hypercoagulable state and high thrombotic risk, correlated with poor prognosis and potentially leading to overt disseminated intravascular coagulation in most severe cases.[2] Epidemiologic and clinical data about COVID-19 in congenital bleeding disorders (CBD) are substantially lacking. To date, to our best knowledge, only a case report about a patient with severe haemophilia A and a mild form of COVID-19 has been published.[3]

Herein, we describe the case of a woman with inherited factor XIII (FXIII) deficiency, admitted because of COVID-19 and a concomitant severe abdominal haematoma.

1.1 | CASE REPORT

This 61-year-old woman was diagnosed in 1973 after postsurgical massive bleeding (FXIII Antigen 1.6%) and thereafter received replacement treatment on demand (1-2 traumatic bleeding episodes per year). She presented on 10th March 2020 fever (up to 38.5°C) and cough after close contacts with her mother affected by COVID-19. Antibiotics (azithromycin and ciprofloxacin) and then hydroxychloroquine were prescribed at home. On March 24th, she went to the emergency room because of persistent cough, abdominal pain and diarrhoea. On admission, laboratory tests showed mild anaemia (haemoglobin 10.2 g/dL) and lymphopenia ($0.85 \times 10^3/\mu L$); normal total leukocyte count and liver and kidney function tests; elevated CPK (880 U/L), D-dimer (2540 ng/mL) and CRP (5.51 mg/dL). The detection of viral RNA at oropharyngeal swab (RT-PCR) confirmed the diagnosis of SARS-CoV-2 infection. Chest computed tomography (CT) revealed small areas of ground-glass opacities in the lung lower lobes (visual score 10%-15% of parenchyma involvement). Low-flow oxygen support (1-2 L/min) was needed. Antiviral treatment (darunavir/cobicistat) was started, together with antibiotic cover with piperacillin/tazobactam. Indeed, due to the patient's history of gallbladder stones, the abdominal pain was initially ascribed to acute cholecystitis. However, the detection of a pelvic mass at abdomen ultrasound (US) led to perform a CT that revealed a large haematoma (23x6 cm) involving rectus muscles from epigastrium to pelvis, with signs of active bleeding after contrast agent injection. The patient received plasmaderived FXIII concentrate (Cluviat®, CSL Behring; 2500 IU, 32 IU/Kg) and underwent arteriography with embolization of the right epigastric artery, which led to cessation of bleeding. FXIII Antigen levels were 57.2% and 44.7%, 20 and 72 hours after the infusion of FXIII concentrate, respectively. A packed red cell unit was transfused due to anaemia (Hb 8.7 g/dL). Five days later, FXIII concentrate (1250 IU) was further administered in order to maintain the haemostatic response. At CT reassessment, decreased dimensions of the haematoma (maximum diameter 15 cm) and absence of active bleeding were shown. Over the following days, the patient's haematological and respiratory conditions improved. The oxygen support was gradually reduced until suspension and COVID-19–related treatments (hydroxychloroquine, azithromycin and antiviral therapy) were stopped by April 03rd. At the same time, stable Hb levels and reduction of abdominal pain and haematoma at US assessment were observed. This clinical picture and the ongoing haemostatic treatment with FXIII concentrate enabled to start thromboprophylaxis, usually prescribed in COVID-19 patients since the admission.[4] According to local protocols, weight-adjusted doses of low molecular weight heparin (enoxaparin 70 IU/Kg/d; body mass index 30.5) were given. FXIII levels were maintained >25%-30% to achieve protection from bleeding risk. Indeed, FXIII concentrate 1250 IU was administered 14 days after the previous infusion (FXIII 29%), and further prophylactic coverage was planned every 10-14 days. After negative RT-PCR on two consecutive oropharyngeal swabs, the patient was discharged on April 15th, being mild anaemia and lymphopenia still present. Enoxaparin was suspended 5 days later. The following clinical course was uneventful. On April 22nd at an outpatient visit at the haemophilia centre, mild abdominal swelling and rigidity were found, together with resolution of anaemia and lymphopenia. The patient's clinical course is represented in Table 1.

1.2 | DISCUSSION

This report of a patient with FXIII deficiency adds information about clinical features and management of COVID-19 in subjects with CBD. In a recent description of a patient with severe haemophilia

TABLE 1 Patient's clinical course, interventions and main laboratory data

Day	Event	Intervention/treatment	Laboratory data	pdFXIII (IU)	FXIII: Ag (%)
1	Admission, COVID-19 diagnosis	Chest CT, oropharyngeal swab Start piperacillin/tazobactam; oxygen 2 L/min	Hb 10.2 g/dL; Ly 0.85 × 10^3/μL PTr 1.3, D.dimer 2540 ng/mL, CRP 5.51 mg/dL		
2	Detection of large haematoma of the abdomen wall, active bleeding	Abdomen CT and angiography Start darunavir/cobicistat, hydroxychloroquine, azithromycin. PRC transfusion	Hb 8.7 g/dL		
3		Arteriography, embolization	Hb 10.1 g/dL	2500	
4					57.2
5					
6					44.7
7	Absence of active bleeding confirmed	Abdomen CT reassessment			
8		Stop darunavir/cobicistat, hydroxychloroquine		1250	
9		Stop piperacillin/tazobactam			
10		Stop azithromycin			
11	Reduction of haematoma dimension	US assessment. Oxygen 1 L/min	Hb 10.5 g/dL		
12		Start enoxaparin 6000 IU/d			
13					
14					
15					
16		Stop oxygen			
17					
18					
19					
20					
21					
22			Hb 10.9 g/dL; Ly 0.98 × 10^3/μL, CRP 0.69 mg/dL	1250	29
23	Discharge				
24					
25			PTr 1.23, D-dimer 1644 ng/mL		
26					
27					
28		Stop enoxaparin			
29					
30	Outpatient visit at HTC		Hb 12.2 g/dL; Ly 2.02 × 10^3/μL		39

Abbreviations: CRP, C-reactive protein; CT, computed tomography; FXIII:Ag, measurement of FXIII antigen level; Hb, haemoglobin; HTC, haemophilia treatment centre; IU, International Unit; Ly, lymphocyte count; pdFXIII, plasmaderived FXIII concentrate; US, ultrasonography.

A, no bleeding symptoms or complications were reported.[3] Similarly to that case, our patient suffered from a mild form of COVID-19. Hospitalization was not due to respiratory insufficiency, but to symptoms of severe bleeding. Indeed, a massive muscle haematoma was diagnosed, likely triggered by persistent coughing fits, which induced abnormal strains of the abdomen wall. This clinical presentation highlights the issue of bleeding risk in CBD patients with COVID-19.[5] Bleeding symptoms are uncommon in COVID-19, and the reported coagulation abnormalities do not result in haemorrhagic tendency; however, additional risks for CBD patients over the course of the disease are due to invasive procedures (arterial punctures for blood gas analysis, central venous access insertion and invasive ventilation)

and some pharmacological treatments.[5] These include corticosteroids, non-steroidal anti-inflammatory drugs and, particularly, antithrombotic strategies. The thrombotic risk in COVID-19, with lung microvascular thrombosis as well venous thromboembolism, is increasingly reported.[4] Therefore, thromboprophylaxis with LMWH at least at standard doses is strongly recommended, with some authors also suggesting therapeutic doses, aimed at affecting thromboinflammatory mechanisms.[4] Thromboprophylaxis is also advised in the prehospital phase and after discharge, according to the individual risk profile.[4] Whether the CBD can modify the thrombotic tendency in COVID-19 is currently unknown. On the other hand, it is now recognized that CBD patients are not protected from cardiovascular/thromboembolic diseases and that they can receive antithrombotic treatments with the same modalities than non-coagulopathic subjects, provided that concomitant anti-haemorrhagic prophylaxis is given.[6-8] Evidence-based guidelines are not available in this setting; therefore, strategies rely on expert suggestions and the careful assessment of individual bleeding and thrombotic/cardiovascular risk.[8] These concepts can be extrapolated to CBD patients with COVID-19, in order to manage their bleeding risk due to thromboprophylaxis and other predisposing conditions, during hospitalization and in the home-treatment setting, if needed.[5] Despite the high bleeding risk, our patient was able to safely receive LMWH, maintaining sustained FXIII levels through specific replacement treatment. Due to the rarity of congenital FXIII deficiency, limited information about treatment and safe factor levels is available. However, the long half-life of FXIII concentrate facilitates the achievement of high trough levels with infusion intervals >7-10 days.[9]

This case also remarks that prompt identification of CBD patients and contact with specialist haemophilia centres are crucial for safe and effective management.[10] FXIII deficiency could be missed as patients show normal first-level coagulation tests. Moreover, specific laboratory testing and replacement products are often not available, particularly in the emergency setting.

Ongoing national and international studies will hopefully help clarify the numerous unanswered issues of COVID-19 in CBD patients.

DISCLOSURES

GQ has acted as a paid consultant to Bayer; AC has acted as a paid consultant to Bayer and Novo Nordisk and received speaker fees by Novo Nordisk and Werfen; AT has acted as an advisory board member to Bayer, Roche and Novo Nordisk and received speaker fees by Novo Nordisk. AR, GFR, EF, FG and EM have nothing to declare.

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