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LETTER TO THE EDITOR

Primary thromboprophylaxis in a patient with type 3 von Willebrand disease and severe COVID-19 infection

To The Editor,

In December 2019, a novel coronavirus—the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—was recognized, causing a global pandemic of the coronavirus disease 2019 (COVID-19) that continues to affect millions of people. A striking feature of the acute COVID-19 infection is its association with hypercoagulability. Large series from China, Europe and North America[1] report a high incidence of venous thromboembolism (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) in hospitalized patients with COVID-19. With growing evidence and experience, most major clinical societies and experts now recommend thromboprophylaxis in patients hospitalized with COVID-19, particularly in adults admitted to the ICU with severe disease.[2,3] However, there is little to no evidence to help clinicians weigh the risks and benefits of prophylactic anticoagulation in patients with COVID-19 and underlying congenital bleeding disorders.

We report our experience of a 65-year-old woman with type 3 von Willebrand disease (VWD) admitted with a severe COVID-19 infection requiring mechanical ventilation and treated with thromboprophylaxis.

A 65-year-old white, obese, female with type 3 VWD (von Willebrand antigen: 3.5%, von Willebrand activity: <1%; FVIII: 18%, absent multimers), adult-onset type 1 diabetes mellitus, hypothyroidism, dyslipidaemia and angiodysplasia presented to a New York hospital in April 2020 with a 4-day history of cough, subjective fever (felt warm to touch), myalgias and shortness of breath on exertion. Before her presentation, she was followed at our Hemophilia Treatment Center and was on prophylactic replacement therapy for two months with a von Willebrand factor/coagulation factor VIII human complex (brand name Wilate) at 35 U/kg every other day along with intermittent courses of tranexamic acid for underlying angiodysplasia and history of gastrointestinal bleeding.

On presentation, she was tachypneic, tachycardiac and hypoxic (oxygen saturation was 94% at rest but 85% on walking). We summarize pertinent laboratory findings in Table 1. She was admitted and required supplemental oxygen via nasal cannula. A nasopharyngeal swab was positive for the SARS-CoV-2 virus PCR. She was diagnosed with COVID-19 pneumonia and started on hydroxychloroquine.

Besides the COVID-19 infection, additional risk factors for VTE included obesity (BMI 44.4 kg/m^2), presence of a peripherally inserted central venous catheter in the right arm (for outpatient von Willebrand factor infusions) and hospitalization. As per the institutional protocol, she was started on intermediate-dose thromboprophylaxis with low molecular weight heparin (LMWH) at 40 mg twice daily. She was continued on her home regimen of von Willebrand factor (VWF) replacement (35 IU/kg every 48 hours). She was monitored closely with trough and peak VWF levels, and the factor dose was adjusted to maintain the VWF activity between 30 and 50%.

On Hospital Day 5, her clinical condition worsened. She developed respiratory failure, was intubated and moved to the ICU for mechanical ventilation. She was then started on systemic corticosteroids and H2 blockers for stomach protection. She continued LMWH thromboprophylaxis and VWF replacement therapy. By Hospital Day 13, she developed worsening anaemia. Her Hb dropped to 7.8 g/dL from 9.4 g/dL, and she received a pRBC transfusion. No source of bleeding was identified, and the anaemia was presumed to be due to her angiodysplasia and dilution from phlebotomy. Her LMWH dose was reduced to 40 mg once daily.

She continued to make gradual progress and was extubated by Hospital Day 14 and transferred to a rehabilitation facility. On Hospital Day 18, she was switched to rivaroxaban thromboprophylaxis (10 mg once daily) and was discharged after 3 weeks from her initial presentation. She did not develop significant haemorrhage and there was no evidence of clinical DVT, PE, arterial thrombosis or VTE post-discharge. No screening imaging for thrombosis was done. She was discharged home on rivaroxaban prophylaxis, which was discontinued 4 weeks post-discharge with no evidence of bleeding. She is now 6 months post-COVID-19 diagnosis and doing well.

COVID-19 infection is distinctly associated with hypercoagulability, and the pathophysiology of this coagulopathy is still under investigation. However, it is now believed that the SARS-CoV-2 can affect all three aspects of Virchow's triad of hypercoagulability through direct endothelial cell injury and invasion, stasis from prolonged hospitalization and immobilization and an acquired hyper-inflammatory and procoagulant state. These patients have higher fibrinogen, markedly increased D-dimer and increased factor VIII and VWF levels[4] suggestive of a hypercoagulable state. It is, therefore, no surprise then that these patients have a high incidence of VTEs. A retrospective study demonstrated patients receiving LMWH prophylaxis had improved survival when compared to patients with no thromboprophylaxis.[5] Due to the high incidence of VTE and increased mortality, major organizations including the ISTH[2] and Anticoagulation Forum[3] now recommend low to

TABLE 1 Laboratory results at significant time points of disease.

Test Performed (reference range)	DAY 1 Presentation	DAY 5 Intubation	DAY 8	DAY 16 Rehab	DAY 21 Discharge
WBC (3.8–10.5 K/uL)	6.97	4.5	14.6	13.59	7.97
Hb (11.5–15.5 g/dL)	9.1	8.4	7.2	9	9.2
PLT (150–400 K/uL)	230	227	311	362	351
ALC (1000-3300/uL)	760		510	2150	1510
CRP (< 0.4 mg/L)	28	>42	30.3		
AST (< 31 u/L)	35	64	48	53	26
ALT (< 32 u/L)	20	34	52	90	37
Ferritin (15–150 ng/ml)	997	3541	3036		
D-Dimer (<229 ng/mL)	325	1017	381	519	1243
VWF activity (43–126%)	110 †,‡	43§	45§	69§	54§
VWF Ag (50–150%)	151†,‡	79§			
Factor VIII assay (45–125%)	173†,‡	157§			
COVID–19 PCR	Positive			Positive	Negative*
CHEST X RAY	Normal	Bilateral diffuse infiltrates	Persistent ARDS		Decreased bilateral opacities
Blood Group	A positive				

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; Hb, haemoglobin; PLT, platelet count; VWF, von Willebrand information; WBC, white blood cell count.

†One week prior to presentation, baseline.

‡Peak activity.

§Trough activity.

intermediate-dose thromboprophylaxis in all patients hospitalized with the COVID-19 infection despite non-availability of data from randomized clinical trials. Though the risk is relatively less, there is a risk of bleeding, and as reported in a recent retrospective study of 144 critically ill patients, the rate of major bleeding was 5.6% (95% CI 2.4–10.7%].[4]

There are very limited clinical data and only a few case reports on the effects of COVID-19 in patients with congenital bleeding disorders. Reports have described COVID-19 infection in patients with mild haemophilia A,[6] severe haemophilia on emicizumab prophylaxis[7] and severe Factor XIII deficiency.[8] However, current guidelines do not definitively recommend anticoagulation in this population and rely on individual caregivers to use their clinical judgment. Furthermore, risk assessment models adopted to estimate the thrombotic and bleeding risks in COVID-19 patients have not been validated. This complicates usage of anticoagulation in patients with COVID-19 and congenital bleeding disorders. A recent publication from Belgium[9] provides practical in-hospital guidance in the care of patients with haemophilia. Thromboprophylaxis with LMWH with concomitant correction of FVIII or FIX with trough levels of 30% and peak levels not exceeding 50% has been recommended based on expert consensus. The recommended dose intensity of thromboprophylaxis was based on the concurrent pro-thrombotic risk factors.

Patients with inherited bleeding disorders can develop VTE from various causes. Reports of factor replacement and high factor VIII levels are reported to be an independent risk factor for VTE in patients with VWD.[10] Moreover, COVID-19 infection can cause increased factor VIII and VWF levels as an inflammatory response.

We started intermediate-dose LMWH in our patient and continued her prophylactic replacement therapy while monitoring peak and trough VWF activity with dosage changes. Intending to maintain that activity between 30 and 50%, we not only could safely continue thromboprophylaxis but also maintain haemostatic VWF activity. With her drop in haemoglobin and concern for bleeding, we decreased her LMWH dose. However, our patient did not develop significant bleeding or any clinical evidence of thrombosis. Therefore, monitoring factor levels on replacement therapy, and the use of standard anticoagulation practices allowed us to safely administer thromboprophylaxis both inpatient (enoxaparin) and outpatient (rivaroxaban) in our patient with severe COVID-19 infection. In an effort to reduce exposure of staff to COVID-19, blood draws were coordinated with VWF trough levels drawn after dosage changes were made. Moreover, anticoagulation dosing for thromboprophylaxis in morbid obesity is an important clinical consideration. Based on few retrospective studies, our institution has developed guidelines for thromboprophylaxis in obese patients. We administer LMWH at 40 mg twice daily for patients with a BMI >30 kg/m^2 and consider anti-Xa level monitoring (target range 0.2–0.4 u/ml). The fact that our patient clearly had ongoing risk factors for VTE post-discharge (obesity, diabetes, central line, reduced mobility) and her refusal to continue subcutaneous injections prompted the use of rivaroxaban

for thromboprophylaxis post-discharge. Given her history of angiodysplasia, she was monitored by weekly blood counts drawn by a home nurse and stool guaiac testing three times a week while on rivaroxaban thromboprophylaxis for early detection of bleeding for which there was no evidence.

Our unique anecdotal experience in a severe congenital bleeding disorder with severe COVID-19 has demonstrated the safety of thromboprophylaxis, along with prophylactic replacement therapy with monitoring of VWF levels to prevent significant bleeding and thrombosis. Issues such as dosing in obese and non-obese patients and duration of inpatient or outpatient thromboprophylaxis warrant a systematic study underscoring the need to enrol patient data of COVID-19-infected bleeding disorder patients in existing national database registries.

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KEYWORDS

anticoagulation, bleeding disorder, COVID-19, LMWH, thromboprophylaxis, von Willebrand disease

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

AV wrote the first draft of the letter. AV, SA and PK designed the manuscript. JS, SM and SA were involved in the care, inpatient management and discharge follow-up of the patient. AV, JS, SM, PK and SA revised and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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