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Case Report

COVID-19-Associated Systemic Thromboembolism: A Case Report and Review of the Literature

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Key Messages

- COVID-19 has affected >188 countries, and it presents as sepsis, acute respiratory distress syndrome, and multiorgan failure in its most severe form.
- Coagulopathy including thrombotic microangiopathy of multiple organs has been observed in COVID-19 patients.
- Elevated D-dimer levels could hint towards a poor prognosis unless timely treatment with high-dose anticoagulation is initiated.
- Anticoagulation could be an essential treatment of COVID-19 patients.

Keywords
COVID-19 · SARS-CoV-2 · Cytokine release syndrome · AKI · ARDS · Thromboembolism · COVID-19-associated coagulopathy · Thrombotic microangiopathy · D-dimer · Anticoagulation

Abstract
Introduction: Coronavirus disease 2019 (COVID-19) is a pandemic that has affected >188 countries, involved >24 million people, and caused >840,000 deaths. COVID-19, in its severe form, presents as acute respiratory distress syndrome (ARDS), shock, and multiorgan failure. Thrombotic microangiopathy of the lungs and kidneys has been observed in these patients. Elevated D-dimer levels have been observed in people with serious COVID-19 illness, and this could be helpful in guiding treatment with anticoagulation in these patients. ***Objective:*** To analyze the role of anticoagulation as a treatment modality for COVID-19. ***Methods:*** We pres-

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ent the unique case of a COVID-19 patient who developed sepsis, ARDS, acute kidney injury, and deep-vein thrombosis (DVT), who was deteriorating clinically. She was treated with anticoagulation. ***Results:*** There was rapid recovery after treatment with systemic anticoagulation. ***Conclusions:*** Systemic anticoagulation could prove to be essential in the treatment of COVID-19. Further studies are required to assess its role in improving long-term morbidity and mortality in these patients.

Introduction

Coronavirus disease 2019 (COVID-19) is a viral illness caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been rapidly spreading throughout the world, causing a pandemic, involving >188 countries, >24 million cases, and >840,000 deaths. SARS-CoV-2 enters cells by endocytosis through angiotensin-converting enzyme 2 (ACE2) receptors, which are present in type 2 alveolar cells of the lung, myocardium, and proximal renal tubules. COVID-19 manifestations can range from asymptomatic infections to multiorgan failure and death. The respiratory system is involved in almost all cases. Additionally, there have been many cases of COVID-like illness where patients display cardinal features of COVID-19 but a negative nasal PCR test. On repeat/more intensive testing, these individuals are found to have COVID-19 and thus represent the false-negative fraction of testing [1]. In both proven COVID-19 and COVID-like illness, fever, cough, dyspnea, chest pain, and oxygen desaturation upon exertion are observed. These symptoms have been associated with increased D-dimer levels and pulmonary microangiopathy on necropsy [2, 3]. The kidneys can be involved, with a similar pathophysiology, presenting with hematuria and rapidly progressive renal failure with oliguria and death. We present the case of a COVID-19 patient who developed acute worsening of the illness but then improved rapidly with anticoagulation. This case highlights the multisystem involvement of SARS-CoV-2, raising the possibility of early and intensive anticoagulation as a supportive treatment measure.

Case Report

A 53-year-old female with a past medical history of uncontrolled type 2 diabetes mellitus, hypertension, and hyperlipidemia presented to the hospital with weakness, shortness of breath, and diarrhea. Five days earlier, she had been to the emergency room (ER) of an outside hospital after she had been notified by the health department that she had come into contact with a COVID-19-positive patient. She tested positive for COVID-19 and was treated for COVID-19-related pneumonia in the hospital for a total of 5 days. She was discharged from that hospital but returned to the ER of our hospital on the same day since she was feeling weak and short of breath after returning home, and her oxygen saturation on pulse oximetry at home was in the range of 80–85%.

In our ER, she was noted to be febrile and tachycardic, and required 4 L/min oxygen via nasal cannula to maintain an oxygen saturation >92%. Laboratory workup showed elevated levels of: serum creatinine 1.14 mg/dL (normal 0.85–1.25 mg/dL; patient's baseline 0.8 mg/dL), lactate dehydrogenase (LDH) 393 U/L (normal 7–55 U/L), ferritin 724 ng/mL (normal 11–307 ng/mL), C-reactive protein (CRP) 44.8 mg/L (normal <10 mg/L), D-dimer 0.67 mg/L (normal <0.5 mg/L), and interleukin (IL)-6 48 pg/mL (normal ≤1.8 pg/mL). Chest X-ray showed patchy bilateral airspace disease, and treatment was initiated with 1 L of intravenous fluid bolus, vancomycin, cefepime, and azithromycin.

Two days later, the patient became tachypneic and hypoxic, requiring a nonrebreather mask. Her respiratory status continued to worsen, and she developed acute hypoxic respiratory failure, for which she was intubated and placed in the prone position in the intensive care unit (ICU). Her inflammatory and coagulation markers continued to worsen, with ferritin 4,848 ng/mL (normal 11–307 ng/mL), LDH 679 U/L (normal

7–55 U/L), CRP 400.79 mg/L (normal <10 mg/L), and D-dimer 4.85 mg/L (normal <0.5 mg/L). She was diagnosed with cytokine release syndrome (CRS) related to COVID-19. Treatment was provided, i.e., corticosteroids, 2 rounds of tocilizumab, and 1 dose of convalescent plasma. The patient's acute kidney injury (AKI) worsened, with creatinine 2.08 mg/dL and urinalysis showing protein, and minimal white and red blood cells. She developed anuria, the treatment for which was continuous venovenous hemofiltration (CVVH). One day later, she developed deep-vein thrombosis (DVT) in the right internal jugular and the left brachial veins, and anticoagulation was started with an intravenous heparin infusion.

In the subsequent days of treatment with anticoagulation, the patient's clinical status started to improve, with resolution of the respiratory failure and shock. Anticoagulant was changed to apixaban, and CVVH was discontinued after her renal function returned to normal. Her PaO_2/FiO_2 ratio started to improve and paralytic agents were stopped. She was ultimately extubated to supplemental oxygen inhalation via a nasal cannula, and then discharged to a skilled nursing facility for rehabilitation.

Discussion

COVID-19 encompasses a wide range of clinical presentations, ranging from being asymptomatic to having multiorgan failure and death. It is caused by a novel coronavirus, SARS-CoV-2. Coronaviruses are a family of enveloped, single-stranded RNA viruses that are extensively present in bats, but also seen in birds, and in mammals including humans. It binds to ACE2 which is highly expressed in human lung alveolar cells, small intestine, endothelial cells, and smooth-muscle cells in the human brain, via its Spike (S) protein [4]. according to Johns Hopkins University, as of 29 August 2020, COVID-19 has affected a total of 24,914,886 people worldwide, causing 841,507 deaths. Despite this high infection rate, only about 15% of people affected have required hospitalization, and 5% required intensive care [5]. The respiratory system is the most commonly involved, characterized by acute respiratory distress syndrome (ARDS), but systemic involvement leading to shock and multiorgan failure can also be observed, and the prognosis is poor.

The most common laboratory abnormalities seen in these patients are neutrophilia, lymphopenia, thrombocytopenia, and elevated serum creatinine, C-reactive protein (CRP), ferritin, prothrombin time (PT), and D-dimer.

Complications related to coagulation abnormalities, including pulmonary and renal microangiopathy, arterial and venous thromboembolism presenting as acute ischemic stroke, DVT and pulmonary embolism, and arterial and venous catheter thrombosis are being reported. These complications are referred to as COVID-19-associated coagulopathy (CAC). They are most likely due to the profound inflammatory cytokine response associated with the illness, including the increased expression of IL-1, IL-6, and tumor necrosis factor (TNF)-α. IL-6 initiates coagulation activation by inducing tissue factor expression on endothelial cells, and IL-1 and TNF-α suppress the endogenous anticoagulant pathways [6]. CAC is postulated to be a cause of ARDS by forming fibrin-platelet microthrombi in the pulmonary microcirculation and parenchyma [7]. This is supported by autopsy findings of increased angiogenesis and microangiopathic thrombosis in the pulmonary vasculature of COVID-19 patients who died from ARDS [3].

It has been proposed that AKI occurs due to similar phenomena, including thrombotic microangiopathy (TMA), acute tubular necrosis (ATN) due to shock, and the direct effect of SARS-CoV-2 on the widely present ACE2 in the kidney [8]. TMA manifests as thrombosis from endothelial involvement of arteriolar and capillary wall, leading to hemolytic anemia, thrombocytopenia, and multiorgan failure [9]. A significant number of COVID-19-related AKI patients have required CVVH, which acts as renal replacement therapy and helps remove cytokines. Clotting in CVVH circuits is already a known complication, but an increasing number of cases are being reported in COVID-19 patients and treated with therapeutic anti-

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Table 1. SIC criteria [16]

Parameters	SIC score[a]		
	0	1	2
PT-INR	<1.2	>1.2	>1.4
Platelet count, 1,000/μL	>150	<150	<100
Total SOFA[b]	0	1	>/=2

SIC, sepsis-induced coagulopathy; PT, prothrombin time; INR, International Normalization Ratio; SOFA, Sequential Organ Failure Assessment.

[a] SIC total score ≥4, with a total score of PT-INR and platelet count ≥2.

[b] The sum of 4 items: respiratory, cardiovascular, hepatic, and renal SOFA.

Table 2. Outcomes of anticoagulation therapy in COVID-19 patients

	Ren et al. [18]	Helms et al. [19]	Klok et al. [20]	Llitjos et al. [21]	Lodigiani et al. [22]	Pavoni et al. [23]	Demelo-Rodríguez et al. [24]	Tang et al. [17]
Study design	Cross-sectional	Prospective	Cross-sectional	Retrospective	Cross-sectional	Retrospective	Prospective	Retrospective
Geographical region	China	France	The Netherlands	France	Italy	Italy	Spain	China
Patients, *n*	48	150	184	26	388	40	156	449
Coagulopathy	n.d.	64	75	24	28	20	23	n.d.
DVT/PE	n.d.	55	68	24	26	20	23	n.d.
ATE	n.d.	4	7	n.a.	13	n.a.	n.a.	n.d.
Other thromboembolisms[a]	n.d.	5	n.a.	n.a.	n.a.	n.d.	n.a.	n.d.
Anticoagulation performed, *n*	41	150	184	26	265	40	153	99
Anticoagulant used	LMW heparin	UF and LMW heparin	UF heparin	UF and LMW heparin	UF heparin, DOAC, and warfarin	LMW heparin	UF and LMW heparin	UF heparin
Anticoagulation mortality	31.20%	8.70%	22%	11.53%	23.71%	12.50%	n.d.	40%[b]
Non-anticoagulation mortality	n.d.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	64%[b]
Risk reduction	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	(adjusted) 24%[b]
p value	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0.029

DVT, deep-vein thrombosis; PE, pulmonary embolism; ATE, arterial thromboembolism. UF, unfractionated; LMW, low-molecular-weight; DOAC, direct oral anticoagulants; n.d., no data; n.a., not applicable.

[a] Includes RRT filter and ECMO oxygenator thrombosis; [b] SIC ≥4.

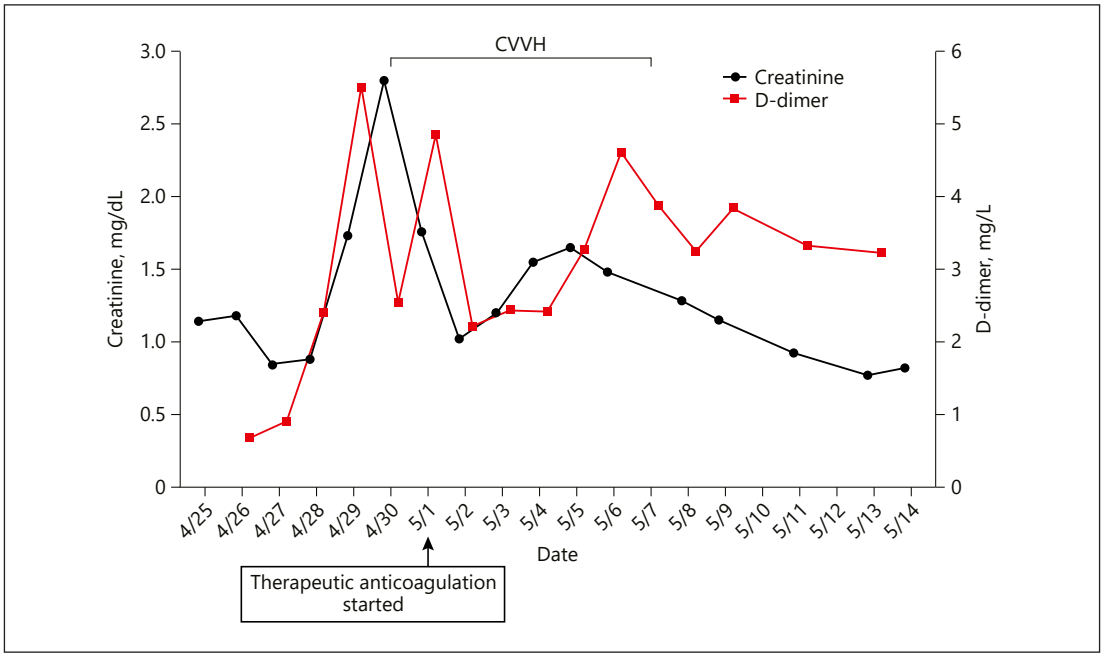

Fig. 1. Trend of creatinine and D-dimer levels.

coagulation [10]. These complications are found to be associated with an increased incidence of death [6].

The severity of COVID-19 and the associated mortality is observed to be higher in patients with elevated D-dimer levels. D-dimer is a fibrin-degradation product whose levels are increased by the breakdown of thrombi. It acts as a marker for the activation of widespread coagulation and fibrinolysis [11]. In a study on 1,099 COVID-19 patients from China, 260/560 patients had elevated D-dimer (>0.5 mg/L) [2]. In another study on 172 patients, 117 had elevated D-dimer (>0.5 mg/L) on admission, and 72 had a level >1 mg/L which was associated with increased mortality (odds ratio [OR] 18.42; 95% confidence interval [CI] 2.64–128.55; p = 0·0033) [12]. A third study showed that patients admitted to the ICU had a significantly higher median D-dimer concentration of 2.4 mg/L (interquartile range [IQR] 0.6–14.4) than patients who did not require ICU care (0.5 mg/L; IQR 0.3–0.8) [13]. In a multivariate retrospective analysis of 440 patients with severe COVID-19, the positive predictors of 28-day mortality were age, prothrombin time, elevated D-dimer, and thrombocytopenia, but not hypofibrinogenemia [14]. For these reasons, COVID-19 patients with elevated D-dimer (i.e., a 3- to 4-fold increase) should be considered for hospitalization, even in the absence of other symptoms, because this signifies an increased generation of thrombin [15]. Elevated D-dimer in COVID-19 patients with sudden respiratory insufficiency should always raise the concern of pulmonary embolism [6].

The International Society on Thrombosis and Haemostasis (ISTH) has identified the preliminary phase of sepsis-associated disseminated intravascular coagulopathy as "sepsis-induced coagulopathy" (SIC), and patients meeting the diagnostic criteria for SIC have a proven benefit from anticoagulant therapy [16] (Table 1).

The role of heparin anticoagulation in CAC was evaluated in a study showing a 20% reduction in mortality in patients with severe COVID-19 (and a SIC score ≥4) with a D-dimer value >3 mg/L given prophylactic-dose heparin anticoagulation [17]. Although in vitro studies of the use of heparin in SARS-CoV showed 50% decreased viral infectivity (the mechanism of

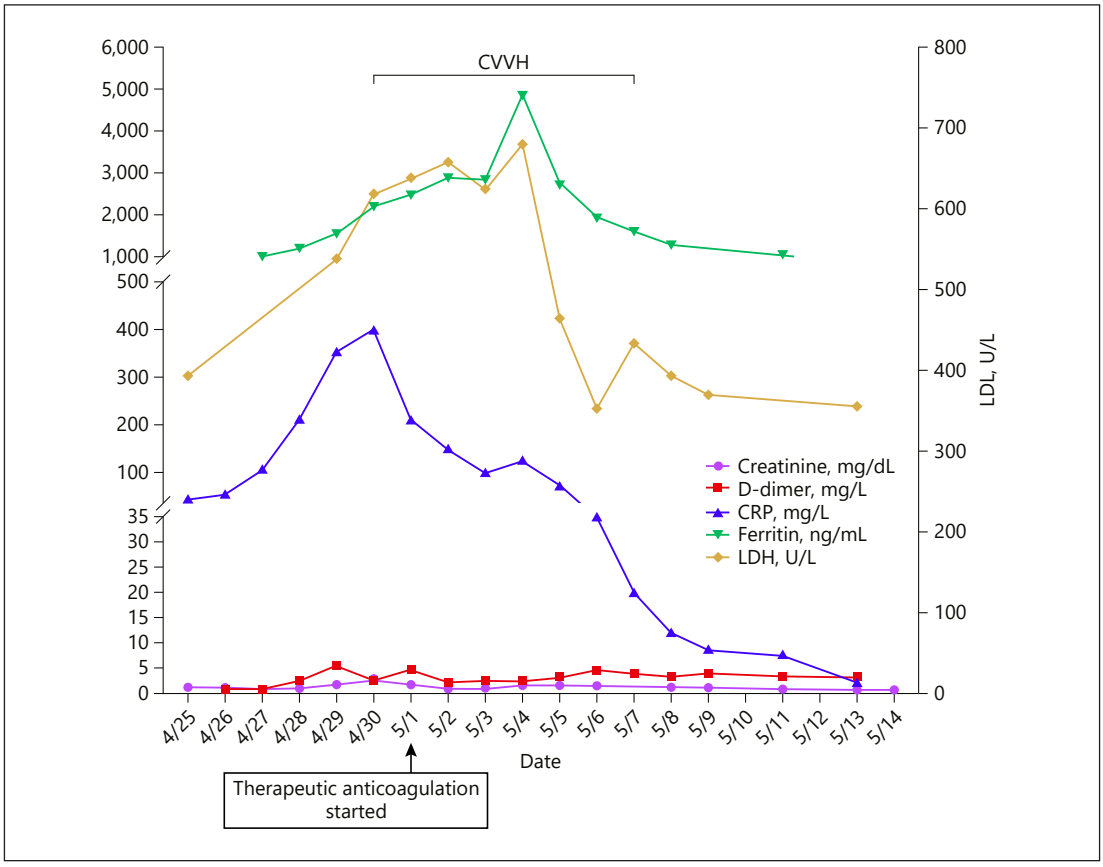

Fig. 2. Trend of renal, inflammatory, and coagulation markers.

responsible for this is still not clear), there are limited data on the interaction of heparin with SARS-CoV-2, and the role of therapeutic anticoagulation in these patients is still not known [7] (Table 2) [17–24]. Also in our patient, the D-dimer level started increasing as the disease progressed, but then decreased within days after starting CVVH and anticoagulation, and the patient experienced a rapid improvement in pulmonary and renal function (Fig. 1, 2).

It is difficult to say if it was the cytokine removal by CVVH or the therapeutic anticoagulation for the DVT that helped the patient recover quickly, but the fact that the elevated D-dimer and the AKI started resolving after the initiation of heparin points towards anticoagulation possibly having a therapeutic role in COVID-19. Even though the initial IL-6 level was elevated, this was subsequently not checked because the patient improved and could be weaned off mechanical ventilation and CVVH. Renal biopsy was not performed in our patient, so this correlation remains unproven.

Studies regarding the beneficial role of convalescent plasma and tocilizumab for the treatment of COVID-19 have shown variable results, but the role of anticoagulation needs to be studied as well, especially since the latest studies hint towards CAC and TMA as the pathogenesis of COVID-19-related multiorgan failure [25, 26]. At the same time, we need to be watchful about the potential complications of anticoagulation, especially the increased risk of bleeding, including intracranial hemorrhage, which has been described in COVID patients receiving anticoagulation treatment.

Further studies are also be required to analyze the role of routine anticoagulation for COVID-19 patients in preventing thrombosis during their hospital stay and after discharge.

Conclusion

It has been observed that COVID-19 is associated with systemic thromboembolism, and an elevated D-dimer level correlates with disease severity and prognosis. Anticoagulation may prove to be a treatment modality for these patients; more studies must be performed to analyze its role.

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Statement of Ethics

The subject gave written informed consent to publish her case. The paper is exempt from ethics committee approval since it is a case report and part of a review of different case reports and papers already published and accessible worldwide.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

P.M.: writing, original draft preparation, methodology, and software. B.D.: data curation, supervision, writing, review, and editing. N.R.: data curation, writing review, and editing. P.A.M.: conceptualization, writing, review, and editing.

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