Case Report

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

Pranav Mahajan^a Bhagwan Dass^b Nila Radhakrishnan^c
Peter A. McCullough^d

^aMBBS, Department of Internal Medicine, Carle Foundation Hospital, Urbana, IL, USA;

^bDivisions of Hospital Medicine and Nephrology, University of Florida, Gainesville, FL, USA;

^cDivision of Hospital Medicine, University of Florida, Gainesville, FL, USA; ^dBaylor University Medical Center, Baylor Scott and White Heart and Vascular Institute, Texas A&M College of Medicine, Dallas, TX, USA

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-

Pranav Mahajan
Department of Internal Medicine, Carle Foundation Hospital
611 W. Park St
Urbana, IL 61822 (USA)
pranav.mahajan@carle.com

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 anti-coagulation. **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.

© 2020 The Author(s)
Published by S. Karger AG, Basel

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 PaO₂/FiO₂ 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-

Table 1. SIC criteria [16]

Parameters	SIC score ^a		
	0	1	2
PT-INR	<1.2	>1.2	>1.4
Platelet count, 1,000/ μ L	>150	<150	<100
Total SOFA ^b	0	1	>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

Study design	Ren et al. [18]	Helms et al. [19]	Klok et al. [20]	Litjens et al. [21]	Lodigiani et al. [22]	Pavoni et al. [23]	Demelo-Rodríguez et al. [24]	Tang et al. [17]
Geographical region	Cross-sectional China	Prospective France	Cross-sectional The Netherlands	Retrospective France	Cross-sectional Italy	Retrospective Italy	Prospective Spain	Retrospective China
Patients, <i>n</i>	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, <i>n</i>	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
<i>p</i> value								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 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.

Acknowledgement

I would like to express my gratitude to Dr. Peter McCullough for his patient guidance and useful critiques of this work. I would like to thank Dr. Bhagwan Dass for his advice and assistance in formulating this paper and keeping my progress on schedule. I would also like to thank Dr. Nila Radhakrishnan for providing data on the patient and valuable feedback.

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.

Funding Sources

There was no funding.

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.

References

- 1 Woloshin S, Patel N, Kesselheim A. False Negative Tests for SARS-CoV-2 Infection — Challenges and Implications. *N Engl J Med*. 2020 Aug;383(6):e38.
- 2 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al.; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020 Apr;382(18):1708–20.
- 3 Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med*. 2020 Jul;383(2):120–8.
- 4 Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020 Mar;579(7798):270–3.
- 5 Campbell CM, Kahwash R. Will Complement Inhibition Be the New Target in Treating COVID-19-Related Systemic Thrombosis? *Circulation*. 2020 Jun;141(22):1739–41.
- 6 Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol*. 2020 Jun;7(6):438–40.
- 7 Connors J, Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020 Jun;135(23):2033–40.

- 8 Gopalakrishnan A, Mossaid A, Lo KB, Vasudevan V, McCullough PA, Rangaswami J. Fulminant Acute Kidney Injury in a Young Patient with Novel Coronavirus 2019. *Cardiorenal Med*. 2020;10(4):217–22.
- 9 George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med*. 2014;371:654–66.
- 10 Stucker F, Ponte B, Tataw J, Martin PY, Wozniak H, Pugin J, et al. Efficacy and safety of citrate-based anticoagulation compared to heparin in patients with acute kidney injury requiring continuous renal replacement therapy: a randomized controlled trial. *Crit Care*. 2015 Mar;19(1):91.
- 11 Weitz JI, Fredenburgh JC, Eikelboom JW. A Test in Context: D-Dimer. *J Am Coll Cardiol*. 2017 Nov;70(19):2411–20.
- 12 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020 Mar;395(10229):1054–62.
- 13 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020 Feb;395(10223):497–506.
- 14 Hess DC, Eldahshan W, Rutkowski E. COVID-19-Related Stroke. *Transl Stroke Res*. 2020;11(3):322–5.
- 15 Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020 May;18(5):1023–6.
- 16 Iba T, di Nisio M, Levy JH, Kitamura N, Thachil J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. *BMJ Open*. 2017 Sep;7(9):e017046.
- 17 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020 Mar;18(5):1094–9.
- 18 Ren B, Yan F, Deng Z, Zhang S, Xiao L, Wu M, et al. Extremely High Incidence of Lower Extremity Deep Venous Thrombosis in 48 Patients with Severe COVID-19 in Wuhan. *Circulation*. 2020 Jul;142(2):181–3.
- 19 Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020 Jun;46(6):1089–98.
- 20 Klok FA, Kruip MJ, van der Meer NJ, Arbous MS, Gommers D, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis [Internet]. *Thromb Res*. 2020 Jul;191:148–50.
- 21 Litjens JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. 2020 Jul;18(7):1743–6.
- 22 Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al.; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy [Internet]. *Thromb Res*. 2020 Jul;191:9–14.
- 23 Pavoni V, Ganesello L, Pazzi M, Stera C, Meconi T, Frigieri FC. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. *J Thromb Thrombolysis*. 2020 Aug;50(2):281–6.
- 24 Demelo-Rodríguez P, Cervilla-Muñoz E, Ordieres-Ortega L, Parra-Virto A, Toledano-Macías M, Toledo-Samaniego N, et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels [Internet]. *Thromb Res*. 2020 Aug;192:23–6.
- 25 Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis*. 2020 Apr;20(4):398–400.
- 26 Radbel J, Narayanan N, Bhatt PJ. Use of tocilizumab for COVID-19 infection-induced cytokine release syndrome: a cautionary case report. *Chest*. 2020 Jul;158(1):15–19.