COVID-19–Associated Ischemic Stroke in a Patient on Therapeutic Anticoagulation

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Introduction: The coronavirus disease 2019 (COVID-19) has been associated with a hypercoagulable state, increasing the risk for ischemic stroke. In select cases, patients are already on anticoagulation therapy. Such examples highlight the severity of COVID-19’s hyperthrombotic state, and raise questions regarding optimal stroke prevention in these patients.

Case Report: An 84-year-old male with past medical history of chronic obstructive pulmonary disease, hypertension, and paroxysmal atrial fibrillation was admitted for respiratory failure secondary to COVID-19 pneumonia. He was continued on his home apixaban 5 mg twice daily. On day 2 of admission, he developed a new aphasia, and right-sided facial droop. Computed tomography (CT) head was unrevealing. CT angiography did not show large vessel occlusion. CT perfusion demonstrated a left middle cerebral artery ischemic penumbra, without core. He was not eligible for thrombolysis or thrombectomy interventions. Later CT head confirmed left middle cerebral artery infarct. The patient’s D-dimer was 1,184 ng/mL on day 1 of admission, and increased to 111,574 by day 4. His hypoxia worsened, requiring intubation and transfer to the ICU. He experienced further clinical decline and eventual demise.

Conclusion: Ischemic stroke in anticoagulated patients with COVID-19 has been previously reported. Such cases emphasize the severity of the coronavirus virus associated hypercoagulable state. A majority of reported cases have occurred in patients continuing their ambulatory therapy. Overall, such cases are likely underreported. There are current trials comparing therapeutic versus prophylactic dose anticoagulation in patients with COVID-19. There are no studies specifically addressing anticoagulation agent failure in these patients. Further research is required this area to determine the optimal therapy for patients with COVID-19.

Key Words: COVID-19, coronavirus, anticoagulation, stroke, ischemic stroke

(The Neurologist 2021;26:108–111)

BACKGROUND

First recognized for an acute viral pneumonia causing severe respiratory distress, the coronavirus disease 2019 (COVID-19) has more recently been associated with a systemic hypercoagulable state. A proposed mechanism of this involves viral binding of angiotensin-converting enzyme 2, interfering with the enzyme’s role in mitigating inflammation and oxidative stress. This, in turn, leads to wide-spread platelet activation, and endothelial injury.1,2 Clinically, patients with severe COVID-19 infection have been shown to have an elevated D-dimer level, reflecting a state of heightened coagulation activation.3,4 As a result, such patients have been shown to have increased incidence of thrombotic events, including ischemic stroke.

Current estimates suggest that anywhere from 0.8% to 6.4% of COVID-19 patients experience an ischemic infarct.5–7 Compare that to the Center for Disease Control’s statistic that ~795,000 people in the United States, roughly 0.2% of the population, have a stroke each year. COVID-19–associated strokes are happening more often, and, on average, in a younger population compared with controls from years prior.8 What is possibly more concerning is that, in some cases, patients are already on therapeutic anticoagulation before experiencing an infarct.9–13 Episodes of venous thromboembolism, either deep vein thrombosis, or pulmonary embolism, while on therapeutic anticoagulation have also been reported.10,14,15 Such examples highlight the severity of COVID-19’s hyperthrombotic state, and raise questions as to which therapies should be used in order to prevent acute ischemic stroke in patients presenting with this disease.

CASE REPORT

An 84-year-old male with a past medical history of chronic obstructive pulmonary disease, hypertension, and paroxysmal atrial fibrillation presented with progressively worsening hypoxia and respiratory failure. He was febrile, tachycardic, and found to be COVID-19 positive. He was admitted to the Internal Medicine Service for further evaluation. His physical examination revealed a temperature of 38.4°C, heart rate of 111 beats per minute, blood pressure of 108/57 mm Hg, and respiratory rate of 25 breaths per minute. Chest examination was remarkable for bilateral inspiratory crackles. Laboratory evaluation revealed a white blood cell count of 11,574 by day 4. His hypoxia worsened, requiring intubation and transfer to the ICU. He experienced further clinical decline and eventual demise.

FIGURE 1. Computed tomography head without contrast. Day 2 of admission.
At that time, the patient was noted to be alert, oriented, and without any neurological deficits. He was continued on his home anticoagulation, apixaban 5 mg twice daily, which he reported compliance with at home. On admission, the patient’s D-dimer was 1,184 ng/mL (reference 0 to 500). Two days into his hospital stay, the patient acutely developed a global aphasia and a right-sided facial droop. A computed tomography (CT) of head without contrast did not show any acute pathology (Fig. 1). Head and neck CT angiography did not show a large vessel occlusion amenable to thrombectomy (Figs. 2, 3). CT perfusion imaging demonstrated a new, left middle cerebral artery territory area of ischemic penumbra, without a measurable core (Figs. 4, 5). As the patient was anticoagulated, he was not a candidate for thrombolysis. The next day, the patients respiratory status worsened, requiring intubation and transfer to the ICU. Neurological deficits progressed, with development of right-sided hemiplegia. Repeat CT head without contrast obtained on day 4 showed an evolving left middle cerebral artery territory infarct (Fig. 6). MRI could not be obtained because of poor clinical stability. Interval labs showed a D-dimer of 5,378 on day 3 of admission, with substantial increase to 111,574 by day 4. While anticoagulation was initially held after the stroke, this rapidly elevating D-dimer, as well as the patient’s progressive deficits, raised concern for an ongoing hyperthrombotic state. Low dose (15 units/kg/h) heparin, without bolus, was started on day 5 of the admission. Unfortunately, the patient experienced further clinical decline in the ICU, eventually resulting in his demise.

METHODS

Case report and initial literature review conducted through PubMed search performed on July 13, 2020. Search terms included “coronavirus,” “covid-19,” “stroke,” and “anticoagulation.” Filters were applied for publications written in the English language and produced within the last 10 years. Cases were included if ischemic stroke was confirmed on imaging, along with a diagnosis of COVID-19, and if patients were on anticoagulation beyond that of standard venous thromboembolism prophylaxis at the time of stroke onset.

While this report was under review, 3 additional cases and 2 case series regarding COVID-19–associated ischemic stroke, some including patients on anticoagulation therapy, were published. Findings from these articles were analyzed and added to this review.

RESULTS

Initial PubMed search resulted in 18 articles, yielding 85 cases of COVID-19–associated ischemic stroke. One report detailed 9 COVID-19–associated infarcts, of which 6 were listed as being on some level of anticoagulation. On further review, 1 patient was listed as being on therapeutic dose low molecular weight heparin (LMWH), while 4 were on a subtherapeutic dose. The final anticoagulated patient from this study was on a vitamin K antagonist with a subtherapeutic internal normalized ratio of 1.2. From this report, only the patient on therapeutic dose LMWH was included.

Secondary review yielded an additional 99 cases of COVID-19–associated stroke. Of these, 5 cases occurred while on therapeutic anticoagulation. One large case series recorded 27 COVID-19–associated strokes where patients were on an antithrombotic medication before admission. The article did not specify whether these were antplatelet versus anticoagulation agents. Therefore, these cases were included in the total number of ischemic strokes analyzed, but could not be added to the number of strokes while on anticoagulation.

In total, out of 184 total cases of COVID-19–associated ischemic stroke, 10 cases (5.4%) were identified with patients on therapeutic anticoagulation at the time of infarct. Our patient made for a total of 11 cases. Ages ranged from 48 to 84 years old (mean: 69 y). Two of the patients were female, and 5 were male. Age and sex were not provided in 4 cases. Anticoagulant agents used included heparin (27.3%), apixaban (27.3%), LMWH (18.2%), warfarin (9.1%), rivaroxaban (9.1%), and an unnamed oral anticoagulant with dual-antplatelet therapy (9.1%).

DISCUSSION

The increased risk of ischemic stroke associated with the coronavirus pandemic is a rapidly emerging concern. The extent of the disease’s hypercoagulable state is further emphasized by cases in which patients who are already being...
Anticoagulated still suffer an ischemic event. In the 11 cases reported of ischemic stroke while on anticoagulation, men were more affected than women and most cases occurred in the elderly. In the 7 cases where age was reported, 4 patients were over the age of 65.

Anticoagulants used in the reported cases varied. Agents included heparin, LMWH, vitamin K antagonists, direct oral anticoagulants, and 1 case of an unspecified oral anticoagulant with dual-antiplatelet therapy. In a majority of cases (54%), patients were continuing their ambulatory therapies. In the case presented here, the patient was taking apixaban. Apixaban, specifically, has a 0.97% to 1.1% yearly failure rate in patients with nonvalvular atrial fibrillation in regards to ischemic stroke.16,17 Such a low failure rate further highlights the severity of COVID-19’s hyperthrombotic risk.

The emergence of ischemic strokes in anticoagulated patients with COVID-19 raises multiple questions that invite further study. Are some anticoagulants more susceptible to failure in this setting? How should anticoagulation be managed in patients with COVID-19? These questions require further investigation.

**FIGURE 4.** Computed tomography perfusion map with 37 mL with $T_{\text{max}} > 6.0$ seconds, and no core volume.

**FIGURE 5.** Computed tomography perfusion demonstrating left MCA penumbra. MCA indicates middle cerebral artery.

**FIGURE 6.** Repeat computed tomography head showing evolved left MCA territory infarct. MCA indicates middle cerebral artery.
setting than others? What is the mechanism by which these agents fail? Most importantly, are there mitigation strategies that could be put in place to prevent these events from occurring? Literature addressing these queries is not yet readily available. Studies exist addressing the prothrombotic state of COVID-19. One New York Health System noticed a decrease in the incidence of COVID-19–associated stroke after implementing a therapeutic anticoagulation protocol for patients with elevated D-dimer levels. There is also an ongoing, randomized trial comparing the safety and efficacy of therapeutic versus prophylactic anticoagulation in these patients.

There are currently no studies specifically addressing anticoagulation failure in patients with COVID-19.

**Limitations**

The incidence of COVID-19–associated ischemic stroke while on therapeutic anticoagulation is likely underreported. This may be due, in part, to the inability of larger case studies to provide extensive patient information, including prior medications. As a result, the number of cases specifying anticoagulation use before ischemic stroke, and the percentages derived here, lack adequate power to reach a valid conclusion. Nevertheless, these cases highlight a need for further research in studying the necessary anticoagulation required in patients with COVID-19.

**CONCLUSION**

Ischemic stroke in COVID-19 while on anticoagulation has been previously reported. Such cases emphasize the severity of the COVID-19–associated hypercoagulable state. A majority of cases occurred in patients continuing their ambulatory therapy. The number of cases is likely underreported. Further targeted research is required in order to elucidate both the mechanism of anticoagulation failure and the optimal therapy for patients presenting with COVID-19.

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