Large Middle Cerebral Artery Ischemic Stroke in a Therapeutically Anticoagulated Patient With Severe SARS-CoV-2 Infection

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Introduction: Coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with hypercoagulability which can predispose infected patients to both arterial and venous thromboembolic complications. Despite therapeutic anticoagulation, there remains a risk of ischemic strokes, which may lead to adverse patient outcomes. Only a few cases are described in the literature regarding SARS-CoV-2 positive patients developing thrombotic ischemic strokes despite therapeutic anticoagulation.

Case Report: The following is a case discussion regarding a 71-year-old female with past medical history of hypertension, diabetes mellitus type 2, hyperlipidemia, and hypothyroidism who was admitted with severe SARS-CoV-2 infection to the intensive care unit and later developed acute left upper extremity weakness on the 5th day of her admission. Initial National Institutes of Health stroke scale (NIHSS) was 15. Subsequent brain imaging was significant for right middle cerebral artery ischemic stroke. The patient was therapeutically anticoagulated with 1.5 mg/kg subcutaneous dose of Enoxaparin since day 1 of her admission. D-dimer upon admission was 1.84 mg/L (< 0.59) and fibrinogen 783.1 mg/dL (200 to 450). Other than past medical comorbidities, our patient had no other known stroke risk factors. Unfortunately, despite early transcatheter thrombectomy, the patient remained comatose and eventually expired after withdrawal of ventilatory support and compassionate extubation.

Conclusion: Because of the severity of inflammation and coagulopathic sequelae of coronavirus disease 2019, anticoagulation failure may occur and lead to adverse patient outcomes. Our case report is one of the few discussions in the current literature regarding large vessel thromboembolic ischemic strokes despite therapeutic anticoagulation.

Key Words: COVID-19, SARS-CoV-2, ischemic stroke, coagulopathy, inflammatory thrombosis

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This manuscript was approved by our Hospital's Ethics Committee for external publication.

Patient consent could not be obtained because of the severity of disease and patient's eventual passing. Exhaustive efforts to contact the next of kin were made without any success. Our hospital's patient privacy and safety HIPAA compliance committee reviewed the case and cleared it for external publication. All efforts have been taken to make sure that no patient identifying information is present in the manuscript.

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CASE PRESENTATION

A 71-year-old female with a known medical history of hypertension, diabetes mellitus type 2, hyperlipidemia, and hypothyroidism was admitted to the intensive care unit with acute hypoxemic respiratory failure. The patient was found to be positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection upon arrival to the emergency department. Chest x-ray was remarkable for bronchovascular prominence concerning for atypical pneumonia. Computed tomography (CT) angiography revealed findings of bilateral opacities consistent with atypical viral pneumonia, such as coronavirus disease 2019 (COVID-19) (Fig. 1). Patient's initial labs included elevated D-dimer, fibrinogen, lactate dehydrogenase (LDH), and C-reactive protein (CRP) (Table 1).

Our patient was given oxygen support with high flow nasal cannula, and started on therapeutic dose of enoxaparin (1.5 mg/kg) because of elevated D-dimer and fibrinogen as per the hospital's COVID-19 treatment protocol at the time. She was also evaluated by infectious disease specialists, who initiated the antiviral, Remdesivir once daily, and Dexamethasone 6 mg daily. Proning was utilized in an attempt to improve oxygenation. Despite treatment, oxygen requirements continued to increase and the patient was escalated to non-invasive ventilation. Echocardiogram at this time was without thrombus or compromised cardiac function.

On hospital day 5, the patient developed a sudden left upper extremity deficit, meeting criteria for an inpatient stroke alert. Initial National Institutes of Health (NIH) stroke scale was 9, and soon worsened to 15. Neurological physical exam was remarkable for severe motor deficit of the left arm as well as left upper and lower extremity sensory deficit. Otherwise, patient was alert and oriented and able to follow commands appropriately. Cranial nerves II-XII were intact and speech was normal.

Teleneurology was consulted and CT angiography of the brain was obtained. Results were remarkable for an acute occlusive thrombus in the M1 segment of the right middle cerebral artery (MCA) (Fig. 2). There were no carotid atherosclerotic changes seen on the imaging. Thrombolytic therapy was held because of an increased risk of intracerebral hemorrhage given the patient had been receiving full dose enoxaparin. In light of these acute neurological findings, patient was transferred to another hospital with neurosurgical capabilities for acute thrombectomy and further neurosurgical intervention. There were no delays experienced in transferring the patient for thrombectomy because of an efficient stroke alert response.

Patient underwent a catheter cerebral angiogram with transcatheter thrombectomy/thrombolysis under general anesthesia without complications and had flow restoration on final angiogram. Following thrombolysis, patient remained intubated and sedated on mechanical ventilation with pressor support. Subsequent magnetic resonance imaging of the brain was remarkable for embolic appearing right hemispheric infarcts with minimal petechial hemorrhages (Figs. 3 and 4). For further neurological assessment, an electroencephalogram (EEG) was obtained showing intermittent, primarily right sided slowing (4 to 5 Hz), but without any epileptiform activities. In addition, the EEG appeared to be isoelectric. There was no response during the EEG to any noxious stimuli. The EEG findings were consistent with severe encephalopathy. Furthermore, in order to prevent post-thrombolysis seizures, patient was started on Levetiracetam 500 mg bis in die by the neurology team. However, despite aggressive intervention, our patient remained comatose without improvement in neurological status.

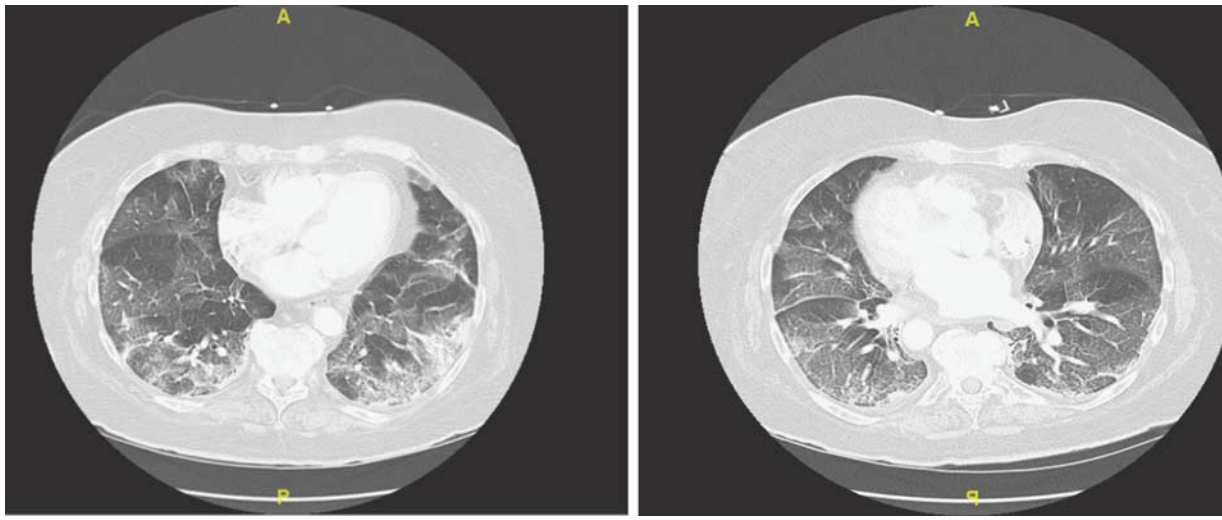

FIGURE 1. Computed tomography angiography chest findings suggestive of atypical pneumonia.

Repeat CT head was concerning for post-thrombectomy hemorrhage within the right posterior frontal infarction zone with extension into the right basilar cistern and bilateral ventricles. The patient was transitioned to do-not-resuscitate status and discharged to Level 4 hospice, as per the power of attorney. Pressor support was removed and terminal extubation was performed. Patient remained encephalopathic and comatose without any improvement and expired shortly after extubation.

DISCUSSION

The underlying etiology of the increased thrombotic state seen in COVID-19 appears to be multifactorial with many components that are still poorly understood. However, initial research proposes a relationship between inflammation and thrombosis being the driving mechanism of coagulopathy seen in COVID-19.[1,2] Furthermore, COVID-19 increases risk for all 3 factors that are responsible for thrombosis as described by Virchow's triad: hypercoagulability, endothelial damage, and stasis.

The initial proinflammatory insult occurs in the pulmonary alveoli cells after infection with SARS-CoV-2.[1,2] Inflammatory cytokines, such as interleukin-2, interleukin-7, tumor necrosis factor-α are hypothesized as being responsible for initiating early inflammation damage.[1,3] After this inflammation-induced damage to the alveoli, various thrombotic factors, including Von Willebrand factor and factor VIII are believed to be released into systemic circulation, activating the coagulation cascade.[4] In addition, this inflammation process leads to endothelial damage and exposes the tissue factor, aiding in thrombosis formation.[1] Finally, because of a severe morbidity burden of COVID-19 and increased oxygen demand, many infected patients are admitted to critical care units and are immobile, further exacerbating the risk of thrombosis secondary to vasculature stasis.

Clinically, these mechanisms can be further explained by increased inflammatory markers, such as CRP, LDH, ferritin, and increased fibrin clot-related markers, such as fibrinogen and D-dimer associated with COVID-19.[2] Specifically, elevated D-dimer may serve as a prognostic factor with higher levels indicating increased risk for thrombosis and related complications.[1,2]

TABLE 1. Inflammatory and Coagulopathy Labs With Normal Reference Ranges

D-dimer	1.84 mg/L (< 0.59)
Fibrinogen	783.1 mg/dL (200-450)
LDH	488 units/L (81-234)
CRP	8.30 mg/dL (0.05-0.3)

CRP indicates C-reactive protein; LDH, lactate dehydrogenase.

The patient treated in our hospital had an elevated D-dimer along with CRP, LDH and fibrinogen. Therefore, she was started on a therapeutic anticoagulation dose (1.5 mg/kg) of Enoxaparin. Of note, Mousavi et al[5] and Poterucha et al[6] have discussed anti-inflammatory properties of heparins, which may be of particular usefulness when treating COVID-19-related inflammatory thrombosis. This may provide another rationale of not only anticoagulating critically ill patients with elevated D-dimer who are without contraindications, but to specifically choose heparin and its derivatives.

Despite anticoagulation, our patient suffered a right MCA infarct resulting in expiration. There are several questions that arise with this case report, with their answers being imprecise and requiring further research. First, arterial thromboembolism is rare when compared with venous thromboembolism, specifically as a COVID-19-related sequela.[1] A limited number of cases of arterial thrombotic infarcts because of COVID-19 have been reported in the literature.[7,8] Secondly, the source of thrombosis in our patient was not confirmed with follow-up studies, thus we cannot ascertain whether thrombosis was a localized event, extracranial embolic event or combination of both. Finally, our patient was therapeutically anticoagulated and yet still had an arterial thrombotic infarct. Shoukry and Kite[8] have discussed a similar presentation of COVID-19-related stroke despite therapeutic anticoagulation.

This rare presentation asks the question whether COVID-19 "inflammatory thrombosis" necessitates a higher therapeutic dose of anticoagulation. Our patient experienced a significant thrombotic event despite therapeutic anticoagulation. In the future, if there are no contraindications, it may be of some benefit in select patients to try a higher therapeutic dose of anticoagulation. However, further studies are needed before this implementation because of increased risk of hemorrhage with higher doses of heparin and its derivatives. Furthermore, risk versus benefit discussion is always important when treating patients with any medication with potentially harmful and life-threatening side effects.

Despite this rare presentation of arterial thrombotic infarct in the setting of anticoagulation, the recommendations of this case report remain the same as the currently accepted COVID-19 treatment discussed in the literature. Routine monitoring is indicated, including trending thromboinflammatory markers, such as CRP,

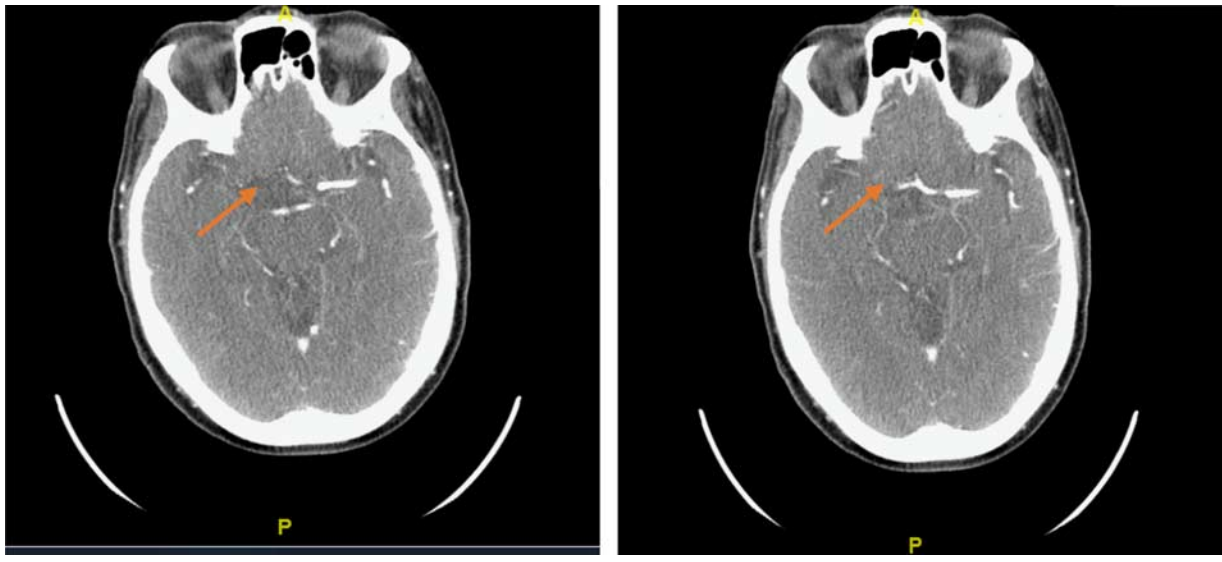

FIGURE 2. Computed tomography angiography brain with 2 frames illustrating occluded right middle cerebral artery. Arrows point to occlusion of right middle cerebral artery.

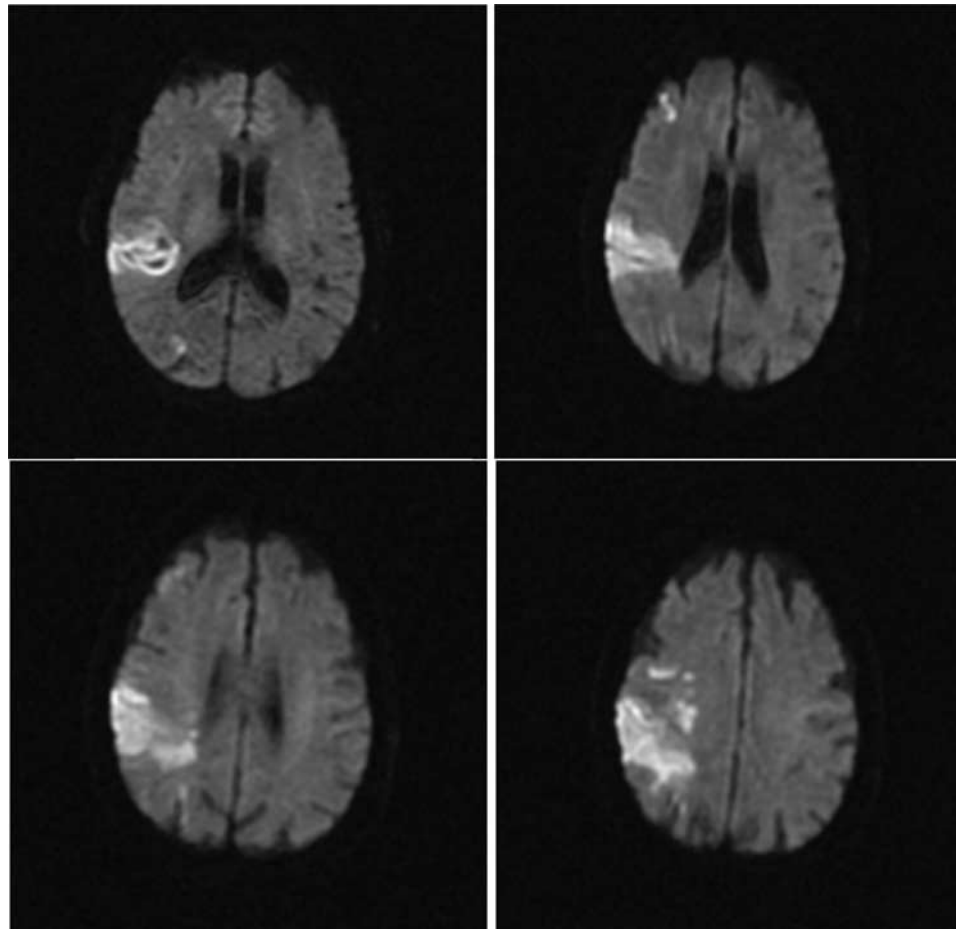

FIGURE 3. Diffusion weighted magnetic resonance imaging of brain without contrast with 4 frames illustrating extensive restricted diffusion in the right parietal and temporal lobes, consistent with acute infarction.

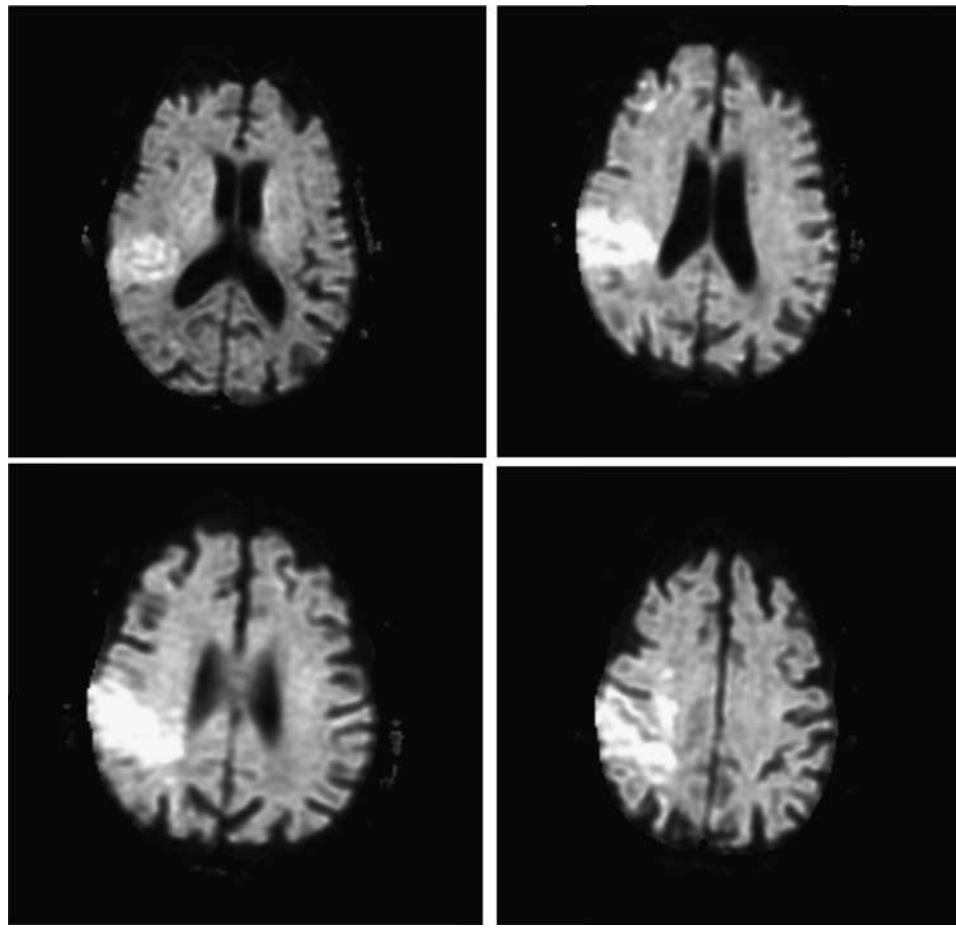

FIGURE 4. Magnetic resonance imaging of brain without contrast with ADC frames with large right sided parietal and temporal lobe infarcts. ADC indicates apparent diffusion coefficient.

LDH, ferritin, fibrinogen, and D-dimer. Routine thromboembolic prophylaxis, including anticoagulating patients, especially those with elevated inflammatory markers (most importantly, D-dimer), and preventing prolonged immobilization if tolerated are of the most importance when treating SARS-CoV-2 positive patients.

A limitation of our case is the inability to assess the origin of the thrombosis in the right MCA. We are uncertain whether the infarct was because of a localized thrombosis, an embolism, or a combination of both. We were also unable to trend inflammatory markers since the patient was transferred to another hospital. Regardless, it would not have changed the outcome or medical management.

CONCLUSION

We discussed a rare case report regarding right MCA infarct in a patient with severe SARS-CoV-2 infection despite therapeutic anticoagulation with enoxaparin. Further research is needed to understand the relationship between inflammation increasing the risk of thrombosis in critically ill patients infected with SARS-C0V-2. While treatment with currently defined therapeutic anticoagulation appears to be effective for most patients, there remains a risk of anticoagulation failure and resulting adverse outcomes associated with COVID-19.

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