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Intracranial Hemorrhage in Hospitalized SARS-CoV-2 Patients: A Case Series

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The SARS-CoV-2 virus causing Coronavirus Disease 2019 (COVID-19) is a global pandemic with almost 30 million confirmed worldwide cases. Prothrombotic complications arising from those affected with severe symptoms have been reported in various medical journals. Currently, clinical trials are underway to address the questions regarding anticoagulation dosing strategies to prevent thrombosis for these critically ill patients. However, given the increasing use of therapeutic anticoagulation in patients admitted with COVID-19 to curtail this prothrombotic state, our institution has witnessed six cases of devastating intracranial hemorrhage as well as thrombosis leading to five fatalities and we examine their hospital course and anticoagulation used.

Key Words: COVID-19—Anticoagulation—SARS-CoV-2—Intracranial hemorrhage

Introduction

The SARS-CoV-2 virus has emerged as a global pandemic causing multiple complications for those who become infected. Upper respiratory tract symptoms are the most common presentations of COVID-19 when first reported from China in December, 2019. For the critically ill, deaths are most commonly caused by acute respiratory distress syndrome (ARDS).1,2 Recently, multiple publications have revealed that SARS-CoV-2 affects the coagulation system, which can lead to increased rates of arterial or venous thrombosis as well as bleeding.3,4 Retrospective studies have suggested that prophylactic anticoagulation may lead to reduced mortality in patients with severe COVID-19 pneumonia who have high sepsis-induced coagulopathy scores.5 D-dimer elevation at admission predicts thrombosis, bleeding, and death in patients with COVID-19 and is now widely used to help triage anticoagulation guidelines upon initial presentation.6 Due to the risk of arterial thrombosis, several studies have reported rates of acute ischemic stroke and even less so, cerebral hemorrhage. One study from Wuhan, China revealed that 10 (4.5%) of 221 inpatients with COVID-19 developed acute ischemic stroke and 1 (0.5%) suffered cerebral hemorrhage; furthermore, from the Netherlands, 3 of 184 critically ill COVID-19 patients had ischemic stroke.4,7 Given the increasing use of therapeutic anticoagulation in patients admitted with COVID-19 ARDS, our institution has witnessed six cases of devastating intracranial hemorrhage as well as thrombosis leading to five fatalities.

Case presentations (Table 1)

Patient #1

A 54-year-old woman with controlled diabetes mellitus type II, hypertension, hyperlipidemia, asthma, sickle cell trait, recurrent supraventricular tachycardia, adrenal insufficiency, and hypothyroidism was admitted for acute hypoxic respiratory failure. On admission, she was SARS-CoV-2 positive. CXR revealed patchy interstitial infiltrates consistent with COVID-19 pneumonia. Inflammatory markers were elevated at presentation. On Hospital Day (HD) 2, she was intubated and started on mechanical ventilation. She was also started on venous thromboembolism (VTE) prophylaxis with low-molecular weight
| TABLE 1. Patient Characteristics |
|---------------------------------|
| Patient 1 | Patient 2 | Patient 3 |
| Age (y) | 54 | 68 | 76 |
| Sex | F | F | M |
| BMI (kg/m²) | 37.2 | 26.8 | 32.3 |
| Past Medical History | Diabetes mellitus, sickle cell trait, adrenal insufficiency, hypothyroidism | Hypertension | Hypertension, hyperlipidemia, gout, GERD |
| Presenting Symptoms | Dyspnea | Left-sided weakness, ataxia, unsteady gait | Fever, cough, dyspnea and diarrhea |
| Admission CXR Findings | Patchy interstitial opacities | Normal | Bilateral lower lobe predominant airspace opacities and bilateral pleural effusions |
| COVID-19 PCR Positivity | 3/27/20 | 5/10/20 | 5/28/20 |
| COVID-19 Treatments | Hydroxychloroquine and doxycycline | None | Remdesivir and convalescent plasma |
| ARDS Treatment | Low tidal volume mechanical ventilation, prone positioning and diuresis | None | Low tidal volume mechanical ventilation, prone positioning and diuresis |
| Days intubated | 24 | N/A | 11 days |
| ECMO | No | No | No |
| Deceased? | Yes | No | Yes |
| Admission Lab Findings | | |
| WBC (K/μL) | 10 | 5.7 | 8.8 |
| ANC | 8.7 | 2800 | 7.8 |
| ALC | 0.6 | 2400 | 0.6 |
| Hb (g/dL) | 15 | 14.2 | 15.1 |
| PLT (K/μL) [150-400] | 131 | 232 | 191 |
| SCr (mg/dL) | 1.34 | 0.5 | 1.0 |
| LDH (U/L) | 384 | NA | 620 |
| D-Dimer (ng/mL) (<500) | 1,469 | NA | 16,107 |
| FBG | 1000 | NA | NA |
| FSP | 40 | NA | NA |
| PT/INR (9.7-13.1 s/0.8-1.20) | 16.3/1.4 | 1.08 | 15.5/1.4 |
| aPTT (25.1-36.5 s) | 45.8 | 28.9 | 27.2 |
| Ferritin (ng/mL) | 800 | NA | 3901 |
| CRP (mg/dL) | 107.08 | NA | 23.4 |
| Procalcitonin (ng/mL) | 0.12 | NA | 0.37 |
| Troponin | 0.03 | NA | 0.54 |
| IL-6 (pg/mL) | N/A | NA | NA |
| Other infection? | Ventilator-associated pneumonia | None | Suspected bacterial pneumonia |
| Confirmed thrombosis? | No | Yes, superficial cortical vein (post-surgical intervention) | No |
| Type of VTE prophylaxis at Admission | LMWH (0.6 mg/kg BID) changed to unfractionated heparin infusion | Subcutaneous heparin every 12 hours (after the bleed) | LMWH 40 mg daily later changed to therapeutic heparin on HD2 due to rise in D-dimer and troponin |
| Type of intracranial bleeding and location | Posterior fossa | Subdural hematoma and postsurgical R frontal lobe intracerebral hemorrhage | Large right frontal lobe intraparenchymal hemorrhage with extension to the intraventricular and subarachnoid spaces (on HD12) |
| Intervention if intracranial bleed | No | Evacuation (craniotomy) | None |
| Location of acute CVA | No | None | None |
| Intervention if acute CVA | No | N/A | N/A |
| Seizures? | No | Yes | No |
| D-dimer level with CVA or ICH | 29,396 | Not done | 3088 |
| | 17.1/1.5 | Same as admission | 16.0/1.4 |
| Patient 1 | Patient 2 | Patient 3 |
|-----------|-----------|-----------|
| **PT/INR with CVA or ICH** (9.7-13.1 s/0.8-1.20) | 10.3/1.0 | NA |
| **aPTT with CVA or ICH** (25.1-36.5 s) | 24/27.6 | NA |
| **PLT count with CVA or ICH** (150-400 K/UL) | 107 | 169 |

| Patient 4 | Patient 5 | Patient 6 |
|-----------|-----------|-----------|
| **Age (y)** | 71 | 79 |
| **Sex** | F | M |
| **BMI (Kg/m²)** | 33.9 | 29.8 |
| **Past Medical History** | Hypertension, diabetes mellitus | Hypertension, hyperlipidemia, diabetes mellitus, CAD, atrial fibrillation |
| **Presenting Symptoms** | Cough, dyspnea, headache | Dyspnea, fever |
| **CXR findings at admission** | Bilateral airspace opacities | Bilateral patchy infiltrates |
| **COVID-19 PCR Positivity** | 3/24/20 | 4/3/20 POCT 10 days prior |
| **COVID Treatments** | Hydroxychloroquine and azithromycin | Ceftriaxone, doxycycline, piperacillin-tazobactam |
| **ARDS Treatment** | Low tidal volume mechanical ventilation, prone positioning and diuresis | Low tidal volume mechanical ventilation |
| **Days intubated** | 26 | 24 |
| **ECMO** | Yes | No |
| **Deceased?** | Yes | No |

### Admission Lab Findings

| WBC (K/ul) | 8.7 | 7.5 | 5.8 |
| ANC | 7.1 | 5500 | 4700 |
| ALC | 0.7 | 1100 | 700 |
| Hb (g/dL) | 9.1 | 12.5 | 15.4 |
| Plt (K/UL) | 426 | 201 | 428 |
| SCr (mg/dL) | 0.6 | 0.93 | 1.17 |
| LDH (U/L) | 396 | 581 | 426 |
| D-dimer (ng/mL) | 5,684 | 1640 | 1585 |
| FBG (mg/dL) | 742 | NA | NA |
| FSP | 40 | NA | NA |
| PT/INR (9.7-13.1 s/0.8-1.20) | 13.1/1.2 | 10.3/1.0 | NA |
| aPTT (25.1-36.5 s) | 40.5 | 27.6 | NA |
| Ferritin (ng/mL) | 967 | 844 | 2289 |
| CRP (mg/dL) | 18.9 | 13.0 | 25.9 |
| Procalcitonin (ng/mL) | 0.33 | 0.04 | 0.15 |
| Troponin I | .02 | 0.05 | 0.0 |
| IL-6 (pg/mL) | n/a | NA | 215.85 |
| Other infection? | Hospital-acquired pneumonia, bacteremia | Presumed bacterial pneumonia |
| Confirmed thrombosis? | No | No | Yes (oclusive thrombi in the distal right common femoral artery extending into the superficial
heparin (LMWH) since her admission D-dimer was <5 times the upper limit of normal (ULN) per institutional protocol. On HD8, her D-dimer rose to 6,677 ng/mL and she was transitioned to LMWH at 0.6 mg/kg twice daily. Her creatinine clearance declined to 46 mL/min; therefore, the LMWH was discontinued and therapeutic heparin was initiated on HD12. On HD15, her hemoglobin dropped, and computerized tomography (CT) of her chest/abdomen/pelvis showed a massive left thigh hematoma. Her anticoagulation was discontinued, and her hemoglobin improved. By HD21, she had shown improvement in respiratory status and was weaned off sedation but was not arousable after three days. CT head (CTH) demonstrated a large cerebellar hemorrhage (Fig. 1). D-dimer at the time was 19,679 ng/mL. She was transitioned to comfort care and expired after terminal extubation on HD27.

### Patient #2

A 68-year-old woman with hypertension initially presented with left-sided weakness and unsteady gait of one-week duration following a mechanical fall at home. On admission, she was SARS-CoV-2 positive. Inflammatory markers along with D-dimer were not evaluated at initial presentation. CTH revealed a mixed density hematoma along the right convexity consistent with acute subdural hematoma that measured 2.4 cm in maximum dimension with a resultant 7 mm midline shift and mild effacement of the right frontal horn of the lateral ventricles. She underwent a right-sided craniotomy with evacuation of the hematoma on HD1. She was subsequently started on prophylactic anticoagulation with subcutaneous heparin. However, her post-operative course was complicated by a right frontal intraparenchymal hemorrhage.

| Patient 4 | Patient 5 | Patient 6 |
|-----------|-----------|-----------|
| Type of VTE prophylaxis at Admission | LMWH (0.6 mg/kg BID) | Home apixaban 5 mg BID | LMWH (0.6 mg/kg BID), increased to 1 mg/kg BID due to concern for PE and worsening respiratory status |
| Type of intracranial bleeding and location | Large intraparenchymal hemorrhage centered in the left frontal lobe | Diffuse bilateral subarachnoid hemorrhage | Bilateral intraparenchymal hemorrhage (Bilateral right temporoparietal and left occipital), with intraventricular extension/SAH |
| Intervention if intracranial bleed | Protamine | None | None |
| Location of acute CVA | No | N/A | Bilateral right temporoparietal and left occipital (with hemorrhagic conversion) |
| Intervention if acute CVA | No | N/A | None |
| Seizures? | No | Yes | No |
| D-dimer with CVA or ICH | 1073 | 15,763 | 13,874 |
| PT/INR with CVA or ICH (9.7-13.1 s/0.8-1.20) | 12.8/1.1 | 14.7/1.3 | 13.5/1.1 |
| aPTT with CVA or ICH (25.1-36.5 s) | 38.9 | 33.3 | 30.4 |
| PLT count with CVA or ICH (150-400 K/UL) | 376 | 380 | 309 |

**Abbreviations:** y: years; F: female; M: male; BMI: body mass index; CXR: chest X-ray; COVID-19: Coronavirus Disease 2019; PCR: polymerase chain reaction; POCT: point of care test; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membranous oxygenation; N/A: Not applicable; HD: hospital day; NA: Not available; WBC: white cell count; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; Hb: hemoglobin; PLT: platelet; SCr: serum creatinine; LDH: lactate dehydrogenase; FBG: fasting blood glucose; FSP: fibrin split product; PT: prothrombin time; INR: international normalized ratio; aPTT: activated partial thromboplastin time; s: second; CRP: C-reactive protein; IL-6: interleukin 6; VTE: venous thromboembolism; LMWH: low molecular weight heparin; BID: twice daily; CVA: cerebrovascular accident; ICH: intracranial hemorrhage
pneumocephalus and localization-related seizures which occurred on HD6. Furthermore, her CTH showed worsening cerebral edema thought to be secondary to new superficial cortical vein thrombosis (Fig. 1). She was managed with supplemental oxygen, lacosamide, levetiracetam and hypertonic saline. She received physical therapy during the admission and discharged to acute inpatient rehab on HD21.

**Patient #3**

A 76-year-old man with hypertension, hyperlipidemia, gastroesophageal reflux disease (GERD), class I obesity and gout who presented with fever, non-productive cough, dyspnea and diarrhea of two days duration. SARS-CoV-2 polymerase chain reaction (PCR) test on admission was positive. CXR revealed bilateral lower lobe predominant airspace opacities and bilateral pleural effusions consistent with COVID-19 pneumonia. Inflammatory markers were elevated at presentation. He was started on prophylactic anticoagulation with LMWH due to initial d-dimer of 16,107 ng/mL on HD1. Prophylactic anticoagulation was escalated to therapeutic heparin due to increasing D-dimer of 23,541 on HD2 and detectable troponin I; he was intubated and placed on mechanical ventilation for ARDS. He received remdesivir from HD3-7 and convalescent plasma on HD10. On HD12, he became unarousable to voice or noxious stimuli and his neurological exam revealed fixed and non-reactive pupils. CTH revealed a large right frontal lobe intraparenchymal hemorrhage with extension to the intraventricular and subarachnoid spaces, associated transtentorial herniation, and a 1.3 cm midline shift. Left lateral ventricle enlargement and diffuse cerebral edema. Additional findings included left lateral ventricle enlargement concerning for entrapment, diffuse cerebral edema and small right cerebellar hemisphere intraparenchymal hemorrhage. Coagulation parameters at the time of the catastrophic hemorrhage showed prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). He expired after terminal extubation on HD14.

**Patient #4**

A 71-year-old woman with diabetes mellitus type II, hypertension, hyperlipidemia, and class III obesity, was transferred from an outside hospital for management of COVID-19 ARDS on HD12. Inflammatory markers were elevated on presentation and HD12 D-dimer was 5,684 ng/mL. LMWH 0.6 mg/kg BID per protocol was initiated. She also had gram negative bacteremia and given a two-week course of antibiotics. On HD15, she developed a right pneumothorax and then left pneumothorax with subsequent chest tube placement. On HD26, a stroke code was called for impaired arousal and a
artery extending into the superficial femoral artery and another occlusive thrombus in the distal right internal iliac artery. These were treated with both percutaneous mechanical thrombectomy and thrombolytic therapy using tissue plasminogen activator (tPA); postoperatively, the loss of left dorsalis pedis and posterior tibial pulsation necessitated the addition of alteplase infusion. He had recurrent surgical site bleeding due to these procedures. On HD8, he reported generalized headache. CTH revealed acute bilateral intraparenchymal hemorrhage, most evident in the left occipital lobe with intraventricular extension, subarachnoid hemorrhage and associated regional mass effect (Fig. 1). There was also a right parietal infarct with hemorrhagic conversion. Therapeutic heparin and tPA were discontinued and cryoprecipitate and tranexamic acid were administered. D-dimer at the time was 13,874 ng/mL. An extensive laboratory evaluation for thrombophilia was performed, including antiphospholipid antibodies was negative. On HD29, he was intubated due to declining respiratory status and subsequently went into septic shock. He was transitioned to comfort care and expired on HD47.

Discussion & conclusion

Here, we describe five critically ill patients with COVID-19 ARDS who developed intracranial hemorrhage while on intermediate or full-dose therapeutic anticoagulation and one patient who was SARS-CoV-2 positive but asymptomatic and suffered intracranial hemorrhage after prophylactic anticoagulation. Five out of six patients received therapy for COVID-19; two with hydroxychloroquine, one with remdesivir and convalescent plasma, one with antibiotics and the last one with tocilizumab. Two patients also had concurrent thrombosis (PE, lower extremity VTE, arterial). All five patients with COVID-19 ARDS had elevated inflammatory markers at presentation including LDH, ferritin, C-reactive protein, D-dimer but only two of five had D-dimer >5x the upper limit of normal (>2500 ng/mL). Additionally, three of five patients had D-dimer levels over 13,000 ng/mL at the time their hemorrhage occurred with all having normal platelet counts and four of five with normal coagulation parameters. Patient #6 also suffered from an acute ischemic stroke with eventual hemorrhagic conversion; due to the finding of arterial thrombosis, antiphospholipid antibodies were sent but not present. As reported in other case series describing intracranial hemorrhage, we are unable to determine if these neurological complications are due to ARDS from COVID-19; however, patient #2 was diagnosed at presentation with a subdural hematoma and then after evaluation had a right frontal lobe intracerebral hemorrhage after prophylactic anticoagulation was begun. None of the patients were treated with extracorporeal membrane oxygenation (ECMO).
COVID-19-associated coagulopathy has been well described. There is growing evidence that patients with COVID-19 have a predisposition to both intracranial hemorrhage and thrombosis.\(^9,10\) It has been proposed that the often-seen elevated hypertension (mediated by binding of SARS-CoV-2 to angiotensin converting enzyme), significant thrombocytopenia and deranged coagulation proteins (as indicated by prolongation of the PT and aPTT) contribute to the development of intracranial hemorrhage in these patients.\(^9,11\) On the other hand, the establishment of a hypercoagulable state as indicated by markedly elevated markers of systemic inflammation caused by a robust inflammatory response resulting in a cytokine storm mediated by IL-1 and IL-6 biochemical cascades. Which in results in denoting ongoing fibrinolysis (e.g. D-dimer and fibrin split products) and other non-specific indicators such as ferritin, C-reactive protein, erythrocyte sedimentation rate, and lactate dehydrogenase which may represent the widespread endothelial damage thought to be associated with COVID-19.\(^9,10,12,13\) However, therapeutic anticoagulation comes with an increased risk of bleeding. Evidence of the overall effect of therapeutic anticoagulation in critically ill COVID-19 patients without confirmed thrombosis is lacking.\(^14\) Prospective clinical trials are needed and are underway to answer these important questions. In the interim, clinicians must carefully weigh the risks and benefits of anticoagulation in the COVID-19 patient; also, given the level of isolation, sedation and paralytics, neurological exams are challenging. When a change is recognized, the disease process has often advanced beyond intervention.\(^9\)

**Declaration of Competing Interest**

None.

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**References**

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristic of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-1720. https://doi.org/10.1056/NEJMoA2002032.
2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323:1061. https://doi.org/10.1001/jama.2020.158.
3. Al-Ani F, Chehade S, Langner-Lazo A. Thrombosis risk associated with COVID-19 infection: A scoping review. Thrombosis Res 2020;192:152-160.
4. Klok F, Kruip M, Meer NVD, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis Res 2020. https://doi.org/10.1016/j.thromres.2020.04.013.
5. 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. https://doi.org/10.1111/jth.14817.
6. Al-Samkari H, Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020;136:489-500.
7. Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020. https://doi.org/10.1136/svn-2020-000431.
8. Oh SB, Bang SJ, Kim MJ. McConnell’s sign; a distinctive echocardiographic finding for diagnosing acute pulmonary embolism in emergency department. Critical Ultrasound Journal 2015;7(S1). https://doi.org/10.1186/2036-7902-7-s1-a20.
9. Abboud H, Abboud FZ, Kharbouch H, Arkha Y, El Abbadi N, El Ouahabi A. COVID-19 and SARS-Cov-2 infection: pathophysiology and clinical effects on the nervous system. World Neurosurg 2020;140:49-53. https://doi.org/10.1016/j.wneu.2020.05.193.
10. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral hemorrhage: causative or coincidental? New Microbes New Infect 2020;35:100669. https://doi.org/10.1016/j.mni.2020.100669. Published 2020 Mar 27.
11. Markus HS, Brainin M. COVID-19 and stroke—a global world stroke organization perspective. Int J Stroke 2020;15(4):361-364. https://doi.org/10.1177/1747493020923472.
12. Coronavirus disease 2019 and stroke: clinical manifestations and pathophysiological insights. J Stroke Cerebrovas Dis 2020;29(8):104941. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104941.
13. Benger M, Williams O, Siddiqui J, Sztriha L. Intracerebral haemorrhage and COVID-19: Clinical characteristics from a case series. Brain Behav Immun 2020;88:940-944. https://doi.org/10.1016/j.bbi.2020.06.005.
14. Thachil J, Tang N, Gando S, et. al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2030;18: 1023–1026.