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Short communication

Intracranial hemorrhage in critically ill patients hospitalized for COVID-19

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ABSTRACT

In this study, we report three cases of spontaneous intracranial hemorrhage in patients who were initially hospitalized at our tertiary care center in Washington, DC with symptoms of COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed in all three patients, who were critically ill, requiring intubation and ventilatory support. During their protracted hospitalizations, subsequent imaging disclosed intracranial hemorrhages, including intracerebral and subarachnoid hemorrhages, in the context of anticoagulation and coagulopathy. We believe this is related to the tropism of SARS-CoV-2 to the endothelial lining of the cerebral vasculature via their angiotensin-converting enzyme (ACE) II receptors. Given our findings, we advocate heightened vigilance for intracerebral hemorrhage events, and scanning when practicable, in COVID-19 patients which have prolonged ventilatory support and depressed neurologic examinations.

We report three cases of spontaneous intracranial hemorrhage in patients who were initially hospitalized at our tertiary care center in Washington, DC with symptoms of COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed in all three patients, who were critically ill, requiring intubation and ventilatory support. During their protracted hospitalizations, subsequent imaging disclosed intracranial hemorrhages, including intracerebral and subarachnoid hemorrhages, in the context of anticoagulation and coagulopathy.

Our first patient was a 57-year-old woman with past medical history of hypertension, obesity, sleep apnea, and asthma who presented to our emergency department (ED) with shortness of breath and fever. After testing positive for SARS-CoV-2, she was initially admitted to the floor and subsequently escalated to the intensive care unit (ICU) and intubated for hypoxic respiratory failure. She developed acute renal insufficiency, requiring continuous veno-venous hemofiltration under coverage of a heparin drip. Following two weeks of mechanical ventilation, a computed tomography (CT) scan of the head was performed given persistent encephalopathy, revealing a subacute lobar right frontal intracerebral hemorrhage (ICH) (Fig. 1A). No coagulation or platelet dyscrasias were uncovered. Repeat CT imaging was stable, and following negative PCR testing for SARS-CoV-2, she was able to undergo contrasted magnetic resonance imaging (MRI), which did not disclosed an underlying pathology for the original ICH and revealed interval development of ICH in the left frontal lobe, despite being off heparization at that time (Fig. 1B and C). Interestingly, it also revealed significant inflammation of the sphenoid sinus – a putative mechanism for neuro-invasion by the virus (Fig. 1D). The patient was subsequently discharged to an acute rehabilitation facility one week later.

The second patient is a 54-year-old female with past medical history of hypertension, obesity, and bilateral mastectomy in 2016 for BRCA2 mutant breast cancer who presented to our ED with four days of myalgia and fever. After testing positive for SARS-CoV-2, she was discharged to home, but was admitted two days later with dyspnea and hypoxia necessitating mechanical ventilation. She continued to deteriorate, entering vasodilatory shock requiring vasopressors and epoprostenol treatment with prone positioning. She had a transient thrombocytopenia and was placed on a heparin drip for thromboembolic protection. At 24 h following cessation of heparin drip, at one week post-intubation, the patient developed dilated and non-reactive pupils on hourly neurologic checks and CT images of the head disclosed diffuse subarachnoid hemorrhage with intraventricular extension and sulcal effacement (Fig. 1E and F). She progressed to brain death and expired due to asystole four days later (Table 1).

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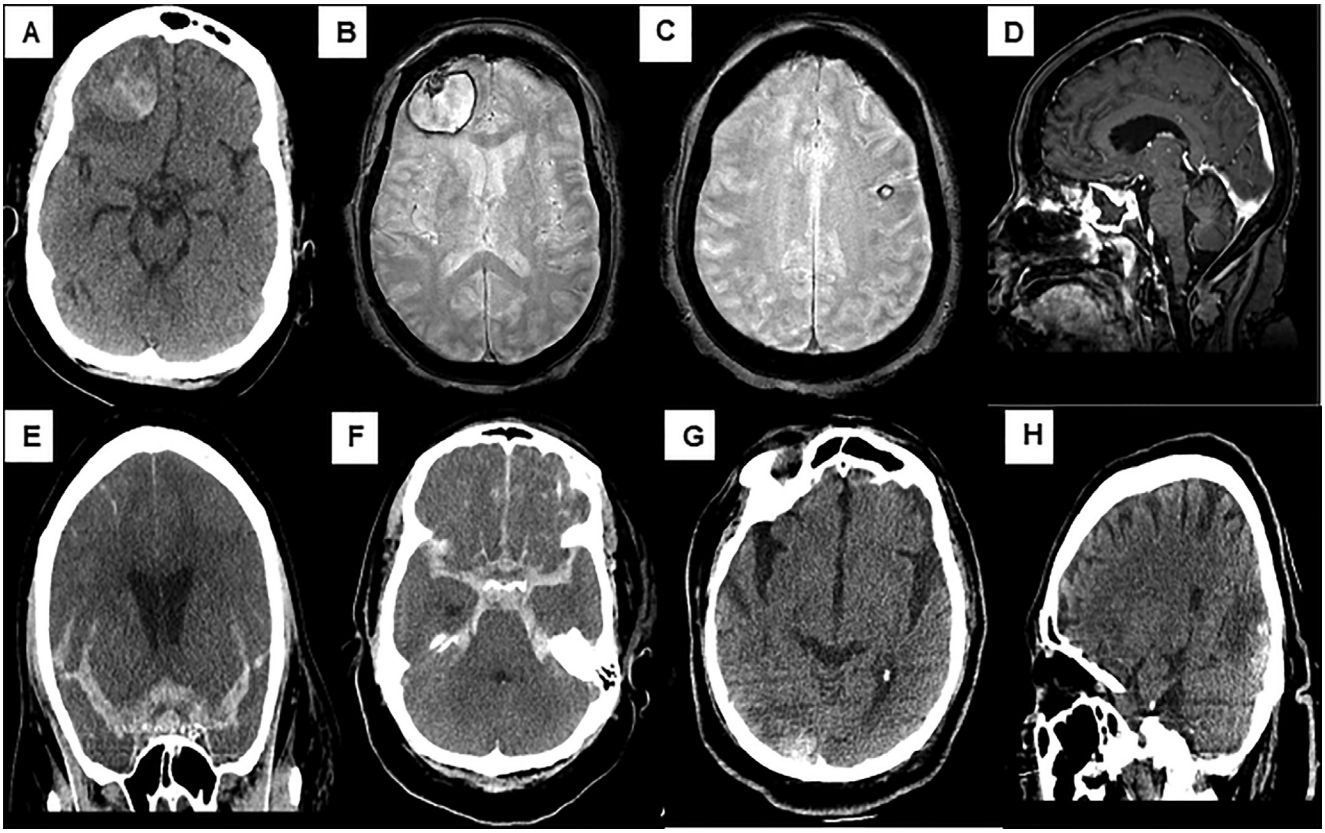

Fig. 1. A: Axial computed tomography (CT) of the head demonstrating a 3.5 × 3.4 × 3.2 cm acute intraparenchymal hematoma with inferior frontal midline shift. B,C: Axial magnetic resonance imaging (MRI) gradient echo (GRE) sequence demonstrating stable 3.2 cm right frontal intraparenchymal hematoma (B) with additional 0.6 cm left frontal intraparenchymal hematoma (C). D: Sagittal post-contrast T1 MRI with evidence of inflammation in the sphenoid sinus, a possible conduit for neuro-invasion by the virus. E, F: Axial (E) and coronal (F) non-contrast CT head demonstrating massive subarachnoid hemorrhage distributed throughout the basal cisterns with effacement of normal sulcal-gyri pattern. G,H: Axial (G) and sagittal (H) non-contrast CT head demonstrating a 2.2 × 2.2 cm intraparenchymal hemorrhage with surrounding hypodensity, suspicious for hemorrhagic transformation of a right-sided posterior cerebral artery (PCA) infarction.

The third patient is a 71-year-old gentleman with past medical history of hypertension, type II diabetes, chronic kidney disease, and B-cell lymphoma in remission who presented to the ED with acute onset shortness of breath and dizziness. After testing positive for SARS-CoV-2, the patient was admitted, progressing from a 15-liter supplement oxygen requirement to intubation, prone positioning, and vasopressor support within 5 days of admission. At two weeks post-intubation, persistent encephalopathy promoted a surveillance head CT, which disclosed a right occipital ICH with surrounding edema suggestive of hemorrhagic conversion of an infarct (Fig. 1G and H). D-dimer and fibrinogen were elevated to 3.2mcg/mL (normal range 0–0.72 mcg/mL) and 1018 mg/dL (normal range 213–536 mg/dL), respectively, indicating a hypercoagulable state. While international normalized ratio (INR) and platelet counts were within normal range prior to the hemorrhage, they subsequently became profoundly hypercoagulable and thrombocytopenic afterwards, suspicious for disseminated intravascular coagulation (DIC). While the ICH remained stable on repeat imaging, the patient ultimately succumbed to multi-system organ failure one week later.

These cases support the predisposition of COVID-19 patients to the development of intracranial hemorrhage during critical illness. The pathophysiology is unclear, but the tropism of SARS-CoV-2 to the endothelial lining of the cerebral vasculature via their angiotensin-converting enzyme (ACE) II receptors, remains a possibility [1,2], and a recent pathology study *The Lancet* demonstrated the presence of virus particles within endothelial cells and an accumulation of inflammatory cells, leading to endothelial cell death [3]. Furthermore, a recent Italian review of animal studies suggests a higher neuro-invasive property of SARS-CoV-2 compared to other coronaviruses [4]. Zhou et al were able to detect SARS-CoV-2 RNA in human cerebrospinal fluid, and neurologic sequelae have been observed in an estimated 36% of COVID-19 patients [5–7]. Postmortem brain studies have also shown direct invasion of neurons and glial cells [8,9]. Several studies have suggested a pro-thrombotic state in these patients, possibly related to antiphospholipid antibodies, which may lead to ischemic complications related to occlusion of the cerebral vasculature [10–15]. Additionally, numerous reports of ICH in COVID-19 have begun to accumulate in the literature [16–20]. Collectively, these findings corroborate the possibility of direct cerebrovascular endothelial injury, vascular injury, and DIC leading to cerebral hemorrhagic events, exacerbated by concomitant anticoagulation therapy in two instances.

The ability to identify and treat these patients is hindered by the strict isolation and precautions mandated by COVID-19 infection. Given our findings, we advocate heightened vigilance for intracerebral hemorrhage events, and scanning when practicable, in COVID-19 patients which have prolonged ventilatory support and depressed neurologic examinations.

Table 1
Clinical Characteristics of Three COVID+ Patients who Developed Intracranial Hemorrhages.

	Case 1	Case 2	Case 3
Age – years	57	54	71
Gender	Female	Female	Male
Medical History	Obesity Sleep Apnea Asthma	Hypertension Bilateral Mastectomy (BRCA2 mutant breast cancer)	Hypertension Type II Diabetes Mellitus Chronic Kidney Disease B-Cell Lymphoma (In Remission)
Relevant Medications	Aspirin 81 mg	Aspirin 81 mg Placebo vs Sarilumab Epoprostenol Desmopressin	N/A
Presenting COVID Symptoms	Shortness of Breath Fever	Body Aches Fever Hypoxia	Shortness of Breath Dizziness
Hospital Stay Prior to ICH – days	20	8	20
Duration of Intubation Prior to ICH – days	18	8	15
Prone Positioning	+	+	+
Other Critical Care Needs	Vasopressors Continuous Veno-Venous Hemofiltration	Vasopressors	Vasopressors
Anticoagulation (Duration)	Heparin drip (6 days)	Heparin drip (30 h)	N/A
Symptom Prompting Head Imaging	Persistent Encephalopathy	Fixed and Dilated Pupils	Persistent Encephalopathy
Type and location of ICH	Right Frontal Lobar Intracerebral Hemorrhage	Diffuse Subarachnoid Hemorrhage	Right PCA distribution infarct with hemorrhagic conversion
Imaging Studies Performed	CT and MRI	CT and Nuclear Medicine Study	CT
Laboratory Values – At Presentation/At Time of ICH/ Minimum-Maximum			
White Blood Cell Count – per mm3	10,700/24,800/8800–91,000	8300/17,300/5200–18,200	10,200/9300/5300–18,600
Platelet Count – per mm3	200,000/181,000/159,00–506,000	135,000/123,000/17,000–137,000	207,000/354,000/64,000–360,000
Prothrombin Time – seconds	13.2/13.9/13.2–15.7	13.0/14.5/13.0–14.8	13.5/20.3/13.2–20.3
Activated Partial-Thromboplastin Time – seconds	33.2/20.8/20.8–40.9	25.1/48.2/25.1–48.2	N/A/57.3/57.3–65.7
International Normalized Ratio	1.0/1.1/1.0–1.2	1.0/1.1/1.0–1.2	1.0/1.7/1.0–1.7
Anti-Xa – IU/mL	N/A/N/A/0.23–1.10	N/A/0.26/0.97–1.10	N/A
Fibrinogen – mg/dL	N/A/638/382–1214	630/308/308–788	672/1276/672–1276
D-dimer – mcg/mL	1.06/14.08/1.06–18.63	0.52/13.79/0.52–20.00	1.44/9.55/1.44–9.88
Outcome	Acute rehabilitation	Cerebral circulatory arrest confirmed by nuclear medicine study	Palliative extubation

ICH: intracranial hemorrhage; CT: computed tomography; MRI: magnetic resonance imaging; PCA: posterior cerebral artery.

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None.

Statement of ethics

This study did not require approval by our institution's Institutional Review Board and did not require patient consent due to the retrospective nature of the analysis.

Disclosure statement

The authors certify that this manuscript is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium. Each named author has substantially contributed to conducting the underlying research and drafting this manuscript. Additionally, to the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.

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