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Fulminant Hemorrhagic Vasculopathy Associated with COVID-19

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Abstract

Background— Coronavirus disease 2019 (COVID-19)–related neurologic complications remain poorly understood. Current literature demonstrates that COVID-19 has been associated with cerebral microbleeds and leukoencephalopathy in as many 30% of critically-ill patients who undergo magnetic resonance imaging suggestive of endothelial inflammation and thrombotic microangiopathy.

Case Description— We report a patient who presented with the sudden onset of status epilepticus and coma. Clinical and neuroimaging findings suggested a diffuse novel severe acute respiratory syndrome coronavirus (SARS-CoV-2)–induced hemorrhagic vasculopathy. Her level of consciousness improved dramatically with high dose corticosteroids, and she made a good recovery.

Conclusions— We report a patient with COVID-19 who developed clinical syndrome and radiological findings most consistent with diffuse cerebral vasculitis.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2), has led to a global pandemic with cases continuing to surge in multiple regions worldwide.[1] SARS-CoV-2 targets the angiotensin-converting enzyme 2 receptors, expressed on multiple tissues, including the lungs, heart, kidney, and also endothelium.[1,2] While COVID-19 is most notable for its pulmonary manifestations, neurological complications have been increasingly reported in the literature.[3-14] The most common nervous system presentations of COVID-19 include loss of smell and taste, altered mental status, dizziness, and headache.[3] COVID-19 also appears to be linked to pro-inflammatory hypercoagulable abnormalities predisposing patients to increased risk of acute ischemic cerebrovascular events.[4] Additionally, a small but growing number of cases have been reported of necrotizing encephalitis, acute disseminated encephalomyelitis, and acute post-infectious neuropathies including Guillain-Barré syndrome.[4–6] Non-specific neurological complications of severe disease, such as hypoxic encephalopathy and critical care myopathy have also been documented.[4]

At the time of this report, four cases of potential central nervous system vasculitis have been reported in association with COVID-19 infection.[7–10] COVID-19 has also been associated with cerebral microbleeds and leukoencephalopathy in as many 30% of critically-ill patients who undergo magnetic resonance imaging, suggestive of endothelial inflammation and thrombotic microangiopathy.[11,12] Here we present a novel case of a COVID-19 patient who presented with the abrupt onset of seizures and coma due to a fulminant small-vessel vasculopathy manifesting as cerebral microhemorrhages and infarcts in the absence of systemic pulmonary disease.

CASE DESCRIPTION

A 66-year-old woman with past medical history of hypertension presented to Westchester Medical Center

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(WMC) after an episode of seizure and unresponsiveness. She had no prior history of stroke, dementia or epilepsy, and no antecedent febrile illness or respiratory symptoms. On July 16, 2020, the patient was in the midst of a phone conversation with her daughter when she was found on the floor by her husband who witnessed tonic-clonic activity, followed by confusion and excessive salivation. She was taken to the nearest urgent care center and subsequently transferred to a hospital. On arrival to the nearest emergency department, she was extremely hypertensive with a systolic blood pressure exceeding 250 mm Hg. Computed tomographic scan of the head demonstrated two small, punctate acute foci of hemorrhage (4 mm) in the right posterior-temporal / inferior parietal lobe (4 mm), and in the upper right parietal convexity (2 mm, Figure 1). There were also scattered hypodensities in the basal ganglia compatible with age-indeterminate lacunar infarcts, and severe white matter disease manifesting as periventricular white matter hypodensities (Figure 1). Patient was stuporous and unable to follow commands. She was intubated for airway protection, loaded with 2 grams of levetiracetam, and transferred to WMC neurologic intensive care unit.

Upon arrival to WMC, COVID-19 was identified with reverse transcription polymerase chain reaction detection of SARS-CoV-2 from a nasopharyngeal swab. Chest radiography and arterial blood gases were normal. Her systolic blood pressure was lowered to 140 mm Hg with intravenous nicardipine. Blood testing demonstrated a systemic inflammatory syndrome with elevated C-reactive protein (13.0 mg/dL), ferritin level (350 µg/L), and D-dimer levels (4.10 mg/L). She also had elevated creatine kinase (409 U/L) and anion gap (15 mEq/L), consistent with convulsive seizures, and relative neutrophilia (85%) and lymphopenia (11%). Off sedation, she continued to be comatose with no eye opening to pain and an intact oculocephalic response (right more than left). In response to sternal pressure, the right upper extremity localized grossly whereas the left showed stereotyped flexion and elevation off the bed. Continuous 24-hour video electroencephalography monitoring demonstrated diffuse bihemispheric slowing with clearly-defined electrographic ictal events originating from the right parietal region with evolution and secondary generalization, consistent with status epilepticus, for which she was loaded with fosphenytoin 20 mg/kg and started on a midazolam infusion at 0.2 mg/kg/hr.

Further imaging was done to look for causes of intracranial hemorrhage, as well for causes of status epilepticus. Computerized tomography venogram demonstrated no dural or cortical venous thrombus. Computerized tomography angiogram demonstrated scattered regions of mild luminal irregularity and variable narrowing involving the anterior and posterior circulation first and second order branches (Figure 2). Brain magnetic resonance imaging on hospital day 6 performed with and without contrast demonstrated a diffuse pattern of cerebral microbleeds involving both the cortex and basal ganglia on T2 fast field echo sequences, and small punctate microinfarcts in the right posterior internal capsule, parietal lobe and bilateral cerebellar peduncles on diffusion weighted imaging (Figure 3). Magnetic resonance angiography of the head and neck again demonstrated mild diffuse narrowing of the visualized intracranial arteries, similar to the changes observed on prior computerized tomography angiogram.

Cerebrospinal fluid analysis did not identify any erythrocytes or leukocytes, with normal protein and glucose levels, and negative meningitis/encephalitis polymerase chain reaction panel. A vasculitis panel for rheumatologic disease was negative with the exception of elevated homocysteine level. Brain biopsy of right frontal cortex demonstrated no definite pathology.

The patient was started on a five-day course of 1000 mg intravenous methylprednisolone daily for the presumptive diagnosis of vasculitis. Coincident with the course of high dose steroids, she recovered consciousness, the flexor posturing resolved, and she was extubated. Thereafter, she was treated with oral prednisone 100 mg daily.

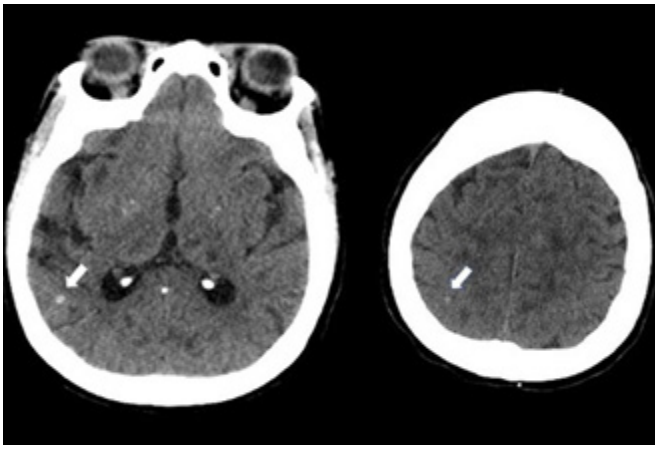

FIGURE 1: Pretreatment admission CT head: Showing two small punctate areas of hemorrhage (arrows), small deep infarcts of indeterminate age affecting the right insula and left thalamus, and white matter hypodensities in the centrum semiovale.

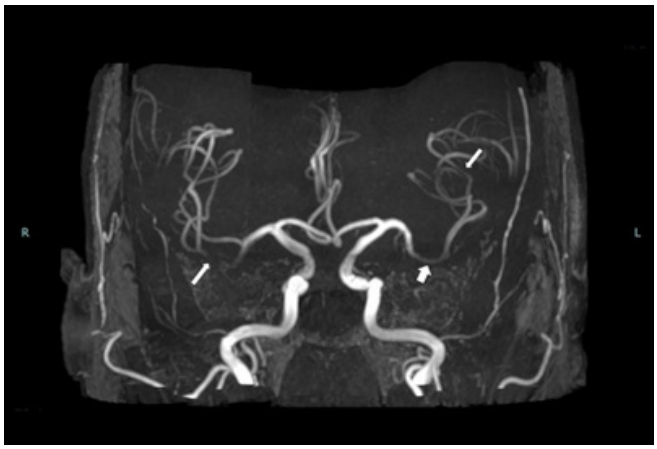

FIGURE 2: Pretreatment CT angiogram: Maximum intensity projection (MIPS) image of a CT angiogram demonstrating several segments of large (thick arrow) and medium-size (thin arrows) vessel narrowing involving the left M1 and bilateral M2 segments of middle cerebral artery.

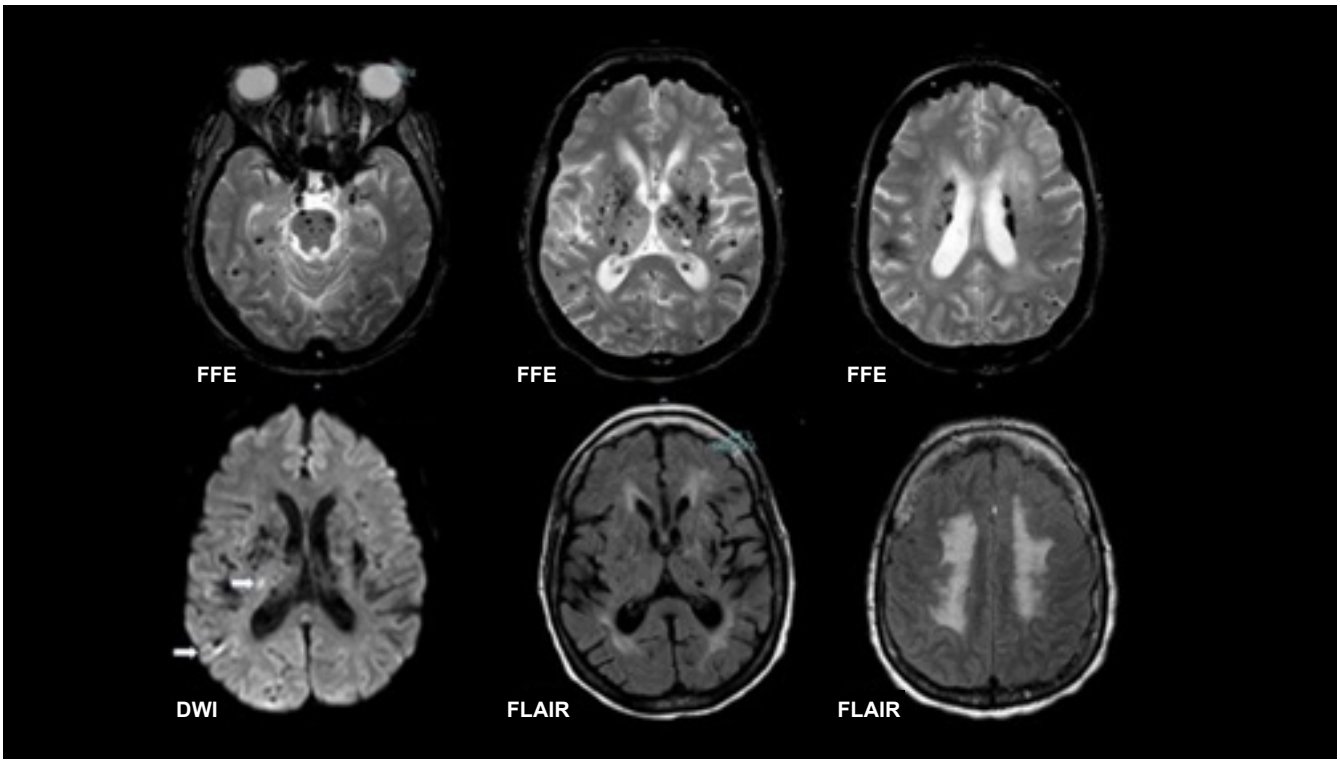

FIGURE 3: Pretreatment MRI: Obtained on hospital day 6 demonstrating a diffuse pattern of microbleeds involving the brain stem, thalamus and basal ganglia, deep white matter and to a lesser extent the cortex on susceptibility-weighted fast field echo (FFE) images; two small punctate infarcts (arrows) on diffusion weighted imaging (DWI); and extensive leukopathy on fluid attenuated inversion recovery (FLAIR) images.

The patient's hospital course was complicated by breakthrough seizures, hospital-acquired pneumonia that was treated with empiric antibiotics, non oliguric acute kidney injury, placement of a percutaneous endoscopic gastrostomy with revisions, and severe refractory hypertension requiring prolonged nicardipine infusion with substitution to oral clonidine, hydralazine, isradipine, and chlorthalidone. Repeat magnetic resonance imaging performed six weeks after admission demonstrated new right frontal and left periatrial white matter infarcts, and multiple new diffusion weighted imaging hyperintensities, without restricted diffusion, involving the right frontal white matter, right putamen, left caudate nucleus, and left cerebral peduncle. Repeat MR angiography demonstrated stable findings compared to prior imaging. Prior to discharge to an acute rehabilitation facility eight weeks after admission the patient had improved to being alert and oriented with hypophonic speech, psychomotor slowing, and generalized weakness with no focal weakness or numbness.

DISCUSSION

Our patient presented with the sudden and abrupt onset of seizures and lethargy, followed by refractory status epilepticus. Computerized tomography imaging showed two small punctate foci of hemorrhage, whereas magnetic resonance imaging showed a striking diffuse pattern of cerebral microbleeds involving the brain stem and deep nuclei more than the cortex, along with a few scattered small ischemic infarcts, severe progressive leukopathy, and evidence of large and moderate vessel segmental narrowing on computerized tomography angiography. Although COVID-19 was diagnosed on the basis of polymerase chain reaction panel performed on nasal swab in addition to elevated pro-inflammatory markers, she had no evidence of pulmonary involvement on presentation and was intubated purely for airway protection due to poor level of consciousness.

The pattern of diffuse microbleeds and infarcts that developed in our patient, combined with the fulminant presentation and lack of antecedent symptoms, points towards a rapidly progressive vasculitis or endothelial inflammation primarily affecting involving small penetrating vessels in the brain. Elevation of pro-inflammatory markers is a sign of a systemic immune response or "cytokine storm," which has been cited as a possible cause of central nervous system vascular inflammation in COVID-19 patients.[13-15] Importantly, our patient experienced immediate clinical improvement after being started on high dose corticosteroid therapy, suggestive of an inflammatory or autoimmune vasculopathy. Similar to our case, another COVID-19 patient in Italy diagnosed clinically with central nervous system vasculitis also showed clinical improvement after being treated with steroids.[10] Fulminant hemorrhagic vasculopathy may be related to endothelial involvement in small arterioles. The spike protein of SARS-COV-2 has a strong affinity for the angiotensin-converting enzyme 2 receptor, which has widespread expression in endothelial cells.[1,2] In a pathological study, Varga et al[2] have documented viral inclusions in endothelial cells in the kidneys, heart, lungs, and small bowel in COVID-19 patients, with associated widespread endothelial dysfunction and apoptosis.

The imaging findings in our patient resemble the cerebral microbleeds and leukopathy reported in 30% of 115 encephalopathic, mechanically ventilated patients with COVID-19 and pneumonia who underwent magnetic resonance imaging.[11] Another report of 11 ventilated COVID-19 patients with microbleeds and leukopathy on magnetic resonance imaging suggested that these findings are primarily a late manifestation of illness caused by exposure to hypoxia,[12] probably representing post-hypoxic demyelination.[16] A case report described an intubated patients with COVID-19 and pneumonia who developed agitated delirium and had evidence of severe leukopathy, microbleeds involving the posterior corpus callosum, and hyperemia of the posterior circulation on arterial-spin-labelling.[17] Our patient differs from these prior reports because of the fulminant mode of presentation and the absence of antecedent respiratory disease.

A comprehensive vasculitis workup in our patient did not elucidate alternate etiologies for the diffuse hemorrhagic vasculopathy identified on magnetic resonance imaging. One limitation of our report is that we were unsuccessful in performing polymerase chain reaction in cerebral spinal fluid sample, which could have confirmed SARS-CoV-2 invasion of the central nervous system. However, majority of COVID-19 patients with neurological manifestations In previous studies[18,19] have negative polymerase chain reaction panel testing for COVID-19 performed on cerebral spinal fluid samples. The brain biopsy in our patient did not confirm the presence of intramural vascular inflammatory infiltrates which may be attributable to limitations in sample acquisition. In conclusion, we report a patient with COVID-19 who developed clinical syndrome and radiological findings most consistent with diffuse cerebral vasculitis.

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