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LETTER TO THE EDITOR

COVID-19 Patients With CNS Complications and Neuropathologic Features of Acute Disseminated Encephalomyelitis and Acute Hemorrhagic Leukoencephalopathy

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To the Editor:

Over the past year, SARS-CoV-2, the novel coronavirus causing COVID-19, has spread across the globe, infecting an estimated 100 million people and causing >2 million deaths thus far, with hundreds of thousands of additional cases occurring daily (1). Typical symptoms include fever, cough, dyspnea, myalgia, and anosmia, however, there is a growing body of evidence which suggests that a wide range of neurologic symptoms may be more prevalent than previously recognized with corresponding pathologies ranging from nonspecific hypoxic-ischemic injury and microvascular injury with microhemorrhage to large infarcts and findings similar to acute disseminated encephalomyelitis (ADEM) (2–7), although there is considerable debate over which neuropathologic findings can truly be attributed to COVID-19 (8–12). These findings are present despite conflicting evidence for viral particles in the brain, spinal cord, and cerebrospinal fluid of patients with neurologic symptoms (13–15). Here, we present 2 cases of fatal COVID-19 with severe neurologic sequalae and neuropathologic findings of ADEM and acute hemorrhagic leukoencephalopathy (AHLE).

CASE 1

A 51-year-old woman with a past medical history of trisomy 21 and medically refractory seizures, documented history of medical noncompliance, status-post corpus callosotomy in 2004 and vagus nerve stimulator placement in 2015 presented to the emergency department with increased seizure activity (6–10 seizures/day) for the preceding 3 days, fever, diarrhea, incontinence, and aphasia. She was intubated and transferred to the neuro ICU and treated for seizures. She tested positive for COVID-19 and remdesivir was started. A CT scan was performed and demonstrated evidence of her prior corpus callosotomy but no evidence of acute intracranial pathology. On hospital day 4 she became hemodynamically unstable and passed away despite full code measures.

At brain autopsy, there was evidence of a disproportionately small cerebellum, and coronal sections demonstrated evidence of prior corpus callosotomy and multifocal tan-gray discoloration throughout the subcortical white matter. Histologically, there was an irregular pattern of demyelination as seen by Luxol fast blue/periodic acid-Schiff (LFB/PAS) (Fig. 1A, B), which corresponded to the white matter discoloration identified grossly. This demyelination centered primarily around veins and venules (Fig. 1C), and although we observed relatively few perivascular CD3+ T-lymphocytes (Fig. 1E), there were frequent perivascular and parenchymal CD68+ histiocytes and activated microglial cells (Fig. 1F), all features consistent with a final diagnosis of ADEM. There was also evidence of focal cortical dysplasia (FCD) type 1c, significant global hypoxic-ischemic injury, and cerebellar hypoplasia with Bergmann gliosis (Fig. 1D). A full workup for neurodegenerative disease demonstrated high-level Alzheimer disease neuropathologic change ([ADNC]; Braak V, Thal 4, CERAD frequent) and mild cerebral amyloid angiopathy (CAA) (Table). Immunohistochemical staining for SARS-CoV-2 was negative in multiple brain sections (mouse monoclonal SARS-CoV-2 spike antibody [1A9], Cat. No. GTX632604, GeneTex, Irvine, CA) (14).

CASE 2

A 64-year-old neurologically intact man with a past medical history of hypertension, hypothyroidism, and heavy alcohol use was admitted to the hospital for persistent fever but tested negative initially for COVID-19. Further workup demonstrated methicillin-susceptible *Staphylococcus aureus* (MSSA) aortic valve endocarditis and he was placed on a 6-week IV antibiotic regimen (which was complicated by left axillary vein DVT), then transferred to a rehabilitation facility where he tested positive for COVID-19. He was placed on remdesivir, convalescent plasma, and corticosteroids. Initial CT scan showed no acute intracranial pathology. During ambulation, the patient collapsed and was nonresponsive with a

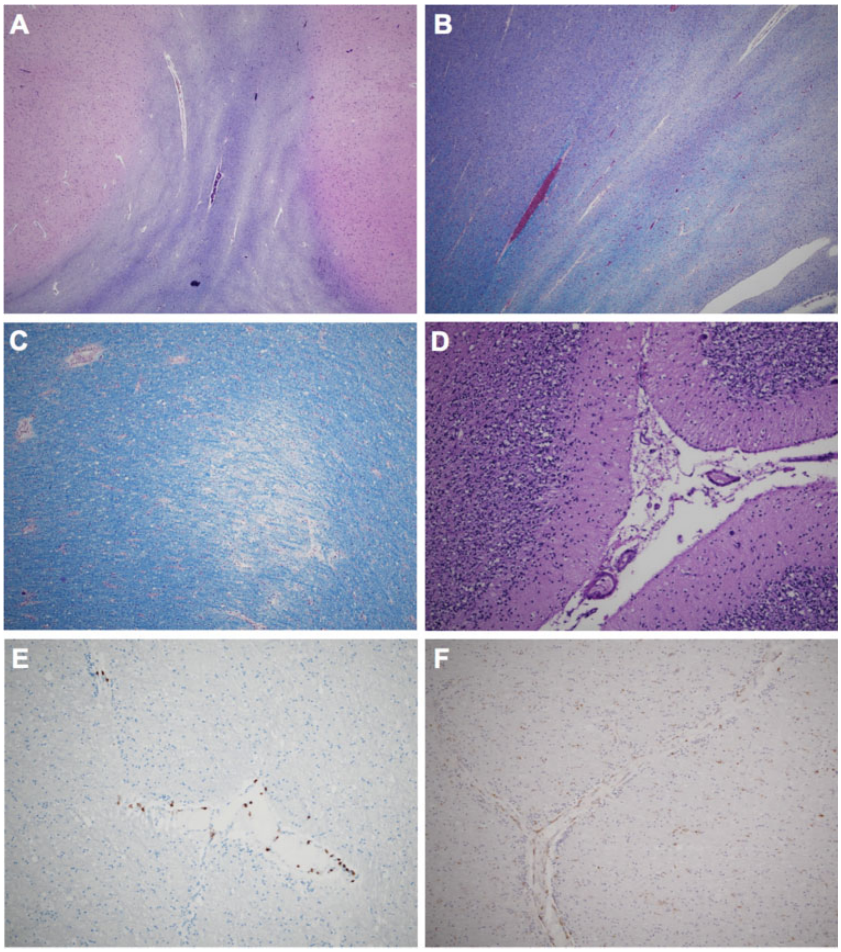

FIGURE 1. Histologic features of Case 1. LFB/PAS stains demonstrating serpiginous myelin pallor in the temporal **(A)** and perihippocampal **(B)** white matter. Higher-power LFB/PAS demonstrating perivascular myelin loss **(C)**. Loss of Purkinje cells and Bergmann gliosis **(D)**. There are multifocal regions of perivascular CD3+ T-lymphocytes **(E)** and perivascular and parenchymal CD68+ histiocytes/activated microglial cells **(F).**

fixed and dilated right pupil. Noncontrast CT scan demonstrated a large right occipital lobe intraparenchymal hemorrhage (Fig. 2A) and right-sided subdural hematoma (Fig. 2B) with significant right-to-left midline shift. The patient passed away soon after.

Brain autopsy demonstrated the acute subdural hematoma, large acute right occipital lobe intraparenchymal hemorrhage (Fig. 2C), and both subfalcine and uncal herniation, as well as multifocal bilateral cerebral white matter hemorrhages. Histologic examination revealed myelin pallor as well as numerous ring- and ball-hemorrhages throughout the white matter with central blood vessels showing fibrinoid necrosis (Fig. 2D, E), most consistent with a diagnosis of AHLE. In addition, there was global hypoxic-ischemic injury, focal neuronophagia in hippocampal sections (Fig. 2F), multifocal areas of myelin pallor, axonal spheroids (Fig. 2G), numerous perivascular CD3+ T-lymphocytes (Fig. 2H) as well as perivascular and parenchymal CD68+ cells (perivascular macrophages and parenchymal microglia) (Fig. 2I). Neurodegenerative workup demonstrated mild primary age-related tauopathy (PART) (Table). Immunohistochemical staining for SARS-CoV-2 spike protein was also negative in the brain.

These 2 cases represent the most severe end of the COVID-19 neuropathologic spectrum. While previous studies have reported neuropathology findings in patients with neurologic symptoms ranging from a complete lack of histologic findings other than hypoxic-ischemic changes (13) to ADEM (2), it remains unclear whether even the most severe pathology is due to the presence of the virus in the brain itself, direct or indirect vascular damage, or parainfectious mechanisms. The findings in these brains are similar to the handful of previously described cases with severe pathology, namely demyelination and axonal injury centered primarily around vessels with perivascular and parenchymal CD3+ and CD68+ cells, ring- and ball-hemorrhages limited to the white matter, and larger hemorrhages. This suggests that COVID-19 could be added to the list of viral syndromes associated

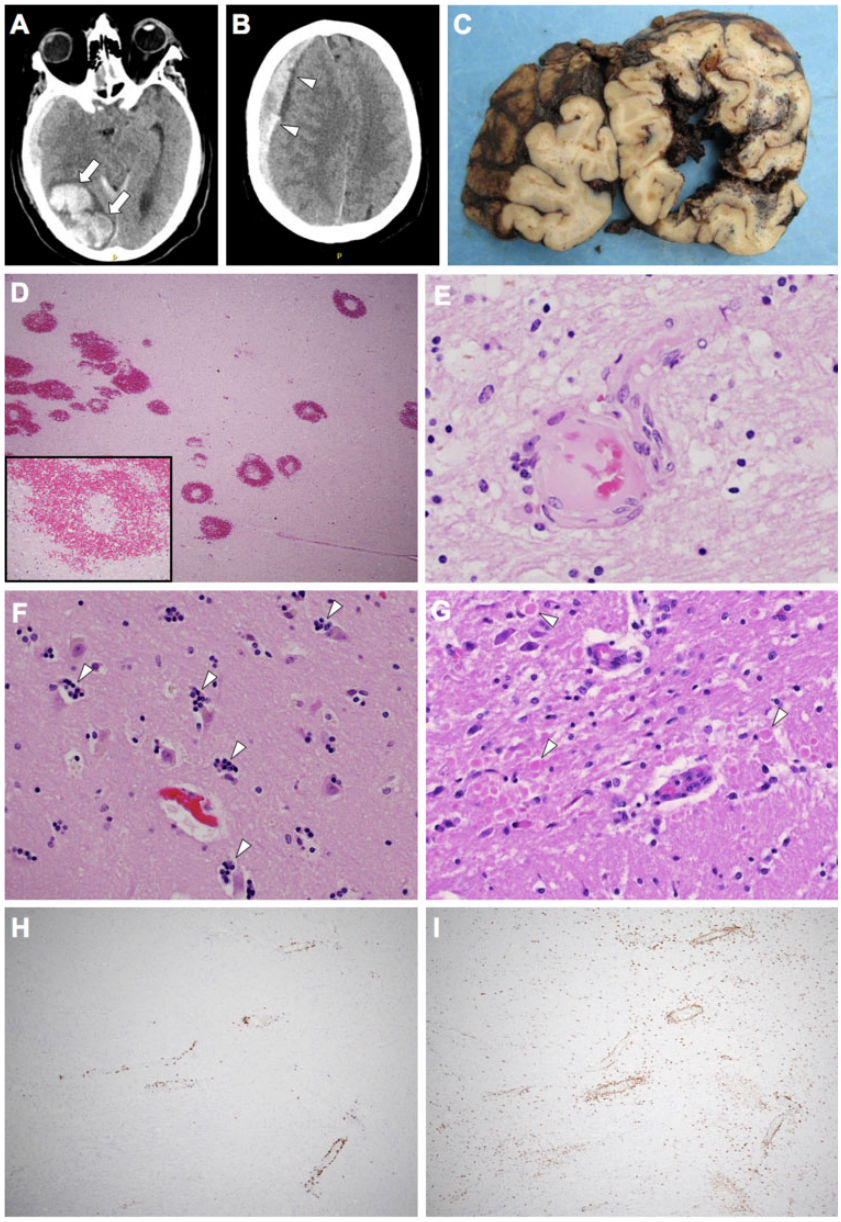

FIGURE 2. Radiologic and pathologic features of Case 2. Antemortem transverse CT scans demonstrating right occipital lobe intraparenchymal hemorrhage (arrows) **(A)** and right cerebral convexity subdural hematoma (arrowheads) **(B)**. Coronal sections of the occipital lobes demonstrating right-sided intraparenchymal hemorrhage **(C)**. Hematoxylin and eosin sections demonstrating ring and ball hemorrhages **(D)** and vessels showing fibrinoid necrosis **(E)**. Hippocampal sections demonstrate neuronophagia in CA1 neurons (arrowheads) **(F)** and basis pontis sections demonstrate frequent axonal spheroids (arrowheads) **(G)**. There are multifocal regions of perivascular CD3+ T-lymphocytes **(H)** and perivascular and parenchymal CD68+ histiocytes/activated microglial cells **(I).**

with demyelinating disease in general and specific syndromes, such as ADEM and AHLE. The damage to both myelin and axons, the lack of immunohistochemical staining for SARS-CoV-2 spike protein, as well as the pathology centering around vessels and evidence for endothelial damage in the brain and other organs (7) suggests an indirect etiologic pathway, such as a primary vascular or parainfectious etiology or a mechanistic route secondary to systemic inflammation and coagulopathy, as opposed to direct central nervous system SARS-CoV-2 infection.

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TABLE. Clinical, Radiologic, and Pathologic Findings

Case	Patient Demographics	Past Medical History	Radiology Findings	Pathologic Diagnoses
1	51-Year-old Female	Trisomy 21 Medically refractory epilepsy Corpus callosotomy (2004) Vagus nerve stimulator placement (2015) History of medical noncompliance with seizure medication	No evidence of acute intracranial processes Evidence of prior corpus callosotomy	Histologic features of ADEM High-level ADNC (Braak V, Thal 4, CERAD 3) Cerebral amyloid angiopathy, mild Focal cortical dysplasia, type 1c Cerebellar hypoplasia with Bergmann gliosis Global hypoxic-ischemic injury Evidence of prior corpus callosotomy
2	64-Year-old Male	Hypertension, hypothyroidism Heavy alcohol use Recent history of MSSA aortic valve endo- carditis with 6-week IV antibiotics, complicated by DVT (July–August 2020)	Right occipital lobe IPH Right-sided subdural hematoma	Histologic features of AHLE Right occipital lobe IPH Right-sided subdural hematoma Global hypoxic-ischemic injury Subfalcine and uncal herniation PART (Braak I, Thal 0, CERAD 0)

ADEM, acute disseminated encephalomyelitis; ADNC, Alzheimer disease neuropathologic change; MSSA, methicillin-susceptible Staphylococcus aureus; DVT, deep vein thrombosis; IPH, intraparenchymal hemorrhage; AHLE, acute hemorrhagic leukoencephalitis; PART, primary age-related tauopathy.

COMPETING INTERESTS

The authors have no duality or conflicts of interest to declare.

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