

LETTER TO THE EDITOR**Postmortem neuropathology in COVID-19**

Dear Editor,

This study concerns the clinicopathologic correlation of 50 decedents of 2019 coronavirus disease (COVID-19) due to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) from among 250 reported patients succumbing to COVID-19 illness (1–7) who underwent detailed postmortem neuropathological studies. This disease, which starts in the lungs, is a multisystem disorder affecting all major organs including the brain. These cases provide a more complete picture of COVID-19 illness, and are important in the development of effective treatment strategies.

As shown in Table 1, older age, male gender, increased serum cytokine and pro-coagulation markers, and critical care hospitalization for ≤ 10 days prior to death characterized the cohort. Immediate causes of death were ascribed to cardiopulmonary and multiple organ failure, intracranial hemorrhage and pulmonary embolus. SARS-CoV-2 detection in brain tissue by polymerase chain reaction was negative in all cases. Seventeen (36%) cases showed focal or diffuse cortical, brainstem, or leptomeningeal inflammation, characterized (in five) as T-cell-mediated based upon flow cytometry. A variety of comorbid pathology in 11 cases (22%) included chronic stroke, Alzheimer, or Lewy body disease and primary brain tumor.

Eight patients had unsuspected encephalitis affecting predominant subcortical white matter (2), brainstem nuclei and white matter tracts (3) and the cerebellum (5). Inflammatory T-cell infiltrates with clusters of macrophages and axonal injury tracking along vessels resembled acute disseminated encephalomyelitis (ADEM) in two cases (2, 5), including one (5) with neuronophagia and microglial nodules, and another with expression of angiotensin converting enzyme (ACE)2 receptor along capillary endothelia cells (2). Six patients of different ages and with differing comorbidity showed histopathological features of encephalitis including localized perivascular and interstitial infiltrates with neuronal cell loss and axonal degeneration involving brainstem nuclei and tracts

without territorial infarctions, or evidence of virus infiltration.

This small cohort of critically ill cases of COVID-19 reveals several important findings. First, hypoxia-ischemia evident in the majority of cases does not account for all relevant neuropathological features of severe COVID-19. Second, patients presenting with elevated levels of circulating interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)- α , suggests activation of innate and adaptive immunity indicative of a cytokine storm. Together with increased serum D-dimer and markers of hypercoagulability in 42% of cases (1, 2), affected patients risk thrombotic, and hemorrhagic parenchymal tissue infarction so noted in nine (18%) cases. Third, eight (16%) cases with ADEM-like features (2, 5) or frank histologic evidence of brainstem encephalitis suggest the need for an index of suspicion in clinically compatible cases.

There were several limitation to this study. First, there was missing data about age, gender, and the cause of death in some cases. Second, case series were often small and unselected. Third, among the various studies included, there were often contradictory conclusions about the significance of inflammatory vascular changes in regards to active central nervous system involvement. In this regard, all patients were in a very critical condition necessitating intensive care due to cardiopulmonary and systemic organ failure. In the absence of comparison to controls, it is not possible to know with certainty whether the histopathological findings suggesting inflammatory vasculopathy, in up to a third of cases, were merely nonspecific.

Awaiting randomized, placebo-controlled trials of antiviral therapy to treat severe COVID-19, or a safe and effective vaccine, this small sample adds to the urgent call to identify neuroprotective therapy. Present research focuses on inhibitors of the cytokine storm using the IL-6 receptor antagonist tocilizumab (ClinicalTrials.gov Identifier: NCT04377659) and the anti-IL-6 monoclonal antibody clazakizumab (ClinicalTrials.gov Identifier: NCT04363502).

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TABLE 1 Clinical and neuropathologic findings of 50 COVID-19 postmortem cases

Observation	Number of cases	Reference
Sex		
Male	24	(1–6)
Female	8	1, 3, 4, 6)
Not reported	18	(1)
Age		
<21	0	
21–49	1	(6)
50–64	5	(3, 6)
>65	7	(2, 3, 5, 6)
Not reported	37	(1, 4)
Serum cytokine and procoagulant levels		
Elevated	21	(1, 2)
Normal	0	
Not reported	29	(3, 4, 5, 6)
Duration of hospital illness to death (days)		
0–1	5	(4, 5, 6)
1–10	18	(2, 3, 4, 6)
>10	9	(3, 4, 6)
Not reported	18	(1)
Cause of death		
Massive intracranial hemorrhage	2	(3)
Cerebellar hemorrhage and herniation	1	(5)
Pulmonary embolism	2	(3, 6)
Cardiopulmonary failure	5	(3, 6)
Multisystem organ failure	1	(2)
Not reported	39	(1, 4, 6)
SARS-CoV-2 reactivity in brain sections		
Positive	0	
Negative	24	(2, 3, 5, 6)
Not Reported	26	(1, 4)
Neuropathology		
Acute microscopic thrombotic ischemic infarcts	4	(1)
Acute microscopic hemorrhagic infarcts	2	(1, 2)
Petechial hemorrhage	3	(3)
Focal perivascular parenchymal T-cell infiltrates	3	(1, 2, 5)
Diffuse perivascular parenchymal T-cell infiltrates	2	(2, 5)
Leptomeningeal inflammation	7	(3, 4)
Interstitial brainstem inflammation with neuronal loss	6	(3)
Capillary endothelium expression of ACE2 receptor	1	(2)


(Continues)

TABLE 1 (Continued)

Observation	Number of cases	Reference
Microglial nodules	1	(5)
Hypoxic ischemia changes and neuronal loss	25	(1, 4, 5, 6)
Associated findings		
Chronic infarction	3	(4)
Alzheimer disease	5	(3, 4)
Lewy body disease	2	(4)
Primary brain tumor	1	(4)

CONFLICT OF INTEREST

The author has no conflicts of interest to report.

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- Bryce C, Grimes Z, Pujadas E, Ahuja S, Beasley MB, Albrecht R, et al. Pathophysiology of SARS-Cov-2: targeting of endothelial cells renders a complex disease with thrombotic microangiopathy and aberrant immune response. The Mount Sinai COVID-19 autopsy experience. *Med Rxiv*. 2020.
- Reichard RR, Kashani KB, Boire NA, Constantopoulos E, Guo Y, Lucchinetti CF, et al. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol*. 2020;140:1–6.
- Von Weyhern CH, Kaufmann I, Neff F, Kremer M. Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. *Lancet*. 2020;395:e109.
- Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological features of Covid-19. *N Engl J Med*. 2020 Jun 12. <https://doi.org/10.1056/NEJMc2019373>. [Epub ahead of print]
- Al-Dalahmah O, Thakur KT, Nordvig AS, Prust ML, Roth W, Lignelli A, et al. Neuronophagia and microglial nodules in a SARS-CoV-2 patient with cerebellar hemorrhage. *Acta Neuropathol Commun*. 2020;8:147.
- Kantonen J, Mahzabin S, Mäyränpää MI, Tynnenen O, Paetau A, Andersson N, et al. Neuropathologic features of four autopsied COVID-19 patients. *Brain Pathol*. 2020 Aug 6. <https://doi.org/10.1111/bpa.12889>. [Epub ahead of print]
- Barth RF, Buja LM, Parwani AV. The spectrum of pathological findings in coronavirus disease (COVID-19) and the pathogenesis of SARS-CoV-2. *Diagn Pathol*. 2020;15:85.