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Letter to the Editor

A Rare Case of Acute Hemorrhagic Leukoencephalitis in a COVID-19 Patient

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Dear Editor,

Neurological manifestations associated with severe COVID-19 infection in the current SARS-CoV-2 pandemic have been gaining attention, with encephalopathy and stroke [1,2] featuring prominently, and a recent account of acute necrotizing encephalopathy [3]. We report a rare case of a Singaporean male with severe COVID-19 pneumonia who developed Acute Hemorrhagic Leukoencephalitis (AHLE).

1. Case Report

A 61-year-old Singaporean male with hypertension, hyperlipidemia and diabetes mellitus presented with a one-week history of fever, cough, and anosmia. On examination, he was alert with normal mental status. He was febrile at 38.0 °Celsius, respiratory rate was 20 breaths per min and oxygen saturation on ambient air was 99%. Physical examination was unremarkable except for crepitations in bilateral lung bases. Initial laboratory investigations revealed lymphopenia (0.58×10^9/L). Chest radiograph showed right lower zone consolidation. SARS-CoV-2 was detected in oropharyngeal and serum samples via real time reverse transcriptase-polymerase chain reaction assays.

On Day 10 of symptoms, the patient developed hypoxic respiratory failure, and progressed to severe acute respiratory distress syndrome on Day 18 requiring intubation and mechanical ventilation under heavy sedation. His mental status had remained normal up to this point. He developed cytokine release syndrome with shock, acute kidney injury requiring continuous renal replacement therapy, and hepatic dysfunction. Inflammatory markers were markedly elevated: LDH 2239 u/L, Ferritin 6575 μg/L, CRP 228 mg/L, D-dimer > 32 mg/L, and interleukin-6 level 154 ng/mL. Remdesivir was initiated on Day 10 and stopped on Day 20. He received subcutaneous enoxaparin 40 mg once daily for venous thromboembolism prophylaxis after admission to the intensive care unit, which was later reduced to renal dosing of 20 mg once daily in view of his subsequent acute kidney injury.

From Day 20, his oxygenation improved, and his ventilatory and sedation requirements were gradually weaned. Repeat serum RT-PCR showed resolution of his viremia, although the endotracheal aspirate remained positive. However, he remained severely encephalopathic. Pain stimuli elicited facial grimacing without any eye opening or limb movement observed, and he had flaccid tetraplegia and absent plantar reflexes. Brainstem reflexes were intact.

Computed Tomography (CT) on Day 27 followed by Magnetic Resonance Imaging (MRI) of the brain (Fig. 1) showed asymmetrical, multifocal lesions in the subcortical white matter of bilateral cerebral hemispheres, with larger lesions involving the overlying cortex. Bilateral thalami and cerebellar hemispheres were also involved. The largest lesion in the left cerebral hemisphere exerted mass effect, causing a 10 mm rightward midline shift. In addition, there were innumerable widespread petechial hemorrhages. Incomplete ring-like enhancement surrounded the thalamic lesions. Diffusion weighted imaging demonstrated only limited areas of restricted diffusion, disproportionate to the greater extent of petechial hemorrhage and vasogenic edema within the lesions. The major dural venous sinuses had normal appearance. 3D time-of-flight magnetic resonance angiography (TOF-MRA) did not reveal any arterial occlusions or irregularities (Fig. 2). These findings favored a diagnosis of AHLE. Lumbar puncture (LP) was not attempted in view of intracranial mass effect. Evaluation for cardiac emboli was negative: transthoracic echocardiogram demonstrated normal cardiac function and did not reveal any intracardiac thrombus or valvular abnormalities, and no atrial fibrillation was detected on telemetry.

Raised intracranial pressure was managed with neuroprotective strategies and mannitol, and enoxaparin was stopped. Therapeutic plasma exchange with regional citrate anticoagulation to prevent filter clotting was initiated, but ceased after one session due to citrate toxicity. Intravenous immunoglobulin therapy (2 g/kg over 5 days) was hence administered. He achieved clearance of SARS-CoV-2 from the respiratory tract on Day 32, and methylprednisolone (1 g daily for 5 days) was administered.

Five days after treatment initiation, Glasgow Coma Score (GCS) improved to E4VTM4. He was extubated, and CT brain performed 3 weeks after treatment showed stable lesions with interval improvement of the hemorrhages and mass effect. His GCS continued to improve further to E4V3M6, although he remains tetraparetic and dysphasic at this time of writing.

2. Discussion

This is the first reported case of AHLE in a critically ill COVID-19

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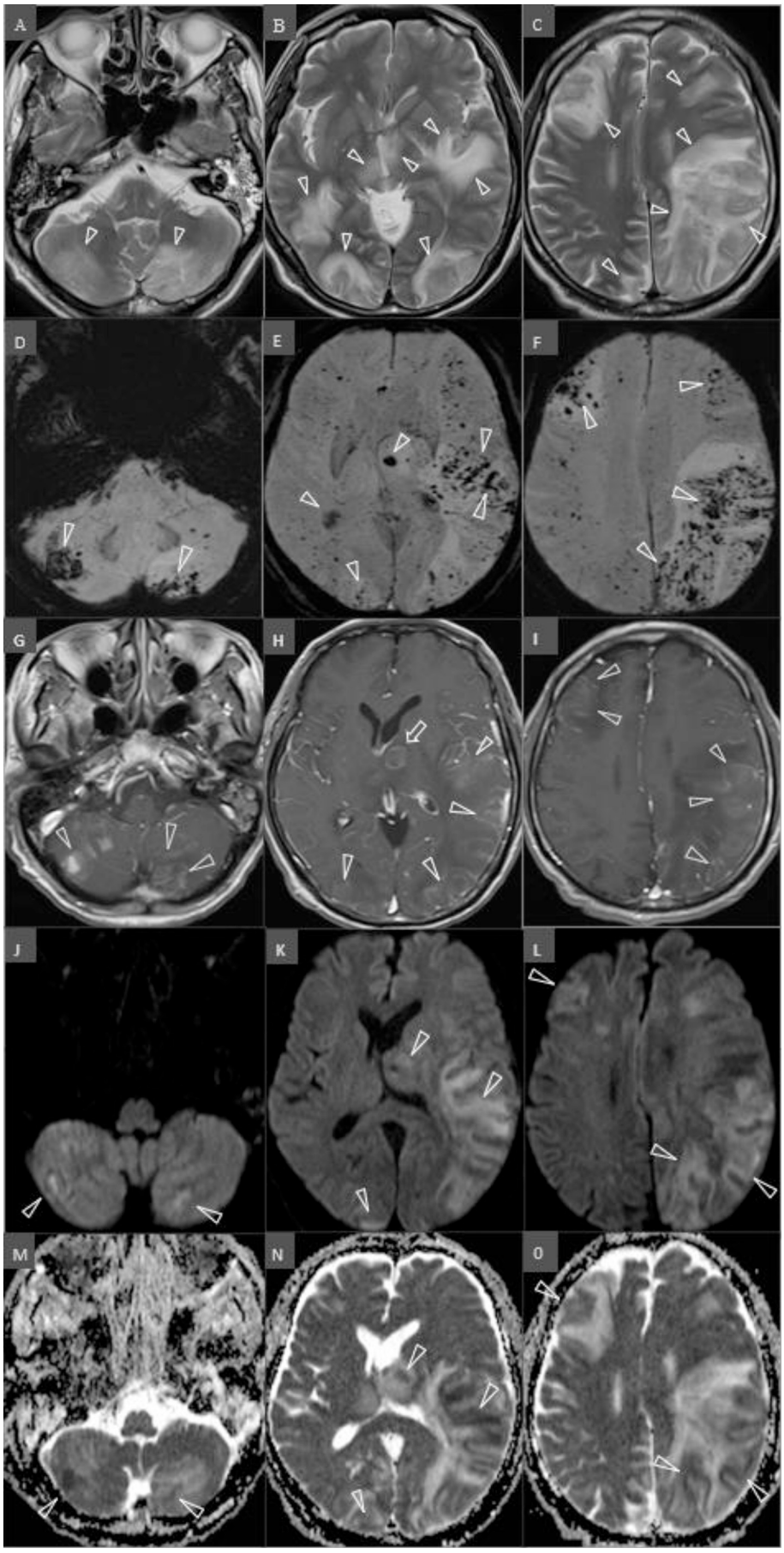

Fig. 1. MRI brain images of our COVID-19 patient with AHLE. MRI Brain axial T2-weighted images at the level of cerebellar hemispheres (A), thalami (B) and frontoparietal lobes (C) demonstrate multifocal asymmetric areas of heterogeneous hyperintensity, predominantly involving the subcortical white matter and thalami (arrowheads). Susceptibility weighted images (SWI) at the corresponding levels (D, E, F) show innumerable foci of punctate hemorrhages scattered throughout the brain parenchyma with several clusters present within aforementioned lesions, including the left thalamus (arrowheads). Post contrast axial T1-weighted images (G, H, I) display subtle patchy enhancement of the majority of the lesions (arrowheads) in addition to incomplete ring enhancement of the left thalamic lesion (arrow in image "H"). DWI (J, K, L) and ADC (M, N, O) images show only limited areas of restricted diffusion within the lesions (arrowheads). There is associated mass effect, best appreciated around the dominant lesion in the left temporo-parieto-occipital lobe.

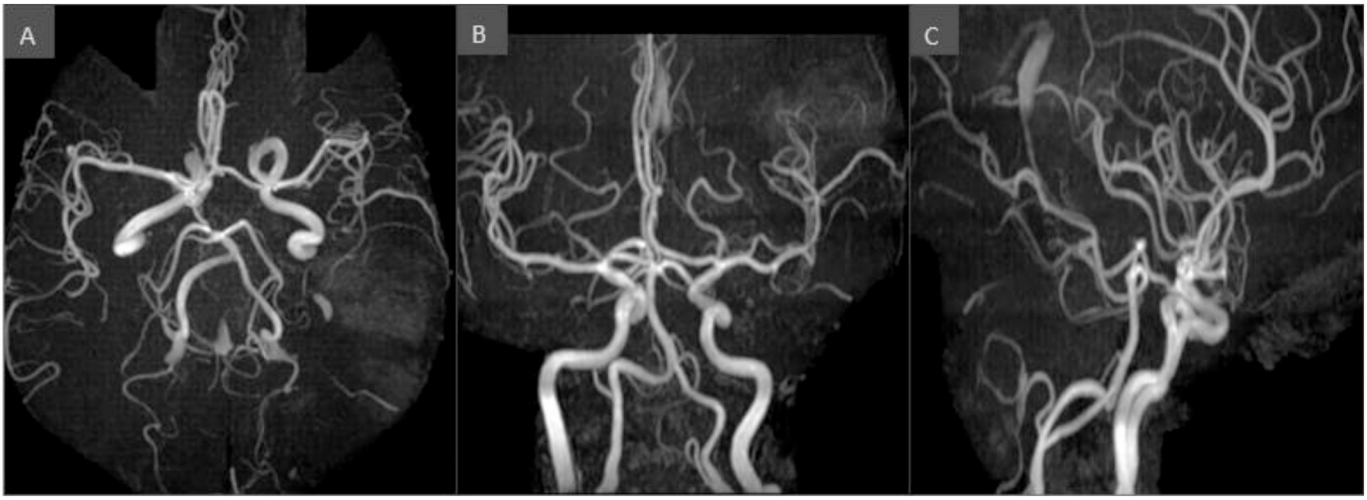

Fig. 2. Maximum intensity projections of 3D TOF-MRA of the circle of Willis in (A) craniocaudal (B) anteroposterior (C) lateral projections show smooth flow signal with no significant proximal vessel stenosis or occlusion. There is displacement and paucity of vessels over the dominant left temporo-parieto-occipital lesion, likely due to mass effect.

patient. Whilst our patient's neuroimaging findings are compatible with AHLE, other important differentials were considered. Acute necrotizing encephalopathy (ANE), which is characterized by bilateral thalamic lesions, has been reported in COVID-19[3] but is postulated to result from cytokine storm causing blood-brain barrier destruction [3,4]. Moreover, the possibility of viral-mediated endothelialitis was considered [5]. SARS-CoV-2 can potentially exploit Angiotensin Converting Enzyme 2 receptors to enter capillary endothelium of cerebral vasculature and cause endothelial inflammation [5]. In addition, reports have recently surfaced demonstrating diffuse leukoencephalopathy, microhemorrhages located predominantly in the corpus callosum and juxtacortical regions, and cortical signal abnormalities on MRI in critically ill COVID-19 patients [6,7].

Although LP was not performed, the likelihood of ongoing direct viral neuroinvasion was considered low, given that he had achieved clearance of SARs-CoV-2 from other clinical sites, and most reported cerebrospinal fluid analyses in the literature have not detected presence of the virus [2,6,7]. Furthermore, the asymmetry and entire distribution of lesions (subcortical white matter, cortex, thalami and cerebellar hemispheres), with incomplete ring contrast enhancement favored AHLE as the diagnosis [4].

Our report serves to raise awareness of the challenges in delivering immunomodulatory treatment in severe COVID-19 disease. Considerations of thrombotic risk and steroid effects on viral clearance [8,9] influenced our patient's treatment described above. A deeper understanding of the mechanisms of COVID-19 related inflammatory response and its contributory role to neurological insults is needed to guide optimization of therapy. Of interest is the potential role of abating the cytokine storm with monoclonal antibodies (such as Tocilizumab) [8]. Trials are ongoing, and whether they benefit the neurological outcome of COVID-19 patients remains to be seen.

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References

[1] L. Mao, H. Jin, M. Wang, et al., Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China, JAMA Neurol Epub (2020), https://doi.org/10.1001/jamaneurol.2020.1127 e201127.
[2] J. Helms, S. Kremer, H. Merdji, et al., Neurologic Features in Severe SARS-CoV-2 Infection, N Engl J Med Epub (2020), https://doi.org/10.1056/NEJMc2008597.
[3] N. Poyiadji, G. Shahin, D. Noujaim, M. Stone, S. Patel, B. Griffith, COVID-19-associated acute Hemorrhagic necrotizing encephalopathy: CT and MRI features, Radiology Epub 201187 (2020), https://doi.org/10.1148/radiol.2020201187.
[4] A. Rossi, Imaging of acute disseminated encephalomyelitis, Neuroimaging Clin. N. Am. 18 (2008) 149–ix, https://doi.org/10.1016/j.nic.2007.12.007.
[5] A.M. Baig, A. Khaleeq, U. Ali, H. Syeda, Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms, ACS Chem. Neurosci. 11 (7) (2020) 995–998, https://doi.org/10.1021/acschemneuro.0c00122.
[6] A. Radmanesh, A. Derman, Y.W. Lui, et al., COVID-19 -associated diffuse Leukoencephalopathy and Microhemorrhages, Radiology Epub 202040 (2020), https://doi.org/10.1148/radiol.2020202040.
[7] S.G. Kandemirli, L. Dogan, Z.T. Sarikaya, et al., Brain MRI findings in patients in the intensive care unit with COVID-19 infection, Radiology Epub 201697 (2020), https://doi.org/10.1148/radiol.2020201697.
[8] D A Berlin, R M Gulick, F J Martinez, Severe Covid-19, N Engl J Med Epub (2020), https://doi.org/10.1056/NEJMcp2009575.
[9] E.J. Needham, S.H. Chou, A.J. Coles, D.K. Menon, Neurological implications of COVID-19 infections, Neurocrit Care Epub (2020) 1–5, https://doi.org/10.1007/s12028-020-00978-4.

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