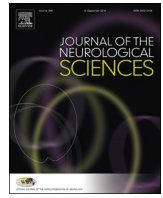




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Letter to the Editor

COVID-19-associated mild encephalitis/encephalopathy with a reversible splenic lesion



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Dear Editor.

Mild encephalitis/encephalopathy with a reversible splenic lesion (MERS) is an infection-associated encephalitis/encephalopathy syndrome that is predominately caused by a viral infection [1]. Herein, we describe the first presumed case of coronavirus disease 2019 (COVID-19)-associated MERS.

On April 8, 2020, a 75-year-old-man with a history of mild Alzheimer's disease visited a general internal medicine clinic, complaining of left-dominant kinetic tremor in his hands, walking instability and urinary incontinence for a few days. During the same period, he had diarrhea but denied history of cough, breathing discomfort or fever history in several days. He denied headache or loss of taste or smell, or convulsion. He had not traveled to foreign countries in several months. On arrival, his temperature was 36.7 °C, his pulse rate was 93 beats/min (regular rhythm), and his oxygen saturation was 94% on room air. His respiratory rate were normal range and physical examinations including lung auscultation did not show any apparent abnormal findings. Neurological examination revealed alerted consciousness and normal eye movement, but the finger-to-nose test showed bilateral marked dysmetria. Mild ataxic gait was observed. Muscle weakness or abnormal tendon reflexes of extremities was not observed. Magnetic resonance imaging (MRI) of the brain revealed an abnormal hyperintensity in the splenium of corpus callosum (SCC) on diffusion-weighted image, suspicious for clinically mild encephalitis/encephalopathy with a reversible splenic lesion (MERS) (Fig. 1A/B). The MRI was otherwise normal.

Initial blood testing revealed a normal range of white blood cell count (5960/ μ L) and platelet (1430×10^2 / μ L) counts, clinically significant for lymphocytopenia (1100/ μ L) and elevated C-reactive protein (5.32 mg/dL). Serum electrolytes were normal. The chest computed tomography (CT) scan routinely performed before the admission demonstrated the presence of ground glass opacities in the bilateral inferior lobes (Fig. 1C/D). Since he did not develop any fever, respiratory disorders and have a history of contact with those who were infected with SARS-CoV-2 at the presentation, health care workers did not suspect that the patient was infected with SARS-CoV-2.

After admission, he received 1.5 g of sulbactam/ampicillin twice per

day. Eight hours after admission, the patient developed a fever of 39.3 °C and rapidly developed severe hypoxemia. Following the news that his daughter tested positive for COVID-19 on reverse-transcription–polymerase-chain-reaction (RT-PCR) the day after admission, the patient received a throat swab RT-PCR test for SARS-CoV-2, which was positive.

On hospital day2, 2020, he was transferred to a hospital designated for COVID-19 treatment. He was disoriented in time and place, but his neurological deficit and cerebellar ataxia had resolved. On April 11, he became alert, coherent and oriented. Although a combination therapy with favipiravir, corticosteroid pulse, ciclesonide and meropenem was carried out at the designated hospital, he died due to respiratory failure 12 days after the first presentation. Invasive mechanical ventilation was not performed at the patient's request.

Discussion

Here we presented novel neurological manifestations of COVID-19. First, we demonstrated the patients with COVID-19 might show an isolated SCC lesion on brain MRI. Second, we also showed that patients with COVID-19 could develop cerebellar ataxia as the initial symptom. We speculated that these findings were associated with MERS, which was diagnosed based on the diagnostic criteria that included complete recovery of neurological symptoms and the hyperintensity lesion in the SCC in the acute stage. Although it is unclear whether the transient mild consciousness disturbance (disorientation) was due to MERS or deterioration in systemic condition, cerebellar ataxia is a common manifestation of MERS. [2] [3] [4].

With regard to the etiology of MERS, we considered that it was caused by COVID-19, because other causes of MERS including abnormal electrolytes disorders, organ failures, and administrations of a certain type of drugs was absent [2]. Virus-related MERS is known to be induced by specific pathogens such as influenza virus, rotavirus, and mumps virus [5]. However, to the best of our knowledge, MERS induced by coronavirus including SARS-CoV, middle east respiratory syndrome coronavirus, or SARS-CoV-2 has not been reported. Recent studies suggested that SARS-CoV-2 infection may cause meningitis/encephalitis [6] and acute hemorrhagic necrotizing encephalopathy

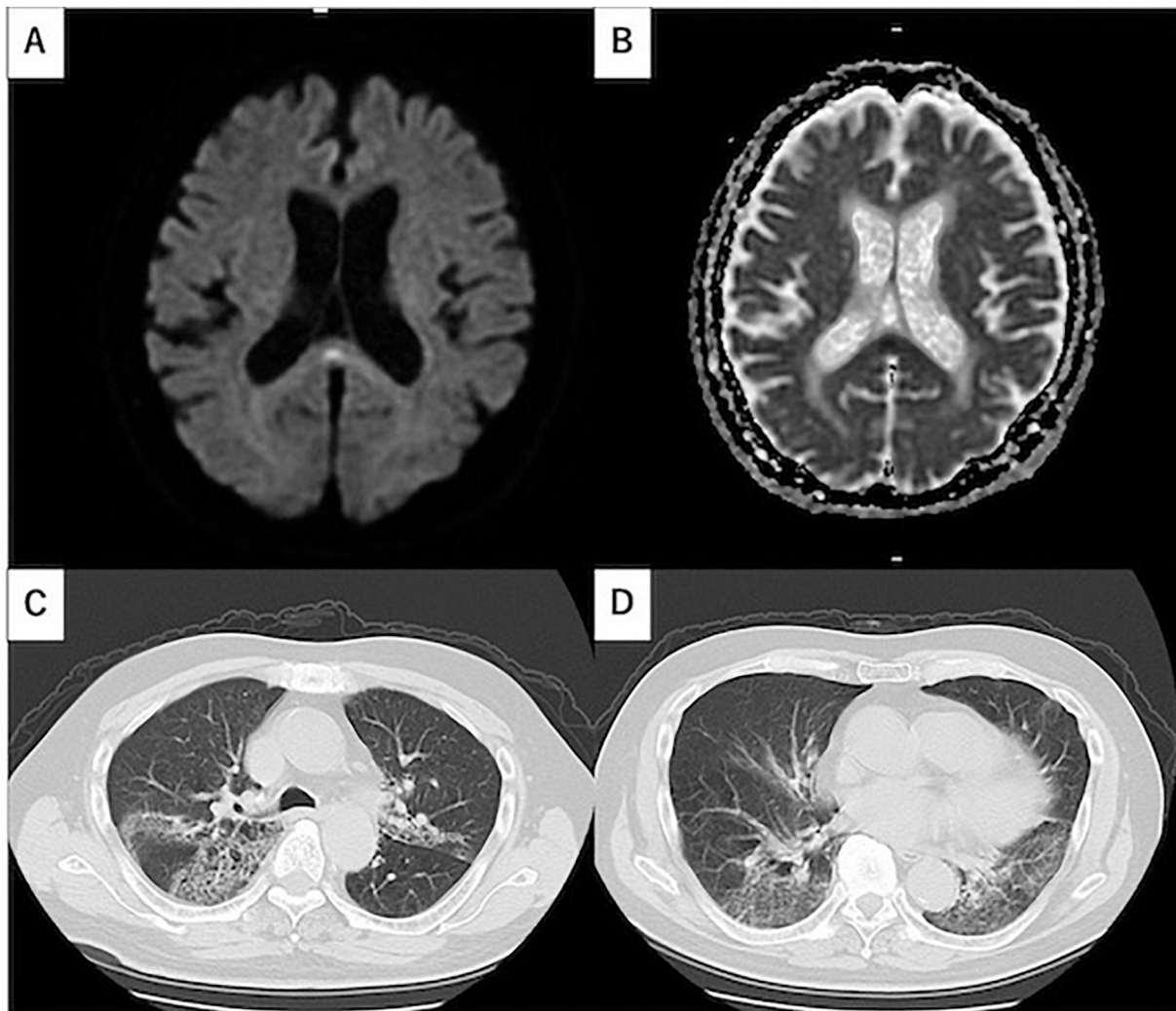


Fig. 1. A: Diffusion weighted images (DWI) of brain MRI performed at the time of presentation showed high signal intensity at the site of splenium of corpus callosum. B: Apparent diffusion coefficient (ADC) map extracted from DWI demonstrated slight decrease in ADC value on the same lesion. C/D: Chest CT images revealed bilateral ground-glass opacity and segmental areas of consolidation.

[7], MERS can be considered as a differential diagnosis for neurological symptoms of COVID-19, especially when patients develop transient cerebellar ataxia or consciousness disturbance.

Contributors/Informed Consent

Hayashi Misayo (HM) cared for the patient, searched the literature and collected the data.

Yuki Sahashi (YS) supervised writing manuscript and conceptualized the idea of the publication.

Yasutomo Baba(YS) cared for the patient in designated hospital for COVID-19.

Hiroyuki Okura (OH) supervised whole process.

Takayoshi Shimohata (TS) edited manuscript, conceptualized the idea of the publication and supervised whole process.

Verbal consent for publication was obtained from the patient's relatives.

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Declaration of Competing Interest

None.

References

- [1] H. Tada, J. Takanashi, A.J. Barkovich, et al., Clinically mild encephalitis/encephalopathy with a reversible splenial lesion, *Neurology*. 63 (10) (2004) 1854–1858.
- [2] M.J. Doherty, S. Jayadev, N.F. Watson, et al., Clinical implications of splenium magnetic resonance imaging signal changes, *Arch. Neurol.* 62 (3) (2005 Mar) 433–437.
- [3] N. Ueda, S. Minami, M. Akimoto, *Mycoplasma pneumoniae*-associated mild encephalitis/encephalopathy with a reversible splenial lesion: report of two pediatric cases and a comprehensive literature review, *BMC Infect. Dis.* 16 (1) (2016) 671.
- [4] N. Imai, N. Yagi, T. Konishi, M. Serizawa, M. Kobari, Legionnaires' disease with hypoperfusion in the cerebellum and frontal lobe on single photon emission computed tomography, *Intern. Med.* 47 (13) (2008) 1263–1266.
- [5] A. Hoshino, M. Saitoh, A. Oka, et al., Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes, *Brain Dev.* 34 (5) (2012) 337–343.
- [6] T. Moriguchi, N. Harii, J. Goto, et al., A first case of meningitis/encephalitis associated with SARS-Coronavirus-2 [published online ahead of print, 2020 Apr 3], *Int. J. Infect. Dis.* 94 (2020) 55–58.
- [7] N. Poyiadji, G. Shahin, D. Noujaim, M. Stone, S. Patel, B. Griffith, COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features published online ahead of print, *Radiology*. 2020 (2020 Mar 31) 201187.

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