Received: 8 July 2021 | Revised: 18 July 2021 | Accepted: 26 July 2021

DOI: 10.1111/cen3.12668

CASE IMAGE

Clinical & Experimental Neuroimmunology WILEY

# Radial linear perivascular emphasis in coronavirus disease 2019-associated acute disseminated encephalomyelitis

Ryo Tanaka[1] | Takamasa Nukui[1] | Ratna Dini Haryuni[1,2] | Makoto Mori[3] | Shigeru Hayashi[3] | Kyo Noguchi[4] | Yuji Nakatsuji[1]

[1]Department of Neurology, Faculty of Medicine, University of Toyama, Toyama, Japan

[2]Center for Radioisotope and Radiopharmaceutical Technology, National Nuclear Energy Agency of Indonesia, Serpong, Indonesia

[3]Department of Neurology, Toyama City Hospital, Toyama, Japan

[4]Department of Radiology, Faculty of Medicine, University of Toyama, Toyama, Japan

**Correspondence**
Takamasa Nukui MD, PhD, 2630 Sugitani, Toyama 930-0194, Japan.
Email: nukkun@med.u-toyama.ac.jp

## 1 | CASE

A 62-year-old woman who had a history of chronic hepatitis B and hypertension presented to a local hospital with cough and fever, and was admitted on day 3. As her chest computed tomography showed bilateral ground-glass opacities, and severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) saliva polymerase chain reaction was positive, she was diagnosed with coronavirus disease 2019 (COVID-19) pneumonia and was treated with favipiravir. On day 7, she was in a relatively good condition, as she was afebrile with a little cough. However, on day 18, she became comatose, which was followed with convulsive seizures, prompting administration of diazepam and levetiracetam.

Afterwards, she was then transferred to our hospital (Toyama University Hospital, Toyama, Japan), presenting with erythema of the extremities and trunk on admission. Furthermore, she was in a coma (Glasgow Coma Scale 7), with isocoric pupils and normal light reflex. She also did not show meningeal signs, such as nuchal rigidity or Kernig's sign. The patient's extremities were flaccid, deep tendon reflexes were increased and the Babinski sign was positive. Laboratory tests showed elevated transaminase levels, but serum anti-myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies were negative. Cerebrospinal fluid (CSF) examination also showed normal cell counts (3/mm$^3$), but protein (871 mg/dL) and myelin basic protein (559.8 pg/mL) levels were elevated. The immunoglobulin G index was 0.59, and the oligoclonal band was negative. Additionally, bacterial culture, CSF viral polymerase chain reaction (including SARS-Cov-2, Herpes simplex virus, varicella zoster virus and human herpesvirus-6) and anti-glial fibrillary acid protein (GFAP) antibody test result were all negative.

In contrast, brain magnetic resonance imaging (MRI) with gadolinium showed diffuse T2/fluid-attenuated inversion recovery hyperintensities in the bilateral white matter (Figure 1a) with radial linear enhancement oriented to the lateral ventricles (Figure 1b,c). The white matter also showed hyperintensities on diffusion-weighted imaging and on apparent diffusion coefficient map. The T2-star images showed no remarkable changes. Whereas spinal MRI with gadolinium showed no abnormalities. Furthermore, an electroencephalogram showed diffuse theta waves.

On reviewing the case, favipiravir was discontinued, as it was assumed to have caused erythema and transaminase elevation. On day 19, the patient was intubated and maintained on sedatives, and methylprednisolone 1 g/day was started and administered for 3 days. Her condition improved, and she was extubated on day 21. Although her consciousness became clearer, and erythema and transaminase levels improved by day 23, higher brain dysfunction remained (Mini-Mental State Examination 22/30). On day 33, her second course of methylprednisolone therapy was initiated, and her higher brain dysfunction finally improved (Mini-Mental State Examination 29/30) on interim. A follow-up CSF examination on day 46 showed no abnormalities, and brain MRI on day 49 showed markedly improved T2/fluid-attenuated inversion recovery hyperintensities and radial linear enhancement (Figure 1d-f).

## 2 | DISCUSSION

Here, we reported the first case of radial linear perivascular emphasis in COVID-19-associated acute disseminated encephalomyelopathy (ADEM). ADEM is a demyelinating CNS disease that commonly

  

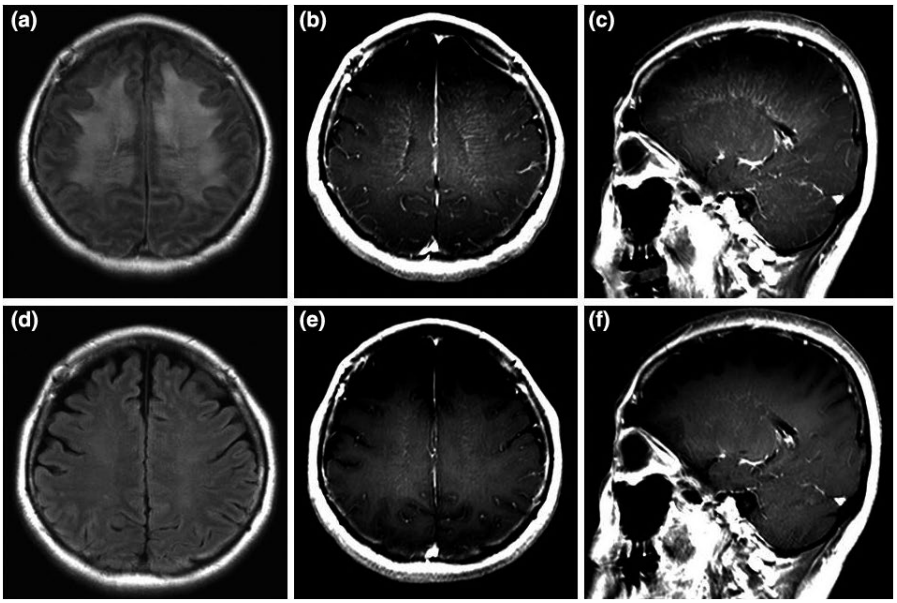


**FIGURE 1** (a) Brain magnetic resonance imaging on day 19 showed diffuse fluid-attenuated inversion recovery hyperintensities in bilateral hemispheric white matter. (b,c) T1-weighted image with gadolinium showed radial linear enhancement oriented to the ventricles. Follow-up brain magnetic resonance imaging on day 49 showed (d) remarkable improvement of fluid-attenuated inversion recovery hyperintensities in the white matter, and (e,f) radial linear enhancement became unclear

occurs after a viral infection. In the present patients, SARS-Cov-2 infection was diagnosed 2 weeks before ADEM onset. As SARS-Cov-2 polymerase chain reaction was negative in the CSF, we speculate that the encephalopathy was not caused by direct viral CNS infection, but by an autoimmune reaction caused by the infection.

The radial linear perivascular enhancement pattern resembles those reported in GFAP astrocytopathy, which is a novel autoimmune meningoencephalomyelitis first reported in 2016.[1] GFAP astrocytopathy is commonly diagnosed with the detection of anti-GFAP antibodies in the CSF and with characteristic MRI findings.[2] Pathological assessment of brain biopsy from a GFAP astrocytopathy patient suggests that the characteristic emphasis reflects perivascular inflammation.[3] Although the CSF anti-GFAP antibody was negative in the present case, COVID-19 ADEM had a characteristic emphasis, suggesting perivascular inflammation, which is pathologically similar to GFAP astrocytopathy. Additionally, perivascular inflammation has been reported as a histopathological finding in the brain of a COVID-19 patient, making it possible that COVID-19-induced perivascular inflammation showed an emphasis that is similar to GFAP astrocytopathy.[4,5]

## ACKNOWLEDGMENTS

The authors thank Dr Akio Kimura, Department of Neurology, Gifu University Graduate School of Medicine, for measuring the anti-GFAP antibody.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DISCLOSURE OF ETHICAL STATEMENT

- Approval of research protocol: N/A
- Informed Consent: The patient gave informed consent.
- Registry and the Registration No. of the study/trial: N/A
- Animal studies: N/A

## ORCID

*Ryo Tanaka* https://orcid.org/0000-0002-2887-2738
*Takamasa Nukui* https://orcid.org/0000-0002-2706-988X

## REFERENCES

1. Fang B, McKeon A, Hinson SR, Kryzer TJ, Pittock SJ, Aksamit AJ, et al. Autoimmune glial fibrillary acidic protein astrocytopathy: a novel meningoencephalomyelitis. JAMA Neurol. 2016;73:1297–307.
2. Wickel J, Chung H-Y, Kirchhof K, Boeckler D, Merkelbach S, Kuzman P, et al. Encephalitis with radial perivascular emphasis: not necessarily associated with GFAP antibodies. Neurol Neuroimmunol neuroinflammation. 2020;7.
3. Shu Y, Long Y, Chang Y, Li R, Sun X, Wang Y, et al. Brain immunohistopathology in a patient with autoimmune glial fibrillary acidic protein astrocytopathy. NeuroImmunoModulation. 2018;25:1–6.
4. Hanley B, Naresh KN, Roufosse C, Nicholson AG, Weir J, Cooke GS, et al. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. Lancet Microbe. 2020;1:e245–e253.
5. Al-Sarraj S, Troakes C, Hanley B, Osborn M, Richardson MP, Hotopf M, et al. Invited review: the spectrum of neuropathology in COVID-19. Neuropathol Appl Neurobiol. 2021;47:3–16.

**How to cite this article:** Tanaka R, Nukui T, Haryuni RD, Mori M, Hayashi S, Noguchi K, et al. Radial linear perivascular emphasis in coronavirus disease 2019-associated acute disseminated encephalomyelitis. Clin Exp Neuroimmunol. 2021;12:281–282. https://doi.org/10.1111/cen3.12668