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Successful treatment of post–COVID-19 acute disseminated encephalomyelitis with urgent immunotherapy and neurointensive management: a case report

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CASE REPORT

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Background: Acute disseminated encephalomyelitis (ADEM)-like white matter disease, a rare complication of coronavirus disease 2019 (COVID-19), is a potentially life-threatening neurological disorder. The objective of this study was to report the successful treatment of post–COVID-19 ADEM with urgent immunotherapy and neurointensive management.
Case Report: A 53-year-old female patient was referred to our hospital with a 2-day history of progressive mental deterioration and was diagnosed with ADEM after COVID-19. The patient's symptoms worsened despite the administration of high-dose steroids, and targeted temperature management was employed to manage brain edema. Additionally, the neurointensivist decided to use intravenous immunoglobulin early for intractable post–COVID-19 ADEM. Her mental status and neuroimaging findings showed rapid improvement at about 3 months after admission.
Conclusion: This case highlights that if the patient's symptoms worsen despite high-dose steroid administration in the acute stage, early use of intravenous immunoglobulin is expected to have a positive effect on the prognosis of patients with post–COVID-19 ADEM.

Keywords: COVID-19; Encephalomyelitis; Acute disseminated encephalomyelitis; Immunotherapy; Neuroimaging

INTRODUCTION

Coronavirus disease 2019 (COVID-19) primarily affects the respiratory system. However, there are several cases and indications where COVID-19 infection can cause neurological complications [1-3]. It has been found that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause central nervous system (CNS) demyelination in humans and animals [4]. Neurological complications related to COVID-19 can be considered direct effects of the virus on the CNS, and are para- or postinfectious immune-mediated processes [5]. A large-scale retrospective study has recently reported that CNS complications occur in 30%–40% of the patients with COVID-19 [3,4].

Acute disseminated encephalomyelitis (ADEM) is a monophasic, postinfectious, or postvaccine acute inflammatory demyelinating disorder of the CNS [6]. It could occur several weeks after a viral infection, including COVID-19 [7]. Prepandemic ADEM is known to have good clinical outcomes and treatment responses

[8]. However, information on post–COVID-19 ADEM is limited. Clinical outcomes seem to be severe and unpredictable. Consequently, immediate initiation of immunotherapy, accompanied by proper diagnosis, is crucial in patients with post–COVID-19 ADEM [9]. Moreover, timely neurological assessment and urgent intervention are critical for preventing rapid aggravation. Herein, we describe a patient with post–COVID-19 ADEM who was successfully treated with immunotherapy and neurointensive management during the early stages of ADEM after COVID-19 infection. To the best of our knowledge, this is the first report on post–COVID-19 ADEM in Korea.

CASE REPORT

A 53-year-old female patient with a 2-day history of progressive mental deterioration was referred to our hospital. She had been diagnosed with COVID-19 by SARS-CoV-2 polymerase chain reaction (PCR) of a nasopharyngeal swab 14 days previously. She had experienced several episodes of self-resolving low-grade fever, dry cough, sore throat, and rhinorrhea for a few days before being diagnosed with COVID-19. The patient had no previous medical illnesses. The patient started to develop unexplained drowsiness and confusion and progressed to stupor 2 days before admission. Neurological examination revealed no focal abnormalities except for decreased consciousness. The pupils were isocoric with bilateral light reflexes (+), and deep tendon reflexes were normoactive. Fundus examination results were normal. The vestibulo-ocular and corneal reflexes were also preserved. Sensory and cranial nerve examinations could not be performed due to poor patient cooperation. She was intubated and mechanical ventilation was initiated. Her initial blood pressure was 122/91 mmHg. Her pulse rate was 66 beats/min, and her temperature was 37.0°C. Chest radiograph was normal. Initial magnetic resonance imaging (MRI) was performed without gadolinium contrast on hospital day (HD) 1. It showed scattered hyperintense lesions on diffusion-weighted imaging (DWI)/apparent diffusion coefficient (ADC) map/fluid-attenuated inversion recovery (FLAIR) imaging in deep and juxtacortical white matter. FLAIR high signal intensity in both hemispheric juxtacortical white matter showed more extensive lesions than DWI (Fig. 1A). Cerebrospinal fluid (CSF) analysis revealed 9 white blood cells, 4,000 red blood cells, 90 mg/dL protein, and 66 mg/dL glucose. Bacterial, tuberculosis, and fungal cultures and PCR panels (including tuberculosis, herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and John Cunningham virus) were all negative. Serum tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies, syphilis, human immunodeficiency virus, myelin oligodendrocyte glycoprotein, and aquaporin-4 antibodies were negative or normal. The CSF venereal disease research laboratory result was negative.

Paraneoplastic autoantibodies in the serum and CSF were negative. Electroencephalography, performed on the day of admis-

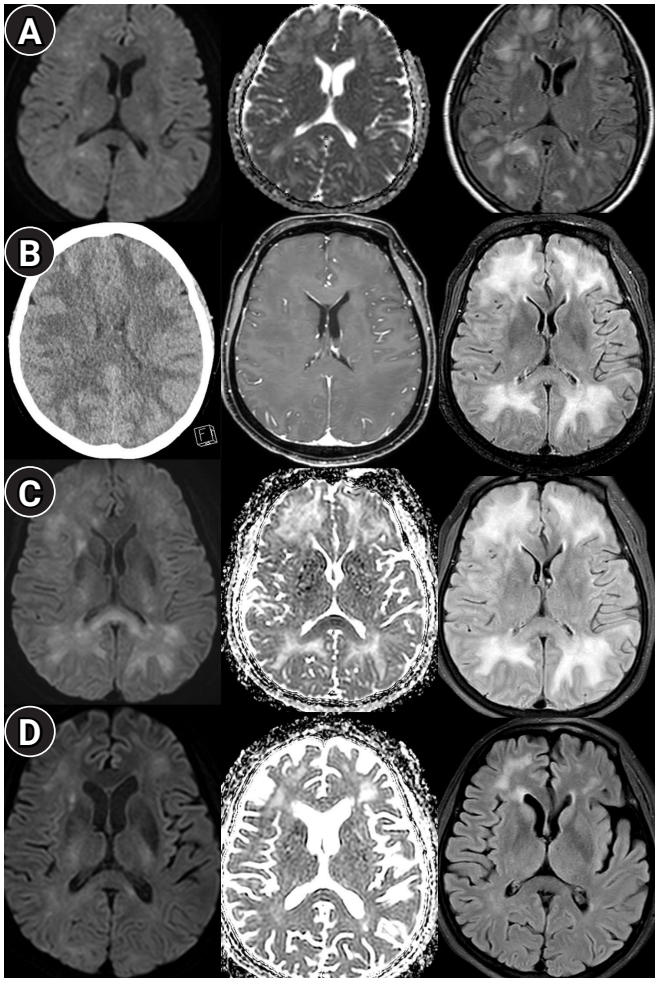

Fig. 1. Serial neuroimaging changes of the patient. (A) Initial magnetic resonance imaging (MRI) showing scattered hyperintense lesions on diffusion-weighted imaging (DWI)/apparent diffusion coefficient (ADC) map/fluid-attenuated inversion recovery (FLAIR) imaging in deep and juxtacortical white matter. A FLAIR high signal intensity in both hemispheric juxtacortical white matter showed more extensive lesions than DWI, suggesting edematous demyelination. (B) Neuroimaging performed during deterioration of the patient. Brain computed tomography showing marked white matter edema with sulcal effacement. There was no significant contrast uptake on T1 or FLAIR enhancement images along the edematous white matter. (C) MRI on hospital day 16 showing more progression and extension of DWI/ADC/FLAIR hyperintensities in the juxtacortical white matter. (D) The last follow-up DWI/ADC/FLAIR performed on the 39th day after admission demonstrating markedly reduced sizes of hyperintense lesions.

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sion, revealed diffuse cerebral dysfunction without significant epileptic discharge. The patient was immediately started on intravenous (IV) methylprednisolone 1 g daily for 5 days after admission. Three days after admission, her pupils were dilated with a decreased neurological pupil index (0.8/1.2). Brain computed tomography showed marked white matter edema with sulcal effacement. There was no significant contrast uptake on T1- or FLAIR enhancement images along the edematous white matter (Fig. 1B). To manage cerebral edema, therapeutic hypothermia was performed using a surface cooling device (Arctic Sun; Medivance, Louisville, CO, USA) at a target temperature of 36°C with emergent administration of 3% hypertonic saline and mannitol. Conscious sedation was performed during the targeted temperature management. The targeted mean arterial pressure was >60 mmHg to maintain the cerebral perfusion pressure. The neurointensivist decided to additionally administer IV immunoglobulin at 0.4 mg/kg daily for 5 days. On HD 12, a follow-up brain MRI was performed. Scattered lesions showed high signal intensity on DWI with slightly restricted diffusion on the ADC, which is inconsistent with ischemic stroke. FLAIR imaging revealed progressive multiple asymmetric hyperintense lesions involving extensive subcortical white matter. On HD 16, the patient was extubated after confirming that the mental status had markedly improved. However, repeat MRI of the brain on HD 16 showed increased progression and extension of DWI/ADC/FLAIR hyperintensities in the juxtacortical white matter (Fig. 1C). The last follow-up DWI/ADC/FLAIR performed on the 39th day after admission demonstrated markedly reduced sizes of the hyperintense lesions (Fig. 1D). Although she showed significant cognitive decline after the illness, independent daily life was possible at about 3 months after admission.

DISSCUSSION

Few reports of post–COVID-19 ADEM have been published [7,9,10]. Our case fulfilled the 2012 revised criteria for ADEM: (1) the first clinical event with a presumed inflammatory cerebral demyelinating cause, (2) typical MRI features of ADEM during the acute phase, and (3) exclusion of other possible causes [11]. Also, our patient developed ADEM at 14 days after the confirmed diagnosis of COVID-19. This temporal relationship supports the diagnosis of post–COVID-19 ADEM. The clinical characteristics of post–COVID-19 ADEM reported that the duration from confirmed COVID-19 infection to the development of ADEM was mostly within 15–30 days. The majority of neurologic manifestations demonstrate subacute progression (between 24 hours and 10 days) of the illness. Initial neurological manifestations showed that progressive encephalopathy was the most common clinical symptom [9].

There are diverse mechanisms for neurologic complications of post–COVID-19 infection, including direct neuroinvasion of the CNS, peripheral nervous system, or muscles and immune response following an infectious trigger [1,10]. ADEM is usually considered a postinfectious immune-mediated disorder [6]. A viral infection, such as COVID-19, can result in nervous tissue damage, which can cause segregated antigens to leak into the systemic circulation through an inflamed blood-brain barrier [6,12]. Structural similarity between viral pathogen and myelin proteins of the patient can also provoke B- and T-cells, which are activated during an immune response to infection [1]. They can enter the CNS and react with the presumed viral antigen presented by the homolog myelin protein.

The post–COVID-19 ADEM should be distinguished from COVID-19 encephalitis and acute autoimmune encephalitis associated with COVID-19. COVID-19 encephalitis occurs as a result of direct infection of the brain parenchyma by the SARS-CoV-2. It is generally infected as part of systemic COVID-19, and additional signs and symptoms of other organ involvement might be present [13]. However, having common clinical features and etiologic pathomechanism with post–COVID-19 infection, the differential diagnosis is not always straightforward. Nevertheless, the most discriminative feature of post–COVID-19 ADEM compared to encephalitis seems to be the neuroimaging pattern. Post–COVID-19 ADEM involves a brief but intense inflammatory attack (swelling) in the brain that damages myelin. Thus, post–COVID-19 ADEM predominantly affects the white matter of the brain, manifesting as an acute-onset encephalopathy associated with multifocal neurologic deficits [7]. Neuroimaging patterns of COVID-19 encephalitis show one or more diffuse areas of high intensity, affecting the cortical gray matter and subjacent white matter. Sometimes, the gray matter of the basal ganglia or brainstem might be involved, which is a very different pattern from that seen in post–COVID-19 ADEM [14]. CSF analysis of post–COVID-19 ADEM usually shows features indistinguishable from that of COVID-19 encephalitis (i.e., lymphocytic pleocytosis, elevated protein levels, normal glucose, and negative cultures) [6]. Unlike the usual encephalitis, a viral culture or the PCR exam of pathogens is negative.

Although post–COVID-19 ADEM rarely occurs, its prognosis is very poor. Approximately 60% of the patients need ventilator care in the intensive care unit [3,4], and approximately 30% of the patients die during follow-up. Post–COVID-19 ADEM occurs mainly in adults, whereas prepandemic ADEM is more common in children with a good prognosis (mortality rates of 1%–3%)

[8,15]. Therefore, determining when and which treatment regimen to use is more important in post–COVID-19 ADEM than in prepandemic ADEM. The rarity of post–COVID-19 ADEM may render the diagnosis difficult, leading to diagnostic delays or misdiagnosis. This can also lead to missed opportunities for early immunotherapy in post–COVID-19 ADEM. Therefore, collecting these cases could facilitate the diagnosis of post–COVID-19 ADEM and improve patient prognosis. Moreover, there are no reports of post–COVID-19 ADEM in Korea. Our patient showed severe neurological deficits and progressive diffuse white matter demyelination at an early stage. Timely initiation of immunotherapy including IV corticosteroids plus immunoglobulin with appropriate neurointensive management of brain edema clearly improved the patient's prognosis.

As in our patient, if the patient's symptoms worsen despite the administration of high-dose steroids, early use of IV immunoglobulin is expected to have a beneficial effect on the patient's prognosis. Additional studies are needed to decipher the mechanisms of massive white matter demyelination in patients with post–COVID-19 ADEM.

ARTICLE INFORMATION

Ethics statement

Ethics approval of Institutional Review Board of Jeju National University Hospital (No. JEJUNUH 2022-07-005) was granted in accordance with the national requirements, and the need for written informed consent was waived.

Conflict of interest

No potential conflict of interest relevant to this article.

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