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CASE REPORT

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COVID-19 related acute necrotizing encephalopathy and acute myocarditis in an adult female: a novel case report of brain injury and myocarditis

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Abstract

Background Acute necrotizing encephalopathy (ANE) and myocarditis are both acute, life-threatening conditions that can be triggered by COVID-19. We report a case of sequential ANE and myocarditis following a COVID-19 infection.

Case presentation A 27-year-old female patient was brought to the emergency department due to episodes of fever for two days and a 9-h altered state of consciousness. Her condition rapidly developed into stuporous and hemodynamic instability within serval hours. Veno-arterial extracorporeal membrane oxygenation (ECMO) was rapidly initiated with other supportive treatments. The following-up MRI showed bilateral, symmetrically distributed lesions in the brainstem, bilateral hippocampal regions, and bilateral basal ganglia, consistent with ANE. The diagnosis was confirmed through the detection of SARS-CoV-2 and the exclusion of other potential causes. After weeks of medical treatment, her condition stabilized, and she was transferred for further rehabilitation treatment.

Conclusions This case study indicates that COVID-19 may simultaneously and rapidly affect the central nervous system and cardiovascular system, leading to poor outcomes. Accurate diagnosis and timely invasive bridging therapy, when necessary, can be lifesaving. Further exploration of potential mechanisms underlying COVID-19 central nervous system (CNS) and cardiovascular system manifestations will be important.

Keywords COVID-19, Acute necrotizing encephalopathy, Myocarditis, ECMO, Case report

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Background

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is characterized predominantly by respiratory symptoms and is recognized as a major global public health emergency. In addition to pulmonary manifestations, COVID-19 is known to have several unusual manifestations. During the COVID-19 pandemic, there was increasing evidence of extrapulmonary organ involvement during SARS-CoV-2 infection, including the cardiovascular system and the neurological system [1, 2].

A significant minority of patients with COVID-19 develop different cardiovascular complications, such as acute heart failure, myocardial infarction, arrhythmias, and rarely, acute myocarditis [3]. COVID-19-related cardiovascular complications are often associated with poor prognosis [4]. A meta-analysis revealed that approximately 22% of critically ill COVID-19 patients exhibited myocardial impairment as measured by troponin I [5]. Initially, it was speculated that cardiac injury could be caused by direct cardiomyocyte infection leading to cardiomyocyte death [6, 7]. However, the theory of direct injury still needs to be further confirmed [8]. Furthermore, cardiac injury might be mediated via indirect mechanisms, such as respiratory failure, hypoxemia or systemic inflammatory response [7]. COVID-19-associated myocarditis has been reported several times [9]. Fulminant myocarditis, a rare and serious manifestation of myocarditis, is characterized by hemodynamic instability necessitating inotropes/vasopressors or mechanical circulatory support (MCS) [10]. Considering the various potential causes of acute heart failure in critically ill patients with COVID-19, it is essential to make a clear distinction and precisely manage the patient's condition.

In addition to the possibility of respiratory and cardiovascular system involvement, increasing evidence suggests that COVID-19 may result in neurological symptoms [11]. A wide variety of clinical syndromes affecting both the central and peripheral nervous systems have already been reported [12]. These symptoms may be the result of direct viral cytopathy or secondary to the local and systemic immune responses [13]. Early in the pandemic, neurology specialists reported a high prevalence of anosmia and dysgeusia [11]. A correlation between COVID-19 and cerebrovascular events, such as stroke, which affects 1–3% of SARS-CoV-2-infected patients, has also been reported [11, 14]. However, it is concerning that reports of severe neurological presentations associated with COVID-19, such as acute necrotizing encephalopathy (ANE), encephalitis, meningitis, and Guillain–Barré syndrome, have started to emerge [15, 16]. Acute necrotizing encephalopathy is a rare complication associated with viral infections such as influenza viruses and is characterized by rapid progression of neurological symptoms with high mortality and disability rates. Notably, the clinical manifestations of infections with different pathogens associated with ANE may vary; for example, rhinovirus infection often leads to moderate illness in humans, while infection with other pathogens, such as dengue virus, are associated with severe and frequently lethal disease. However, the potential clinical symptoms of COVID-19-related ANE have not yet been fully investigated.

Here, we describe the rare case of an adult woman who simultaneously suffered from COVID-19-associated severe ANE and fulminant myocarditis. To manage these rare but fatal diseases concurrently, prompt diagnosis and timely supportive treatment may be associated with reduced mortality. In this case, the patient was treated with veno-arterial extracorporeal membrane oxygenation (ECMO) and immunomodulatory therapies promptly and ultimately her condition stabilized. We hope our work will be useful for clinicians making decisions for patients suffering from this potentially devastating condition.

Case presentation

A 27-year-old woman (165 cm, 44.5 kg), who had a two-month history of depression and tested positive for SARS-CoV-2 antigen two days prior presented to our emergency department with episodes of fever for two days and a 9-h altered state of consciousness. Two days prior, she developed intermittent fever with a maximum body temperature of 39.5 °C. Additionally, she experienced a sore throat, but without chest tightness, chest pain, hemoptysis, dyspnea, abdominal pain, or diarrhea. Despite receiving antipyretics, it resulted in minimal improvement. 9 hours prior to the presentation, she began to present with reduced consciousness. There were no staring eyes, limb convulsions, and urinary and fecal incontinence. She had been vaccinated three times of inactivated vaccine CoronaVac (Sinovac Biotech) and the last vaccination was a year and a half ago. Upon hospital arrival, physical examination revealed a reduced level of consciousness (Glasgow Coma Scale score, 13 [E4/V4/M5]), a body temperature of 39℃, tachycardic (130 beats/min) with a blood pressure of 102/60mmHg, a respiratory rate of 26 breaths per minute, and oxygen saturation of 94% in room air. Her cardiac examination revealed cool extremities, jugular venous distention, ventricular gallop rhythm, and rales at the lung base, with no murmur heard in any valve auscultation area. Neurologic examination revealed that the pupils were each 2 mm in diameter with reactivity to light, nuchal rigidity, and bilateral positive Babinski signs. Her abdomen was soft, and her liver and spleen were nonpalpable. Blood samples were collected immediately upon emergency department admission. The initial blood tests revealed

that normal white blood cell, red blood cell and platelet counts (5.4×10^9/L, 4.5×10^9/L and 124×10^9/L, respectively); absolute lymphopenia (0.3×10^9/L); a normal hemoglobin level (134 g/L); and an increased C-reactive protein (CRP, 16.50 mg/L) and interleukin 6 (IL-6, 668.36 pg/ml). Other laboratory indicators including liver function parameters, kidney function parameters, the cardiac troponin I (cTnI) level, the creatine kinase-muscle/brain (CK-MB) level, and blood ammonia level, were all normal. Her nasopharyngeal swab was detected positive for SARS-CoV-2 via reverse transcription polymerase chain reaction (RT-PCR). Nucleic acid extraction was performed using magnetic bead method. Cycle threshold (Ct) values of RT-PCR were used to approximately represent the viral load (inversely related to the Ct value). The nucleic acid testing for SARS-CoV-2 targets two genes: the open reading frame 1ab (*ORF1ab*) and the nucleocapsid (*N*) gene. The Ct values of RT-PCR were 23.1 for *ORFlab* gene and 21.57 for *N* gene, respectively. Whole-body computed tomography (CT) revealed hypodensity in the right basal ganglia region and indications of bilateral pneumonia (Fig. 1). The electroencephalograph (EEG) showed mild to moderate abnormal brainwave patterns (a widespread increase in slow waves, Supplementary Fig. S1). Bedside transthoracic echocardiography revealed a pronounced weakening of left ventricular wall motion (left ventricular ejection fraction [LVEF], 17%) (Fig. 2). The electrocardiogram (ECG) showed sinus tachycardia, poor R-wave progression in V1-3, and mild ST-T changes and displayed no indications of acute coronary syndrome (Fig. 3). The patient's condition rapidly deteriorated and she became stuporous, shortness of breath, and went into cardiogenic shock within 4 h after emergency department admission. Orotracheal intubation was immediately performed. The ventilator settings were: a fraction of inspired oxygen (FiO_2) of 60%, a positive end-expiratory pressure (PEEP) of 10 cm H_2O, and a driving pressure of 12 cm H_2O. Then, she was transferred to the intensive care unit (ICU).

On admission to the ICU, her vital signs were extremely unstable, including sinus tachycardia (150/min) and hypotension (90/46 mmHg) with 0.5 μg/kg/min norepinephrine maintenance. The blood tests revealed an elevated lactate level (5.0 mmol/L), an increased cTnI level (4.98 ng/ml), severely impaired central venous oxygen saturation (ScvO2 89%), and a high central venous-to-arterial carbon dioxide tension difference (PCO2gap 15 mmHg). Bedside ultrasound-guided femoro-femoral veno-arterial ECMO was performed, with a 21-F drainage catheter (Maquet Cardiopulmonary AG, Rastatt, Germany) placed from the left femoral vein to the level of the right atrium and a 15-F arterial catheter (Maquet Cardiopulmonary AG, Rastatt, Germany) inserted into the right femoral artery. In addition, a 6-F distal perfusion cannula (Cordis, USA) was placed through the right superficial femoral artery to prevent distal lower limb hypoperfusion. The initial settings were 3155 rpm, 100%, 2 L/min of oxygen. Thereafter, her hemodynamics began to stabilize. Next-generation sequencing (NGS) of bronchoalveolar lavage fluid only detected the presence of SARS-CoV-2. The nasopharyngeal swab sample tested by Ningbo Municipal Center for Disease Control and Prevention reported that the strain type of SARS-CoV-2 was Omicron EG.5.1. She was started on Piperacillin-Tazobactam. Molnupiravir (800 mg twice daily for 5 days) was used for COVID-19 treatment. For immunosuppressive therapies, she received intravenous methylprednisolone (0.5 g/day for 5 days followed by a tapering dose of prednisone) and intravenous immunoglobulin (IVIG, 0.4 g/kg/day for 5 consecutive days).

During subsequent treatment, her body temperature returned to normal, the dose of vasopressors was reduced, and her daily urine output increased. The levels of the cardiac injury markers cTnI, CK-MB and aspartate aminotransferase (AST) gradually decreased during ICU stay (Fig. 4). On Day 12, her cardiac function significantly improved. Considering her blood pressure (BP) could be maintained under an ECMO blood flow of 1 L/min, she was successfully weaned from veno-arterial ECMO on Day 13.

However, she remained comatose, and no significant changes were observed in her neurological function. In

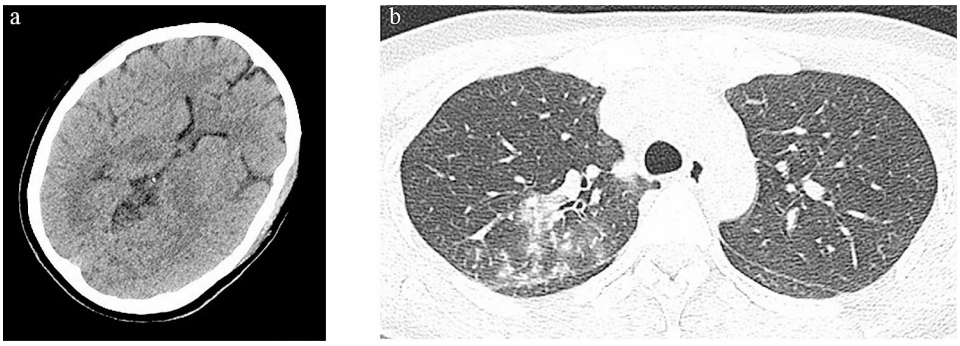

Fig. 1 Brain and chest CT

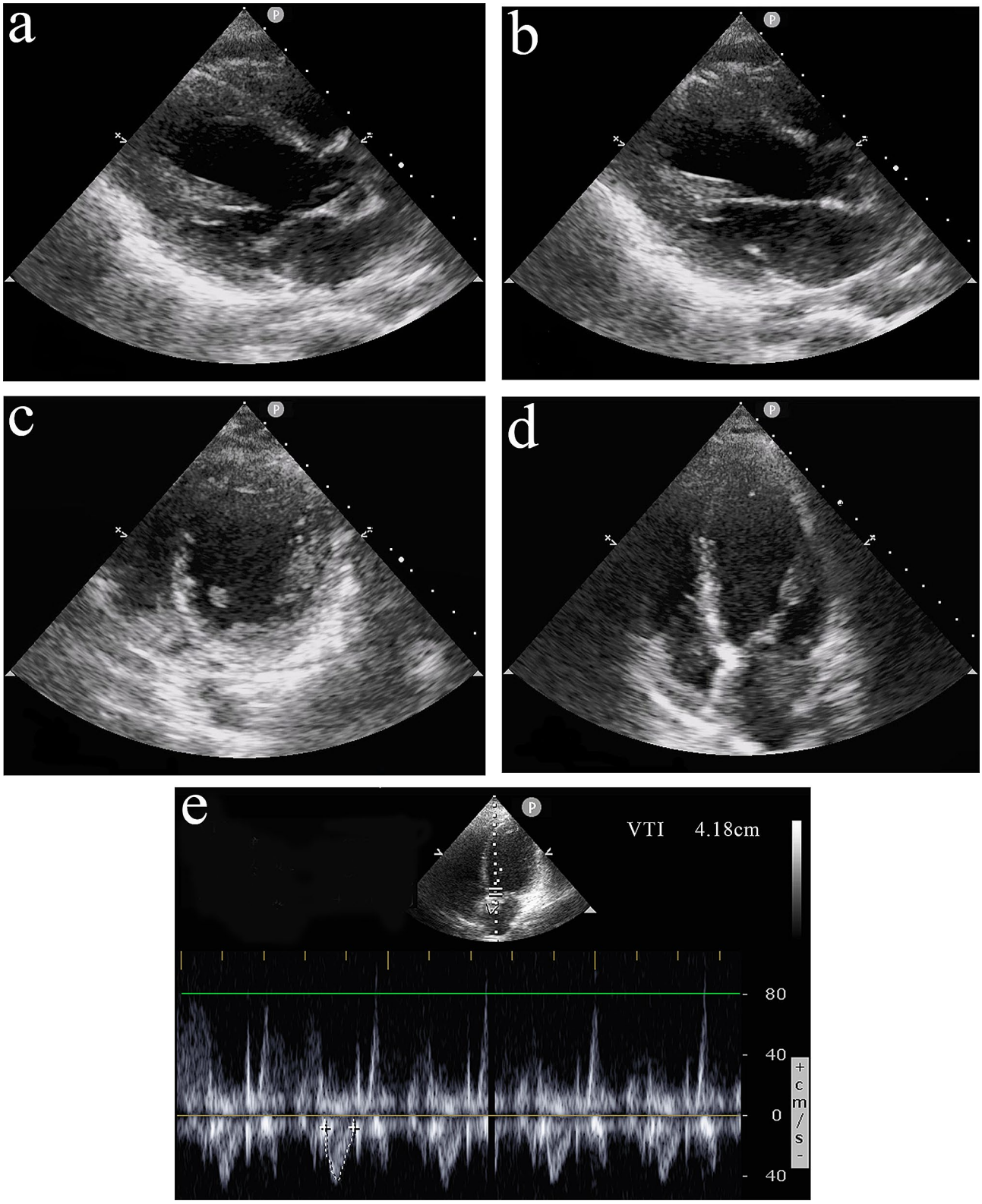

Fig. 2 Transthoracic echocardiography on ICU Day 1. TTE presented severe cardiac dysfunction, left ventricular ejection fraction (17%), left ventricular outflow tract velocity time integral (LVOT VTI 4.18 cm), left ventricular end-diastolic (LVEDd, 50 mm), left ventricular end-systolic diameter (LVEDs, 43 mm) and interventricular septum thickness (7 mm). No regional wall motion was observed. (**a**) Parasternal long-axis views in systolic phase (**b**). Parasternal long-axis views in diastolic phase. (**c**) Parasternal short-axis view. (**d**) Apical four-chamber view. (**e**) Apical five-chamber view. Abbreviations: LVOT VTI, left ventricular outflow tract velocity time integral; LVEDd, left ventricular end-diastolic; LVEDs, left ventricular end-systolic diameter.

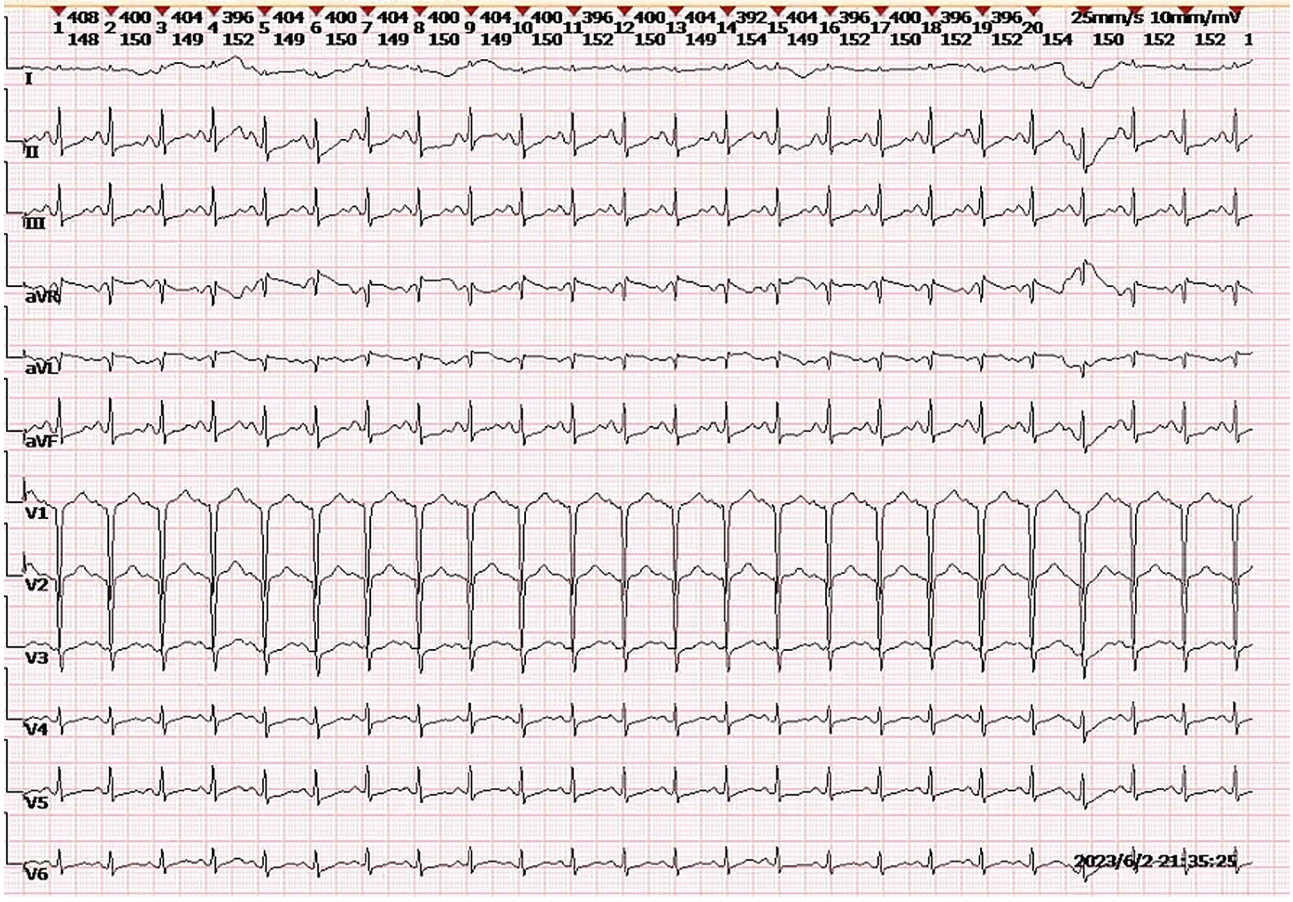

Fig. 3 Twelve-lead electrocardiogram on ICU admission. ECG showed sinus tachycardia, poor R-wave progression in V_{1-3}, and mild ST-T changes. ECG recorded at 25 mm/s and 10 mm/mV

order to further clarify the diagnosis and etiological factors. We thought it would be useful to procure cerebrospinal fluid (CSF) to assist in ruling out specific infectious or inflammatory conditions. On Day 15, she underwent a lumber puncture (opening pressure of 13 cmH_2O) that, in the absence of pleocytosis (cell count of 3×10^6/L, protein level of 0.498 g/L and glucose level of 5.36 mmol/L), did not indicate a central nervous system infection (Supplementary Fig. S2). NGS for SARS-CoV-2 and other pathogens in the CSF was negative. The CSF sample was negative for both autoantibodies and oligoclonal bands. Percutaneous tracheostomy was performed on Day 16. After clinical improvement and the restoration of spontaneous respiration, she was further weaned from mechanical ventilation on Day 22. On Day 25, 1.5T enhanced magnetic resonance imaging (MRI) revealed bilateral, symmetrically distributed lesions in the pons, bilateral hippocampal regions, and bilateral basal ganglia, compatible with ANE (Fig. 5). Considering her nasopharyngeal swabs were consecutively tested positive (Fig. 4) with low Ct values and the severity of her condition, we extended the course of molnupiravir for antiviral therapy with her husband's consent. The antiviral therapy was continued to 20 days with no signs of toxicity.

Despite the improvement in cardiac function, she could not perform instructed actions. On Day 31, a repeat CT revealed that the lesions in the head and chest had reduced (Supplementary Fig. S3). On Day 32, she was discharged to a rehabilitation facility for further treatment.

Discussion

In this case report, we presented a rare case of a patient who experienced COVID-19- associated severe ANE and fulminant myocarditis. She received aggressive extracorporeal cardiovascular support and immunosuppressive therapies. Ultimately, her condition stabilized and she was transferred for rehabilitation. This case provides valuable insight into the management of severe neurological and circulatory complications related to COVID-19.

Recent research has shown that the number of SARS-CoV-2 extrapulmonary manifestations has gradually increased. However, the understanding of the neurological complications associated with COVID-19 remains limited. Acute necrotizing encephalopathy, commonly observed in children after viral respiratory infections, has

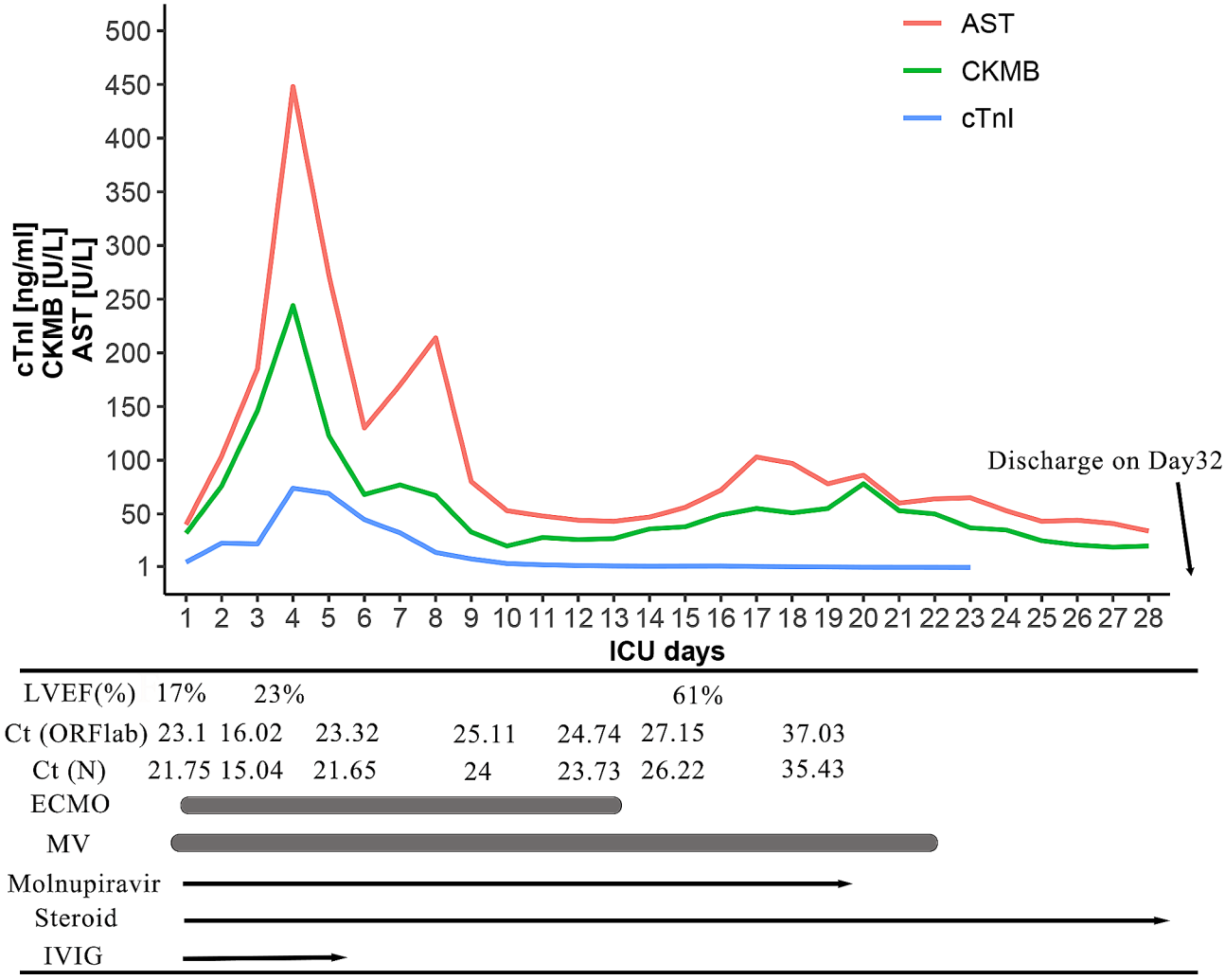

Fig. 4 Clinical course of the patient after ICU admission. Abbreviations: AST, aspartate aminotransferase; CK-MB, creatine kinase-muscle/brain; cTnI, cardiac troponin I; ICU, intensive care unit; LVEF, left ventricular ejection fraction; Ct, Cycle threshold; ECMO, extracorporeal membrane oxygenation; MV, Mechanical ventilation; IVIG, intravenous immunoglobulin.

been recognized as a rare complication of SARS-CoV-2 infection [17]. Prior research has shown several cases of ANE caused by SARS-CoV-2 [18]. Poyiadji et al. reported the first case of a patient with COVID-19 and ANE in March 2020 [18]. In that case, the patient exhibited radiologic findings similar to those of the patient whose case is reported here: symmetric thalamic lesions. The patient in our study experienced severe neurological dysfunction, and her condition rapidly deteriorated. As in this case, ANE is often characterized by a rapid progression of neurological symptoms following a febrile systemic illness, including seizures, altered mental status and focal neurological deficits. Despite its association with viral infection, ANE is not typically considered an inflammatory encephalitis. CSF analysis often reveals an increase in protein concentration and the absence of pleocytosis [19]. The exact cause and pathophysiology of ANE are still unclear. Neurotropism caused by coronaviruses and the association of coronaviruses with demyelinating lesions have been established through studies involving both humans and animals [20]. Recently, Paniz-Mondolfi et al. showed that SARS-CoV-2 was detected in brain tissue at autopsy, and neuronal infection by the virus was confirmed [21]. The trigeminal and olfactory nerves serve as possible routes for entry [22]. There are multiple potential causes for the failure to identify the virus in the CSF in our case and other similar cases [23]. First, the virus primarily remains bound to cells and spreads through direct cell-to-cell transmission. Second, the amount of virus was below the detection limit of the testing method. Recently, Virhammar et al. reported a case of COVID-19-related ANE, in which SARS-CoV-2 RNA was detected in CSF via third lumbar puncture [24]. This finding emphasizes the importance of repeated lumbar punctures in COVID-19 patients with neurological symptoms. Third, CSF contains low concentrations

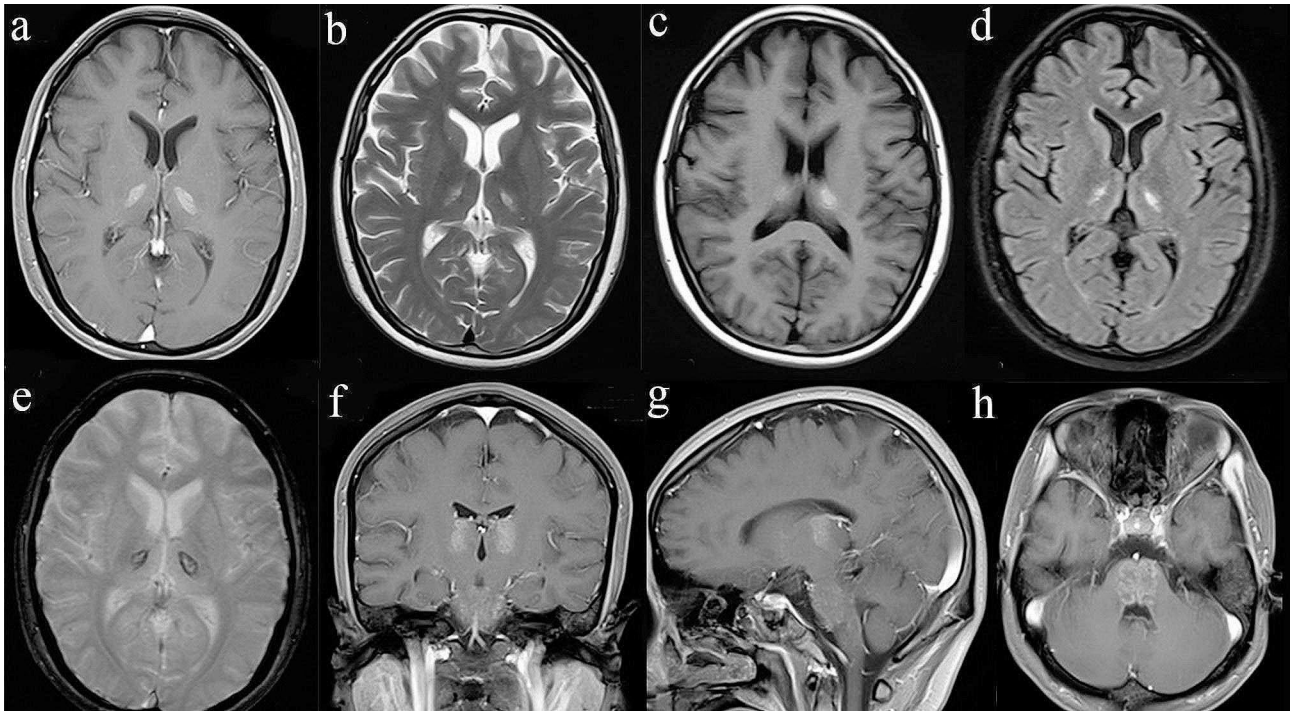

Fig. 5 MRI findings in the patient with acute necrotizing encephalopathy. Patchy and uneven elongated T1 and T2 signals were observed in the pons and bilateral hippocampal regions, with unclear borders, punctate and patchy enhancements. Patchy short T1 and slightly long T2 signals were seen in the basal ganglia regions on both sides, with low signal rims at the edges

of endonucleases/exonucleases and proteins that function as inhibitors [25]. Moreover, ANE is recognized as the outcome of an immune-mediated process that involves the activation of proinflammatory cytokines. A recent observational study demonstrated an association between COVID-19-related encephalitis and changes in neuronal/glial biomarkers, as well as a specific cytokine pattern that indicates underlying inflammatory-mediated mechanisms linked to SARS-CoV-2 infection complications [26]. Further large studies are required to explore potential COVID-19-related central nervous system (CNS) pathologies. Further investigation of whether the pathophysiology of ANE is mainly caused by direct viral invasion or an autoimmune response is also needed.

In this case, the heart function was successfully recovered through timely mechanical hemodynamic support like ECMO. The underlying mechanism of COVID-19-related myocarditis may be multifactorial, including direct viral infection of cardiomyocytes and subsequent inflammation-mediated cardiac injury [27, 28]. Although endomyocardial biopsy (EMB) is the gold standard for myocarditis, it is rarely used due to facility limitations, insufficient clinical experience, and patient instability [29]. In our case, EMB was not feasible due to the patient's hemodynamic instability, which suggested viral myocarditis. Despite the unavailability of EMB results, the patient's clinical presentation met the diagnostic criteria for myocarditis (based on ECG and echocardiography findings, and troponin levels) in the absence of significant coronary artery disease, preexisting cardiovascular conditions, or extracardiac factors that could account for the syndrome [9]. Viral myocarditis exhibits variable clinical manifestations, ranging from minor chest tightness and pain to fulminant myocarditis, a rare but life-threatening type of myocarditis with rapidly progressing myocardial dysfunction, as in our case. If primary COVID-19 myocarditis is the principal condition, a fulminant course characterized by a significant deterioration in cardiac function should be expected. According to previous research, the presence of significant myocardial edema with lymphocytic infiltration is apparent [30]. This phenomenon could be found sonographically in our patient. Thus, early diagnosis and close monitoring are pivotal in the management of acute myocarditis. The efficacy of ECMO in managing patients with fulminant myocarditis who were developed hemodynamically unstable has been reported in patients with COVID-19 [31]. According to previous reports, the occurrence of additional acute respiratory distress syndrome (ARDS) or other organ involvement in COVID-19 was considered to be of great importance for the clinical prognosis [32, 33]. Early communication with critical care specialists about providing mechanical circulatory support, such as ECMO, may be lifesaving for patients with acute fulminant myocarditis.

Conclusion

The simultaneous incidence of myocarditis and acute necrotizing encephalopathy in patients with COVID-19 is rare and is associated with high mortality. Early and accurate diagnosis and timely treatment are crucial for increasing survival rates. The initial acute fulminant presentation of myocarditis can resolve and heart function can recover within days. Thus, rapid invasive bridging therapy may be lifesaving. Further exploration of potential mechanisms underlying COVID-19 CNS and cardiovascular systems will contribute to preventing progression to severe SARS-CoV-2 infection and creating personalized treatment plans. Further investigation of the potential of an immune-mediated process and its therapeutic implications is also needed.

Abbreviations

ANE	Acute necrotizing encephalopathy
ECMO	Extracorporeal membrane oxygenation
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MCS	Mechanical circulatory support
CRP	C-reactive protein
IL-6	Interleukin 6
cTnI	Cardiac troponin I
CK-MB	Creatine kinase-muscle/brain
RT-PCR	reverse transcription polymerase chain reaction
Ct	Cycle threshold
ORF1ab	Open reading frame 1ab
N	Nucleocapsid
CT	Computed tomography
EEG	Electroencephalograph
LVEF	Left ventricular ejection fraction
ECG	Electrocardiogram
FiO2	Fraction of inspired oxygen
PEEP	Positive end-expiratory pressure
ICU	Intensive care unit
ScvO2	Central venous oxygen saturation
PCO2gap	Central venous-to-arterial carbon dioxide tension difference
NGS	Next-generation sequencing
AST	Aspartate aminotransferase
CSF	Cerebrospinal fluid
MRI	Magnetic resonance imaging
EMB	Endomyocardial biopsy
ARDS	Acute respiratory distress syndrome

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions

CX and YS were involved in the design of the study, data analysis, data interpretation, and manuscript preparation. JP, TP, and XZ were involved in data curation, investigation, and interpretation. HW and ZX were involved in data interpretation and the revision of the manuscript. BC was involved in the oversight of the study and the revision of the manuscript. All authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Human Research Ethics Committee of Ningbo No. 2 Hospital (No. YJ-NBEY-KY-2023-144-01).

Consent for publication

Written informed consent was obtained from the patient's parents and husband for the publication of this article and any accompanying images.

Competing interests

The authors declare no competing interests.

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