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A rare case of managing near sudden unexpected death in status epilepticus with COVID-19 infection in rural area: what is the possible cause?

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ABSTRACT

COVID-19, a pandemic caused by the SARS-CoV-2 infection, has many fatal complications related to neurological and cardiovascular events such as seizures and arrhythmia leading to cardiac arrest. The direct and indirect mechanisms of SARS-CoV-2 played a significant role to generate its clinical manifestation. Near-sudden unexpected death in epilepsy (SUDEP) is a reversal of cardiopulmonary arrest in an epileptic patient which is very dangerous if not treated well. Here we present a 27-year-old man with VF and near sudden unexpected death due to status epilepticus (SE) and COVID-19 infection that was successfully managed in a rural area emergency setting. Prompt treatment in the emergency room followed by supportive management is important for patient survival. This rare and complex case possibly happened and should be differentiated whether the cause is COVID-19 or SUDEP to establish definitive management though the supportive management is still the same. Prevention of COVID-19 complications and SUDEP should also be done to reduce morbimortality.

Keywords: near-sudden unexpected death in epilepsy, covid-19, status epilepticus, ventricular fibrillation

INTRODUCTION

COVID-19 caused by the SARS-CoV-2 virus has been the most discussed disease since early 2020 due to its rapid transmission across the nations via droplets to the lung as their main target organ, but multiorgan involvement has been reported since various clinical manifestations were found. Pulmonary manifestations such as cough, dyspnoea, and respiratory failure were the most common symptoms. Neurological manifestations were found in almost one-third of hospitalized patients where dizziness and taste impairment were the most reported symptoms [1], yet they also had very extensive features ranging from stroke to seizures including de-novo status epilepticus as one of the unusual manifestations [2]. Cardiovascular manifestations such as arrhythmias and myocardial injury were reported in some cases and associated with increased morbimortality, but the incidence and nature of cardiovascular manifestation in COVID-19 were still poorly documented across studies. Status epilepticus (SE) and ventricular fibrillation (VF) are rare manifestations of COVID-19. Little is known about the information that explained the mechanism of COVID-19-induced status epilepticus and arrhythmias. Invasive properties of the virus to related cells which had angiotensin-converting enzyme 2 (ACE2) receptor (neurotropism and cardiotropism) remained to be the main mechanism reported in several studies [3,4]. Otherwise, many reports were confirming seizure-induced cardiac arrest which is known as sudden unexpected death in epilepsy patients (SUDEP). Most SUDEP cases are due to a cascade of respiratory disturbances causing dysregulation of the respiration center in the brainstem and

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leading to cardiac events [5,6]. This can be a challenge for medical workers in rural area emergency setting to establish the diagnosis and give the best care available to the patients. Here we reported a rare case of a VF and near sudden unexpected death in SE patient with COVID-19 infection that was successfully managed with cardiopulmonary resuscitation (CPR), defibrillation, and supportive management in a rural area located in East Indonesia.

CASE ILLUSTRATION

A 27-year-old man came at night to the emergency department with chief complaints of fatigue, malaise, and dizziness in the last two days before admission. Further alloanamnesis revealed that the patient had fieldwork one week before admission and his colleague had mild symptoms of cough and fever but no further examination was done. The patient had received 2 times COVID-19 vaccines (Sinovac©) 3 months before admission. No other past medical history was identified. He was fully alert without any neurological deficit, initial vital signs showed sub-febrile condition (T: 37,5°C) with normal heart rate (HR: 90 bpm), oxygen saturation 98% in room air. Minimal rhonchi were found in the lateral-basal area of both lungs. The patient suddenly had a tonic-clonic seizure for 1 minute followed by cardiac arrest when under monitoring in the emergency room. Initial resuscitation was initiated with

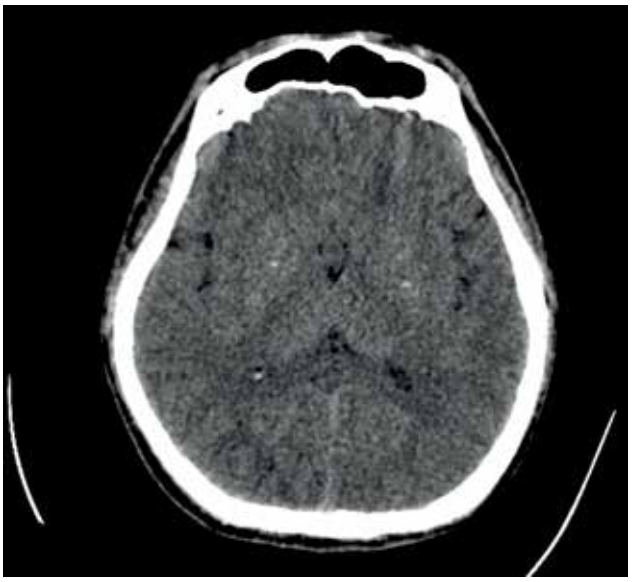

FIGURE 1. Non-contrast CT brain showed multiple hyperdense lesions around the basal ganglia. Neither infarction nor hemorrhage was found and other parts of the brain were within normal limits

CPR, followed by 2 times defibrillation due to VF detected in a manual external defibrillator (HR: 178 bpm), intubation, and supportive management were done. After the return of spontaneous circulation (ROSC), the patient had 5 episodes of status epilepticus in the first 30 minutes of ROSC. Valproic acid as antiepileptic drug (AED) and sedative agents

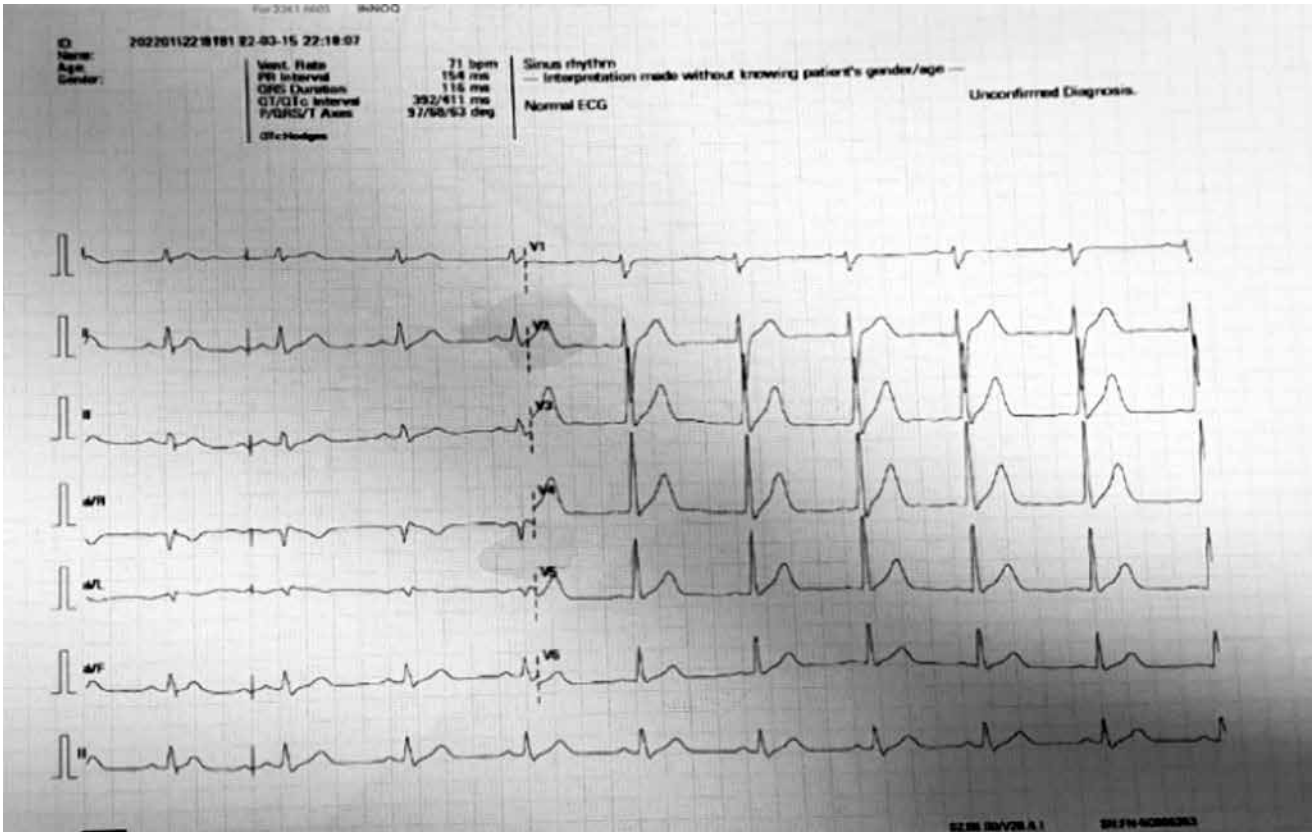

FIGURE 2. Normal ECG was recorded after ROSC. No abnormality was found

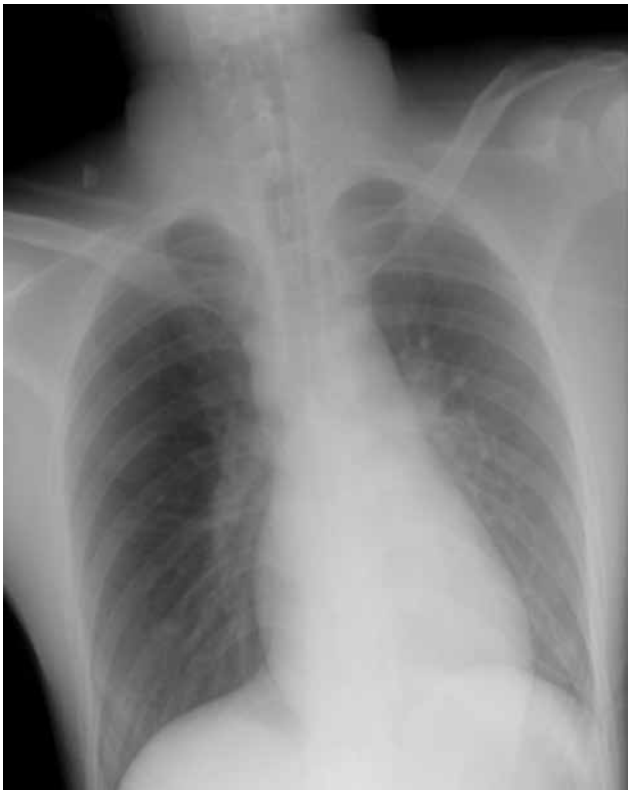

FIGURE 3. From the chest x-ray, bilateral infiltrates around the parahilar-paracardial area were found. Mild pneumonia can be established from the chest x-ray and positive PCR result

were administered. Diagnostic examinations were carried out to find the possible cause of the patient's condition. Laboratory results showed a slight increase in D-dimer (0.60 mg/mL) and hypokalaemia (3.0 mmol/L) with normal C-reactive protein (5.17mg/L). Blood gas analysis revealed metabolic and pulmonary acidosis (pH: 7.312, pCO_2: 43.8mmHg, pO_2: 124.6mmHg, HCO_3^-: 21.7mmol/L) while other laboratory results were within normal limits. Non-contrast computed tomography (CT) scan of the brain suggested intracranial infection (Figure 1). Electrocardiogram (ECG) was recorded when the patient was in stable condition after ROSC was normal sinus rhythm (Figure 2). The Real-Time Polymerase Chain Reaction (RT-PCR) of nasopharyngeal and oropharyngeal swabs tested positive for COVID-19 with CT value of 21.6 confirming pneumonic appearance in patient's chest x-ray (Figure 3).

The patient was admitted to an isolated intensive care unit (ICU), given ventilation support, treated with drugs listed in the Indonesian national guideline for COVID-19 (remdesivir, dexamethasone, antibiotic, and supportive vitamins), AED, and sedative agents. Anticoagulant was not given until the 2nd day of treatment due to upper gastrointestinal bleeding detected on the nasogastric tube. Clinical improvement was shown on the 3rd day of treatment with no episode of seizure and source of bleeding found. The weaning process went well and the patient was extubated on the 4th day of treatment. The patient was discharged on the 6th day in good and stable condition with advice to self-isolate. He did a follow-up visit to the neurology policlinic one month after discharge with no complaints. Mini mental status examination was done and showed no deterioration of cognitive function.

DISCUSSION

Since COVID-19 was declared a pandemic, many neurological and cardiac manifestations were reported as complications of the viral infection. SARS-CoV-2 binds to its receptors that are located in adipose tissue, lung, brain, heart, naso-oral mucosa, vascular endothelium, and liver using ACE2 receptors [7]. Sepsis and ARDS are the most common complication in COVID-19, but other complications such as shock, arrhythmia, or acute cardiac injury could also happen and contributed to mortality if not treated quickly and precisely. The heart and brain are the two most important organs that regulate all the autonomic systems and coordinate other body organs. Any pathological condition from one of those can dysregulate each other.

An acute seizure can arise from a hypoxic state, febrile, or metabolic dysfunction even though all of them are rare [8]. Despite lack of evidence, the mechanism of SE might be the same mechanism with Guillain-Barre Syndrome and encephalomyelitis in COVID-19 patients. The mechanism of neurological manifestations can be direct or indirect. Direct neuroinvasion of SARS-CoV-2 in the brain is caused by ACE2 receptors that are expressed in the motor cortex, middle temporal gyrus, substansia nigra, posterior cingulate cortex, ventricle, thalamus, and olfactory bulbs that contain high numbers of neurons, astrocytes, and oligodendrocytes. This virus can dysregulate the blood-brain barrier and can be detected in cerebrospinal fluid. The indirect mechanism suspected to be neuroinflammatory is the activation of T lymphocytes, macrophages, and endothelial cells resulting in inflammatory response and cytokine storm that lead to disseminated intravascular coagulation (DIC) and multiorgan dysfunction syndrome (MODS) [8-10]. Frequently, the indirect mechanism can be found when the IL-6 and IL-8 values elevate in the serum, while IL-8 can be detected in CSF [10]. The mechanism of cardiovascular manifestations was also reported to be similar to neurological manifestation. Direct invasion of the virus to myocardial or endothelial cells via ACE2 receptor-induced myocarditis and cardiomyopathy while indirect mechanisms such as hyperinflammatory state also played a role in worsening arrhythmia condition [3,11]. Currently, along with standard supportive care, antiviral agents were needed to

prevent further viral replication of SARS-CoV-2 and immunomodulators if needed to alleviate the hyper inflammation and tissue damage caused by it. Proper management can reduce the incidences of complication and morbimortality in the later and post COVID-19 stage.

In our case, SE can be the result of direct neuroinvasion due to hyperdense intracranial lesions found in CT brain, though the exact mechanism can't be ruled out due to the limitation to perform a lumbar puncture in the rural area. Another hypothesis known as SUDEP explained that prolonged seizures can make respiratory disturbance from laryngospasm, central and obstructive apnoea, and also dysregulate the respiration center in the brainstem, which can lead to cardiac events such as tachyarrhythmia, bradyarrhythmia, asystole, and AV block [6,12]. It is known to possibly occur in severely epileptic patients, multiple drugs combination usage, and have uncontrolled risk factors. All patients with epilepsy are susceptible to SUDEP [12].

Cardiac arrhythmias can happen in every sequence of seizures, whether it's preictal, ictal, interictal, or postictal episodes. Ictal asystole was the most reported case of cardiac arrhythmias. However, ictal arrhythmia was reported to be self-limited since no death was reported. Near-SUDEP is a reversal of cardiopulmonary arrest with subsequent survival for more than one hour by resuscitation effort [5]. Sinoatrial abnormality and ventricular arrhythmia were presented in patients with chronic epilepsy or under AED [13]. This cause of cardiac arrhythmia can be ruled out in our patient because he has no history of seizures. VF was reported to be a rare case of cardiac arrhythmia that occurred during postictal and is frequently associated with SUDEP [14,15]. Therefore, malignant ventricular arrhythmia such as VF in our patient may be occurred due to SARS-CoV-2 effect or SE, but the exact mechanism is still unknown.

Choosing the right AED for epileptic patients with any complications is important. Some cardiac arrhythmias occurred due to cell disturbance in regulating bioelectrical activity or as the adverse effect of the AED itself. AED such as phenytoin, carbamazepine, and levetiracetam are proven to worsen the cardiac cells activity [13]. Valproic acid can be drug of choice in epilepsy patients with cardiac arrhythmia. Not only to control the repeated seizure episode but also can influence cardiac conduction and can be used as an anti-arrhythmic agent [16]. Electroencephalogram (EEG) evaluation is needed to adjust the AED and prevent its adverse effect. Prevention of SUDEP also includes using monitoring devices to reduce the occurrence of seizures and cardiopulmonary distress, preventing airway obstruction, and reducing central hypoventilation to prevent central apnea [17].

Many challenges have been faced by medical workers in rural areas. EEG examination, CSF viral analysis, and serum inflammatory markers such as procalcitonin, IL-6, and IL-8 can't be done due to limited facilities in the rural area. Prompt treatment in an emergency situation such as SE is important for patient survival followed by supportive management and treating the cause of cardiac arrest immediately. Prevention of COVID-19 complications and sudden cardiac arrest in all types of epileptic patients should also be done.

CONCLUSION

Malignant ventricular arrhythmia and near sudden unexpected death in SE patient with COVID-19 infection is a rare and complex case. Nowadays, one should always keep in mind that sudden cardiac arrest as COVID-19 complication or epileptic-induced is possibly happened and should be differentiated to establish definitive management though the supportive management is still the same. Malignant ventricular arrhythmia in COVID-19 is caused by direct and indirect mechanism while in SUDEP is caused by cardiac-respiratory-brainstem dysfunction cascades. Prevention of COVID-19 course of disease and complication by giving proper management, and prevention of sudden cardiac arrest in all type of epileptic patient especially in detection of seizure and choosing right AED should also be done to reduce morbimortality.

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