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Case Report

Acute myocarditis associated with diffuse cerebral edema in a patient with Covid-19: case report*

Miocardite aguda associada a edema cerebral difuso em paciente com Covid-19: relato de caso

Isabella Cristina Mendes Rossa[1], Gustavo Lenci Marques[2], Carlos Alexandre Twardowschy[3]

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ABSTRACT: Infection with severe acute respiratory syndrome virus 2 (SARS-CoV-2), in addition to causing serious damage to the respiratory system, can trigger heart and brain damage. Studies suggest that both the brain parenchyma and the myocardium can be directly infected by the virus. Furthermore, the secondarily triggered hyperinflammatory state promotes endothelial, vascular and myocardial inflammation, plaque instability, hypercoagulative state and electrolyte imbalance. This paper aims to describe the case of a patient with COVID-19 with acute myocarditis associated with cerebral edema. This was a 44-year-old female patient admitted with symptoms of COVID-19. During her hospital stay, she presented elevated cardiac troponin I, as well as diffuse hypokinesia on transthoracic echocardiography, which suggested the diagnosis of myocarditis. Then, a cranial tomography showed diffuse cerebral edema and tonsillar herniation, and the patient evolved with brain death. The case reported here shows a probable impact of myocarditis on the central nervous system, and it is even less possible that low output can reduce cerebral perfusion, causing a worsening of the prognosis, due to the endogenous response process of the edema. In addition, it presents the possibility of direct damage by the virus to the myocardium and brain parenchyma, since this fact could trigger an outcome of equal severity. In this sense, there is a need for further studies to investigate the effects of SARS-CoV-2 on these tissues, as it was not possible to rule out the direct action of the virus on heart and brain tissue.

KEY WORDS: COVID-19; SARS-CoV-2; Myocarditis; Brain edema.

RESUMO: A infecção pelo vírus da síndrome respiratória aguda grave 2 (SARS-CoV-2), além de provocar danos graves ao sistema respiratório, pode desencadear lesões cardíacas e cerebrais. Estudos sugerem que tanto o parênquima cerebral quanto o miocárdio podem ser infectados diretamente pelo vírus. Ademais, o estado hiperinflamatório secundariamente desencadeado promove inflamação endotelial, vascular e miocárdica, instabilidade de placas, estado de hipercoagulabilidade e desbalanço eletrolítico. O presente trabalho tem como objetivo descrever o caso de uma paciente com COVID-19 com apresentação de miocardite aguda associada a edema cerebral. Tratava-se de uma paciente do sexo feminino, 44 anos, admitida com sintomas da COVID-19. Ao longo da internação, ela apresentou elevação de troponina cardíaca I, assim como hipocinesia difusa na ecocardiografia transtorácica, o que sugeriu o diagnóstico de miocardite. Em seguida, uma tomografia de crânio evidenciou edema cerebral difuso e herniação tonsilar, sendo que a paciente evoluiu com morte encefálica. O caso relatado mostra um provável impacto da miocardite sobre o sistema nervoso central, sendo possível inferir que o baixo débito pode reduzir a perfusão cerebral, provocando a piora do prognóstico, devido ao processo de resposta endógena do edema. Além disso, apresenta a possibilidade de dano direto do vírus ao miocárdio e ao parênquima cerebral, visto que esse fato poderia desencadear um desfecho de igual gravidade. Nesse sentido, existe a necessidade de outros estudos para investigação dos efeitos do SARS-CoV-2 nesses tecidos, pois não foi possível descartar a ação direta do vírus no tecido cardíaco e cerebral.

PALAVRAS-CHAVE: COVID-19; SARS-CoV-2; Miocardite; Edema cerebral.

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[1.] Pontifícia Universidade Católica do Paraná. ORCID: 0000-0002-5885-7854. Email: isabella.rossa@pucpr.edu.br.
[2.] Hospital Marcelino Champagnat, Departamento de Cardiologia. ORCID: 0000-0002-6057-0350. Email: gustavolencimarques@gmail.com
[3.] Hospital Marcelino Champagnar, Departamento de Neurologia. ORCID: 0000-0003-3667-0412. Email: carlos.twardowschy@pucpr.br
Correspondence: Isabella Cristina Mendes Rossa. Rua Capitão Amin Mosse, nº 11, Alto Boqueirão, Curitiba, Paraná, CEP: 81850-150. Email: isabella.rossa@pucpr.edu.br.

INTRODUCTION

In December 2019, a series of cases of pneumonia of unknown etiology, but with characteristics similar to a viral condition, emerged in Wuhan, Hubei province, China[1]. Researchers identified the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the cause of this infection, which was named COVID-19[1]. Patients infected with SARS-CoV-2 usually present with fever, cough, and dyspnea for a period of 2 to 14 days and can develop pneumonia[1]. Like other coronaviruses, SARS-CoV-2 uses Angiotensin Converting Enzyme II (ACE2) as a ligand-binding receptor before entering the cell by receptor-mediated endocytosis[2]. The ACE2 receptor is a membrane protein present in cardiomyocytes, type 2 pneumocytes, astrocytes, and other cells[3].

In addition to causing damage to the respiratory system, SARS-CoV-2 can trigger heart and brain damage[4]. The mechanisms of damage to these two systems are not fully understood and are probably multifactorial[3]. In some cases of myocardial damage, SARS-CoV-2 particles have been identified in the myocardium, reinforcing the hypothesis of cardiotoxicity[5]. Regarding the brain, studies suggest that SARS-CoV-2 can infect it directly, reaching the brain parenchyma through the blood and via the olfactory system[6]. In addition, the hyperinflammatory state triggered by COVID-191 promotes vascular inflammation, plaque instability, myocardial inflammation, electrolyte imbalance, and a state of hypercoagulation[7], contributing to the occurrence of myocardial and brain damage[3].

Recent studies indicate that 7-14% of patients diagnosed with COVID-19 have myocardial damage[21], and this condition is related to higher mortality rates[1,5,22] and more severe disease outcomes5. Cases of myocarditis are rare in patients diagnosed with COVID-19, but when a case of fulminant myocarditis occurs, it is associated with fatal outcomes for these patients[6]. Therefore, additional studies of cases of myocarditis in patients infected with SARS-CoV-2 are needed.

OBJECTIVE

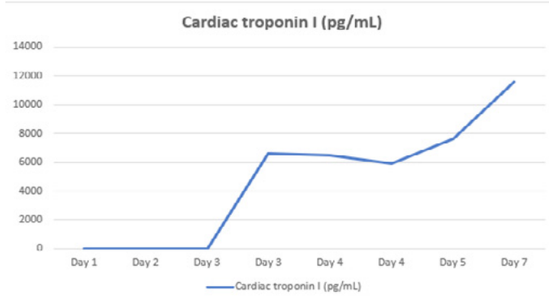
To describe the clinical course of a patient affected by COVID-19 with acute myocarditis associated with cerebral edema.

METHOD

Descriptive observational study. The project was approved by the Ethics Committee of the Pontifical University of Paraná (PUCPR) under opinion number 3.944.734. The Free and Informed Consent Form was waived.

RESULTS

A 44-year-old woman sought medical attention with a dry cough, dyspnea on moderate exertion, odynophagia, prostration, and myalgia. On admission, the patient had a body temperature of 37.1°C (afebrile), blood pressure of 128/79 mmHg, heart rate of 94 bpm, and oxygen saturation (O2) of 96%, with the only alteration found on physical examination being crackles at both lung bases. She had a history of dyslipidemia, for which she was taking a statin, and was also overweight (Body Mass Index: 27.68 kg/m2). The patient had been diagnosed with COVID-19 4 days earlier using the reverse transcriptase polymerase chain reaction (RT-PCR) test. On the first day of hospitalization, a chest CT scan showed acute inflammatory pulmonary changes affecting around 50% of the lung parenchyma. Laboratory tests showed a cardiac troponin I level of 4.8 pg/mL (reference value: less than 11.6 pg/mL), C-reactive protein of 71.5 mg/L (reference value: less than 5 mg/L), and normal blood cell counts. On the second day, the patient developed acute respiratory failure, and orotracheal intubation was performed. A transthoracic echocardiogram revealed a left ventricular ejection fraction of 44%, diffuse hypokinesia, and an increase in the size of the left ventricle, all findings suggestive of myocarditis. On day 6, the patient improved, with O2 saturation of 93%, mild acidosis, and permissive hypercapnia on arterial blood gas analysis. However, she developed hemodynamic instability due to circulatory shock (mean arterial pressure 55 mmHg and heart rate 125 bpm), leading to the need to increase the dose of vasoactive drugs. She also had pupils fixed mydriasis and the absence of corneal-palpebral reflex. On the same day, the level of cardiac troponin I found was 11,576.6pg/mL (reference value: less than 11.6pg/mL), the highest since day 1 (Figure 1). The electrocardiogram showed sinus tachycardia and no signs of myocardial ischemia (Figure 2). The patient underwent a CT scan of the skull, which showed reduced differentiation between the white and gray matter in the cerebral hemispheres, associated with an expansive effect and tonsillar herniation, suggestive of diffuse cerebral edema. The patient was under suspicion of brain death, and sedation was switched off and hemodynamic, respiratory, and cardiac monitoring was maintained. The patient did not undergo Cardiovascular Magnetic Resonance Imaging and Cardiac Catheterization due to her worsening hemodynamic condition. On the seventh day, the patient died.



*Troponin values were not obtained on days 6 and 8

Figure 1 - Elevation of cardiac troponin during hospitalization

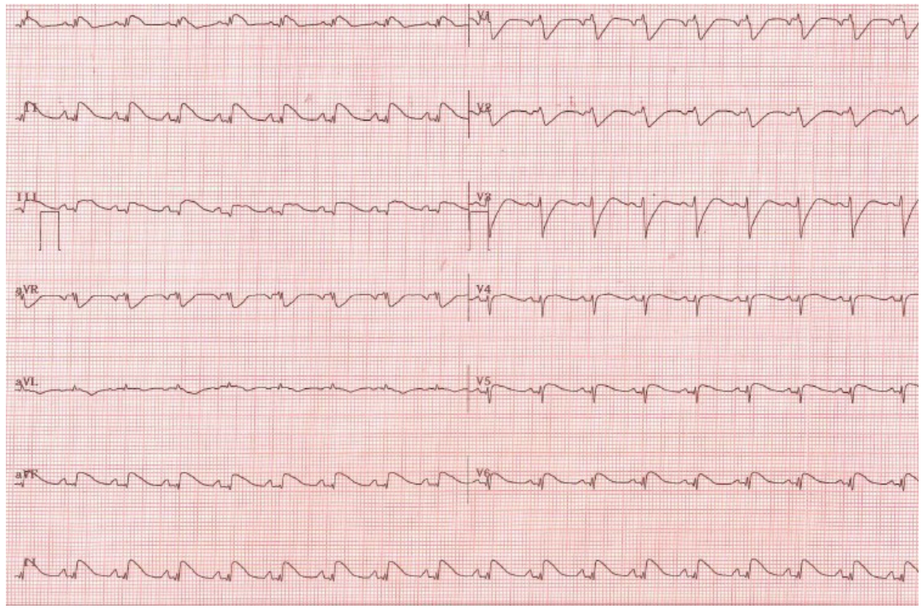


Figure 2 - Electrocardiogram obtained on day 6

DISCUSSION

In addition to lung involvement, SARS-CoV-2 infection can compromise myocardial function, triggering cases of acute myocarditis[4,12-13]. Myocarditis, an inflammatory disease of the myocardium, is one of the manifestations of myocardial damage. Viral infections, such as enterovirus and adenovirus infections, are common causes of this condition, which causes focal or global myocardial inflammation, necrosis, and, in some cases, ventricular dysfunction[8]. The diagnosis of myocarditis is based on various parameters since this condition can manifest itself as anything from subclinical disease to sudden death. The symptoms of myocarditis usually manifest as chest pain, palpitations, fatigue, and syncope; however, in many cases, additional tests are necessary. Increased markers of myocardial necrosis, non-specific ST segment and T wave changes on the electrocardiogram, global hypokinesia, and pericardial effusion on the echocardiogram, as well as histological changes on the biopsy, are used as criteria for the diagnosis of myocarditis[9]. Furthermore, in the absence of evidence of coronary artery disease, high levels of cardiac troponin can suggest the occurrence of myocarditis, since this marker has high specificity for this diagnosis[9]. The pathogenesis of this involvement may reflect a process of viral replication and dissemination through the blood or lymphatic system of the respiratory tract. In addition, it may be associated with the infectious process triggered by SARS-CoV-2, which characteristically induces an exaggerated inflammatory response capable of causing myocardial damage10. In addition, during pulmonary infection, fever, and tachycardia increase the demand for oxygen by cardiac tissue. However, impaired gas exchange due to continuous blood flow to low-ventilation lung regions causes a ventilation-perfusion disorder, resulting in blood hypoxemia and, consequently, a worsening of cardiac tissue oxygenation[11]. In the patient in this case, the diagnosis of acute myocarditis was obtained due to the clinical picture of circulatory shock, elevated cardiac enzymes, absence of signs of myocardial ischemia on the electrocardiogram, and findings suggestive of myocarditis on the transthoracic echocardiogram.

Yokoo et al.[4] described the case of a patient diagnosed with COVID-19, aged over 80, with a history of systemic arterial hypertension and ischemic stroke. Laboratory tests showed high levels of troponin T, the electrocardiogram showed no signs of ischemia and the echocardiogram showed an ejection fraction of 35%. This patient underwent a Cardiovascular Magnetic Resonance which revealed areas of late enhancement with ischemia in the septal wall of the base of the left ventricle, as well as diffuse hypokinesia and impaired global systolic function[4]. Cases of myocarditis associated with COVID-19 have been reported from young to old. Paul et al.[12] described the case of a 35-year-old patient who was overweight as the only cardiovascular risk. This patient's electrocardiogram showed changes in repolarization and laboratory tests showed a high level of cardiac troponin I with high sensitivity. Cardiovascular MRI showed subepicardial enhancement predominantly in the lateral and inferior walls, a typical finding of myocarditis12. The two cases described presented patients with pre-existing cardiovascular risk, but acute myocarditis associated with COVID-19 can also manifest in patients without cardiovascular risk factors. Inciardi et al.[13] published a case of acute myocarditis in a patient with no cardiovascular risk, who presented elevated troponin T, as well as diffuse hypokinesia and reduced ventricular ejection on transthoracic echocardiography. In this

sense, repolarization changes on the electrocardiogram, elevated cardiac troponin, as well as detection of left ventricular diastolic impairment on echocardiography are indicative of myocarditis associated with COVID-19[13,14].

Patients with heart damage associated with SARS-CoV-2 infection have a more severe acute manifestation of COVID-19, characterized by high levels of C-reactive protein and creatinine, as well as more intense lung involvement, a condition similar to that of the patient in this case[13]. The mortality rate is also influenced by the myocardial damage associated with COVID-19 and is higher than 50% among patients with heart damage compared to 5% among those without[14].

In this case report, in addition to myocarditis, the patient had diffuse cerebral edema. Several mechanisms have been proposed for the neurological complications caused by COVID-19. The main hypothesis about direct infection of the brain parenchyma by SARS-CoV-2 is based on the retrograde hematogenous or axonal route with viral accumulation in endothelial cells, pericytes, inflammatory cells, neurons, or glial cells[15]. Brain damage may also be related to pneumonia caused by SARS-CoV-2, because when the virus passes through the lung parenchyma, it triggers an exaggerated accumulation of neutrophils, increased vascular permeability, and the formation of exudates, leading to hypoxemia. In the brain, hypoxia promotes increased anaerobic metabolism, causing vasodilation and cerebral edema15. In this sense, the patient's brain involvement in this case was probably due to severe hypoxia, which was also related to the occurrence of circulatory shock. In addition, pneumonia caused by SARS-CoV-2 infection causes an exaggerated inflammatory response known as a "cytokine storm"[1]. This hyperinflammatory state appears in the advanced stages of severe COVID-19, causing damage to various organs16. Increased cytokine levels cause plaque destabilization, which can lead to plaque rupture, triggering heart and brain damage[16,17].

Another point to analyze is the presence of dyslipidemia as a comorbidity in the patient. A meta-analysis of several studies highlighted the existence of a relationship between the presence of dyslipidemia and severe COVID-19 outcomes[18]. After the occurrence of a viral infection, macrophages can interact with cholesterol in atherosclerotic plaques or be involved in the activation of an inflammasome, increasing the secretion of pro-inflammatory cytokines[19]. Thus, the presence of dyslipidemia can cause endothelial dysfunction and increase the risk of cardiovascular complications[20].

CONCLUSION

In addition to causing respiratory complications, SARS-CoV-2 infection can impair heart and brain function. Acute myocarditis, a manifestation of myocardial damage, is associated with more severe COVID-19 outcomes, as well as leading to poor cerebral perfusion, culminating in edema and brain death. In addition, dyslipidemia has a major influence on the progression of COVID-19 and its presence is related to more severe outcomes of the disease. The case described represents the risk of cardiac and cerebral involvement in patients with COVID-19, given that the patient presented with brain death just 7 days after hospital admission. Furthermore, it remains unclear whether the diffuse cerebral edema was directly associated with acute myocarditis, whether it derived from an exacerbated inflammatory response, or whether it was caused by direct viral damage to the brain parenchyma. These findings could not be obtained mainly due to the lack of cardiac catheterization, cardiac and cerebral magnetic resonance imaging, as well as myocardial and cerebral parenchymal anatomopathological analysis. In this sense, it is not possible to rule out the hypothesis of the direct action of the virus on heart and brain tissue, which reinforces the need for further studies of the effects of SARS-CoV-2 on these organs.

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