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Myocarditis as a serious complication of COVID-19

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***Abstract*—** *Recently, the identification of a new line of coronavirus, which was called SARS-CoV-2, has become the subject of studies worldwide, reaching pandemic proportions. In line with this, this virus was identified as the etiological agent of a clinical entity called COVID-19, characterized by potentially severe pneumonia. In addition to respiratory involvement, the cytokine storm inherent to the pathophysiology of the disease constitutes a cascade of inflammatory activation, mediated by cytokines, which can lead to numerous multisystemic complications, including myocarditis. It is also postulated that myocardial involvement is due to direct viral cytopathic effects, as well as lymphocytic cell cytotoxicity, generating myocardial injury and cardiac dysfunction. This study aimed to describe the presence of myocarditis as a serious complication of SARS-CoV-2 infection, to better guide health professionals to consider this association as a diagnostic hypothesis in the face of the current scenario, in order to promote early diagnosis and management. The reported patient, aged 32, presented with typical manifestations of COVID-19, did not have cardiovascular risk factors and had preserved cardiac function at admission. We report the evolution of the condition with impaired cardiac function within 72 hours, describing the investigation, management and positive outcome with recovery of ventricular function.*

I. INTRODUCTION

At the end of 2019, a new line of coronavirus emerged in China, called SAR-CoV-2. Its origin is attributed to a spillover process, possibly related to the contact and consumption of wild animals, such as bat and pangolin. High transmissibility of the viral agent, even in asymptomatic and convalescent phases, has made contact with infected people an important source of viral spread, so that the virus has quickly spread throughout the world, reaching worrying pandemic proportions [1,2].

Likewise, the new coronavirus was appointed as the etiological agent of Coronavirus Disease of 2019

(COVID-19), an entity whose clinical course has multiple possible facets, from asymptomatic to severe pneumonia, with extensive pulmonary involvement, serious complications and even death. SARS-CoV-2 pneumonia is characterized by a rapid evolution from a focal presentation to diffuse involvement of both lungs, evidenced by a frosted glass pattern in the image. In addition to respiratory manifestations, general symptoms such as fever, asthenia, prostration, headache, flu-like prodrome, nausea, vomiting, diarrhea and anosmia stand out, with great variability, depending on the age group. In view of the multiple clinical courses of this recent disease, management is challenging, given the lack of consensus on first-line drug therapies [3,4].

Numerous complications have been reported in patients with COVID-19, many of them, with multisystemic consequences, with pathophysiological mechanisms that are still not very well elucidated. Among them, it is possible to mention thromboembolic manifestations, encephalitis, Guillain-Barré syndrome, delirium, acute kidney injury and even cardiac involvement, such as arrhythmias and myocarditis [5,6,7].

Myocardial involvement does not yet have its pathophysiological pillars completely elucidated; however, it is postulated that the cytokine storm intrinsic to COVID-19 plays a key role in the genesis of myocardial tissue inflammation. In addition, a possible direct viral cytopathic effect on cardiomyocytes is questioned, which may lead to the appearance of this potentially fulminant complication [8,9,10].

II. OBJECTIVE

To describe the association of COVID-19 with myocarditis of viral etiology as a serious complication, through the construction of a case report, aiming to highlight the importance of early diagnosis and treatment in optimizing the prognosis.

III. METHODOLOGY

Construction of a case report based on information obtained through analysis of the patient medical record, presenting a description of the condition, results of exams and procedures adopted, correlating them with the available literature and other cases already reported.

IV. CASE REPORT

Case presentation

A 32-year-old male patient, without cardiovascular risk factors, with a history of dry cough for 9 days, associated with continuous fever for 4 days and moderate dyspnea for 2 days. He was admitted to the emergency room with hypoxemia, 87% pulse oximetry and tachypnea of 26 incursions per minute, being admitted to the Intensive Care Unit (ICU).

Initial Management

Treatment with oxygen therapy by nasal catheter at 4 liters/minute, ceftriaxone, azithromycin, olsetamivir and hydroxychloroquine. Initial pulmonary ultrasound (Lung score 7), echocardiogram with preserved right and left ventricular systolic function (LVEF (Left ventricular ejection fraction): 64%, absence of segmental alteration), computed tomography of the chest with evidence of approximately 25 to 50% of frosted-glass pattern and PCR-RT SARS-CoV-2 positive.

Evolution and Investigation

After 72 hours of hospitalization, he presented with acute respiratory failure and severe hypoxemia, requiring orotracheal intubation. Pulmonary ultrasound was performed again, evidenced by LUS 18, and the echocardiogram showed a new segmental alteration, lower hypokinesia and left inferior-lateral ventricle and reduced ventricular function (LVEF: 44%).

Conduct and Follow-up

Hemodynamic optimization measures, association of positive inotropes (dobutamine) and diuretics were started, with improvement after 48 hours. After 14 days of hospitalization, the patient was discharged with drugs for ventricular dysfunction (beta-blocker, angiotensin-converting enzyme (ACE) inhibitors, diuretic and spironolactone). He was asked to return to the cardiology outpatient clinic and a new echocardiogram was performed after 30 days with improved ventricular function (LVEF: 64%).

V. DISCUSSION

COVID-19: General Aspects and Cytokine Storm

The emergence of the disease by the new coronavirus and its rapid distribution around the globe, causing hundreds of thousands of fatal victims, points to the need for understanding the pathophysiological mechanisms and complications that this disease causes. SARS-CoV-2 is a single-stranded RNA virus of the coronavirus family and has an envelope and four structural proteins: spike, membrane, envelope and nucleocapsid. Glycoprotein that makes up the spikes has an affinity for receptors for the angiotensin-converting enzyme 2 (ACE-2), where the virus adheres and invades cells. This receptor is expressed in several cells, and has been widely identified in epithelial cells of upper respiratory tract, pneumocytes I and II, myocardial cells and the renal epithelium [11,12,13].

The new coronavirus is transmitted from person to person through aerosols dispersed in the air and through fomites. Once in contact with the respiratory epithelium, the virus invades the cell and begins its viral replication

process. The degree of clinical repercussions varies not only by the direct cytopathic lesion caused by the virus, but also by the systemic inflammatory reaction triggered by the host's immune system [14,15,16].

Apoptosis of infected cells generates an inflammatory reaction with a storm of cytokines and chemokines produced by immune cells. IFN-γ production triggered by intracellular infection by means of auxiliary standard CD4+ T cells (Th1) causes cytotoxic cell lysis. Auxiliary lymphocytes Th17 recruit neutrophils and macrophages through the production of IL-17, IL-21 and IL-22. The production of these cytokines and activation of the Th1 and Th17 patterns lead to the extensive production of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α. These cytokines alter the function of the vascular endothelium and interact with these cells, activating the coagulation system and causing an increase in the activity of the coagulation system, provoking arterial and venous thromboembolisms [17,18,19,20].

In addition, once in the bloodstream, virus can reach other systems and invade cells that have the ECA-2 receptor. Considering that cardiomyocyte has this receptor, it is evident the relationship that the virus has with these cells, and it is imperative to understand the mechanisms permeating this relationship, in order to avoid important cardiovascular complications and decrease morbidity and mortality rates [21,22,23].

Myocarditis and SARS-CoV-2: Presentation and Mechanisms Involved

Myocarditis consists of an inflammatory-based disorder of the myocardial tissue, characterized by inflammatory infiltrates and cardiac damage without association with ischemic causes, which mostly affects males. It is commonly correlated with viral etiologies, and its pathophysiology is related to the combination of direct cell damage and cytotoxicity mediated by lymphocyte activity. In this light, the participation of cytokines such as interleukin 6 (IL-6) seems to be a central trigger in the cytokine storm cascade, orchestrating the activation of lymphocytes with the consequent production of more cytokines, in a hyperbolic manner, leading to a pro-inflammatory loop and consequent tissue damage, including myocardial. Moreover, a possible T cell cardiotropism is postulated, mediated by molecular interactions [8,24].

Myocarditis can present clinically in several forms, and it is possible to mention symptoms such as thoracalgia, fatigue, palpitations and even under presentations with high morbidity and mortality, such as cardiogenic shock and sudden cardiac death associated with ventricular arrhythmias. It is common for the myocardial condition to be preceded by a viral prodrome, manifesting through fever, respiratory distress, myalgia and gastrointestinal complaints [9,24].

Myocarditis has been reported as a complication in patients with COVID-19 of different age groups. Indeed, viral RNAs from the Middle East Respiratory Syndrome (MERS-CoV) and SARSCoV coronaviruses, agents extremely similar to the new coronavirus, were found in cardiac tissue of infected animals, evidencing a probable cardiotropism inherent to coronaviruses [8,9].

Furthermore, as already mentioned, the entry of SARS-CoV-2 into cells is known to be mediated by the connection between viral protein spikes and the ECA2 membrane protein. This enzyme was not only found in the respiratory epithelium and type II pneumocytes, but also expressed in cardiomyocytes, making them possible targets for the virus. Thus, a cardiac involvement related to a positive regulation of these receptors is postulated [8,25,26].

Myocarditis Associated with COVID-19: Investigation, Associated Complications and Management

Echocardiography is an important tool to aid in the diagnosis of myocarditis, allowing, through a non-invasive procedure, to make differential diagnoses and rule out other cardiac conditions of similar clinical presentation, such as valve diseases, ischemic events, septic and stress-induced cardiomyopathy (Takotsubo Syndrome). Possible suggestive findings visible on transthoracic echocardiography include: global left ventricular hypokinesia, ventricular dilation and/or hypertrophy, regional abnormalities in wall movement and reduced left ventricular ejection fraction, which is the most commonly reported finding in cases of myocarditis associated with COVID-19 [8,27].

The investigation may still use other alternatives that support the determination of the diagnosis. In fact, electrocardiogram is an accessible and non-invasive alternative, which may show conduction abnormalities. In addition, cardiac enzymes such as troponins and brain natriuretic peptide may have elevated serum levels. Inflammatory markers such as C-reactive protein, even though nonspecific, may be increased, contributing to diagnostic direction. Imaging tests such as magnetic resonance and computed tomography can also be used in more detailed investigations. In the event of an unviable or doubtful diagnosis, myocardial biopsy can be suggested, which may demonstrate inflammatory infiltrate, edema, necrotic areas and detection of viral particles [28,29,30].

Nevertheless, a possible complication strongly related to myocarditis is arrhythmia. Arrhythmogenesis in myocarditis related to SARS-CoV-2 infection has acute and chronic pathophysiological mechanisms. Among the

acute mechanisms liable to precipitate arrhythmias are direct viral effects on cardiac cells, pericardial edema and effusion, and microvascular ischemia. While the chronic processes include dysfunction of intercellular junctions secondary to the action of cytokines, such as IL-6, especially in predisposed patients, as well as the formation of scar and fibrotic tissue. Among the possible arrhythmias, it is possible to mention bradyarrhythmias and supraventricular and ventricular tachyarrhythmias. Early recognition and intervention of this complication are essential to avoid fulminating outcomes [22,31,32].

Therapeutic management presents variability, according to the clinical presentation and consequences of myocarditis in each patient. In general, potentially fulminant cases include the adoption of a cardiogenic shock protocol, with administration of inotropic agents and vasoactive drugs, as well as mechanical ventilation. In some cases, the use of ECMO (Extracorporeal Membrane Oxygenation) is a rescue alternative and bridge for effective and beneficial lung transplantation, as well as the use of External Ventricular Assist Devices. In cases of greater hemodynamic stability, pharmacological therapy with inotropes and vasopressors is sufficient to promote improvement in cardiac function. In general, habitual therapy for acute ventricular dysfunction is established, obtaining resolution of the condition and prognosis correlated with the patient's severity through prognostic scores. The use of immunosuppressants as corticosteroids and the use of immunoglobulins remains controversial, given the results of studies that do not demonstrate the benefit of this therapy. The use of Tocilizumab, anti-IL-6, may be beneficial in reducing the cytokine storm, however, further studies that support its clinical use should be encouraged [8,9,33].

Correlating Reported Cases

The case described here demonstrates in a patient without cardiovascular risk factors, who, during a confirmed diagnosis of COVID-19, developed a cardiac complication, acute myocarditis. Initially, heart function was shown to be preserved on echocardiogram, however, after 72 hours of admission to the ICU, he presented severe hypoxemia, so that the new echocardiographic examination already showed a reduction in cardiac function, with LVEF of 44%. Supportive therapeutic measures and classic heart failure therapy were adopted, with improvement in 48 hours. The patient in question evolved well, with a good prognosis and discharge with preserved cardiac function.

We reported here a patient with a typical presentation of COVID-19, manifested by fever, dyspnea and hypoxemia. However, myocarditis can be a complication even in cases with atypical manifestations of SARS-CoV-2 infection. The case report described by Rehman et al. [34] demonstrates a 39-year-old male patient whose clinical presentation was chest pain, with no fever and respiratory symptoms. The patient evolved with increased levels of troponin and the electrocardiogram was inconclusive, after a thorough investigation, the diagnosis of COVID-19 and associated myocarditis was established.

In addition, we demonstrate here a patient with a good evolution and prognosis, however, the scenario is not always this. In the case reported by Khatri, Wallach [35], the patient developed acute hemodynamic dysfunction, myocardial injury and reduced ventricular function, refractory to supportive therapy and management of SARS-CoV-2 infection and myocarditis, presenting an outcome of fulminant myocarditis. The heterogeneity of myocarditis as a serious complication of COVID-19, with potential mortality, points to the need to consider this association in the current scenario, in order to identify and intervene early.

VI. FINAL CONSIDERATIONS

Myocarditis as a complication of COVID-19 is heterogeneous, so the prognosis depends on the severity of the patient's condition and associated organ dysfunctions. It is known that myocardial involvement associated with SARS-CoV-2 can manifest itself through unspecific cardiac complaints and present from resolution and improvement of cardiac function with appropriate drug therapy, to potentially lethal conditions. Also noteworthy is the prevalent association with arrhythmia, a contributing factor to the aggravation of cardiac morbidity and mortality in COVID-19. Therefore, the report shows the need for an early diagnosis of myocarditis as a serious complication of COVID 19, as well as rapid and effective management. The early diagnosis of myocarditis in an intensive care unit in the face of the current scenario of COVID-19 is necessary to implement intervention measures at an early stage, aiming to minimize negative outcomes. The construction and publication of reported cases can help guide health professionals to consider myocarditis as a possible complication in the presence of patients with COVID-19, in order to further encourage the establishment of early diagnosis and interventions.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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