Viral Cardiomyopathies Associated With SARS-CoV-2 Infection

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ABSTRACT

CONTEXT: Since the end of 2019 with the identification of the new coronavirus SARS-CoV-2 and the disease it produces, named COVID-19, various manifestations have been described, initially pulmonary due to acute and severe respiratory syndromes, now systemic manifestations have been described.

CASE REPORT: We report 3 cases of patients with cardiovascular manifestations associated with SARS-CoV-2 infection, highlighting the diagnostic approach and variety of presentation, from acute myocardial infarction, myocarditis, heart failure, shock, arrhythmias to sudden death.

CONCLUSIONS: Every day is more frequent to find reports of patients with cardiovascular compromise during COVID-19 affecting the development and prognosis of this disease.

KEYWORDS: Myocarditis, pericarditis, SARS-CoV-2, endomyocardial biopsy, Arrhythmias, COVID-19

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Introduction

Inflammatory myocarditis or cardiomyopathy is defined as inflammation of the heart muscle associated with degeneration and necrosis of myocytes of non-ischemic origin[1]; It is diagnosed by invasive techniques via Endomyocardial Biopsy (EMB) through histological, immunological and immunohistochemical parameters established in the Dallas criteria.[1] Noninvasive techniques such as electrocardiogram, biomarkers, and imaging are used to help rule out other diagnoses and identify indirect signs of cardiomyopathy. Within the imaging tests, the echocardiogram allows the evaluation of contractility, wall thickness and other non-inflammatory heart diseases, valvular heart disease. Cardiac Magnetic Resonance Imaging (CMR) can be useful after the use of 3 combined techniques and if they meet the Lake Louise criteria.[2]

The clinical presentation is nonspecific, ranging from chest pain with ischemic characteristics, syncope, acute heart failure, arrhythmias, pulmonary embolisms, to cardiogenic shock with impaired ventricular function and sudden death,[2] sometimes associated with electrocardiographic changes and positive biomarkers. The etiology of myocarditis is heterogeneous, including systemic diseases mediated by immune systems, drugs, and toxic substances, and infectious agents.[1]

Viral infections are the most common cause of myocarditis, with cardiotropic viruses being the main cause in developing countries.[2] SARS-CoV-2 is a single-stranded RNA virus, causing the COVID-19 pandemic, whose pathophysiology remains unknown; however, an increase has been seen in the mortality of these patients due to cardiovascular causes than due to other viruses.[1] Possible mechanisms include cytokine storm myocardial damage following T-cell dysregulation; hypoxia-induced; due to the decrease in activity of the ACE2-angiotensin axis that affects the expression of ACE2, the entry receptor for SARS-CoV-2, influencing cardiomyocytes causing direct cardiotoxicity.[1,3]

Herein, we present 3 cases of patients with COVID-19 who developed cardiomyopathies with diverse clinical manifestations in different scenarios, highlighting the importance of cardiovascular expressions associated with SARS-CoV-2.

Case 1

An unvaccinated 54-year-old hypertensive female patient, consulted for oppressive retrosternal chest pain that began at rest and was not associated with other symptoms, vital signs, and physical examination were unremarkable. Blood tests showed positive ultrasensitive troponin T (238 ng/ml) and CK-MB (52U/L), normal chest X-ray, electrocardiogram with sinus tachycardia (HR133bpm) and diffuse ST-segment elevation (Figure 1A). A transthoracic echocardiogram was performed with evidence of ischemic heart disease, conserved biventricular function (LVEF 64%). She was transferred to the intensive care unit (ICU) due to acute coronary syndrome for coronary

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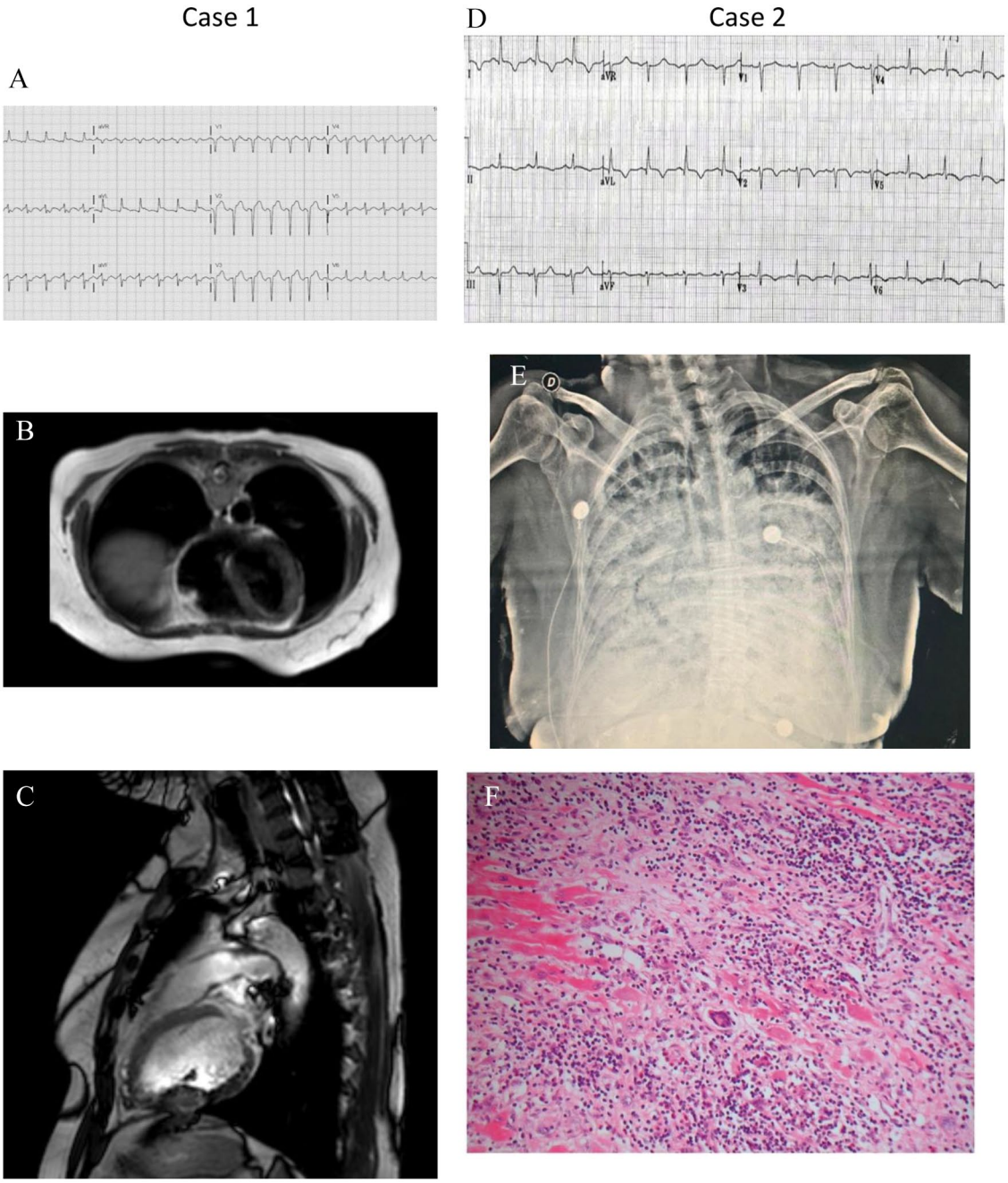

Figure 1. (A) 54-year-old female electrocardiogram with diffuse ST-segment elevation (B) Cross-sectional CMR of a 54-year-old female showing enhancement suggestive of pericardial edema. (C) CMR sagittal section of a 54-year-old female with ventricular thickening. (D) 75-year-old female electrocardiogram with diffuse t-wave inversion. (E) 75-year-old female chest X-ray with signs of vascular congestion cephalization of flow. (F) Appearance of inflammatory cell infiltration in the myocardium.

angiography. In her ICU stay, patient refers respiratory symptoms 2 weeks ago, RT-PCR COVID-19 test is performed, resulting positive. The angiography showed healthy coronary arteries, compatible with MINOCA (myocardial infarction with nonobstructive coronary arteries), supportive management continued with a decrease in biomarkers, favorable clinical evolution, and discharge. Considering a possible viral myocarditis, an outpatient CMR was performed at 5 days, confirming a non-ischemic late enhancement pattern, sequelae of myocarditis (Figure 1B and 1C). EMB was not performed. Currently in the follow-up patient remain asymptomatic.

Case 2

An unvaccinated 75-year-old female with a history of COPD consulted for 3 days of ill-defined chest and epigastric pain with oppressive characteristics in the absence of respiratory symptoms. On admission saturation was 89% with nasal cannula at 2 l/min, blood pressure 96/54 mmHg, respiratory rate 28 rpm, temperature 38.5°C physical examination with signs of tissue hypoperfusion, tachypnea, and work of breathing: subcostal and intercostal retractions, cardiopulmonary auscultation tachycardia and scattered crepitus. Support with crystalloids fluids and norepinephrine was started, with no

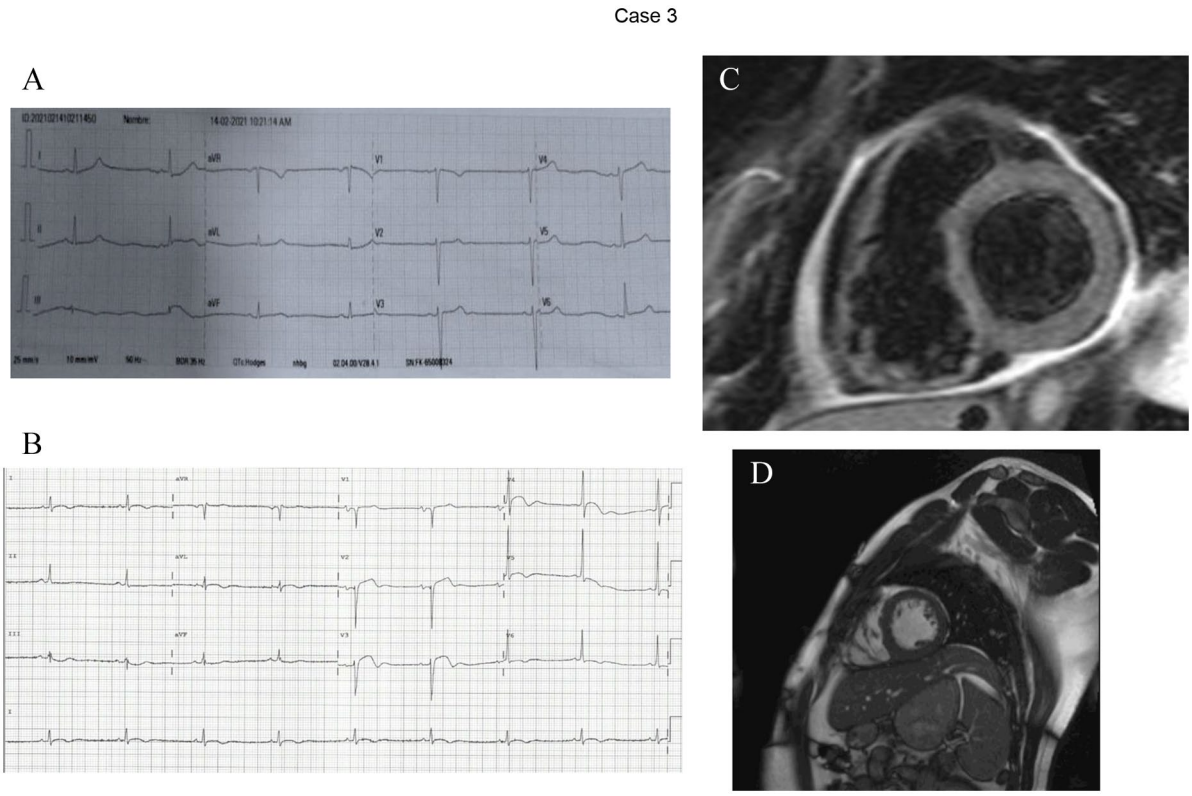

Figure 2. (A) 32-year-old female electrocardiogram with sinus bradycardia. (B) electrocardiogram during an episode of pain showing concave elevation of the ST segment. (C) CMR in sagittal section with enhancement. (D) CMR sagittal section with ventricular thickening and pericardial effusion.

improvement. Blood tests revealed respiratory acidosis and moderate hypoxemia and hyperlactacidemia (PaO2/FiO2 ratio 169, lactate 3 mmol/l), leukocytosis (leukocytes 22.800/mm^3, neutrophils 90%), BNP negative (59 pg/mL reference value: normal less than 100 pg/mL), positive C-reactive protein (12.5 mg/l), LDH (1870 IU/L), D-dimer (25.937 ng/ml) and troponin (1.874 ng/ml). Electrocardiogram with diffuse T-wave inversion (Figure 1D), Chest X-ray with signs of vascular redistribution-congestion and flow cephalization (Figure 1E). Patient with progressive respiratory deterioration who required orotracheal intubation, due continuos hemodynamic instability, dobutamine and supportive treatment were started, including tocilizumab and antibiotic therapy. A bedside echocardiogram showed a dilated ventricle with moderate dysfunction (LVEF 27%), pericardial effusion (110 mL), and diffuse myocardial edema. No valvular disease. Normal right cavities. There were no signs of constriction of compression.

Patient continues with torpid evolution, hemodynamic instability, and 2-days later develops signs of cardiac tamponade. Repeat echocardiogram showed an increase in effusion with right heart compression. An ultrasound guided pigtail catheter was inserted. Over the next hours straw-colored fluid was drained. The characteristic findings of fluid were exudative. Nevertheless, she died the next day due to multi-organ failure. The nasopharyngeal swab and RT-PCR of pericardial fluid were positive for SARS-CoV-2. Autopsy revealed commitment by mononuclear inflammatory cells at the level of the myocardium (Figure 1F).

Case 3

A 32-year-old female diagnosed with COVID-19 pneumonia was admitted due to pleuritic chest pain, asthenia, adynamia, and a sensation of dyspnea of 24 hours of evolution. Refers outpatient management with beta-lactam and macrolide. She received the Janssen COVID-19 vaccine 6-month-ago. Upon evaluation, heart rate 48 bpm, saturation at room air was 94%, the rest of the physical examination normal. Blood tests were unremarkable with negative cardiac biomarkers. Chest CT showed ground glass consolidation with 15% lung involvement. Electrocardiogram with sinus bradycardia (Figure 2A). An echocardiogram revealed a normal-sized left ventricle, preserved global and segmental systolic function (LVEF 68%), altered myocardial strain –17%, moderate right retroatrial pericardial effusion. Cardiac Holter was taken showing predominantly sinus rhythm, average heart rate 65 bpm, adequate chronotropic competence, maximum heart rate 133 bpm and minimum 36 bpm, without significant pauses. During her stay, she presented an episode of chest pain in 8/10, an electrocardiogram (Figure 2B) was performed and indicated oral analgesics. Given symptoms of viral myopericarditis, management was initiated with colchicine and NSAIDs. CMR with late

gadolinium enhancement was performed as a non-invasive evaluation strategy of the disease, showing a subepicardial late enhancement pattern that corresponded to 23.9% of the total ventricular mass, pericardial effusion, preserved biventricular function, absence of alterations in regional myocardial contractility (Figure 2C and 2D). After 10 days of hospitalization, satisfactory evolution improvement of pain, discharge. EMB was not performed.

Discussion

In December 2019, the first report of 2019 coronavirus disease (COVID-19) was made, in the city of Wuhan, China, with respiratory symptoms predominating. Today systemic manifestations and extrapulmonary complications are known, which have become clinically relevant, for this reason it is important to highlight their forms of presentation, clinical course, and diagnostic approach. The identification of cardiac involvement in patients with SARS-CoV-2 infection has been associated with an increased risk of in-hospital mortality (51% vs 4%) and long-term adverse outcomes.[4] One of the cases described presented an accelerated clinical deterioration with rapid progression to cardiogenic shock and death. Epidemiological data on myocarditis or pericarditis associated with COVID-19 are limited to case reports.[5,6]

The clinical presentation of this entity is varied, including dyspnea, acute myocardial infarction, acute heart failure, cardiogenic shock, myocarditis, and malignant arrhythmias.[1,5] It is unclear what the severity of cardiovascular disease depends on or if there is a relationship with viral load, sex, age, or comorbidities.[6] In this series, 3 different forms of manifestation of the disease are exposed, all female, 2 of them with comorbidities of cardiovascular risk such as COPD and hypertension. No guidelines have been established for the diagnosis of myocarditis associated with COVID-19, an approximation is made based on the information available to date and knowledge of other viral cardiomyopathies.[5]

The diagnosis of myocarditis is not based solely on the elevation of biomarkers of myocardial damage, such as troponin.[1,6] A recent study found a prevalence of 36% in troponin elevation in patients hospitalized for COVID-19, in addition for individuals with troponin $\geqslant$0.09 ng/ml, the Hazard ratio (HR) for mortality was 3.03 (95% CI 2.42-3.80).[6] These findings suggest a high prevalence of myocardial injury in patients with COVID-19, which could be associated with worse outcomes.[5,6] Patients with underlying cardiovascular disease have a higher risk of developing a serious heart injury,[6] consistent with what happened in case 2. The electrocardiogram is an easily accessible screening tool, it reveals nonspecific and multiple abnormalities such as atrioventricular blocks, atrial fibrillation, sinus dysfunction, premature ventricular contractions, ST segment and T wave abnormalities. It is noteworthy that QRS widening is considered an important predictor of poor prognosis in these patients.[1,6] Being the study of initial approach to a patient with cardiovascular manifestations. In this series, 2 cases presented diffuse alterations of the ST segment and elevation of biomarkers.

Although an EMB must be performed to establish the diagnosis to evaluate histological, immunological and immunohistochemical parameters, the ideal time for performing it is not clear, and its routine use is not standardized.[6] Sometimes hemodynamic instability, multi-organ compromise and coagulopathy inhibit its performance. Likewise, complications related to this procedure such as cardiac perforation, tamponade and bleeding have been described. Therefore, the diagnosis of myocarditis associated with COVID-19 could be based on abnormal findings on echocardiography or CMR[7]; as indeed occurred in 2 of the cases described.

The echocardiographic findings are not specific, but allow an evaluation of cardiac structure and function, ruling out additional secondary etiologies: ventricular dysfunction, intracavitary thrombi, or pericardial effusion.[6] CMR continues to be the non-invasive gold standard for diagnosing myocarditis, based on the Lake Louise criteria[1,5]; being performed in 2 of the cases presented.

Regarding the therapeutic field, there is no staggered proposal for the management of myocarditis due to COVID-19.[8] Different drugs have been used in other infectious scenarios, based on the inflammatory mechanisms of myocardial injury, such as glucocorticoids, colchicine or inhibitors IL-6, without studies supporting these interventions at the moment.[6,7] The cases described were managed with ventilatory and hemodynamic support measures; in those requiring supplemental oxygen or critically ill, management with steroids was indicated based on the results of the Recovery study and antibiotic therapy for bacterial superinfection.

Myocardial involvement by SARS-CoV-2 and its complications have been described more frequently in the literature, recent results support its negative impact on the prognosis of these patients, given its high morbidity and mortality. The need to develop new studies aimed at defining non-invasive diagnostic criteria and therapeutic proposals is created.

Author Contributions

The authors confirm contribution to the paper as follows: Study conception and design: Juan Camilo Gutierrez, María Carolina Paternina, María Cristina Martínez. Data collection: María Cristina Martínez, Juan Camilo Gutierrez, María Carolina Paternina. Analysis and interpretation of results: Tomás Rodriguez, Amilkar Almanza. Draft manuscript preparation: Gino Gomez, María Cristina Martínez. All authors discussed the results and contributed to the final manuscript.

Consent for Publication

No written consent has been obtained from the patients as there is no patient identifiable data included in this case report

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