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Case Report

Pathophysiology and Cardiac Autopsy in COVID-19 related Myocarditis

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Abstract

On the 11th of March 2020, the coronavirus disease-2019 (COVID-19) was declared a global Pandemic by the World Health Organization. This infectious disease is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which emerged in Wuhan, China, in December 2019, and rapidly spread across the world. Respiratory involvement ranging from a mild flu-like illness to potentially lethal acute respiratory distress syndrome is the predominant clinical manifestation. However, major cardiovascular complications have also been reported, with myocarditis contributing to mortality in up to a third of cases with severe COVID-19. In the presence of normal coronary arteries, acute myocarditis in SARS-CoV-2 cases may present with varying clinical severity, including myopericarditis, fulminant myocarditis, and cardiogenic shock. The pathophysiology of myocardial injury caused by SARS-CoV2 is not fully understood. The extent to which direct viral cytopathic effects contribute to the pathophysiology, compared with indirect systemic toxicity, remains unclear. The autopsy-proven myocardial localisation of the virus has rarely been reported.

Keywords: Myocarditis; Acute myocardial injury; COVID-19; SARS-CoV-2

On the 11th of March 2020, the coronavirus disease-2019 (COVID-19) was declared a global Pandemic by the World Health Organization. This infectious disease is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which emerged in Wuhan, China, in December 2019, and rapidly spread across the world. As of June 2020, the World Health Organization reports 7 553 182 cases, with 423 349 deaths worldwide.

Respiratory involvement ranging from a mild flu-like illness to potentially lethal acute respiratory distress syndrome is the predominant clinical manifestation of SARS-CoV-2 [1]. However, major cardiovascular complications have been reported [2] [3]. Analysis of current literature revealed that 5-25% of COVID-19 related hospital admissions was a result of acute myocardial injury of multifactorial pathophysiology [4] [5]. Myocardial injury significantly contributed to patient morbidity and mortality. In particular, myocarditis was a contributing factor to mortality in up to one third of cases with severe COVID- 19 [6]. In the presence of normal coronary arteries, acute myocarditis in SARS-CoV-2 can present with varying clinical severity, including myopericarditis, fulminant myocarditis, and cardiogenic shock. The pathophysiology of myocardial injury caused by SARS-CoV2 is not yet fully understood and the extent to which direct viral cytopathic effects contribute to this, compared with indirect systemic toxicity, remains unclear [7].

Methods

The authors conducted a comprehensive literature review and searched for papers using the following key words: “myocarditis”, “acute myocardial injury”, “COVID-19”, and “SARS-CoV-2”. A total of 44 articles were selected. Retrospective studies, prospective studies, systematic reviews and meta-analyses, narrative reviews, clinical guidelines and case reports was included in this analysis. Pre-printed articles were also included. No language restrictions were applied.

Discussion

Epidemiology and Clinical Manifestations

Acute myocardial injury, defined by high sensitivity-cardiac Troponin (hs-cTn) above the 99th percentile of upper reference limit, was found in 5-25% of COVID-19 cases admitted to hospital [4] [5].

Shi and colleagues analysed a single-centre cohort of 416 patients hospitalized due to COVID-19, and 19.7% of the sample size reported acute myocardial injury. Patients with cardiac injury reported a greater rate of mechanical ventilation (22.0% vs 4.2%; $p<0.001$), and mortality (51.2% vs 4.5%; $p<0.001$) [3].

A correlation between cardiac biomarkers and intensive care unit (ICU) admissions was published by Wang in a clinical cohort of 138 patients (hs-cTn level 11.0pg/mL vs 5.1pg/mL; $p=0.004$) [5].

Guo has classified 187 patients presenting with SARS-CoV-2 according to their levels of cTn (reported to be high in 27.8% of these cases) and demonstrated that higher levels of cTn were correlated with greater complications and higher mortality (59.6% vs 8.9%) [8].

In Ruan’s analysis of 68 deaths in a cohort of 150 patients positive for SARS-CoV-2, 7% were attributed to myocarditis with hemodynamic collapse, whilst in

33% of cases, myocarditis could have been a significant contributing factor to mortality [6].

The true incidence of myocarditis in COVID-19 cases remains unknown. Case reports worldwide have provided evidence of SARS-CoV-2 related myocarditis. Despite this, the pathophysiology of how SARS-CoV-2 causes myocardial damage still remains unclear.

Myocarditis is inflammation of the myocardium which can affect the contractility and the electrical signalling of the heart. This can lead to impaired systolic function and arrhythmias.

The diagnosis of myocarditis is often challenging. The cardinal diagnostic tools include clinical examination, electrocardiogram (ECG), echocardiography, cardiac magnetic resonance imaging (MRI) and endomyocardial biopsy. Clinical diagnosis can be obtained via the 2013 European Society of Cardiology's position statement that includes a clinical symptom such as chest pain, as well as a diagnostic criterion, for example high levels TnT or TnI [9]. The classical echocardiographic signs of myocarditis include increased wall thickness, chamber dilatation, pericardial effusion and, of course, ventricular systolic dysfunction [10]. The revised Lake Louise consensus criteria for the diagnosis of myocarditis with the cardiac MRI include (A) oedema, (B) irreversible cell injury, and (C) hyperaemia or capillary leak [11]. Endomyocardial biopsy is recommended by both the American Heart Association (AHA) and the European Society of Cardiology (ESC), and typical histological findings are inflammatory infiltrates and viral RNA/DNA [9,12]. Nevertheless, early diagnosis of cardiac involvement in COVID-19 can be misguided in patients with chronic cardiac conditions by symptoms like fatigue (51%, 95% CI: 34-68%), dyspnoea (30%, 95% CI: 21-40%), and cough (67%, 95% CI: 59-76%), as these can also be manifestations of decompensated heart failure [13].

Patients with acute myocarditis related to SARS-CoV-2 can present with varying clinical severity (Table 1 [14-27]) including myopericarditis, fulminant myocarditis, and cardiogenic shock, in the presence of normal coronary arteries. Clinical symptoms vary from nonspecific flu-like symptoms to anginal chest pain. Similarly, a variety of ECG changes have been reported; bradyarrhythmias with high degree atrio-ventricular block and tachyarrhythmias (such as ventricular tachycardia), including ST elevation and T wave inversion. Conversely, almost all case reports document raised inflammatory markers, cTn and NT pro-BNP. Furthermore, left ventricle ejection fraction (LVEF) appears to be reduced, up to a severe degree, in the majority of patients. Cardiac MRI, when performed, shows a varying degree of myocardial oedema and ventricular hypokinesis. Finally, prior to discharge, echocardiography and/or cardiac MRI can demonstrate a full recovery of the LVEF.

Cases of pericardial effusion requiring emergency pericardiocentesis have also been reported [23,24].

Rapid deterioration into cardiogenic shock or acute respiratory distress syndrome (ARDS) makes the use of intra-aortic balloon pump (IABP) and veno-arterial extracorporeal membrane oxigenation (VA-ECMO) common among COVID-19 patients with a suspicion of myocarditis [15,23,24,26].

Beri's article focused on the sudden cardiac death of a COVID-19 patient. The history of chest pain, dyspnoea and ventricular tachycardia (VT) on ECG pointed towards myocarditis [28].

Analysis of the paediatric population is beyond the aim of this review, however cases of suspected myocarditis in COVID-19 paediatric patients have been reported worldwide. A multicentre study analysed a case series of febrile paediatric patients admitted to ICU for cardiogenic shock, left ventricular dysfunction and severe inflammatory state, potentially associated with SARS-CoV-2. LVEF <30% was reported in one third and 28% required ECMO. The high levels of inflammation markers were suggestive of cytokine storm and macrophage activation, indicating indirect myocardial damage [29]. A further multicentre analysis described a case series of acute myocarditis and major systemic inflammation following SARS-CoV-2 infection in 20 critically ill children. LVEF was 35% (25–55) and cTn 269 ng/mL (31–4607) [30].

Authors	**Age**	**Clinical Presentation**	**cTn and NT pro-BNP**	**ECG**	**Echocardiography**	**cMRI**
Asif et al	64	Dyspnoea	0.17 ng/ml	Diffuse ST elevation	LVEF 70-75%	-
	71	Fever, cough, dyspnea	1.6 ng/ml	ST elevation in (V2–V6); Q waves (V4–V6)	LVEF 65-70%	-
Zeng et al	63	Fever, dyspnoea, exertional chest tightness	11.37 g/L and 22,600 pg/mL	Sinus tachycardia	LVEF 32%	-
Cizgici et al	78	Chest pain, dyspnea	998.1 ng/ml	AF and diffuse ST elevation	-	-
Kir et al	49	Fever, cough, dyspnea	<0.012 ng/mL and 38.3 pg/mL	high-degree AV block (VR<20 bpm)	Preserved LVEF	-
Coyle et al	57	Fever, dyspnoea,cough, myalgia, diarrhea	Raised	Sinus rhythm	LVEF 35-40%	Diffuse oedema
Doyen et al	69	Dyspnoea, cough, diarrhoea, fever	9002 ng/L	Diffuse T wave inversion	Preserved LVEF	subepicardial enhancement of the apex and inferolateral wall
Paul et al	35	Chest pain, fatigue	2885 ng/L	repolarization changes in the precordial leads	Preserved LVEF	subepicardial enhancement in the inferior and lateral walls
Hu et al	37	Chest pain, dyspnoea, diarrhea	10 000ng/L and 21 025ng/L	ST elevation (III, aVF)	LVEF 27%	-
Inciardi	53	Cough, fever and	0.24 ng/mL	Diffuse ST elevation,	Increased wall	increased wall thickness,

et al		fatigue	and 5647pg/mL	T wave inversion (V1, aVR)	thickness, LVEF 40%	diffuse biventricular hypokinesis, marked biventricular myocardial interstitial oedema
Irabien-Ortiz et al	59	Fever, chest pain	220-1100 ng/dL and 4421 ng/L	ST elevation and PR depression	severe biventricular failure and diffuse myocardial oedema	-
Khalid et al	34	Chest heaviness, fever, generalised weakness	0.55 ng/ml	sinus tachycardia, poor R wave progression (anterior leads)	LVEF 25%, large pericardial effusion	-
Kim et al	21	Dyspnoea, cough, fever and diarrhea	1.26 ng/mL and 1929 pg/mL	Nonspecific intraventricular conduction delay, premature ventricular complexes	Severely reduced LVEF	diffuse high signal intensity in the myocardium, myocardial wall oedema
Tavazzi et al	69	Dyspnoea, cough, weakness	4332 ng/L	-	dilated LV, LVEF 34%	-
Warchoł et al	74	-	72 ng/l to 102 ng/l and 2451 ng/l	Ventricular tachycardia	-	LVEF 20%, no myocardial oedema, inferior and inferolateral wall fibrosis subepicardially and intramurally

Table 1: Case reports on COVID-19 related myocarditis

cTn: cardiac Troponin. NT pro-BNP: N-terminal pro B-type natriuretic peptide. LVEF: left ventricle ejection fraction. AV: atrio-ventricular. cMRI: cardiac magnetic resonance imaging. AF: atrial fibrillation. VR: ventricular rate. LV: left ventricle

Pathophysiology

The acute myocardial injury caused by SARAS-CoV-2 appears to have a multifactorial pathophysiology which is not yet fully characterized. Several explanatory theories have been postulated. Case reports of myocarditis in COVID19 provide evidence for cardiac inflammation but do not reveal the mechanism, thus it remains unclear how much of the cardiac injury is attributable to direct viral infection (cytopathic damage) versus indirect systemic toxicity [7,31].

Prior acute myocarditis experience with alternative viruses suggests that direct cellular injury is related to a combination of cardiotropic viral entry into myocytes and the subsequent innate immune response that can lead to focal or diffuse myocardial necrosis

[32,33]. Within a few days of this direct cellular injury, oedema and necrosis can lead to contractile dysfunction and clinical symptoms [32,33].

Chronic cardiovascular diseases may become unstable in the setting of a viral infection as a consequence of the imbalance between the infection-induced increase in metabolic demand and reduced cardiac reserve [5,34].

A key role in the pathophysiology of myocarditis is played by the prompt and severe downregulation of myocardial ACE-2 (angiotensin-converting enzyme 2) pathways. Beyond its function in cardiovascular homeostasis, ACE-2 is also a functional receptor widely expressed in the lungs, as well as other organs, including the heart, and constitutes a portal of entry for SARS-CoV-2 [7]. The binding of SARS-CoV-2 to ACE-2, particularly in the epicardial adipose tissue [35], results in alteration of the neurohumoral signalling pathways, thereby resulting in direct myocardial injury [36]. Importantly, brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) transcripts are co-upregulated in ACE2-postive cardiomyocytes (CMs). BNP, ANP, and ACE2 may form a feedback loop associated with the RAAS (renin-angiotensin-aldosterone-system)/Ang II signalling pathway. One of the most interesting findings is that ACE-2 appears not to be equally expressed in all of the ventricular and atrial CMs, but only expressed in approximately 5% normal ventricular or atrial CMs. Conversely, ACE-2 expression is increased to 30% in the ventricular CMs of failing hearts, indicating that heart failure patients are more prone to develop myocardial injury if SARS-CoV-2 positive [37].

Other proposed mechanisms of myocardial injury include a cytokine storm triggered by an imbalanced response by type 1 and 2 T-helper cells [4,38], and strong interferon-mediated immunopathological events [39], resulting in indirect injury. IL(interleukin)-6, IL-2, IL-7, TNF (tumor necrosis factor)-α, IFN (interferon)-γ IP (inducible protein)-10, MCP (monocyte chemoattractant protein)-1, MIP (macrophage inflammatory protein)-1α, G-CSF (granulocyte-colony stimulating factor), CRP (C-reactive protein), procalcitonin, and ferritin activate immune cell differentiation and the trafficking of leukocytes to sites of infection [7,40].

Finally, respiratory dysfunction and hypoxemia caused by COVID-19 can lead to myocardial cell damage [34].

Autopsy Results

Thus far, the data demonstrating the presence of SARS-CoV-2 within myocardial tissue is inconsistent [7].

For the first time, Tavazzi and colleagues were able to demonstrate the presence of viral particles in the heart of a COVID-19 patient in cardiogenic shock. The pathologic study showed low-grade interstitial and endocardial inflammation, as well as large (>20μm), vacuolated, CD68-positive macrophages. The ultrastructural study demonstrated single or small groups of viral particles with the morphology (dense round viral envelope and electron-dense spike-like structures on their surface) and size (variable between 70 and 120 nm) of coronaviruses, in cytopathic, structurally damaged interstitial cells with loss of the cytoplasmic membrane integrity. Cardiac myocytes

showed non-specific features consisting of focal myofibrillar lysis, and lipid droplets [26].

In New Orleans, examination of the heart in 9 deceased COVID-19 cases was carried out. Cardiomegaly and right ventricular dilatation were the main gross abnormalities. Histologically, there was scattered individual cell myocyte necrosis, and rare small interstitial collections of lymphocytes were noted. There was no obvious viral cytopathic effect by light microscopy. These findings might represent an early stage of viral myocarditis [41].

Similarly, the autopsy performed in a SARS-CoV-2 positive patient in Houston showed multifocal lymphocytic infiltrates in the epicardium with enlarged hyperchromatic nuclei, suggestive of an acute injury [42].

Cardiac autopsy from a deceased SARS-CoV-2 patient showed a few interstitial mononuclear inflammatory infiltrates, but no other substantial damage in the heart tissue. However, during hospitalization, the patient did not show any clinical signs of myocardial involvement as their symptoms were mainly respiratory [43].

Interestingly, Craven reported a case of eosinophilic myocarditis in a SARS-CoV-2 positive 17-year-old patient. Microscopically, diffuse inflammatory infiltrates composed of lymphocytes, and macrophages, with prominent eosinophils were detected. This inflammation was primarily in the interstitium, and was associated with multiple foci of myocyte necrosis in both ventricles [44].

Conclusions

Since the outspread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remarkable efforts have been made to increase the understanding of the pathophysiology of myocardial injury in COVID-19 patients. Whether this is a result of a direct cytopathic effect of the virus on the myocardium (SARSCoV-2 viral myocarditis), or an indirect result of the complications of the disease remains unclear.

It would be highly desirable that the future studies on COVID-19 specifically described the incidence, outcomes and cardiac autopsy results of patients with a diagnosis of myocarditis.

Limitations

This review consists of some limitations, which merit consideration. Firstly, the significant heterogeneity in study design, patient selection and outcomes. Secondly, different criteria for the diagnosis of myocarditis may be used, and this may affect incidence between studies. Finally, due to the current pandemic, a consistent amount of literature is published in a preprint form, prior to full peer review.

Disclosure

Authors declare no conflict of interest.

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