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COVID-19

Acute Myocarditis Related to COVID-19: Comparison to SARS and MERS

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Abstract

Myocardial involvement has been described during previous SARS and MERS outbreaks. Infection by SARS-CoV-2 (COVID-19) can range from asymptomatic to life-threatening multi-system disease. Heart involvement most commonly occurs during severe COVID-19 infection. Myocardial injury, based on elevated levels of myocardial enzymes, has been noted in up to 30% of patients with COVID-19 infection and could be a marker for worse prognosis. A few cases of possible myocarditis due to SARS-CoV-2 have been described, providing variable degree of evidence of direct myocardial involvement. We reviewed in detail those cases in comparison to relevant literature on SARS and MERS and attempted to draw initial conclusions in regard to clinical presentation, treatment and prognosis.

Keywords COVID-19 · Myocarditis · Myocardial injury · Troponin · Corticosteroids · Treatment

Introduction

Infection by the new coronavirus SARS-CoV-2 (COVID-19 infection) is a multi-systemic illness [1]. Cardiac injury has been reported in 20% to 30% of hospitalised patients [2]. Reported cardiac involvement includes arrhythmias, acute myocardial infarction, heart failure and cardiogenic shock [2], (https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance).

Acute myocarditis is another condition which has been reported to complicate the COVID-19 infection [3]. Ten cases have been reported so far. Cases of acute myocarditis have been previously attributed to other coronaviruses such as SARS-CoV and MERS-CoV [4, 5]. In fact, postmortem real-time polymerase chain reaction analyses of heart tissue from the SARS epidemic, detected the viral genome in 35% of patients ($n = 7/20$) who died from SARS (https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance). SARS-COV-2 mRNA has also been detected in autopsy specimens as well as endomyocardial biopsies in patients with suspected myocarditis. [6, 7]

Pathogenesis of Myocardial Injury

Increases in troponin I and CK-MB, which are suggestive of myocardial injury, are frequent findings in COVID 19 disease and associated with adverse prognosis. Huang et al. reported that 31% of patients with COVID-19 hospitalised in ICU had an increase in troponin I compared to 4% of non-ICU patients [8]. In a meta-analysis, including 341 patients, levels of troponin I were significantly increased in critically ill patients as opposed to those with milder illness [9]. Suggested mechanisms of myocardial injury during COVID-19 infection are the following:

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1. Direct injury through connection to ACE2 receptors that are expressed in the myocardium.
2. Indirect injury due to the systemic inflammatory response syndrome (SIRS) and the cytokine storm that the infection provokes [10].
3. Infection-induced vasculitis attributed either to contamination of the endothelial cells or to immunological response [3].

Binding to ACE2 receptors is the entrance point of SARS-CoV-2. These receptors are expressed, among others, in the epithelial cells of lungs, heart and enterocytes [10, 11]. These same receptors were also found to be the entrance point of SARS-CoV. Both viruses seem to be able to modulate the ACE2 myocardial and pulmonary pathways, leading to inflammation of the heart, pulmonary oedema and acute respiratory failure [12]. Myocardial inflammation in SARS-CoV infection can also be mediated by macrophages entering the myocardial tissue and producing cytokines [4].

Clinical Presentation—Symptoms and Signs

Acute myocarditis may present with chest pain, fever, dyspnoea, signs of heart failure and ECG abnormalities like ST-interval or T-wave changes. [13]

SARS-CoV-2 We reviewed ten published case reports of infection by SARS-CoV-2, presenting as acute myocarditis [14–23]. The cases included 6 male and 3 female patients, aged between 17 and 69 years. In one case, a 17 year old male, eosinophilic myocarditis was diagnosed postmortem after experiencing out of hospital cardiac arrest. Five of the patients presented with chest pain [14, 15, 19, 21, 23]. Dyspnoea was another main symptom reported in 6 cases [15, 16, 18, 21–23]. More details regarding their clinical presentation are presented in Table 1.

MERS-CoV We found a single case report involving a MERS-CoV infection complicated with acute myocarditis. The case involved a 60-year-old man who presented with pneumonia and congestive heart failure. Main symptoms were fever, dyspnoea, cough with sputum and left-sided chest pain. On clinical examination he had widespread crackles and elevated jugular venous pressure [5].

Laboratory Findings

SARS-CoV-2 All reported cases (except the case which included the 17-year-old patient) presented with increased levels of troponin ranging from 590 to 11.000 ng/L [14–23]. Four of them had elevated NT-pro-BNP levels that ranged between 1300 and 8465 pg/ml [16–19] and two had elevated NT-BNP levels which peak accounted for 22.600 pg/ml [15, 21]. Other markers suggestive of myocardial injury that were found elevated in certain patients were myoglobin and CK-MB [15, 17, 21]. Detailed information on laboratory findings is available in Table 2.

Regarding the full blood count leukocytosis and lymphocytopenia were noticeable in four patients. These findings are common among COVID-19 patients and can predict the severity of the infection [24].

Patients with COVID-19 and acute myocarditis were also found to have increased levels of IL-6, IL-1β and IL-10 [15, 17, 25]. The virus is known to induce production of IL-6 and IL-1, among other cytokines, through at least 2 distinct pathways, as recently described [26].

Electrocardiogram was available in all 9 patients. ST-segment elevation was evident in 3 cases [17, 19, 21] and T-wave inversion in 2 cases [17, 22] while the rest had non-specific findings such as sinus tachycardia, intraventricular conduction delay or non-specific repolarization abnormalities.

Echocardiography revealed a wide range of findings. Seven out of nine patients had moderate to severe left ventricular dysfunction (left ventricular ejection fraction ranging between 25 and 40%) [15, 17, 19, 21, 23]. Other findings included increased wall thickness, hypokinesia and pericardial effusion [15, 17–19, 21, 23].

Definite diagnosis with cardiovascular magnetic resonance was available in six cases. Myocardial oedema and late gadolinium enhancement demonstrated in all cases [14, 16–18, 22, 23]. More information regarding investigations is available in Table 3.

SARS-CoV SARS-CoV infection can also be complicated with acute myocarditis as indicated by SARS-CoV genome detected in the heart tissue [3]. A 30-day follow-up study measured cardiac output in patients infected by SARS-CoV during hospitalisation and at follow-up. Measurements were significantly lower during hospitalisation. Infection-induced myocarditis may lead to myocardial dysfunction [27].

MERS-CoV Acute myocarditis can also be one of the manifestations caused by MERS-CoV. A case presented with increased troponin I and pro-BNP levels. ECG showed diffuse T-wave inversions and echocardiography revealed severe left ventricular systolic dysfunction. MRI findings were in accordance with clinical suspicion revealing myocardial oedema and late gadolinium enhancement (LGE) [5].

Pathologic Findings

The 17-year old patient who had the postmortem diagnosis of COVID-19 had undergone autopsy. The microscopic

Table 1 Demographics of the patients and symptoms

	Case 1 [13]	Case 2 [14]	Case 3 [15]	Case 4 [16]	Case 5 [17]	Case 6 [18]	Case 7 [19]	Case 8 [20]	Case 9 [21]	Case 10 [22]
Age/sex/country	35/M/France	63/M/China	21/F/South Korea	53/F/ Italy	57/M/USA	59/F/Spain	17/M/USA	37/M/China	69/M/Italy	64/M/Switzerland
Fever	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Chest pain	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes
Fatigue	Yes	Yes	No	Yes	No	No	No	No	No	No
Shortness of breath	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
Other respiratory symptoms	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No
Overweight	Yes (BMI 29 kg/m2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 2 Laboratory findings

	Case 1 [13]	Case 2 [14]	Case 3 [15]	Case 4 [16]	Case 5 [17]	Case 6 [18]	Case 7 [19]	Case 8 [20]	Case 9 [21]	Case 10 [22]
Troponin	Peak hs I 2.88 ng/mL	Peak 1.13×10^7 ng/mL	1.26 ng/mL	Peak hs T 0.59 ng/mL	Peak I 7.33 ng/mL	Peak T 11 ng/mL	N/A	*T* > 10 ng/-mL	hs I 9 ng/mL	hs T 0.26 ng/mL
NT-BNP	N/A	22.6 ng/mL	N/A	N/A	N/A	N/A	N/A	21.02 ng/mL	N/A	N/A
NT-pro-BNP	N/A	N/A	1.92 ng/mL	Peak 8.46 ng/mL	Peak 1.30 ng/mL	4.42 ng/mL	N/A	N/A	N/A	N/A
CK-MB	N/A	N/A	N/A	Peak 39.9 ng/mL	N/A	N/A	N/A	0.11 ng/mL	N/A	N/A
Myoglobin	N/A	390.97 ng/mL	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Haemoglobin	N/A	N/A	N/A	Min 11.2 g/dL (on day 7)	N/A	N/A	N/A	N/A	15.4 g/dL	N/A
White blood cell count	N/A	N/A	N/A	Max 13.73×10^9/L	4.7×10^9/L	14.1×10^9/L	N/A	N/A	14.9×10^9/L	18.7×10^9/L
Lymphocyte count	N/A	N/A	N/A	Min 0.9×10^9/L	0.5×10^9/L	2.59×10^9/L	N/A	N/A	1.04×10^9/L	N/A
Cytokine measurements	N/A	Peak IL-6272.40 pg/ml	N/A	N/A	Peak IL-6 18 pg/mL	N/A	N/A	N/A	N/A	N/A

Table 3 Investigations and results

	Case 1 [13]	Case 2 [14]	Case 3 [15]	Case 4 [16]	Case 5 [17]	Case 6 [18]	Case 7 [19]	Case 8 [20]	Case 9 [21]	Case 10 [22]
Electrocardiogram	Repolarisation changes in precordial leads	Sinus tachycardia	Non-specific intraventricular conduction delay	Diffuse ST segment elevation, ST segment depression and T-wave inversion in V1 and aVR	Sinus tachycardia	ST segment elevation, PR-segment depression, low voltages	N/A	ST segment elevation inferior leads	Left ventricular hypertrophy, diffuse T-wave inversions	Unremarkable
Cardiac echo	Normal systolic function, no pericardial effusion	Diffuse myocardial dyskinesia, left ventricular ejection fraction 32%, pulmonary artery hypertension (PAP 44 mmHg)	Severe left ventricular systolic dysfunction	Increased wall thickness, diffuse hypokinesis, LVEF 40%, pericardial effusion max. 11 mm	Moderate diffuse hypokinesis, LVEF 35–40%	Admission: concentric hypertrophy, moderate pericardial effusion, diminished intraventicular volumes with preserved LVEF 2 h after admission: biventricular failure and diffuse myocardial oedema	N/A	Enlarged heart, decreased ventricular systolic function, LVEF 27%, pericardial effusion 2 mm, increased cardiac chamber dimensions	Known left ventricular hypertrophy, normal systolic function	LVEF 47% after extubation
Cardiac CT	N/A	N/A	Myocardial hypertrophy, left ventricular subendocardial perfusion defect	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cardiac MRI	Late subepicardial enhancement predominating in the inferior and lateral walls	N/A	Myocardial wall thickening and extensive transmural late gadolinium enhancement (LGE)	Increased wall thickness, diffuse biventricular hypokinesis, LVEF 35%, myocardial interstitial oedema, diffuse late gadolinium enhancement (LGE)	Diffuse bi-atrial and biventricular oedema, late gadolinium enhancement (LGE)	N/A	N/A	N/A	Subepicardial late gadolinium enhancement (LGE) of the apex and inferolateral wall	LVEF 42%, hypokinesia of the lateral wall, myocardial oedema, late gadolinium enhancement (LGE)

Table 4 Treatment in acute myocarditis due to COVID-19 and prognosis

	Case 1 [13]	Case 2 [14]	Case 3 [15]	Case 4 [16]	Case 5 [17]	Case 6 [18]	Case 7 [19]	Case 8 [20]	Case 9 [21]	Case 10 [22]
Corticosteroids	No	Yes	N/A	Yes	Yes	Yes	N/A	Yes	Yes	No
Interferon/lopinavir/ritonavir	No/no	Yes/yes	N/A	No/yes	No/no	Yes/yes	N/A	No/no	No/no	No
NSAIDS/colchicine	No/no	No	N/A	No/no	No/yes	No/no	N/A	No/no	No/no	No
Immunoglobulin	N/A	Yes	N/A	No	No	Yes	N/A	Yes	No	No
β-blocker	Yes	No	N/A	Yes	No	No	N/A	No	No	No
ACE-inhibitor	Yes	No	N/A	No	No	No	N/A	No	No	No
Inotropes/CRRT/ECMO use	No/no/no	No/yes/yes	N/A	Yes/no/no	Yes/No/No	Yes/no/Yes	N/A	Yes/no/no	No/no/No	Yes/no/no
Prognosis	Near normal (3 weeks)	Death after 33 days (healthcare-acquired pneumonia)	N/A	Improvement (on day 6: reduction of LV wall thickness, LVEF 44%, slight decrease of pericardial effusion)	Improved (LVEF 82%) and discharged	Regained biventricular function within few days but required ECMO	Death on arrival	Improvement (normal myocardial injury markers 3 weeks later)	Improved and discharged	Discharged on day 12 completely recovered

examination of the heart revealed biventricular necrosis and infiltration of inflammatory cells, mostly eosinophils [20]. Sporadic in other cases cardiac biopsies have revealed lymphocytes and other inflammatory cells residing in the myocardium [28].

Treatment

SARS-CoV-2 Almost all patients received corticosteroids as part of their treatment [15, 17–19, 21, 22]. IV methylprednisolone was the drug of choice. Corticosteroids (namely dexamethasone) are included in a recently proposed therapeutic algorithm from Athens, Greece [29] and have been shown to offer a survival advantage in severe COVID-19 infection according to a recent announcement by the RECOVERY investigators (https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19). Immunoglobulin [15, 19, 21] and anti-viral therapy were administered to less than half of the patients. Antiviral therapy included lopinavir/ritonavir (400 mg/100 mg) and was administered twice daily [15, 17, 19]. Additionally, two out of seven patients required ECMO during their hospitalisation [15, 19]. A detailed course of treatment of each case is presented in Table 4.

MERS-CoV The only reported case presenting with acute myocarditis received broad-spectrum antibiotics and IV furosemide [5].

Prognosis

SARS-CoV-2 Among the aforementioned cases with COVID-19 two died, the 17-year-old patient who experienced out of hospital cardiac arrest and a patient who recovered from fulminant myocarditis only to die at the 33rd day of his hospitalization due to secondary infection [14, 20]. The rest of the patients improved within several days (6–20 days). Their troponin levels dropped [14, 21], the LVEF improved [17, 18, 23] and myocardial wall thickness was restored [17].

SARS-CoV Patients with SARS-COV infection and traceable genome of the virus in their heart tissue had poorer prognosis compared to those with non-traceable virus. The latter's shorter hospitalisation period (7 days vs. 13 days) indicates that cardiac involvement may lead to severe illness and earlier death [4].

MERS-CoV The only registered case with MERS-COV infection complicated with acute myocarditis showed no

improvement in left ventricular systolic function 3 months after being discharged [5].

Conclusions

Previous experience with SARS-CoV and current reports of COVID-19 infection mandate a high level of clinical suspicion for cardiovascular involvement, myocardial injury and possibly acute myocarditis. Diagnosis of acute myocarditis as a result of COVID-19 may be challenging for clinicians. High levels of troponin I and NT-BNP along with ECG abnormalities and the appropriate clinical context should raise suspicion. Cardiac magnetic resonance has proven to be a useful diagnostic tool in acute myocarditis cases. So far, most patients have favourable outcomes but the limited data cannot allow us to draw safe conclusions.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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