Life-threatening cardiogenic shock in a pediatric patient with SARS-CoV-2-associated myocarditis treated with remdesivir: a case description and report of similar cases from the Literature

Silvia Molinari (✉ s.molinari3@campus.unimib.it)
Università degli Studi di Milano-Bicocca, Fondazione MBBM, Azienda Ospedaliera San Gerardo, Monza (MB), Italy

Lucia M.D. Colasanto
Università degli Studi di Milano-Bicocca, Fondazione MBBM, Azienda Ospedaliera San Gerardo, Monza (MB), Italy

Maria L. Melzi
Università degli Studi di Milano-Bicocca, Fondazione MBBM, Azienda Ospedaliera San Gerardo, Monza (MB), Italy

Alessandro Cattoni
Università degli Studi di Milano-Bicocca, Fondazione MBBM, Azienda Ospedaliera San Gerardo, Monza (MB), Italy

Roberto Panceri
Università degli Studi di Milano-Bicocca, Fondazione MBBM, Azienda Ospedaliera San Gerardo, Monza (MB), Italy

Michela Bombino
Università degli Studi di Milano-Bicocca, Azienda Ospedaliera San Gerardo, Monza (MB), Italy

Giuseppe Lapadula
Università degli Studi di Milano-Bicocca, Azienda Ospedaliera San Gerardo, Monza (MB), Italy

Andrea Biondi
Università degli Studi di Milano-Bicocca, Fondazione MBBM, Azienda Ospedaliera San Gerardo, Monza (MB), Italy

Case report

Keywords: Severe Acute Respiratory Syndrome Coronavirus 2, Coronavirus disease 2019, fulminant myocarditis, cardiogenic shock, child, interleukin-6, cytokine release syndrome, remdesivir

DOI: https://doi.org/10.21203/rs.3.rs-34802/v1
Abstract

Background

Children are relatively spared from Coronavirus disease 2019 (COVID-19), but some severe cases have been reported. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children may affect the cardiovascular system. We hereby report about a case of myocarditis evolving to cardiogenic shock in a SARS-CoV-2 positive child.

Case presentation

An otherwise healthy 12-year-old patient was admitted with fever, vomiting, diarrhoea and drowsiness, without any respiratory symptoms. He was diagnosed with COVID-19 on nasopharyngeal swab. He developed hypotension and cardiogenic shock. Bedside echocardiography revealed left ventricular impairment with an ejection fraction (LVEF) below 25%. Plasmatic markers of myocardial injury were remarkably raised, as well as inflammatory biomarkers, including procalcitonin (highest recorded value: 66 ng/mL) and interleukin-6 (8209 pg/mL). The child was transferred to Intensive Care Unit and he was treated with catecholamine support, mechanical ventilation and empiric anti-infectious therapy, including broad spectrum antibiotics and the antiviral agent remdesivir. All additional microbiological investigations yielded negative results.

We observed a gradual improvement of LVEF within 5 days. A cardiac magnetic resonance confirmed the suspicion of myocarditis. After 21 days of hospitalisation, the child was discharged without sequelae.

Conclusions

Our hypothesis is that the child suffered from SARS-CoV-2-induced fulminant myocarditis, probably in the setting of cytokine release syndrome (CRS). The peculiarity of this SARS-CoV-2 infection is the presence of cardiac failure in a previously healthy child without a respiratory illness. The positive outcome is in line with published Literature about the overall better prognosis of COVID-19 children compared to adults. Remdesivir, an investigational antiviral therapy, may have played a role on the clinical improvement of the child.

Background

The World has recently witnessed the epidemic outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, spreading globally and rapidly evolving into a pandemic phenomenon.

In spite of its utmost and potentially life-threatening involvement of the respiratory system, the novel coronavirus disease 2019 (COVID-19) has been recently reported as a causative factor for severe cardiac injury in adult patients. Whether the impairment of cardiac function results from direct detrimental
effect of the virus on the myocardium or should be regarded as a secondary outcome of the systemic inflammatory response elicited by COVID-19 is still debated.

Indeed, an increasing number of Authors have been highlighting the onset of severe cytokine storms in COVID-19 patients. When cytokine release syndrome (CRS) targets the cardiovascular system,(3) the clinical picture includes tachycardia, hypotension, troponin elevation, arrhythmias, QT prolongation, cardiomyopathy and acute heart failure.(3) In COVID-19 patients, all the previous clinical pictures have been described.(4) Interleukin-6 (IL-6) seems to play a pivotal role in CRS, activating complement and the coagulation pathway and inducing endothelial damage. Moreover, IL-6 has been reported to depress the myocardial function.(3,5,6) In COVID-19 patients high levels of IL-6 and C-reactive protein (CRP) appear to be negative prognostic markers.(7,8)

Most children experience no or just mild signs and symptoms of SARS-CoV-2 infection, even though severe cases, mainly occurring in patients with an underlying disease, have been described.(9–11) Pediatric COVID-19 patients may experience respiratory, gastrointestinal, neurological symptoms, but few is known about cardiovascular involvement.(9,10)

We hereby report the first pediatric case of myocarditis in a child affected by COVID-19 and presenting with cardiogenic shock.

Case Presentation

An otherwise healthy 12-year-old boy was admitted to a peripheral hospital (Lombardy – northern Italy), with complaints of fever, vomiting, diarrhoea and drowsiness for the previous three days. Though no respiratory symptoms were reported, both his parents have been presenting with cough and low-grade fever for several weeks. Patient’s past medical history was unremarkable.

On admission, blood tests showed normal full blood count but raised CRP (23.4 mg/dL, reference range < 0.5) and procalcitonin (PCT – 3.3 ng/ml, reference range < 0.5). Despite negative findings at chest x-ray, based on the clinical and family history, COVID-19 was suspected and a nasopharyngeal swab was performed, showing positive result for SARS-CoV-2 infection by real-time reverse transcriptase–polymerase chain reaction (RT-PCR). Later, also nasopharyngeal swab of patient’s father revealed to be positive.

Twenty-four hours later, a remarkable increase of both CRP (33.1 mg/dL) and PCT (44.22 ng/ml) prompted the collection of peripheral blood culture, the start of systemic antibiotic treatment with intravenous Ceftriaxone and patient’s transferral to the Pediatric Department of our tertiary care Centre.

Upon arrival, the patient was ill-appearing, highly febrile (body temperature: 39.0°C) and tachycardic (140 beats per minute), though he presented with normal blood pressure (110/70 mmHg) and room-air pulse-oximetry (98%).
Repeated laboratory investigations showed a further worsening of inflammation markers (CRP 43.11 mg/dL, PCT 58.84 ng/mL), neutrophilia (neutrophils 12.18 x10³/µL) and raised D-Dimer (2396 ng/mL, reference range <250), with an International Normalized Ratio (INR) of 1.4 and increased lactate (4 mmol/L). Venous gas analysis and baseline electrocardiogram provided normal results.

Given the overall worsening of both clinical and biochemical picture despite ongoing antibiotic treatment, Ceftriaxone was empirically switched to a combination of intravenous meropenem and vancomycin. In addition, antithrombotic therapy with intravenous unfractioned heparin was introduced.

In a few hours the child developed severe hypotension (blood pressure: 70/40 mmHg) and clinical signs consistent with progressive peripheral hypoperfusion, refractory to intravenous fluid resuscitation (saline solution: 20 mL/Kg in 15 minutes) and vasoactive amines infusion (norepinephrine). Urgent bedside echocardiography showed a severe decrease in ventricular systolic function, with a left ventricle ejection fraction (LVEF) of 25%, increased left ventricular dimensions with diffuse hypokinesis but retained right ventricular function. Both troponin T (TnT, 602 ng/L with reference range < 14) and N-terminal brain natriuretic peptide (NT-proBNP, 27075 pg/mL with reference range < 300) were found to be remarkably raised.

Due to a progressive deterioration of the clinical picture and the need for mechanical ventilation, invasive hemodynamic monitoring and combined norepinephrine and dobutamine infusion, the patient was transferred to our Intensive Care Unit (ICU).

As showed in figure 1, after an initial improvement, the patients experienced a steep exacerbation of both clinical and biochemical data within 48 hours. Interleukin-6 was tested at this stage and showed a peak value of 8209 pg/ml (reference range: < 7). A chest and abdomen CT scan showed radiological signs consistent with uncomplicated colitis, while pulmonary findings were unremarkable.

The patient was therefore started on antiviral treatment with remdesivir, an investigational nucleoside analogue prodrug with supposed efficacy on SARS-CoV-2, at the loading dosage of 200 mg, followed by 100 mg every 24 hours. Vancomycin was discontinued and replaced with tigecycline and clindamycin, while treatment with meropenem was continued unchanged. Support therapy including vasoactive and inotropic amines, short course hydrocortisone (due to its mineralocorticoid effect), furosemide and captopril was undertaken. With the exception of SARS-CoV-2, all the remaining microbiological investigations performed yielded negative results, including peripheral blood cultures for fungi and bacteria and serologies for cardiotropic infectious agents (echoviruses, coxsackieviruses, cytomegalovirus, adenovirus and mycoplasma) and PCR essays on blood and stool for enterovirus genus nucleic acids.

During the following days, patient's clinical condition progressively improved. Figure 1 shows how the gradual drop of inflammation and myocardial damage markers corresponded to a concomitant increase of LVEF, leading to restoration of cardiac function by the fifth day of intensive care. In two additional days’ time, the patient was progressively weaned from vasoactive support and definitely extubated. The
SARS-CoV-2-targeted nasopharyngeal swab and bronchoalveolar lavage performed seven days after the start of antiviral treatment showed negative results, and remdesivir was therefore discontinued.

Gadolinium-enhanced cardiac Magnetic Resonance Imaging (MRI), performed on day 13, detected an area of subepicardial delayed enhancement within the left ventricle, consistent with recent myocarditis (See figure 2 for detailed description of radiological findings).

After 21 days of hospitalization, the child was discharged with no sequelae.

**Discussion And Conclusions**

We hereby report about a 12-year-old SARS-CoV-2-positive patient who presented with biochemical and clinical signs of acute cardiac injury (raised necrosis markers, severely depressed left ventricle function) in the presence of radiological signs consistent with myocarditis and no signs of respiratory involvement.

In our opinion, several points are worthy of discussion.

Firstly, we presented a rare case of SARS-CoV-2-related cardiac involvement in childhood. Viral infections are the commonest cause of myocarditis in children(12) and myocardial involvement has already been reported in a few SARS-CoV-2-positive patients. Table 1 compares the clinical, laboratory and diagnostic features of all the cases published hereinbefore. (13–21)

Secondly, in our patient, acute onset with progressive clinical deterioration and refractory cardiogenic shock met the diagnostic criteria for fulminant myocarditis (FM).(22,23) This is not unexpected in adulthood, as 4 out of the 9 published cases involving adult patients diagnosed with myocarditis met the criteria of COVID-19-related FM (Table 1). Our case highlights that in case of rapid otherwise unexplained deterioration of clinical conditions in SARS-CoV-2-positive patients, also pediatricians should keep a high index of suspicion and deem FM as a potential diagnosis.

Other than myocarditis, myocardial infarction, disseminated intravascular coagulation (DIC)-associated damage, stress induced cardiomyopathy and CRS-associated damage have been described as possible clinical presentations of cardiac involvement in COVID-19.(4) Indeed, cardiac injury in COVID-19 probably has a multi-factorial genesis. Many Authors agree that different mechanisms may interplay leading to cardiac injury: direct viral damage on myocardial cells, overwhelming inflammation process due to cytokine storm and hypoxia due to the imbalance between increased myocardial oxygen demand and decreased pulmonary oxygen supply during acute respiratory syndrome.(1,24)

As showed in Figure 1, in our case increased TnT and NT-pro-BNP levels, as well as decreased ejection fraction at echocardiography were significantly correlated with IL-6 and CRP levels over time. Similar data have already been described in published Literature.(24) A recent meta-analysis demonstrated that elevated IL-6 values are associated with increased severity and mortality of SARS-Cov-2 disease (8) and patients treated with IL-6 inhibitors, such as Tocilizumab, have reported a clinical improvement.(25) We
decided not to administer tocilizumab to our patient because clear demonstrations of the safety and clinical effectiveness of this anti IL-6 drug is currently lacking.(8,26)

As showed in table 1, both in our pediatric case and in several adult patients, cardiac failure due to myocarditis in otherwise healthy patients may occur without any associated respiratory symptoms. On the other hand, the complete lack of electrocardiographic signs found in our patients is infrequent amongst adults.

Third, there are few reports of remdesivir use in children, and none of them in patients with acute myocarditis. Remdesivir has recently been associated with some clinical benefit in adult patients with COVID-19 (27), leading the US Food and Drug Administration to issue an emergency use authorization for the treatment of COVID-19 in adults and children hospitalized with severe disease. Similarly, remdesivir has been proposed as the preferred agent in children, when antiviral treatment is regarded as potentially beneficial.(28) Nonetheless, most COVID-19 pediatric patients with either mild or severe disease described so far, recovered with supportive care only. Accordingly, ascertaining whether antiviral therapy played a central role on the clinical improvement experienced by our patient is challenging and potentially misleading.

Finally, we are aware that the present case report has some limitations. Firstly, in a highly febrile patient who presented with remarkably raised CRP and PCT, it may be argued that the cardiac impairment could be secondary to concomitant septic shock. Cardiac biopsy could have demonstrated the primary myocardial involvement, but it was contraindicated due to the procedure-related risk in a hemodynamically instable patient. However, cardiac MRI, increasingly used to diagnose myocarditis(29) on the back of the non-invasiveness of the technique, confirmed the diagnosis throughout pathognomonic findings. In addition, the lack of etiological agents other than SARS-CoV-2 identified at repeated cultures decreases the likelihood of a cryptogenic bacterial systemic infection.

Furthermore, our patient was treated with supportive therapy, empirical antibiotics and remdesivir. Assessing the relative contribution of each of these treatments and discerning between therapeutic effectiveness and natural history of the disease in an otherwise healthy child may be misleading. However, the timing of remdesivir administration suggests that it may have played a role in the positive evolution of the overall clinical picture.

In conclusion, although rare, SARS-CoV-2 infection in children may affect the cardiovascular system and result in a life-threatening disease. Pediatricians should take into account fulminant myocarditis amongst the clinical conditions elicited by COVID-19 and potentially resulting in a fatal outcome.

**Abbreviations**

COVID-19: Coronavirus disease 2019, CRP: C-reactive protein, CRS: cytokine release syndrome, CT: computer tomography, DIC: disseminated intravascular coagulation, FM: fulminant myocarditis, ICU: Intensive Care Unit, IL-6: Interleukin-6, INR: International Normalized Ratio, LVEF: Left ventricular ejection fraction,
fraction, MRI: Magnetic Resonance Imaging, NT-pro-BNP: N-terminal brain natriuretic peptide, PCT: procalcitonin, RT-PCR: real-time reverse transcriptase–polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, TnT: troponin T

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the legal parent for publication of this case report and any accompanying images.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was secured for this study

Authors’ contributions

SM, LC and AC, developed the idea of the study, participated in its design and coordination and helped to draft the manuscript. SM, LC, MML and AC contributed to the acquisition and interpretation of data. MML, AC, RP, MB, GL and AB were involved in critically reviewing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The Authors would like to thank Lucia Boffi4, M.D., pediatric cardiologist, for her intellectual contribution and Filiberto Di Gennaro5, M.D., radiologist, for providing us with a clear interpretation of the radiological data.

4Department of Cardiology, Università degli Studi di Milano-Bicocca, Azienda Ospedaliera San Gerardo, Monza (MB), Italy

5Department of Radiology, Università degli Studi di Milano-Bicocca, Azienda Ospedaliera San Gerardo, Monza (MB), Italy
Dr. Boffi and Dr. Di Gennaro have no conflicts of interest, funding sources, and industry-relation to disclose.

References

1. Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. Int J Cardiol. 2020 Jun;309:70–7.
2. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020 Apr 11;
3. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. J Immunother Cancer. 2018 Dec 15;6(1):56.
4. Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, et al. Cardiovascular manifestations and treatment considerations in covid-19. Heart. 2020 Apr 30;2:heartjnl-2020-317056.
5. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016 Jul;8(8):959–70.
6. Pathan N, Hemingway CA, Alizadeh AA, Stephens AC, Boldrick JC, Oragui EE, et al. Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. Lancet. 2004 Jan;363(9404):203–9.
7. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020 Jun;127:104370.
8. Aziz M, Fatima R, Assaly R. Elevated Interleukin-6 and Severe COVID-19: A Meta-Analysis. J Med Virol. 2020 Apr 28;jmv.25948.
9. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents. JAMA Pediatr. 2020 Apr 22;
10. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. N Engl J Med. 2020 Apr 23;382(17):1663–5.
11. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020 Mar 16;e20200702.
12. Dancea AB. Myocarditis in infants and children: A review for the paediatrician. Paediatr Child Health. 2001 Oct;6(8):543–5.
13. Kim I-C, Kim JY, Kim HA, Han S. COVID-19-related myocarditis in a 21-year-old female patient. Eur Heart J. 2020 Apr 13;
14. Inciardi RM, Lupi L, Zacconce G, Italia L, Raffo M, Tomasoni D, et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Mar 27;
15. Zeng J-H, Liu Y-X, Yuan J, Wang F-X, Wu W-B, Li J-X, et al. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. Infection. 2020 Apr 10;
16. Irabien-Ortiz À, Carreras-Mora J, Sionis A, Pàmies J, Montiel J, Tauron M. Fulminant myocarditis due to COVID-19. Rev Española Cardiol (English Ed. 2020 Apr;
17. Paul J-F, Charles P, Richaud C, Caussin C, Diakov C. Myocarditis revealing COVID-19 infection in a young patient. Eur Hear J - Cardiovasc Imaging. 2020 Apr 27;
18. Doyen D, Moceri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. Lancet. 2020 Apr;
19. Fried JA, Ramasubbu K, Bhatt R, Topkara VK, Clerkin KJ, Horn E, et al. The Variety of Cardiovascular Presentations of COVID-19. Circulation. 2020 Apr 3;CIRCULATIONAHA.120.047164.
20. Sala S, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D, et al. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J. 2020 Apr 8;
21. Marie-Laure Oberweis, MD, Andrei Codreanu, MD, Wolfgang Boehm, MD, Damien Olivier, MD, Charlotte Pierron, MD, Chantal Tsobo, MD, Michel Kohnen, MD, Tamir T. Abdelrahman, MD, PhD Nguyen T. Nguyen, MD, Kerstin Wagner M, and Isabel de la Fuente Garcia, MD Ms. Pediatric Life-Threatening Coronavirus Disease 2019 With Myocarditis. Pediatr Infect Dis J. 2020;online fir.
22. Ammirati E, Cipriani M, Lilliu M, Sormani P, Varrenti M, Raineri C, et al. Survival and Left Ventricular Function Changes in Fulminant Versus Nonfulminant Acute Myocarditis. Circulation. 2017 Aug 8;136(6):529–45.
23. Veronese G, Ammirati E, Cipriani M FM. Fulminant myocarditis: Characteristics, treatment, and outcomes. Anatol J Cardiol. 2018;
24. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Mar 27;
25. Alzghari SK, Acuña VS. Supportive Treatment with Tocilizumab for COVID-19: A Systematic Review. J Clin Virol. 2020 Jun;127:104380.
26. Radbel J, Narayanan N, Bhatt PJ. Use of Tocilizumab for COVID-19-Induced Cytokine Release Syndrome. Chest. 2020 Apr;
27. NIH. NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19. NIH Press Release. 2020.
28. Chiotos K, Hayes M, Kimberlin DW, Jones SB, James SH, Pinninti SG, et al. Multicenter Initial Guidance on Use of Antivirals for Children With Coronavirus Disease 2019/Severe Acute Respiratory Syndrome Coronavirus 2. J Pediatric Infect Dis Soc. 2020 Apr 22;
29. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013 Sep 1;34(33):2636–48.
| Gender | Symptoms | Cardiac Comorbidities | Pulmonary Findings | Cardiac Findings | Descriptive Findings | LV on Gadolinium T2 Weighted | IL-6 (pg/mL) Peak | CRP (mg/dL) Peak | PCT (ng/mL) Peak | Fulminant T9 |
|--------|----------|----------------------|-------------------|-----------------|---------------------|-----------------------------|----------------|----------------|----------------|-----------|
| Male   | Fever, No vomiting, diarrhea | None None | None None | Increased LV dimensions, diffuse LV hypokinesis | 25% Incr. LV diam | Intense Focal intramyocardial delayed enhancement | 8209 43,11/6 | 0,602 | 27075 | Yes |
| Female | Fever, cough, dyspnea, diarrhea | Bilateral Cardiac al multi hyper trophy; subendocardial perfusion defect | Bilateral Myocardial Ground-hyper trophy; opacification | Multipl e premature ventricular complexes | Not Severe; LV hyper trophy; Pericardial effusion | Intense Extensive signal transmural late enhancement | Not describ ed describ ed | 1.26 1929 | No |
| Female | Fatigue | None None | Not describ ed describ ed ed | Elevated ST tract; | 40% Elevat ed dyskin eisis; Low voltage; T wave inversion in V1 and aVR | Intense Extensive signal transmural late enhancement | Not describ ed describ ed | 1.3/- 0.24 5647 | Yes |
| Male   | Fever, No dyspnea | Ground-Glass opacification | Bilateral None | Sinus tachycardia | Diffuse dyskinesia; LV hyper trophy | Not describ ed describ ed | 272 Not 11.37 22600 | Yes |
| Female | Hypertension, degenerative cervical arthropathy, | Vascular redistribution with no signs of primary | Not describ ed describ ed | Elevated ST tract; | 32% Elevat ed dyskin eisis; LV hyper trophy | Not describ ed describ ed | Not describ ed describ ed | 1.0/- 11.00 4421 | Yes |
| Gender | Chest Pain, Fatigue | None | None | Repolarization abnormalities | Not Subependymal gadolinium enhancement | Not Not 2.88 None | No |
|--------|---------------------|------|------|-----------------------------|----------------------------------------|-------------------|---|
| Male   | Fever, Hypertension, diarrhea, cough, dyspnea | None | None | LV hypertrophy | Normal cardiac allograft function | Not ND/No 9.00 Not described | No |
| Female | Chest Pressure, Hypertension, Hyperlipidemia | None | None | Sinus tachycardia, low QRS voltage, diffuse ST and PR elevations, ST depression in aVR | LV hypertrophy, 30% dilated and severely hypokinetic right ventricle | Not 0.0054 7.9 Not described | Yes |
| Male   | Fever, Renal Cough, and dyspnea heart transplant | None | None | Normal Normal | Not Not descried | 120 12.9/- 0.016 3212 No |
| Female | Chest Pain, Dyspnea | Subtle | None | Bilateral Mid basal patchy LV ground-hypokinesi | Inferior wall hypokinesi | Not 1.8/- 0.135 512 No |
| Male | Fever, None | Not described | Bilateral pneumonia of the inferior lobes, bilateral pleural effusion, | Discrete ST elevation in V3 | Impaired left ventricular function, small pericardial effusion, mitral insufficiency | 21% | Not described | Subepicardial late gadolinium enhancement | 1023 | 7.3/- | 0.044 | 5112 | Yes |
|------|-------------|---------------|---------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------|------|---------------------------|-----------------------------------------|-------|-------|--------|--------|-----|

**Table 1. Clinical characteristics of COVID-19 patients with myocarditis** (suspected or diagnosed according to European Society of Cardiology.(18)

Abbreviations: LVEF: left ventricle ejection fraction, MRI: magnetic resonance imaging; LV: left ventricle; IL-6: interleukin-6; CRP: C Reactive Protein; PCT: Procalcitonin; Pro-BNP: pro-brain natriuretic peptide; ND: not determinable.

a diagnosis of fulminant myocarditis according to Veronesi et al. and Ammirati et al.(13,14)

**Figures**
Figure 1

Cardiac MRI showing radiological signs consistent with myocarditis Panel 2A: short tau inversion recovery (STIR) sequences showing a spot of intramyocardial signal hyperintensity (residual edema – yellow arrow); Panel 2B: 3D-two chambers view showing intramyocardial delayed enhancement (subepicardial/"mild-wall", not ischemic pattern) at inferior basal segment of left ventricle (yellow arrow); Panel 2C: post-contrast image revealing focal delayed enhancement at the same location (yellow arrow)
**Figure 2**

Course of laboratory inflammation and cardiac necrosis markers and changes in left ventricle ejection rate. Concomitant treatments administered are reported in the panels at the bottom of the picture.

Abbreviations: CRP: C Reactive Protein; PCT: Procalcitonin; IL-6: interleukin-6; TnT: troponin T; CPK MB: creatine phosphokinase MB; LVEF: Left Ventricle Ejection Fraction; pro-BNP: pro brain natriuretic peptide; LMWH: low molecular weight heparin.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- CARECHECKLIST.pdf