Myocardial localization of coronavirus in COVID-19 cardiogenic shock

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Abstract

We describe the first case of acute cardiac injury directly linked to myocardial localization of severe acute respiratory syndrome coronavirus (SARS-CoV-2) in a 69-year-old patient with flu-like symptoms rapidly degenerating into respiratory distress, hypotension, and cardiogenic shock. The patient was successfully treated with venous-arterial extracorporeal membrane oxygenation (ECMO) and mechanical ventilation. Cardiac function fully recovered in 5 days and ECMO was removed. Endomyocardial biopsy demonstrated low-grade myocardial inflammation and viral particles in the myocardium suggesting either a viraemic phase or, alternatively, infected macrophage migration from the lung.

Introduction

Acute myocardial involvement in coronavirus disease 2019 (COVID-19) is currently described as 'acute cardiac injury', defined as blood levels of cardiac biomarkers [high-sensitivity troponin I (hs-TnI)] above the 99th-percentile upper reference limit. It is described in more than 20% of patients and seems to be related to increased mortality.[1], [2] The pathogenesis of acute myocardial injury is unknown. The diagnosis is based upon clinical data, imaging and biomarkers of acute cardiac damage[3], [4]; the identification of the cause, either myocardial inflammation (myocarditis or myopericarditis[5]), or necrosis, is clinically relevant for the correct diagnostic and therapeutic management of patients, especially those with severe infections admitted to the intensive care unit (ICU).

We describe a COVID-19 patient with flu-like symptoms rapidly degenerating into respiratory distress, hypotension, and cardiogenic shock. He was successfully treated with mechanical ventilation and venous-arterial extracorporeal membrane oxygenation (VA-ECMO) implantation as a bridge to recovery. Endomyocardial biopsy (EMB) showed low-grade myocardial inflammation and coronavirus particles. Twelve days after weaning from ECMO, with complete normalization of cardiac function, the patient died of Gram-negative septic shock. This first case unquestionably shows that the heart can be directly involved in the infection with clinical manifestations similar to those of fulminant myocarditis but with pathology evidence of very low-grade myocardial inflammation.

Case description

Acute clinical manifestation and evolution

A 69-year-old patient presented to the emergency department of the main hospital of a 'red zone' town in Lombardy, Italy. He had been complaining of worsening dyspnoea, persistent cough, and weakness since 4 days. A lung computed tomography scan showed diffuse bilateral interstitial inflammation with sub-pleural consolidations. The nasopharyngeal swab tested positive for COVID-19 on real-time reverse transcriptase-polymerase chain reaction assay. Blood analysis demonstrated high inflammatory markers and lymphopenia (white blood cell count 23080/mm^3, neutrophils 91.4%, lymphocytes 1.4%, C-reactive protein 52.7 mg/L) and increased hs-TnI (4332 ng/L). Arterial blood gas analysis showed severe metabolic acidosis with hyperlactacidaemia (pH 7.2, excess basis –6 mEq/L, lactates 9 mmol/dL) and hypoxaemia. Non-invasive ventilation was initiated. The first echocardiography showed a dilated left ventricle [left ventricular (LV) end-diastolic diameter 56 mm], severe and diffuse LV hypokinesia (LV ejection fraction 34%). Three hours later, LV ejection fraction dropped to 25% and estimated cardiac index was 1.4 L/min/m^2. Coronary angiography findings were unremarkable. An intra-aortic balloon pump (IABP) was placed on top of adrenaline (0.07 µg/kg/min), and noradrenaline (0.1 µg/kg/min) was added for worsening hypotension (systolic blood pressure: 80/67/60 mmHg). The mobile team from our third level ECMO center was activated for on-site implantation of VA-ECMO and patient retrieval to our hospital. After ECMO institution, the patient developed sudden and marked desaturation requiring orotracheal intubation. On admission to our ICU, due to maintenance of minimal ventricular ejection and aortic valve opening, the inotropic support was gradually decreased and eventually stopped to prevent adrenergic stimulation to the myocardium (online supplementary *Appendix S1*). EMB was performed and a venous cannula was added at the right jugular vein site for persistent severe hypoxaemia, thus upgrading the VA-ECMO to venous-arterial-venous ECMO. LV function progressively recovered up to normal levels on day 5, when both ECMO and IABP were discontinued. Twelve days after weaning from ECMO, the patient suddenly developed Gram-negative pneumonia (*Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) and died of septic shock within a few hours, without any further LV function impairment.

Endomyocardial biopsy

Endomyocardial biopsy was performed as per protocol in non-ischaemic cardiogenic shock. Myocardial samples were rapidly processed for light (n = 3) and electron microscopy (n = 1). The pathologic study showed low-grade interstitial and endocardial inflammation (*Figure* **1***A* and **1***B*). Large (>20 µm), vacuolated, CD68-positive macrophages were seen with immune-light microscopy (*Figure* **1***C* and **1***D*); they were ultrastructurally characterized by cytopathy, with membrane damage and cytoplasmic

vacuoles (*Figure* **1***E*). 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 (*Figure* **2**). COVID-19 infected Vero cells were used as control. The viral particles were observed in cytopathic, structurally damaged interstitial cells that demonstrated loss of the cytoplasmic membrane integrity (*Figure* **3**).

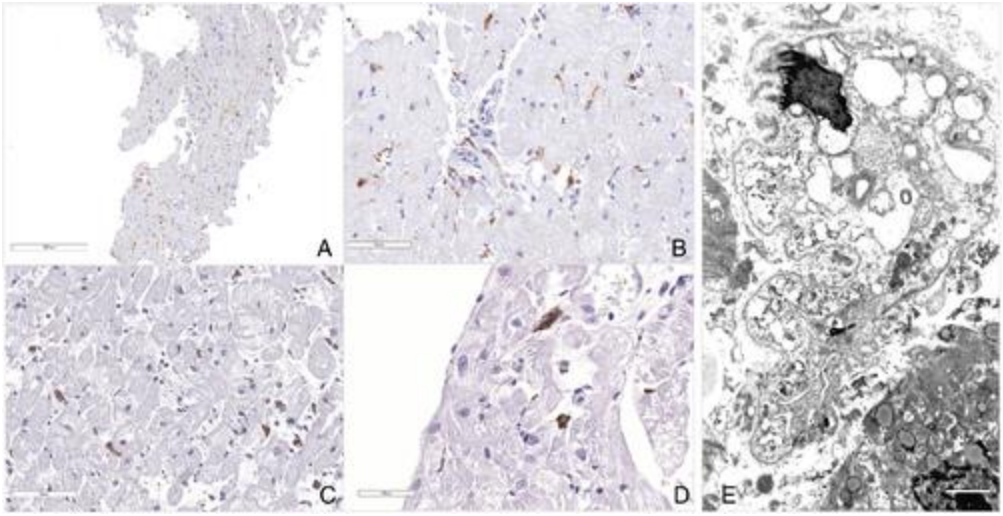

Figure 1

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Light microscopy immunostaining of the inflammatory infiltrate. (*A*,*B*) Low- and high-power views of endomyocardial biopsy, with sparse CD45RO positive interstitial cells. (*C*,*D*) Large, vacuolated macrophages immunostained with anti-CD68 antibodies. (*E*) Ultrastructural morphology of a large and cytopathic macrophage. (*A*–*D*: the bar scale is in the left low corner of each panel. *E*: the bar scale is in the right low corner of the panel and corresponds to 2 μm).

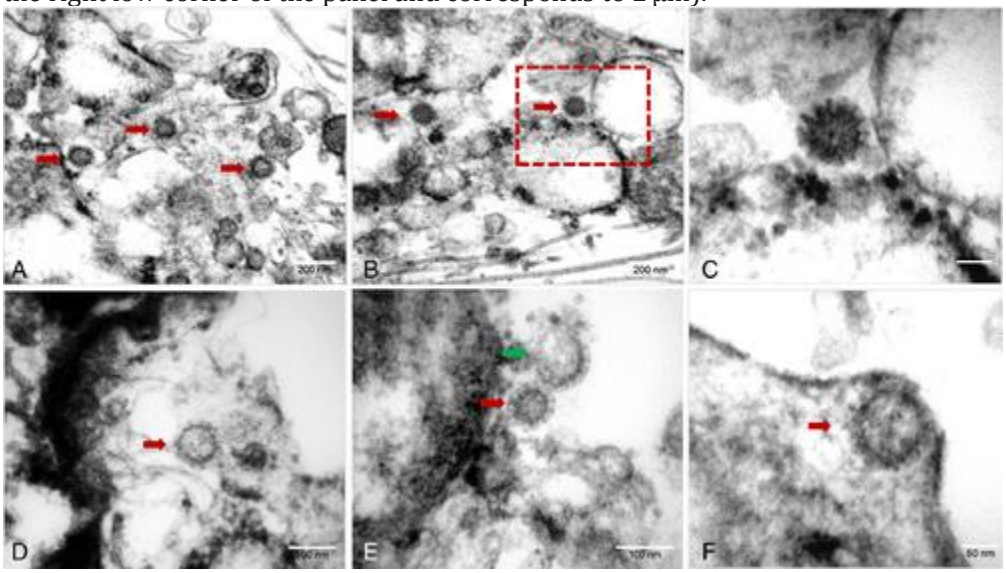

Figure 2

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Examples of small groups of viral particles (*A* and *B*; panel *C* shows a higher magnification of one of the viral particles squared in dashed red box of panel *B*) or single particles (*D*–*F*) observed within the

interstitial cells of the myocardium of the patient. The red arrows indicate the most typical and easy-to-recognize viral particles, whose size varies from about 70 nm to 120 nm (see the white bars in the panels). Morphology also shows small differences with more or less prominent spikes of the viral crown. The morphology may also show viral particle disruption (*E*, green arrow) or attenuation of spikes of the crown (*D* and *F*), or viral particles in budding attitude (*F*). (Bar scale: *A* and *B*, 200 nm; *C*, 50 nm; *D*, 100 nm; *E*, 100 nm; *F*, 50 nm).

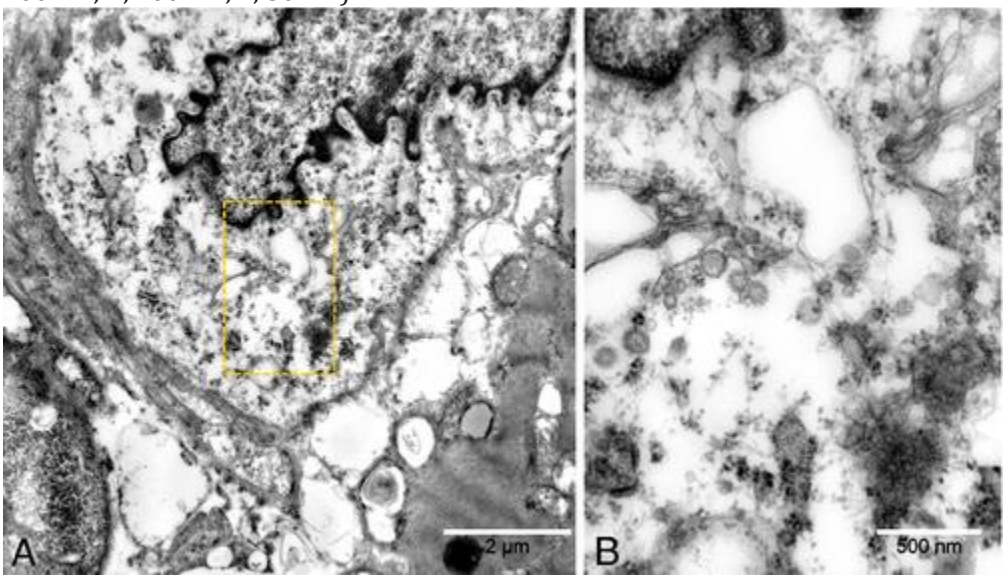

Figure 3

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Electron micrograph showing a cytopathic interstitial inflammatory cell (*A*) that contains viral particles (some of them are magnified in panel B that corresponds to the yellow squared area of panel *A*). The interstitial cell is in close contact with the adjacent cardiac myocyte (left). The viral particles show diameter variability in the range of 70–120 nm. Although the inflammatory cell and myocyte are closely adjacent, no viral particles are observed in the myocyte.

Cardiac myocytes showed non-specific features consisting of focal myofibrillar lysis, and lipid droplets. We did not observe viral particles in myocytes and endothelia. Small intramural vessels were free from vasculitis and thrombosis. EMB did not show significant myocyte hypertrophy or nuclear changes; interstitial fibrosis was minimal, focal, and mainly perivascular.

Discussion

We describe the first case of biopsy-proven myocardial localization of viral particles with morphology and size typical of coronavirus in a COVID-19 patient presenting with cardiogenic shock. While the clinical presentation was suggestive for severe and necrotizing acute myocarditis, the pathologic study demonstrated low-grade myocardial inflammation and absence of myocyte necrosis. Pathologic studies are especially needed for the characterization of acute myocardial injury in COVID-19 patients admitted to the ICU. Our ultrastructural findings are similar to those observed in autopsy samples from a patient with T-cell lymphoma and Middle East respiratory syndrome coronavirus (MERS-CoV),**6** where viral particles were found in the cytoplasm of pneumocytes and alveolar macrophages, renal proximal

tubular epithelial cells, and macrophages infiltrating the skeletal muscle. Our observation of myocardial localization implies either a viraemic phase or, alternatively, the migration of infected alveolar macrophages in extra-pulmonary tissues. Although the main target cells for the virus to infect are epithelial cells and macrophages of the respiratory tract,[7] COVID-19 RNA has been detected in the small and large intestine, lymph nodes, spleen, liver, heart, kidney, skeletal muscle, adrenal gland, and cerebrum, suggesting extra-pulmonary dissemination and virus localization in different types of tissues and fluids.[8] We observed viral particles in interstitial cytopathic macrophages and their surroundings. Vice versa, we did not observe viral particles in cardiac myocytes and, therefore, we cannot infer on viral cardiotropism. Cardiac myocytes showed non-specific damage that was mainly characterized by focal myofibrillar lysis. In addition, we did not observe cytopathic endothelia and small intramural vessel inflammation or thrombosis. Other cases are needed to confirm this observation.

Cardiogenic shock clinically mimicked fulminant myocarditis and was treated according to standard protocols,[9], [10] including implantation of VA-ECMO[11] that prevents an excessive and detrimental catecholaminergic stimulation to the myocardium. VA-ECMO as a bridge to recovery should be considered for COVID-19 patients with severe acute myocardial injury.[12], [13] Since different mechanisms (oxygen supply/demand imbalance with or without coronary artery disease, increased right ventricular afterload due to respiratory acidosis, hypoxaemia and positive pressure ventilation) can cause acute myocardial injury,[14] the precise identification of the cause is essential to target the treatment accordingly. The extent of local tissue damage and the cytokine storm triggered by the host immune response may both contribute to the severity of the disease. On the basis of the theoretical hyper-inflammatory response and on a re-analysis of data from a controlled trial on interleukin-1 blockade in sepsis, showing significant survival benefit in patients with hyper-inflammation,[15] randomized controlled trials on specific anti-inflammatory treatments are advocated.

This unique case demonstrates that COVID-19 can localize in organs/tissues other than the lung. Either transient viraemia or infected macrophage migration from the lung likely occurs in COVID-19 patients with non-ischaemic acute myocardial injury. Identification of the cause of acute myocardial injury may contribute to explain the different evolution of the severe SARS-CoV-2 infection and to plan treatments according to the type of myocardial injury.

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