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Case Report

Fatal Takotsubo syndrome in critical COVID-19 related pneumonia

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ABSTRACT

COVID-19 can involve several organs and systems, often with indirect and poorly clarified mechanisms. Different presentations of myocardial injury have been reported, with variable degrees of severity, often impacting on the prognosis of COVID-19 patients. The pathogenic mechanisms underlying cardiac damage in SARS-CoV-2 infection are under active investigation.

We report the clinical and autopsy findings of a fatal case of Takotsubo Syndrome occurring in an 83-year-old patient with COVID-19 pneumonia. The patient was admitted to Emergency Department with dyspnea, fever and diarrhea. A naso-pharyngeal swab test for SARS-CoV-2 was positive. In the following week his conditions worsened, requiring intubation and deep sedation. While in the ICU, the patient suddenly showed ST segment elevation. Left ventricular angiography showed decreased with hypercontractile ventricular bases and mid-apical ballooning, consistent with diagnosis of Takotsubo syndrome. Shortly after the patient was pulseless. After extensive resuscitation maneuvers, the patient was declared dead. Autopsy revealed a subepicardial hematoma, in absence of myocardial rupture. On histology, the myocardium showed diffuse edema, multiple foci of contraction band necrosis in both ventricles and occasional coagulative necrosis of single cardiac myocytes. Abundant macrophages CD68+ were detected in the myocardial interstitium. The finding of diffuse contraction band necrosis supports the pathogenic role of increased catecholamine levels; the presence of a significant interstitial inflammatory infiltrate, made up by macrophages, remains of uncertain significance.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causal agent of COVID-19 pandemic. Viral infection most commonly manifests with fever and respiratory illness of variable severity, although several organs and systems can also be affected. Cardiovascular complications of COVID-19 disease are increasingly recognized, and acute myocardial injury with increased troponin levels is reported as the most common cardiac abnormality in this setting [1].

Takotsubo syndrome (TTS) also known as stress cardiomyopathy, is characterized by acute left ventricular dysfunction, which is transient and reversible in most cases, often secondary to an emotional or physical trigger. Patients usually present with chest pain and show ST-segment elevation on ECG, as well as mild increase in the serum troponin levels. Regional wall motion abnormalities (apical ballooning or other forms) are detected by cardiac imaging. The reported frequency of TTS in patients with symptoms of acute coronary syndrome ranges between 0.7% and 2.5% [2]. Among the cardiovascular manifestations of COVID-19 there are a few reported cases of TTS, suggesting a possible role of SARS-CoV-2 infection in the onset of this syndrome [3-10] which, however, is yet to be determined.

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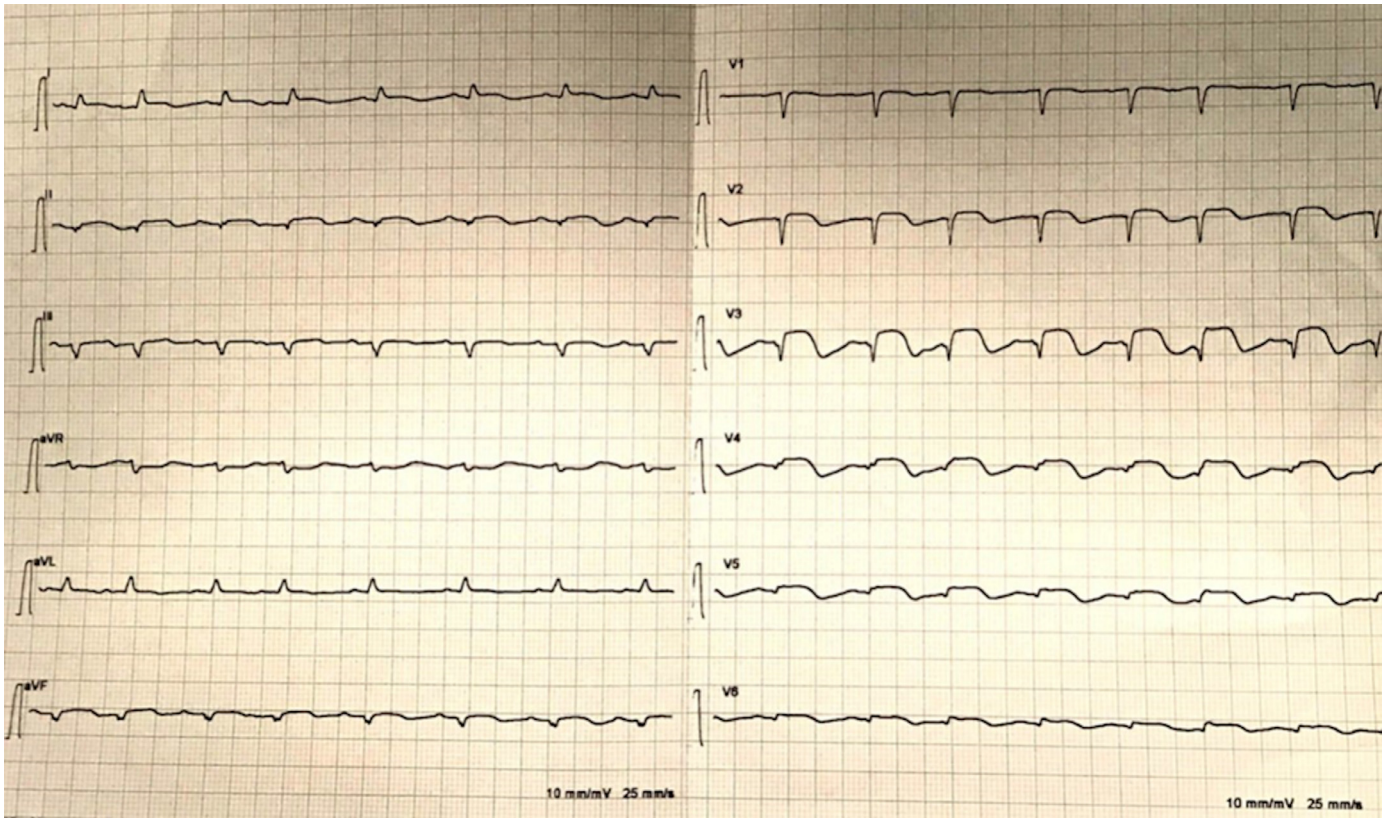

Fig. 1. Electrocardiogram with diffuse ST segment elevation, more evident in the precordial leads (V3-V5), and Q waves in precordial and peripheral inferior leads.

We report the clinical and autopsy findings of a case of fatal TTS occurring in an 83-year-old man with critical COVID-19 pneumonia.

2. Clinical case

An 83-year-old man was admitted to the Emergency Department in the last week of March 2020, for the acute onset of dyspnea following three days of fever and diarrhea. His blood pressure was 120/80 mm Hg, temperature 37 °C, heart rate 95 bpm. In the past medical history, the patient reported chronic obstructive pulmonary disease, systemic hypertension, diabetes mellitus and dyslipidemia. His BMI was 34. A naso-pharyngeal swab test for SARS-CoV-2 was positive. The first blood gas analysis (without O_2 therapy) showed blood oxygen saturation of 95%, partial pressure of oxygen 68 mm Hg, partial pressure of CO_2 32 mm Hg, pH 7.45 and P/F ratio of 324. Physical exam revealed bilateral, basal decreased breath sounds with crackles.

A chest CT scan showed lung ground glass opacities and subpleural patchy areas of consolidation. Pericardial thickening and aneurysmal dilatation of the thoracic aorta (53 mm) were also observed. Over the next 4 days the patient progressively worsened with an increase in respiratory rate and desaturation, requiring the positioning of a continuous positive airway pressure (CPAP). Three days later the patient was intubated after deep sedation (propofol 100 mg, fentanest 100 mcg and rocuronium 100 mg iv) due to the worsening of his respiratory conditions. He was then transferred to the intensive care unit (ICU) with tocilizumab (600 mg die) and hydroxychloroquine (400 mg die) and continuous infusion of norepinephrine in medical therapy. A central venous catheter was placed in the internal jugular vein and blood pressure invasive monitoring was started.

On the fourth day of invasive ventilation in ICU ECG monitoring. showed diffuse ST segment elevation, more evident in the precordial leads (V3-V5), and Q waves in precordial and peripheral inferior leads (Fig. 1). The patient became severely hypotensive, with increased levels of blood lactates, therefore norepinephrine dosage was increased to 0.1 mcg/kg/min.

An echocardiogram was immediately performed, which, due to the suboptimal acoustic window, only allowed to detect a severe global reduction of the left ventricular contractility with mild pericardial effusion. Urgent coronary angiography showed only a 70% stenosis in the posterolateral branch which originated from the circumflex (left dominance). Considering the electrocardiographic and clinical findings, intravascular ultrasound was performed to exclude the presence of coronary dissection, thrombi or plaques not recognized by angiography (Fig. 2). The exam was implemented with a left ventricular angiography, which showed LV severe dysfunction with hypercontractile ventricular bases and mid-apical ballooning (Fig. 3), consistent with the diagnosis of TTS.

In consideration of the severely reduced left ventricular systolic function, Levosimendan was administered without bolus at 0.05 mcg/Kg/min continuous infusion. About 4 hours after the return to the ICU, the patient became pulseless. During resuscitation, a fast echocardiogram showed LV dilation with RV compression, and pericardial effusion. Urgent pericardiocentesis was performed with drainage of 100 ml hemorrhagic fluid. After 50 minutes the resuscitation was interrupted, and an autopsy was requested.

3. Autopsy findings

On gross examination, the pericardium contained 100 ml of blood. There was moderate left ventricular hypertrophy (heart weight: 400 g) and dilation. The coronary arteries were unremark-

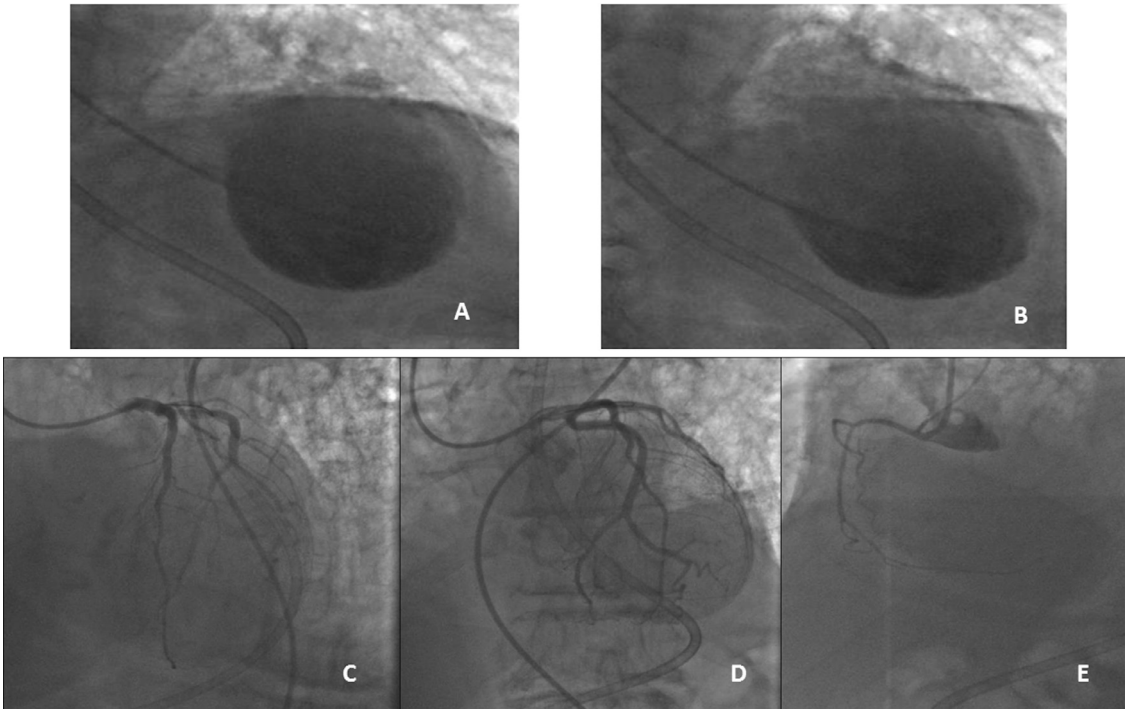

Fig. 2. Ventriculography and coronary angiography. (A) Left ventricular ballooning is evident both in systole and (B) in diastole. Coronary angiography. (C) The anterior descending branch of the left coronary artery is unremarkable. (D) The posterolateral branch of the left circumflex artery shows a 70% stenosis. (E) The right coronary artery is unremarkable.

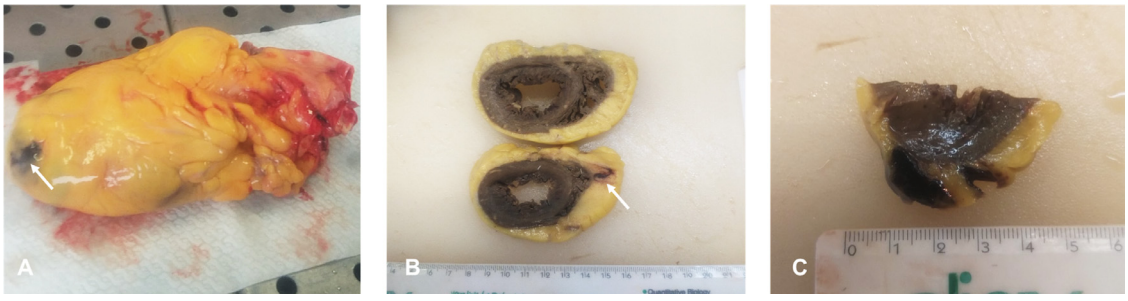

Fig. 3. (A) Gross picture of the heart at autopsy, showing a hemorrhagic area (arrow) on the epicardial surface at the apex. (B) The same lesion is evident on cut surface after fixation (arrow). (C) The hemorrhagic infiltrate involves only the subepicardial fat extending for a depth of 2 mm into the subepicardial myocardium in the apical region.

able, except for the presence of an eccentric plaque in the posterolateral branch, consistent with the angiographic findings. The epicardial surface at the apex showed a linear breach, measuring 8 mm, associated with a hemorrhagic infiltrate involving the subepicardial fat and extending for a depth of 2 mm into the subepicardial myocardium, in absence of a transmural myocardial rupture (Fig. 3). The lesion was not spatially related with the anterior descending branch of the left coronary artery. The lungs showed acute edema and bilateral interstitial pneumonia, with sub-pleural honeycombing.

Histologic examination was performed on multiple myocardial samples (n = 16) obtained from both ventricles, including the left ventricular apex. On histology, the myocardium showed diffuse edema, multiple foci of contraction band necrosis in both ventricles (Fig. 4A) and occasional coagulative necrosis of single cardiac myocytes (Fig. 4B). There were no lymphocytic infiltrates, however abundant macrophages CD68+ were detected in the myocardial interstitium (Fig. 4C). This finding has been recently reported as a frequent feature in hearts from COVID-19 autopsies, and could result from the elevated systemic levels of proinflammatory cytokines [11].

Additional features included focal myocyte stretching and waviness (Fig. 4D) interstitial hemorrhages in the apical region and occasional presence of microthrombi in the small coronary vessels (Fig. 4E, F). Overall, cardiac findings were consistent with the clinical diagnosis of TTS.

The SARS-CoV-2 genome was detected by qualitative reverse transcriptase polymerase chain reaction (RT-PCR) in the lung, but not in the myocardium.

4. Discussion

TTS typically manifests as a transient left ventricular systolic dysfunction with complete recovery of the normal ejection fraction within a variable period of time (generally few days). It is more frequent in postmenopausal women, and most often occurs after a physical or emotional stress [2,12].

Clinical and instrumental features mimic acute coronary syndrome with ECG ST-elevation or depressions, precordial T-wave in-

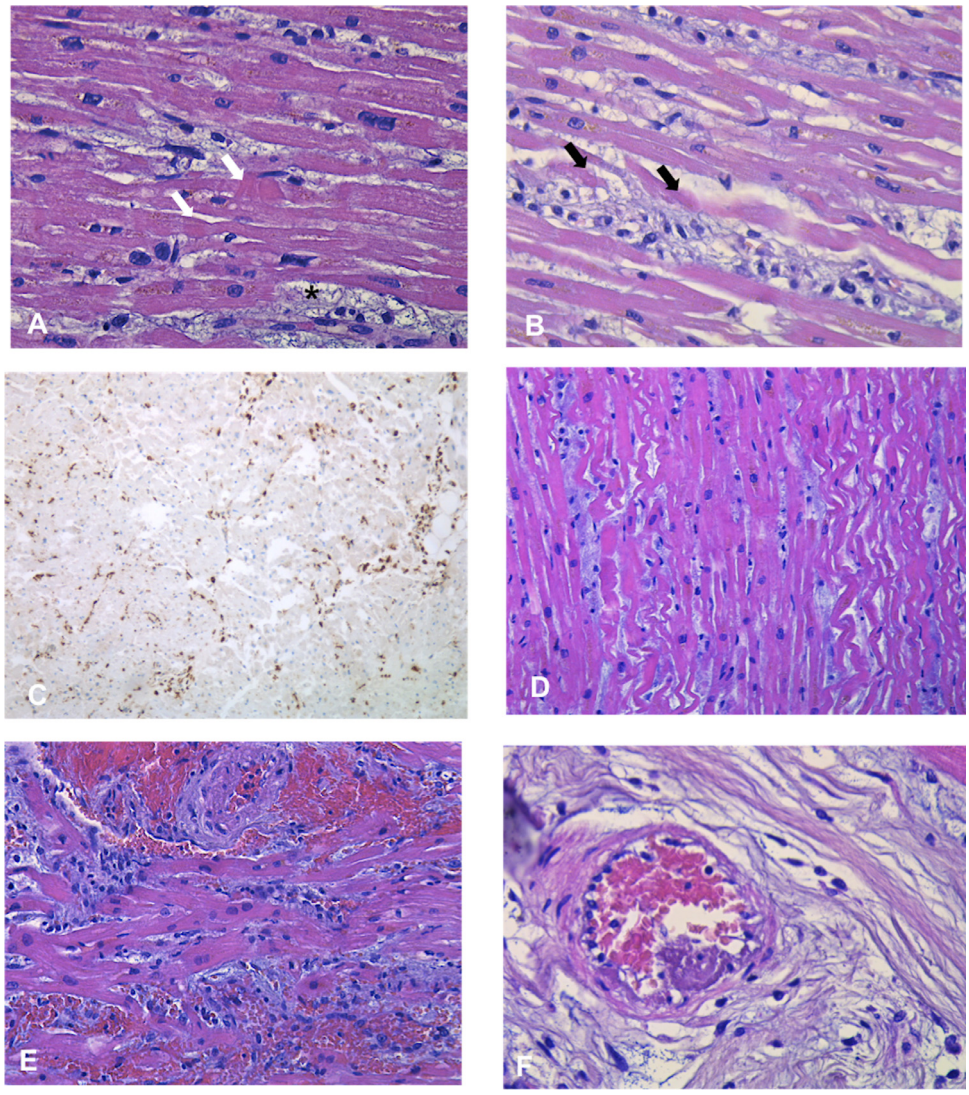

Fig. 4. (A) Cardiomyocytes showing contraction bands (arrows). There is marked interstitial edema (asterisk). (B) Necrotic cardiomyocytes (arrows) admixed with macrophages. (C) The interstitial infiltrates are made up by abundant CD68+ macrophages. (D) Groups of stretched and wavy myocytes. (E) Acute interstitial hemorrhages in the apical region. (F) Occasional, nonocclusive thrombi in coronary microvessels. Hematoxylin-eosin, original magnification 20x, and CD 68 immunostaining, original magnification 5x (C).

versions and, as in our case, transient Q-waves. Serum indicators of myocardial damage are often not particularly high, and in several cases troponins remain below the limit for the diagnosis of probable acute coronary syndrome [13].

Despite the transient nature and the and the benign prognosis in most cases, ventricular disfunction associated with TTS can lead to acute heart failure, low cardiac output, and/or pulmonary edema. The etiology of TTS is still not completely clear. Current evidences show that in the acute phase there is an increased concentration of catecholamines that might cause myocardial injury and coronary spasm, mostly at the microvascular level, together with an increased cardiac workload that contribute to an acute situation of "supply-demand mismatch" followed by post-ischemic stunning [14]. Some triggers are often detectable in emotional or physical stress, however in several cases no events are reported in the clinical history [13]. With the progression of the COVID-19 pandemic, a significant increase in the incidence of TTS has been reported in subjects with negative RT PCR swab test. This phenomenon has been attributed to psychological, social, and economic stress associated with the pandemic itself [15]. However, there is an increasing number of reported cases of TTS in patients with COVID-19 [3-10] suggesting the hypothesis that SARS-CoV-2 infection poses a greater risk of developing the syndrome. In addition, a high mortality rate has been reported for TTS in COVID-19 patients [10]. Cardiac pathologic findings in COVID-19 complicated by TTS are largely unknown. Therefore, the mechanism underlying the onset of stress cardiomyopathy in COVID-19 patients still remains unknown. Endomyocardial biopsy findings of lymphocytic myocarditis have been recently reported in a young woman with a reverse TTS and SARS-CoV-2 infection [8], suggesting that inflammation may contribute to development of stress cardiomyopathy.

Autopsy reports are crucial for the understanding of the type and extent of cardiac involvement in COVID-19 [16]. To our knowledge, this is the first report providing the cardiac autopsy findings of a fatal case of TTS in a COVID-19 patient.

In the case described the patient was intubated and deeply sedated for 4 days before TTS manifestation, without any episode of awakening or superficialization. The general and respiratory conditions were stable since the entry in ICU, and after intubation, the analysis of blood gases did not show significant variations. The

condition of deep sedation should have prevented the onset of an emotional trigger, however the patient had been treated with high-dose norepinephrine, which could explain the onset of stress cardiomyopathy in this case. The presence of diffuse contraction band of myocytes, involving both ventricles, is in line with this hypothesis. In addition, the finding of abundant interstitial macrophages, recently reported as a characteristic finding in autopsy hearts from COVID-19 patients [11], could represent distinctive pathologic feature of SARS-CoV-2 infection in our case. The mechanisms underlying this phenomenon, as well as its possible clinical impact, are still unknown. For example, it is not known whether the virus is able to interfere with the role of ACE2 (SARS-CoV-2 receptor) in the central regulation of anxiety and sympathetic nervous system output [17].

The subepicardial myocardial laceration observed at the cardiac apex in our case could be explained by a severe increase in the ventricular filling pressures following the spherical remodeling and the reduction of contractility. Iskander reported a case of left ventricular free wall rupture due to Takotsubo cardiomyopathy with literature review for a total of about 15 cases published until 2018. In almost all of these cases the clinical presentation was ST elevation with wall motion presenting the typical apical ballooning pattern, as in our case. Therefore, this evolution has already been reported, although it is very rare (about 0.5%) [18].

5. Conclusions

Stress cardiomyopathy is increasingly reported in COVID-19 patients. The mechanisms underlying myocardial injury in this particular setting are unknown. The cardiac autopsy findings herein reported support the pathogenic role of increased catecholamine levels and highlight the presence of a significant interstitial inflammatory infiltrate, made up by macrophages, which remains of uncertain significance.

Disclosure statement

The authors declare that they have no conflicts of interest and nothing to disclose.

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