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CASE REPORT

Progressive chronic SARS-CoV-2-positive giant cell myoendocarditis with atrial standstill and sudden cardiac death

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Abstract

Giant cell myocarditis (GCM) is a rare condition. Its association with SARS-CoV-2 has not been described before. The 46-year-old female patient was admitted to the clinic on September 2020. She had 7 year adrenal insufficiency history and infarct-like debut of myocardial disease in November 2019. After COVID-19 in April 2020, cardiac disease progressed. The examination showed low QRS voltage, QS complexes in V_1–V_5 leads, atrial standstill, left ventricular systolic and restrictive dysfunction, elevated anti-heart antibodies, and subepicardial late gadolinium enhancement by magnetic resonance imaging. Endomyocardial biopsy and pacemaker implantation were performed, but the patient died suddenly due to ventricular tachycardia or ventricular fibrillation (the resuscitation was ineffective). The autopsy revealed GCM, SARS-CoV-2, and Parvovirus B19 were detected in the myocardium. The role of SARS-CoV-2 in the pathogenesis of autoimmune myocarditis is discussed.

Keywords SARS-CoV-2; Giant cell myoendocarditis; Atrial standstill; Sudden cardiac death; Endomyocardial biopsy

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Introduction

In 2020, severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has taken its place among the established etiological factors of myocarditis. According to the mechanism of action, the experts classify it as ACE2-tropic virus with possible cardiotoxicity.[1] The development of RNA-positive coronavirus myocarditis was demonstrated in COVID-19 patients.[2] However, the ability of the virus for long-term persistence and its role in maintenance of chronic myocarditis have not been studied. It was reported only that in the acute phase of coronavirus pneumonia, almost three-fourth of patients had significantly elevated titers of anti-heart antibodies, which correlated with cardiac injury and prognosis.[3] There are still no definite ideas about the role of COVID-19-associated autoimmune heart damage, and treatment options for coronavirus myocarditis remain unclear.

Case report

A 46-year-old female patient was first admitted to the clinic on September 10, 2020. She complained of shortness of breath during physical exertion, palpitations, weakness, chest pain, episodes of blood pressure elevation up to 160 and 90 mmHg and transient leg oedema. Her medical history was remarkable for primary adrenal insufficiency with recurrent Addisonian crises for 7 years; she received hydrocortisone and fludrocortisone replacement therapy. TEE parameters at that period of time were normal.

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In November 2019, after an intestinal infection, chest pain and shortness of breath appeared. Since February 2020, after a number of upper respiratory tract infections, weakness and dyspnoea deteriorated, episodes of hypotension occurred. TEE revealed pulmonary hypertension and left ventricular ejection fraction (EF) decline to 37%. Electrocardiogram (ECG) recorded a sinus rhythm. The coronary angiography showed no abnormalities. Chest computed tomography findings were consistent with right-sided pneumonia without signs of pulmonary embolism. Heart failure treatment was carried out. There was a 3 day long episode of fever up to 38C. Nasopharyngeal swab for SARS-CoV-2 was negative. The patient noted an increase in dyspnoea, weakness and leg oedema. Chest computed tomography revealed bilateral viral pneumonia with less than 50% of lung parenchyma affected. Antibacterial and symptomatic therapy was performed. In July 2020, SARS-CoV-2 serum IgG level was 139 units/L (normal value less than 10), NT-proBNP up to 1000 pg/mL.

Physical examination: BMI 26.7 kg/m^2, vitiligo, diminished breath sounds over the lower lungs fields, blood pressure 100/60 mmHg, heart rate 55 beats per min, no murmurs, liver was not enlarged. Blood tests showed slight leukocytosis (9.9 × 109), erythrocyte sedimentation rate 15 mm/h, CRP 14 mg/L, fibrinogen 4.64 g/L, hypogammaglobulinemia (9.1%), creatinine 107–127 μmol/L (glomerular filtration rate 54–43 mL/min), uric acid 471 μmol/L, and thyrotrophic hormone 2.2 μME/mL. Anti-heart antibodies were significantly elevated: anti-cardiomyocyte antibodies 1:160 (N 1:40), anti-smooth muscle antibodies 1:160 (N 1:40) and anti-cardiac conducting tissue antibodies >1:320 (N 1:40). The IgG to SARS-CoV-2 decreased to 18 units/L.

Electrocardiogram series and 24 h ECG monitoring registered nodal rhythm with alternating bundle branch block, low QRS voltages, and QS complexes in V_1–V_5 leads (*Figure 1*). Based on TEE, left ventricle was not enlarged (EDD 2.5 cm/m^2) while left and right atria (39 and 40 mL/m^2) and right ventricle (3.5 cm) were dilated. There were both systolic and diastolic dysfunction (EF 48%, VTI 11.3 cm, E/A 2.9, E/E 14.3), pulmonary hypertension (52 mmHg), severe mitral and tricuspid regurgitation, and pericardial separation (5–8 mm). Cardiac MRI revealed intramyocardial LGE in ventricular septum and subepicardial LGE in basal segments of left ventricle and in atrial myocardium (*Figure 2*). Cardiotropic therapy included spironolactone and furosemide only due to hypotension and rhythm disturbances.

The endomyocardial biopsy was postponed due to relapse of febrile fever. A month later, the patient was admitted to the clinic again with increasing dyspnoea, leg oedema, and slight ascites. EF decreased to 37% (*Figure 2*), 24 h ECG monitoring recorded more than 1000 premature ventricular beats and episodes of non-sustained ventricular tachycardia.

Figure 1 Electrocardiograms of patient. (A) Electrocardiogram (ECG) at the admission to the clinic dated 10.09.2020 (nodal rhythm without signs of atrial activity, narrow QRS complex, heart rate 55 per min, right axis deviation, low QRS voltage, QS in V_1–V_5 leads). (B) ECG dated 14.09.2020 (change to left axis deviation). (C) ECG dated 25.10.2020 (no atrial activity, ventricular pacing with 60 per min rate). (D) ECG from 28.10.2020 during unsuccessful resuscitation (ventricular fibrillation with pacing spikes). Paper speed 25 mm/s.

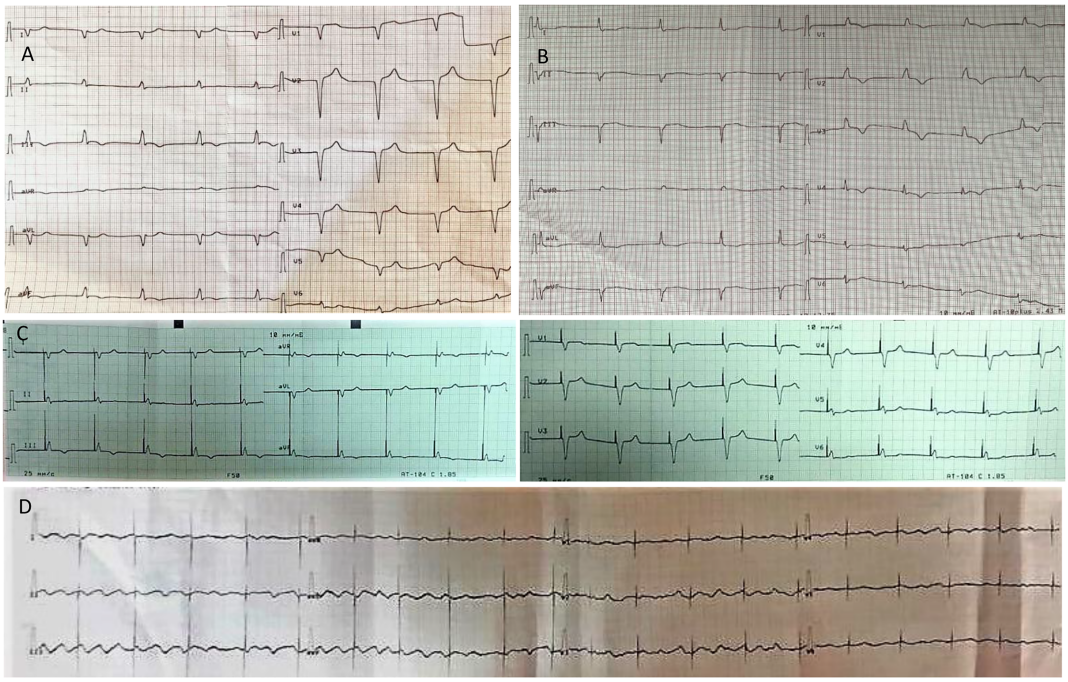
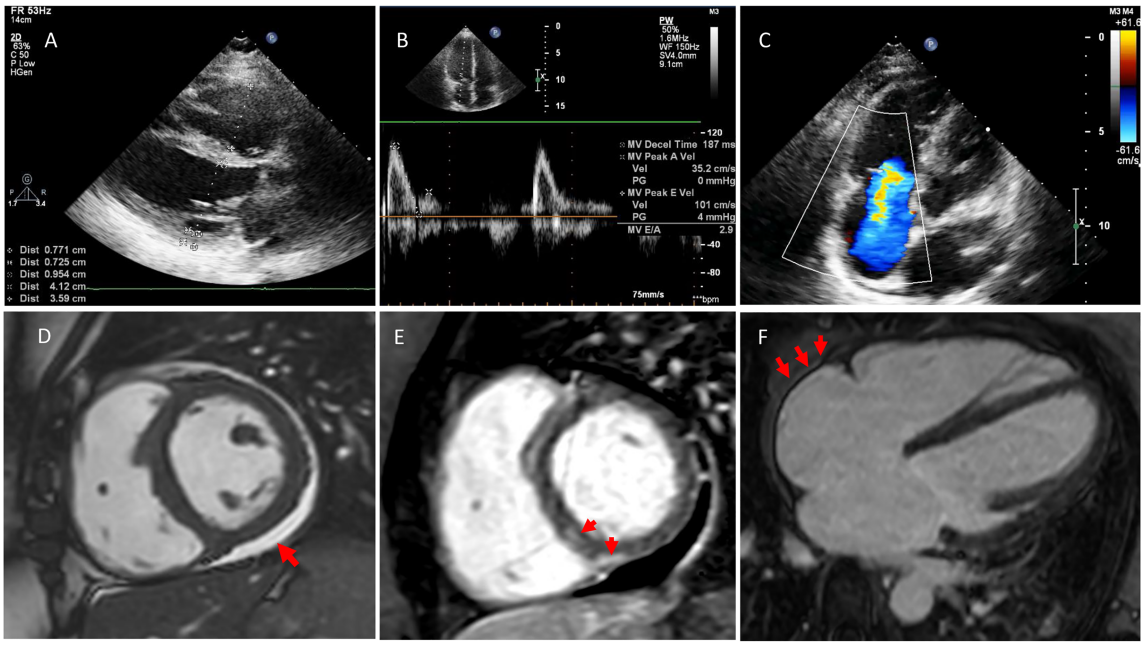


Figure 2 Cardiac visualization of patient. (A–C) Echocardiograms. (A) Enlangered right ventricle and normal size of left ventricle; (B) restrictive dysfunction of left ventricle; (C) sever tricuspid regurgitation by Doppler. (D–F) Cardiac MRI with gadolinium. (D) Short axis view at mid-level, arrows show fluid in the pericardial cavity, E - short axis view, foci of late gadolinium enhancement along posterior wall of LV and posterior septal segment, F - four-chamber view, areas of late gadolinium enhancement along the right atrium myocardium.



During implantation of a dual-chamber pacemaker, AV nodal rhythm with complete atrial electrical inactivity («atrial standstill») and low ventricular electrical activity were observed. Atrial electrode implantation failed because of ineffective stimulation. Ventricular pacing with 60/min frequency was performed (*Figure 1*). Endomyocardial biopsy of the right ventricle showed active lymphocytic myocarditis and thrombotic masses in the endocardium; parvovirus B19, adenovirus and herpetic viruses were not detected.

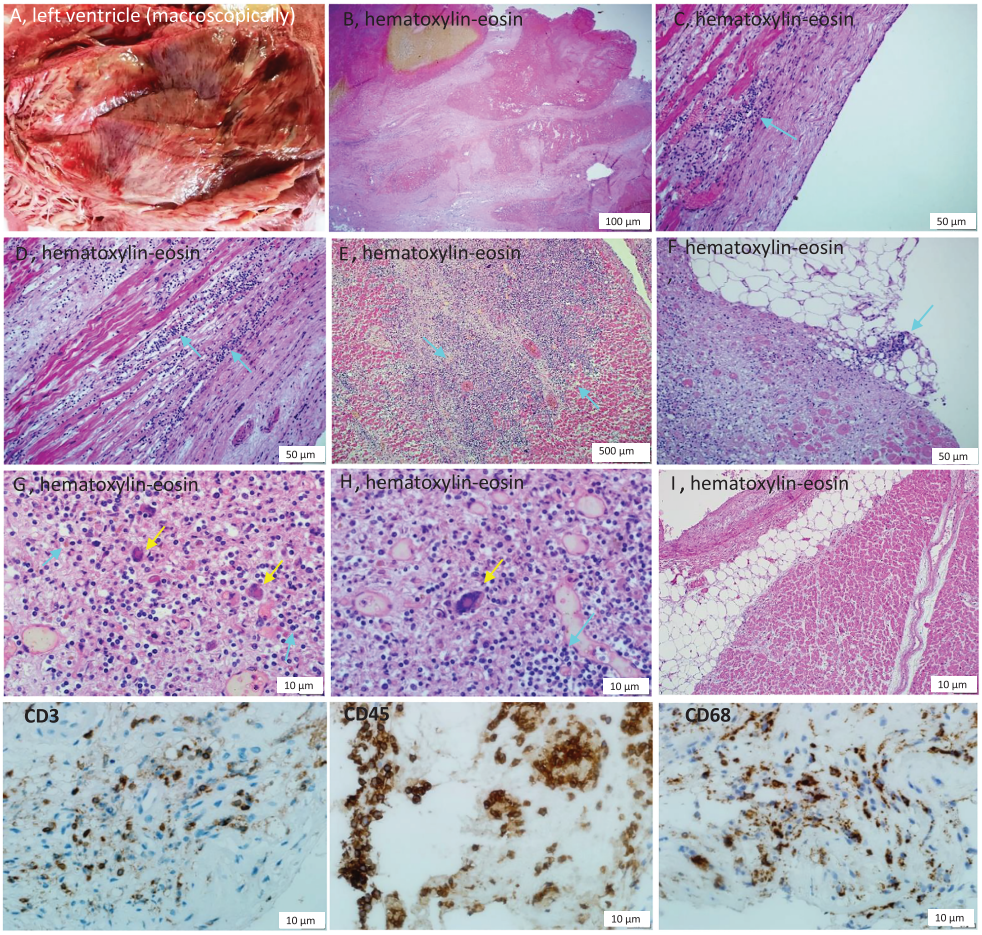
In view of the biopsy results and increasing mineralocorticoid insufficiency (potassium up to 7 mEq/L, sodium 133 mEq/L), pulse therapy with methylprednisolone 500 mg (two times) combined with fludrocortisone was started. As a result electrolyte levels normalized. However, on October 28, 2020, the patient developed cardiac arrest; initially, ventricular tachycardia 240 per min was registered with further conversion to ineffective stimulation (*Figure 1*). Resuscitation was unsuccessful. The diagnosis was formulated as chronic SARS-CoV-2-associated active lymphocytic endomyopericarditis, autoimmune polyglandular syndrome type 2. The autopsy showed presence of SARS-CoV-2 and Parvovirus B19 in myocardium samples (by PCR), diffuse myocardial changes on macroscopic examination (mottled flabby myocardium), highly active lymphocytic myocarditis with giant cells, interstitial oedema, cardiomyocyte necrosis, microvasculitis, massive replacement fibrosis and lipomatosis, and lymphocytic tromboendocarditis and pericarditis (*Figure 3*).

Discussion

According to World Health Organization, myocarditis is an inflammatory disease of the myocardium diagnosed by established histological, immunological, and immunohistochemical criteria. The same criteria are used in the diagnosis of coronavirus myocarditis, which requires myocardial biopsy. The mechanisms of COVID-19–related myocarditis include the direct viral injury (by binding spike protein of the SARS-CoV-2 to the membrane protein angiotensin-converting enzyme 2) and immune-mediated cardiac damage.[4] Microvascular pathology (endotheliitis, coronariitis, and microthrombosis) plays an independent role in coronavirus-induced myocardial injury. The myocarditis is usually diagnosed in the absence of ischemic causes, but in case of COVID-19–related myocarditis, microvascular ischemia may contribute to myocardial injury as well. The associated pericarditis may result in arrhythmias.

Giant cell myocarditis (GCM) is one of the rarest and most malignant forms of myocarditis. Its association with SARS-CoV-2 infection has not yet been described. During the pandemic, the wish of clinicians to rule out a COVID-19 diagnosis

Figure 3 Post-mortem morphological study of the myocardium. (A) Macroscopic study (myocardium is flabby, patchy, red-brown, without any focal lesions). (B,C) Microscopic study of right ventricle, (D–I) microscopic study of left ventricle; haematoxylin and eosin staining: thrombotic masses adhered to the endocardium (B), endocardium is thickened, with lymphocytic infiltrates (C, blue arrows), interstitial oedema, massive lymphocytic infiltration of the myocardium (blue arrows) with focal fibrosis, cardiomyocyte dystrophy and necrosis (D,E), lymphocytic pericarditis, severe substitutive fibrosis in the myocardium (F), diffuse lymphocytic infiltration of the myocardium with giant cells (G,H, yellow arrows), focal lipomatosis in the myocardium, microvasculitis (I). Low series—immunohistochemical (IHC) study with antibodies to CD3, CD45 lymphocytes and CD68 macrophages (massive clusters of IHC-positive cells in the left ventricular myocardium). Magnification 50× (E), 100× (B), 200× (C, D, & F), and 400× (G, I, IHS).



could be the reason of delayed endomyocardial biopsies.[5] This problem is fully confirmed by the case report: we had to wait for a whole month for a biopsy due to the onset of febrile fever in patient.

In the pathogenesis of GCM, autoimmune reactions play vital role. Up to 15–19% of cases of GCM occur in patients with other autoimmune conditions such as Hashimoto thyroiditis, Graves' disease, inflammatory bowel disease, myasthenia gravis, rheumatoid arthritis, polymyositis, or lymphoma.[6] Viral-positive GCM cases have also been described.[7] In our case, GCM developed in a patient with a polyglandular syndrome. Despite the autoimmune nature of both diseases, this combination was described only once.[8]

The greatest interest in the present case is the specifics of clinical course of GCM and its possible relationship with a new coronavirus infection. In the beginning, the disease manifested itself with an infarct-like picture. The following deterioration of dyspnoea was associated with a non-specific viral infection. The third episode of infection contributed to the cardiac disease progression (Spring 2020) was identified as COVID-19. Therefore, we cannot claim that there is an exclusive etiological role of SARS-CoV-2 in the development of myocarditis.

We also do not know when exactly myocarditis acquired the signs of GCM—from the very beginning or just after COVID-19. Due to slow progression of systolic dysfunction until summer 2020, we favour the second hypothesis. SARS-CoV-2 could be a powerful inducer of anti-heart antibodies production, because high anti-heart antibodies titers were observed. Myocarditis rapidly progressed directly after COVID-19: decline in systolic function, onset of ventricular arrhythmias and atrial standstill occurred. There is evidence

that proinflammatory cytokines (IL-6) could cause fibrofatty replacement and displacement of desmosomal proteins from the cardiomyocyte membrane.[4]

In addition, thrombovasculitis and thromboendocarditis, so typical for coronavirus cardiac injury, were found. Examination of autopsy material revealed DNA from parvovirus B19. This virus is tropic to the endothelium that may have played a role in the infarct-like debut of myocarditis. However, parvovirus B19 can be only a bystander in the myocardium. Its presence, regardless of activity, does not affect negatively the results of immunosuppressive therapy for myocarditis.[9] More significant is the detection of SARS-CoV-2 RNA in the myocardium five months after COVID-19. Previously, only cases of borderline SARS-CoV-2-positive myocarditis 4 weeks after COVID-19 were described.[10] Our data not only prove long-term persistence of coronavirus in the myocardium but also suggest a direct role of the SARS-CoV-2 in aggravation of autoimmune myocarditis.

The most difficult in such cases is the choice of the optimal way of myocarditis treatment. When coronavirus is detected in the myocardium, standard cardiotropic therapy is usually used.[1,11] There is still no effective antiviral therapy. However, in our case was an indication for parenteral corticosteroid therapy such as decompensated adrenal insufficiency. Electrolyte disorders due to mineralocorticoid insufficiency, cardiac conduction abnormalities, and hypotension made optimal treatment of heart failure impossible.

Our case demonstrates the great importance of autoimmune reactions in the pathogenesis of post-COVID myocarditis. We believe that immunosuppressive therapy should be considered in many cases of post-COVID chronic myocarditis with high immune activity. As a positive example, we can cite a case of retrospective diagnosis of coronavirus nature of myocarditis: immunosuppressive therapy for «virus-negative» myocarditis with good results was carried out for 2 months before the virus in myocardium was detected.[12]

Conflict of interest

All authors declare no conflict of interest.

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