DOI: 10.15825/1995-1191-2020-4-173-182

VERIFIED CHRONIC SEVERE GIANT CELL MYOCARDITIS: AN INEVITABLE CHOICE FOR HEART TRANSPLANTATION

O.V. Blagova[1], Yu.A. Lutokhina[1], D.H. Ainetdinova[1], V.P. Sedov[1], A.N. Volovchenko[1], D.A. Parfenov[1], N.P. Mozheiko[2]

[1] Sechenov University, Moscow, Russian Federation
[2] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

Myocarditis has polymorphic clinical manifestations and is one of the main causes of heart transplantation. We present a clinical case of a 43-year-old female patient who was admitted to the clinic with biventricular heart failure (NYHA class 3–4). She periodically noted exacerbations of bronchitis against the background of prolonged smoking. Twenty-one months prior to hospitalization, she first noted a shortness of breath without an obvious connection with the infection. Her ejection fraction (EF) decreased to 34%, pleural and pericardial effusion was revealed. Coronary angiography found no abnormalities. However, MRI showed subendocardial contrasting of the left ventricular (LV) apex. The diagnosis was myocarditis. Within six months, the patient received therapy with 30 mg/day prednisolone and cardiotropic therapy. Her shortness of breath intensified, and the lower extremities swelled. Examination in the clinic showed a sharp decrease in QRS voltage, QS complexes in the V1–V6 leads, dilation of all heart chambers, thrombus in the LV apical aneurysm, 16% EF, 3.9 cm VTI, 454 mmHg dp/dt, and a sharp increase in anticardiac antibody titers (up to 1:320). Endomyocardial biopsy was not performed due to the patient's rapidly deteriorating condition, the need for cardiotonics, and signs of multiple organ failure. She was transferred to Shumakov National Medical Research Center of Transplantology and Artificial Organs, where extracorporeal membrane oxygenation was performed; orthotopic heart transplant was successfully performed. The patient's condition was stable for the next year. Investigation of the explanted heart revealed a picture of giant cell myocarditis. Issues of diagnosis, possibility of a long-term chronic course, as well as methods of treatment of this variant of myocarditis, including the key role of heart transplantation, are discussed.

Keywords: giant cell myocarditis, heart failure, left ventricular aneurysm, anticardiac antibodies, heart transplantation.

INTRODUCTION

Myocarditis is an inflammatory lesion of the myocardium. It has various origins and it is one of the main causes of heart failure in young people, including incurable heart failure and requiring heart transplantation (HT). Unrecognized myocarditis is often what lies behind the diagnosis "dilated cardiomyopathy" (DCM), which competes on equal terms with coronary heart disease (CHD) as a reason for referral to HT, and according to some reports, it is ahead of it [1]. At the same time, myocarditis is a potentially curable disease, and its timely detection can be critically important for patient prognosis.

The main problem of myocarditis diagnosis in clinical practice, including in Russia, is the almost complete inaccessibility of endomyocardial biopsy (EMB), an invasive interventional technique that is often indispensable for verifying myocarditis diagnosis and determining the scope of therapy. European experts, the authors of the first guidelines on myocarditis in 2013, consider EMB to be absolutely necessary in all cases of suspected myocarditis [2]. American experts recommend performing EMB in acute DCM syndrome with intact coronary arteries, inotropic support if necessary, in the presence of 2nd-degree and 3rd-degree AV block, sustained ventricular tachycardia or treatment failure within 1–2 weeks, i.e. if not in all, then in very many cases of suspicion of severe chronic myocarditis [3].

The main advantages that distinguish EMB from all non-invasive techniques (including the best among them – contrast-enhanced magnetic resonance imaging of the heart) are the ability not only to make myocarditis diagnosis reliable, but to determine its morphological type and the presence/absence of a viral genome in the myocardium, which largely determines the treatment [1]. If myocarditis diagnosis (most often lymphocytic) can be made with a high degree of probability based on non-invasive comprehensive examination, including the use of the proposed and tested algorithm [4], then non-invasive diagnosis of rare and prognostically most unfavorable histological variants without biopsy is absolutely impossible.

Corresponding author: Olga Blagova. Address: 6/1, B. Pirogovskaya str., Moscow, 119992, Russian Federation. Phone: (499) 248-62-33. E-mail: blagovao@mail.ru

These variants include, first of all, giant cell myocarditis (GCM), which was described by S. Saltykov in 1905. Its distinctive morphological feature lies in the presence of inflammatory lymphocytic infiltrates, including giant cells and eosinophils, and cardiomyocyte necrosis, but without formation of sarcoid granulomas [4]. The true incidence of this type of myocarditis is unknown due to the difficulties of its in vivo diagnosis; as a rule, only descriptions of individual clinical cases are given. The largest multicenter registries include a few dozen patients, and transplant surgeons are the most likely to have such observations. Each case is unique and presents physicians with the challenge of aggressive diagnosis and therapy, as well as timely determination of indications for HT [5–7].

We present a clinical case of a patient with severe chronic myocarditis, which illustrates the long-term course of unrecognized GCM and the current possibilities of saving the patient's life through surgery quickly even in the end stage of the disease.

CLINICAL CASE

Patient L., female, 43 years old, was admitted to the Vinogradov Faculty Therapeutic Clinic at Sechenov University on November 11, 2019, presenting with general weakness, shortness of breath at minimal exertion, nausea, swelling of the legs and feet, and increased abdominal volume.

From medical history. *Family history of cardiomyopathy is not burdened. The patient is a psychologist by profession, lives in Krasnoyarsk, travels a lot, smokes up to 30 cigarettes a day for a long time, periodically notes exacerbations of bronchitis with prolonged (up to a month) cough, has not taken antibiotics, no other bad habits. Over 20 years ago, post-tuberculous changes were detected in her lungs; X-rays were regularly performed; there were no dynamics, and she did not need any treatment. She had a history of two spontaneous vaginal deliveries (the last one at the age of 39), there were no heart complications. Until 2018, she considered herself healthy. In February, she felt unwell, difficulty breathing without apparent fever, and regarded it as another exacerbation of bronchitis. For 2 weeks, while on vacation, she noted a decrease in tolerance of previously habitual physical activities. In March 2018, she for the first time noted the emergence of severe shortness of breath, cough, a feeling of lack of air, mainly at night, and progressive weakness. She consulted cardiologists on an outpatient basis, no adequate examination and treatment was carried out.*

In April, due to further deterioration in her health, the ambulance team took her to the hospital, where she was hospitalized. Initially, her condition was treated as pneumonia. However, her ever-first EchoCG revealed a decreased ejection fraction (EF) to 34% or less, diffuse left ventricular (LV) hypokinesis, mitral regurgitation grade 3, increased pulmonary artery systolic pressure (PASP) to 54 mm Hg., pleural and pericardial effusion. Coronarography showed no abnormalities. MRI revealed delayed gadolinium accumulation mainly in the LV apex; there was no evidence of thrombosis. The condition was regarded as myocarditis; therapy with oral prednisolone was administered per os 30 mg/day for 6 months (there were no recommendations on the duration of treatment), torsemide, beta-blockers and angiotensin-converting enzyme (ACE) inhibitors. Against this background, she noted decreased shortness of breath. According to EchoCG from April and June 2018, EF was 37–39%. However, cushingoid manifestations appeared (visceral obesity, "moon-shaped face", "hump"), she on her own gradually withdrew prednisone. Outpatient examinations revealed elevated cytomegalovirus (CMV) IgG antibody titers, and other herpetic viruses were detected.

In February 2019, she noted a deterioration in her health in the form of increased shortness of breath and increasing general weakness. The condition was regarded as DCM. Ivabradine 10 mg/day, sacubitril-valsartan 200 mg/day (withdrawn due to episodes of blood pressure dropping to 60/30 mmHg), digoxin 0.125 mg/day, torsemide 20 mg/day, nicorandil 20 mg/day, eplerenone 50 mg/day were administered. Despite feeling unwell, she went on vacation three times a year, tolerated the trips relatively satisfactorily, and attempted unconventional remedies. In October 2019, she noted renewed dyspnea with minimal physical exertion, a constant feeling of shortness of breath and nausea, increasing edema of the legs and feet. An EchoCG test performed on October 22, 2019 revealed LV apex aneurysm, EF did not exceed 18–20%. The patient was hospitalized for further examination and treatment.

On admission, *her condition was severe. Height 180 cm, weight 76 kg, BMI = 23.46 kg/m^2. Body temperature 36.50 °C. Her skin was moderately pale with normal moisture. Moderate swelling of the legs, feet, thighs. Respiratory rate (RR) 20/minutes, hard breathing, $SatO_2$ 95%. In the lungs, breathing was vesicular in all parts of the lungs, there was no wheezing. Dull heart sounds, systolic murmur at the apex. Heart rate 84/min, correct rhythm, blood pressure 70/40 mm Hg. The abdomen was somewhat tense, painless, moderately enlarged due to ascites. The liver and spleen were not enlarged.*

Blood tests showed *slight leukocytosis (10.9 × 10^9/L, lymphocytes 33.3%, neutrophils 53.2%, eosinophils 2.3%), Hb 156 g/L, platelets 273 × 10^9/L, ESR 5 mm/hour, minimal increase in AST (49 U/L), total bilirubin (27.3 μmol/L) due to direct bilirubin (11.2 μmol/L), normal albumin (35 g/L), creatinine (103.3 μmol/L), lipids, electrolytes, hyperuricemia (606 μmol/l). Blood group AB (IV), Rh factor positive.* ***Urine tests*** *showed decreased specific gravity (1010), urobilinogen 3+.*

ECG *(Fig. 1) revealed a sharp decrease in QRS voltage in standard leads and almost complete absence of R*

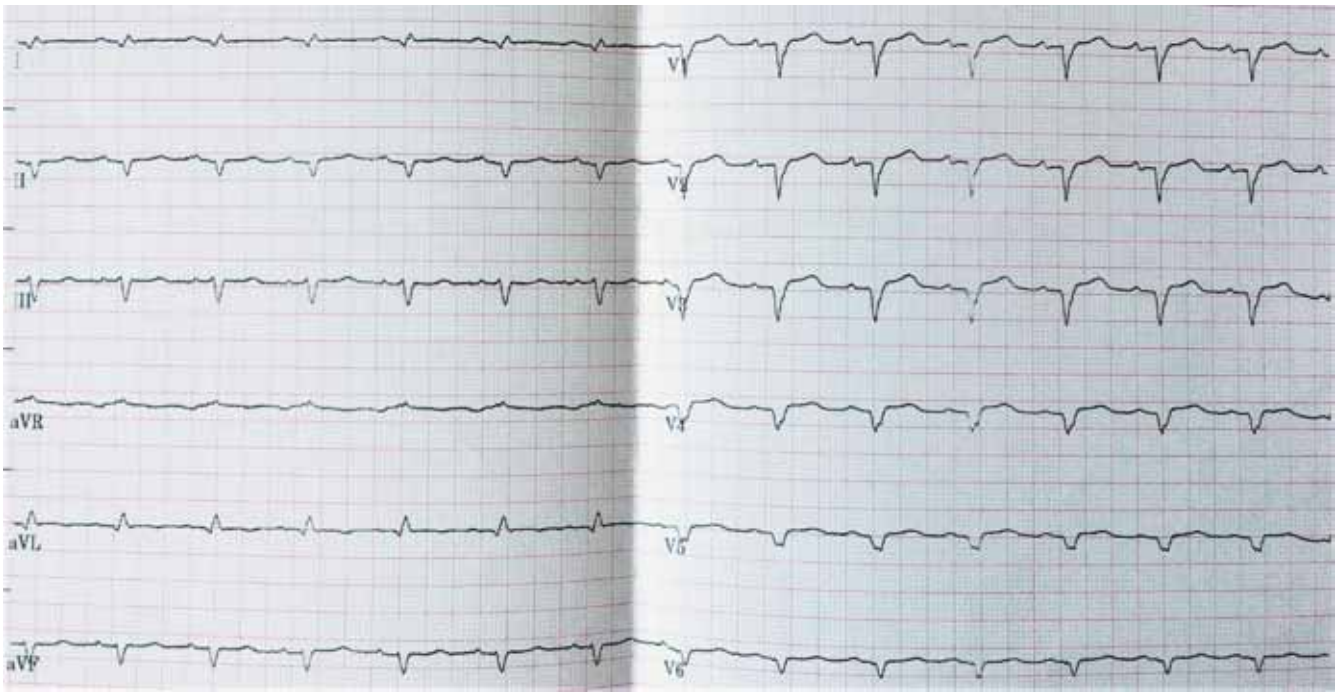

Fig. 1. Patient's ECG upon admission at the hospital. Recording speed 25 mm/s. Sinus rhythm, sharp decrease in QRS voltage in standard leads, QS complexes in the V1–V6 leads, minimum R waves in the II, III, aVF leads, QRS duration 120 ms, PQ 190 ms

waves (QS complexes in V1–V6 leads, minimal R in leads II, III, aVF); QRS lasted for 120 ms, PQ 190 ms, which indicated a pronounced decrease in viable myocardial volume. Holter ECG monitoring revealed no significant ventricular arrhythmias.

***EchoCG** (Fig. 2) confirmed expansion of all heart chambers (LV end-diastolic diameter 6.2 cm, end-diastolic volume 155 mL, end-systolic volume 129 mL, left atrium 4.4 cm, 87 mL, right atrium 103 mL, right ventricle 3.5 cm), LV apex aneurysm lined with thrombus (3.3 × 1.2 cm), a sharp decrease in LV contractility (EF not exceeding 16%, VTI 3.9 cm, dp/dt 454 mm Hg), impaired LV diastolic function according to the pseudonormal type (E/A = 1.17, E/Em 9.2 at the norm <8) in the absence of hypertrophy of its walls (interventricular septal thickness 8 mm, posterior wall thickness 9 mm), mitral and tricuspid regurgitation grade 3, pulmonary hypertension (PASP 45 mmHg), small amount of fluid in the pericardial cavity (posterior wall 1.2 cm, lateral wall 0.7 cm, front wall 0.4 cm, in the right atrium 0.7 cm).*

***Chest X-ray** showed an enlarged heart, a calcified focus with 7 mm in diameter in the right lung, no effusion in the pleural cavities. **Ultrasound** confirmed the presence of free fluid in all parts of the abdominal cavity, the liver at the upper limit of the norm.*

*An **MRI** conducted in May 2018 showed no signs of non-compact myocardium, a scar in the LV apex is clearly defined, no blood clots. Cardiac MRI could not be repeated due to the deterioration of the patient's condition.*

So, there was no doubt about severe myocardial injury with the development of DCM syndrome and biventricular heart failure. But the nature of the lesion was not completely clear. Emergence of dyspnea more than 2 years after her second birth did not allow us to speak of peripartum cardiomyopathy, although we could not completely rule out delayed decompensation of primary (genetically determined) cardiomyopathy. Regular exacerbations of chronic bronchitis and not quite distinct connection of the onset of the disease and one of the exacerbations of chronic bronchitis, as well as a winter trip to India, could become a background (trigger) for myocarditis development. Taking into account the severity of decompensation in April 2018 with clinical of anginal pain, severe dyspnea, ECG (QS complexes in all chest leads), EchoCG (LV apical akinesis and thrombus), and MRI (subendocardial contrasting of the apex over 50% of myocardial thickness), infarct-like debut of severe myocarditis with its subsequent chronicity seemed to be the most likely.

Myocarditis was also supported by a clear positive response to medium-dose prednisolone therapy (clinical and echocardiographic) in the anamnesis. However, insufficient improvement and rapid loss of effect could indicate insufficient monotherapy doses, a particular myocarditis severity, its viral nature, and the presence of an initial genetic myocardial disorder. For the first time, blood tests for anti-cardiac antibodies revealed a concomitant sharp increase in antibody titers to most heart antigens, including cardiomyocyte antigens (Table), which indicated in favor of a highly immune component

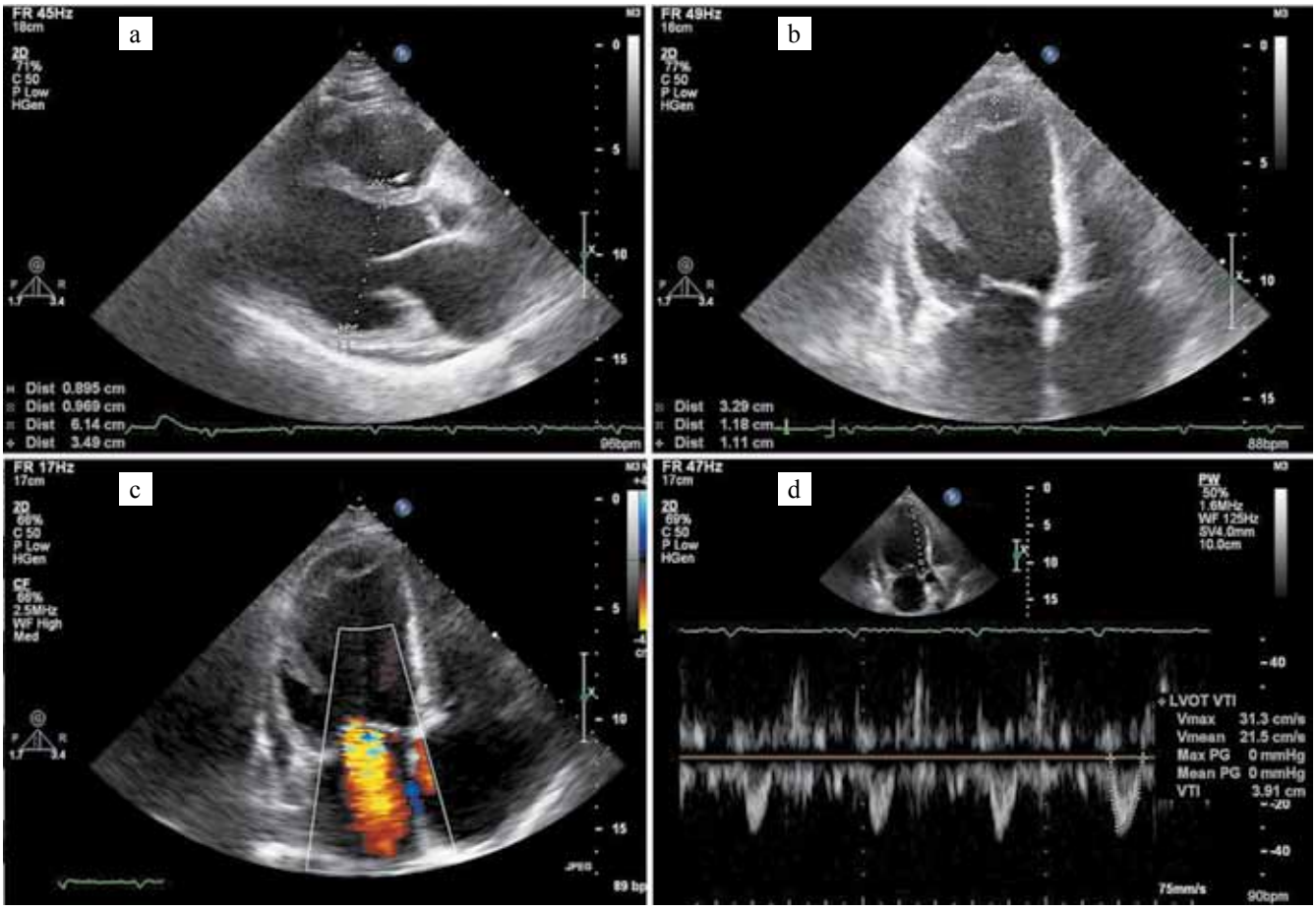

Fig. 2. Patient's ECG upon admission at the hospital. a) two-chamber position, increase in the size of the left and right ventricles; b) four-chamber position underlying thrombus in the left ventricular apical aneurysm; c) color flow Doppler, flow of grade 3 mitral regurgitation (up to the left atrial roof); d) low cardiac output syndrome (sharp decrease in VTI)

of myocarditis. However, this did not allow to completely rule out active viral infection in the myocardium or determine the extent of immunosuppressive therapy.

The only study that could have answered the question about further drug treatment tactics is EMB. However, the severity of the patient's condition increased the risk of this study and made the prospects for baseline therapy for myocarditis questionable, especially given the age of the disease. Despite the high likelihood of active myocarditis, the time for its treatment was obviously missed, the only way to avoid an unfavorable outcome seemed to be HT.

Table

Titers of various anti-heart antibodies in the blood

Indicator	Result	Norm
Antibodies to cardiomyocyte nuclear antigens	none	none
Antibodies to endothelial antigens	1:40	1:40 antibody titer
Antibodies to cardiomyocyte antigens	1:320	1:40 antibody titer
Antibodies to smooth muscle antigens	1:320	1:40 antibody titer
Antibodies to antigens of fibers of the cardiac conduction system	1:160	1:40 antibody titer

Despite attempts at complex cardiotropic therapy (enoxaparin, furosemide, eplerenone), the patient's condition did not improve during her stay in the clinic. Due to pronounced oliguria (100–150 mL of urine for two days) against the background of persistent hypotension (80/60 mmHg or less), which persisted despite complete discontinuation of bisoprolol, she was transferred to the intensive care unit, where, as a result of constant infusion of low doses of dopamine and administration of lasix 240 mg/day resulted in positive diuresis (3900 mL per day) with some reduction in dyspnea. However, diuresis decreased to 700 mL again after dopamine withdrawal and lasix infusion continuation. EchoCG (on November 18, 2019) showed no positive dynamics (EF less than 20%, VTI 3 cm, severe valve regurgitation).

Infusion of dobutamine, lasix and potassium chloride (due to progressive hypokalemia) was resumed, followed by addition of norepinephrine. However, hypotension, oliguria persisted, nausea and vomiting appeared (regarded as a manifestation of ischemic hepatitis); there was an increase in the level of liver enzymes (by November 22, the AST level was 826 IU/L, ALT – 678 U/L). Asym-

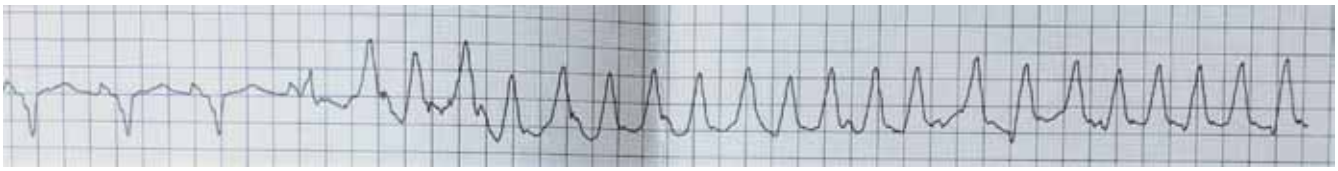

Fig. 3. Patient's ECG in the intensive care unit. Bedside monitor recording, speed 25 mm/s. An episode of nonsustained ventricular tachycardia

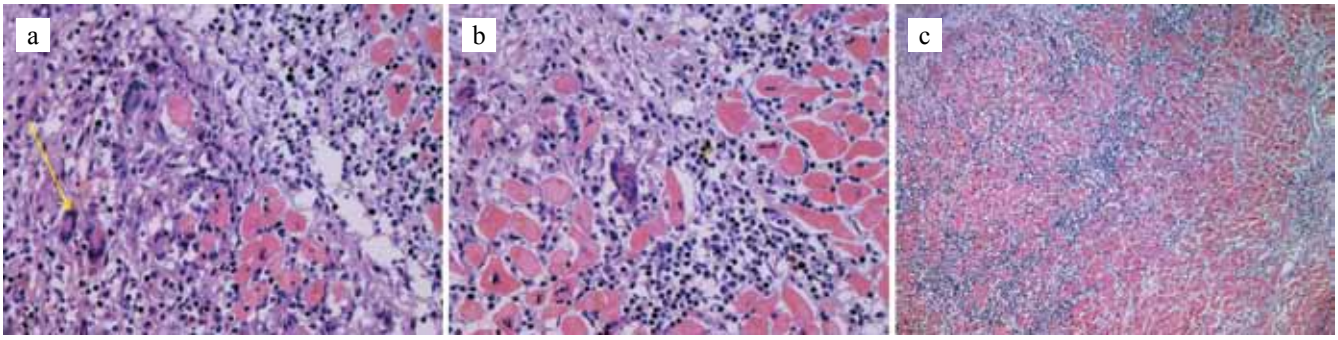

Fig. 4. Results of morphological examination of the explanted heart. a) giant multinucleated cells among diffuse inflammatory infiltration in loose fibrous connective tissue in the interstitium and between cardiomyocytes; b) giant multinucleated cell among diffuse inflammatory infiltration in loose fibrous connective tissue in the interstitium and between cardiomyocytes; c) diffuse focal mononuclear inflammatory infiltration in the edematous interstitium and in sclerosis zones; among inflammatory cells there are multinucleated giant cells. H&E stain. 200× (a, b), 100× (c) microscope magnification

ptomatic episodes of unstable ventricular tachycardia were recorded on the monitor screen (Fig. 3).

*Multi-slice computed tomography (**MSCT**) of the brain and abdominal organs revealed no volumetric lesions; thoracic examination revealed a group of calcified foci, a zone of severe fibrosis, and pleural adhesions in the upper lobe of the right lung. There was emergency consultation with a phthisiatrician: residual changes after spontaneously healed tuberculosis of the upper lobe of the right lung. Performing HT was not contraindicated. When prescribing immunosuppressive therapy, it was rational to administer a course of preventive chemotherapy with isoniazid (0.6/day) against the background of vitamin B_6 (0.06/day) and pyrazinamide 1.5/day.*

After consultation at the Shumakov National Medical Research Center of Transplantology and Artificial Organs with clinical diagnosis of DCM of unspecified genesis, she was on November 22, 2019 transferred to the intensive care unit of the Center, where extracorporeal membrane oxygenation (ECMO) was immediately initiated. Clinical picture at the time of transfer: myocardial infarction (necrosis) of the anterior apical localization of April 2018. Chronic infectious-immune (viral-immune?) myopericarditis, severe course, high degree of immunological activity, in the acute phase? Left ventricular apex thrombosis. Low ejection syndrome. Arrhythmia: ventricular extrasystole, unstable ventricular tachycardia. Relative mitral and tricuspid insufficiency grade 3. Moderate pulmonary hypertension. Chronic heart failure, NYHA FC 3–4, stage IIB: peripheral edema, bilateral hydrothorax, ascites. Acute ischemic hepatitis. CKD stage 3b. Hyperuricemia. Chronic bronchitis without exacerbation. Post-tuberculous changes in the right lung.

Orthotopic HT was performed on the first day of stay at the Shumakov National Medical Research Center of Transplantology and Artificial Organs (on the night of November 23, 2019). Morphological examination of the explanted heart revealed highly active giant cell myocarditis (Fig. 4). During the following year, the patient's condition remained stable, there were no signs of graft rejection.

DISCUSSION

The presented case demonstrates a number of peculiarities of the course and management of myocarditis in general (and GCM, in particular), the analysis of which seems to be very instructive for the entire team of doctors handling such patients.

The debut of the disease and the diagnosis of myocarditis during that period deserve discussion. The following were the clinical grounds for the diagnosis of myocarditis in March 2018: highly probable association with a respiratory infection (another exacerbation of chronic bronchitis, rapid development of severe myocardial dysfunction with increasing dyspnea, ECG changes that were retrospectively (but not at the first visit to the doctor) considered as infarction-like and became one of the grounds for immediate hospitalization. At the same time, there were no data on troponin levels in the blood during that period, no thrombus was detected (including by MRI) in the LV.

Given the complete absence of CHD risk factors, diagnosis of myocardial infarction was rejected at the place of residence (which was also confirmed by normal coronarograms), although the development of infarction with unchanged coronary arteries (so-called MINOCA) could be discussed. MRI findings indirectly confirmed the diagnosis of myocarditis; there were no other possibilities (EMB, determination of the anti-cardiac antibody levels).

With an infarct-like onset of myocarditis, there are several possible courses – quite favorable, typical for young patients, easily diagnosed without the use of EMB, does not lead to a significant drop in LV contractility even in an acute period, does not leave irreversible consequences and is not prone to chronicity and is completely different, having a particularly severe course from the very beginning, with a diffuse drop in contractility and a persistent EF decrease [8], as it happened in our patient. In severe infarct-like onset of myocarditis, along with "banal" lymphocytic myocarditis, several special nosological forms should be considered, namely eosinophilic myocarditis, myocarditis within sarcoidosis, systemic vasculitis (eosinophilic granulomatosis with polyangiitis), and in this series – GCM. However, with GCM, this type of opening is described only in 6–9% of cases [9, 10]. Even less common are LV aneurysms [11], which are considered more characteristic of sarcoidosis and are characterized by high arrhythmogenicity (which was not the case in our case). Thrombus formation in the LV indicates a particular severity of inflammation with necrosis and endocardial involvement. In our case, delayed thrombus formation is likely to reflect a prolonged inflammatory process that remains highly active.

In any variant of myocarditis, the development of persistent cicatricial changes is an unfavorable prognostic factor, which in most cases does not allow counting on a persistent improvement in LV function as an outcome of immunosuppressive therapy (IST) [12]. In the absence of EMB data, several treatment options could be considered – only cardiotropic therapy (which had been used for some time, but did not give sufficient effect); immediate referral to HT (which is practiced in such patients, but cannot be considered optimal tactics in the absence of an accurate diagnosis); implantation of artificial LV in order to buy time and wait for the possible effect of drug treatment (hardly feasible); and, finally, use of IST (in fact, ex juvantibus therapy), which has been undertaken.

This tactic is at variance with the recommendations by European experts, but consistent with Russian realities. In many cases, such treatment gives the desired effect, since lymphocytic myocarditis is the most common option, and among about half of virus-positive cases, myocarditis (associated not with herpes or enteroviruses, but with parvovirus B19, whose impact on IST prognosis and effectiveness remains unclear) predominates. In our case, administration (essentially uncontrolled) of medium-dose prednisolone gave only short-term and insufficient clinical improvement. Further treatment tactics could not be determined without EMB.

Its implementation was one of the main objectives of hospitalization; however, upon admission it became obvious that the degree of myocardial dysfunction had reached a critical level. Diagnosis of highly immune myocarditis remained the most likely, especially based on the results of a blood test for anti-cardiac antibodies. EMB was not possible due to the patient's constant need for cardiotonic support and an increased risk of complications from the procedure. Thus, the decision to carry out immediate HT was the only possible one; retrospective GCM diagnostics confirmed the correctness of rejection from further attempts to verify the diagnosis and IST at this end stage.

Naturally, the question arises whether a timely EMB and GCM diagnostics at the onset of the disease with administration of an adequate IST could change the prognosis and allow avoiding HT or performing it in a less urgent mode. GCM is one of the rarest and probably the most malignant forms of myocarditis. The registry of the Shumakov National Medical Research Center of Transplantology and Artificial Organs contains only four cases of GCM [13]. One of the first multicenter studies of GCM included only 63 cases, patients' mean age was 43 years, men and women had the disease equally often [8]. The only transplant center in Finland with HT facilities has experience diagnosing 46 cases of GCM from 1991 to 2015, with rates increasing significantly every five years; women were twice as likely to have the disease, with a mean age of 51 years [9].

GCM is considered to be an idiopathic autoimmune variant of myocarditis, although virus-positive cases have also been described, e.g. fatal GCM induced by cytomegalovirus infection [12]. In our patient, GCM may have been supported by maximal anti-cardiac antibody titers (despite IST performed a year ago), but this sign is not absolutely specific for GCM, it only suggests the potential benefit of aggressive IST. GCM may indicate the presence of other autoimmune diseases, which are associated with GCM in 15–19% of cases [4, 8, 9] – primarily thymomas with the development of myasthenia gravis, which is characterized by the appearance of antibodies to a wide range of muscle antigens (to acetylcholine receptors, titin, myosin, smooth muscles, [14]), as well as ulcerative colitis, rheumatoid arthritis, polymyositis, Graves' disease, lymphoma, etc. The high activity of the disease with massive myocardial injury explains the high sensitivity of MRI (100%) and positron emission tomography (93%) [9]. However, there is no visual pattern specific to GCM.

The optimal extent of IST in the treatment of GCM has not been determined, although there is no doubt about its feasibility – GCM is one of the few myocarditis options for which IST is definitely recommended [2]. European and American experts also agree that GCM requires a more aggressive IST than other myocarditis options.

Over 20 years ago, an international GCM study group recommended the use of a 3-component combination (prednisolone, azathioprine and cyclosporine), although HT remained the method of choice [8]. Taking into account the importance of T cells in the pathogenesis of GCM, the use of muromonab-CD3 and antithymocyte globulin in addition to cyclosporine is being developed [15]. Attempts are being made to use cytostatics and bioactive drugs (methotrexate, mycophenolate mofetil, sirolimus, tacrolimus, rituximab, basiliximab, [16]), many of which are also used in transplantology.

However, according to various data, adverse outcomes (death and/or HT) can be avoided only in 11–42% of cases, depending on the extent of IST [4]. In a 1997 study, there were 89% adverse outcomes (with a mean time of just 5.5 months from symptom development) [8]. A five-year graft-free survival of 42% in a recent Finnish study was achieved with combined IST (70% of patients), ICD implantation in 57%, and was associated with less necrosis and fibrosis on EMB, as well as baseline troponin levels (also reflecting the severity of necrosis) of <85 ng/L and a positive response to treatment – an increase in EF by 5% or more, a decrease in NT-proBNP levels by 1000 ng/L or more [9].

Unusual for GCM is the prolonged chronic course with periods of improvement observed in our patient. In typical cases, GCM proceeds as fulminant, i.e. it requires intensive cardiotonic and respiratory support already in the acute period [5]. Its most common manifestations are acute heart failure, ventricular arrhythmias, blockages, and cardiogenic shock. Most often, it is in the acute period of GCM that the use of mechanical circulatory support is required, including ECMO, which is one of the most effective technologies for GCM. In the French intercenter register of fulminant GCM, it was applied in 85% of cases and ended with HT in 8 out of 11 patients; in 87% of fulminant GCM cases, HT or death was not avoided. However, EMB and IST were performed in a smaller proportion of patients, which brings this register closer to our observation [17]. We should refer to the experience of E. Ammirati from Milan, who conducts EMB even in patients on ECMO and total anticoagulation, understanding the critical importance of accurate GCM diagnosis for determining further treatment tactics [4].

Our patient required ECMO only in the end stage of the disease as a bridge to successful HT, which reflects a more favorable course of her GCM for almost two years. Regarding the possibility of a long course of GCM, it is worth noting the encouraging results obtained in a recent multicenter study, which included 26 patients with GCM. After 1 year, the 5-year survival rate without transplantation was 72%, the maximum period reached 20 years. However, the work does not contain information about patients who died or underwent HT in the first year of the disease [5]. In any case, it can be judged that the successful experience of the first year is a favorable prognostic sign. Cases of more than 10-year course of GCM with maintenance of EF at 30–35% level through cardiotropic therapy and IST, but still HT in the outcome of the disease have been described [18]. With timely diagnosis of GCM and adequate IST, one could hope for a similar variant of the course in our patient.

The special significance of GCM in the practice of transplantologists depends on the possibility of its recurrence in a transplanted heart (which once again proves its autoimmune nature). The relapse rate in 1997 was 26%. In 1 case out of 9, GCM recurrence resulted in death [9]. Probably, no other myocardial disease has such a malignant course. At the same time, improvement in IST protocols after HT, including in patients with GCM, has led to significant decrease in the number of relapses. Thus, in the French registry (the results were published in 2018), not a single case of GCM development in the transplanted heart was reported [18, 19]. An increased risk of acute rejection has also been reported in patients with GCM compared with DCM (16% vs 5%, $p = 0.021$), but 1.5 and 10-year survival rates do not differ from those for other HT reasons (94%, 82% and 68%, respectively) [20].

Our patient showed no signs of GCM rejection or recurrence by the end of the first year.

CONCLUSION

Giant cell myocarditis is one of the rarest and most severe forms of myocarditis that cannot be definitely diagnosed by any method (including MRI) other than endomyocardial biopsy. Acute development of severe heart failure, up to cardiogenic shock, is typical for GCM. Auxiliary blood circulation is often required in the first days of the disease; much less typical is the infarction-like debut with aneurysm formation, noted in the presented case. Its feature was a weak and short-lived, but distinct positive response to monotherapy with medium doses of prednisolone, which are usually completely insufficient for GCM treatment, and a long (almost two years) relatively favorable course of the disease. The particular severity of myocarditis and the need for aggressive immunosuppression could be indicated by sharply increased titers of anti-cardiac antibodies. However, the time for performing EMB and conducting an adequate IST was missed, which made HT the only reasonable and possible way out. The severity of the patient's condition at the time of transfer to the Shumakov National Medical Research Center of Transplantology and Artificial Organs made it necessary to immediately connect ECMO and perform urgent HT on the first day of hospitalization. Despite the risk of recurrence in the transplanted heart, HT remains the treatment of choice for the majority of patients diagnosed with GCM both preoperatively and retrospectively.

The authors declare no conflict of interest.

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The article was submitted to the journal on 1.10.2020