Acute Myocarditis in a Patient with Parainfluenza Infection, Seven Years After Bone Marrow Transplantation

N. Marinov, I. Simova, I. Petrov

Clinic of cardiology, University Hospital Acibadem City Clinic Cardio-vascular center

Abstract.

Myocarditis is an inflammatory disease of the myocardium, with heterogeneous etiology. Although rare, myocarditis can be a complication of the influenza infection. In the majority of cases, viral myocarditis is a self-limiting infection passing without permanent changes in the myocardium. We present a clinical case of a 30-year-old woman with acute heart failure in the course of respiratory infection accompanied by severe systolic dysfunction [left ventricular (LV) ejection fraction (EF) 19%]. The patient was treated according to the current guideline recommendations for the treatment of acute and chronic heart failure with the conjunction of immunostimulating and metabolic therapy. During hospitalization from microbial and viral testing, acute-phase antibodies to parainfluenza virus were identified. Following the treatment, a complete resolution of heart failure symptoms and restoration of LVEF to baseline (40%) was observed. Timely initiation of treatment in myocarditis, followed by good clinical course and regression of LV systolic dysfunction, in some cases may cancel invasive procedures such as endomyocardial biopsy.

Key words: acute myocarditis; heart failure; parainfluenza

Address

Nikolay Marinov, Clinic of cardiology, University Hospital Acibadem City Clinic Cardio-vascular center, Okolovrasten Pat St. № 127, Bg – 1407 Sofia tel: 089599825; e-mail: nikolay.valeriev.marinov@gmail.com
**Introduction**

Myocarditis is a challenging diagnosis, given the heterogeneous clinical presentation and numerous etiologic causes. According to the World Health Organization, myocarditis is an inflammatory disease of the myocardium diagnosed by histological, immunological, and immunohistological criteria [1]. It is difficult to determine the exact incidence of myocarditis, given that endomyocardial biopsy (EMB), which is the gold standard for diagnosis [1-3], is rarely used [2-3]. Patients presenting with mild symptoms and minimal LV dysfunction usually proceed to spontaneous resolution without specific treatment [4]. However, up to 30% of biopsy-proven cases of myocarditis can progress to dilated cardiomyopathy, which is a poor prognostic sign [1-6]. The prognosis in patients with myocarditis differs depending on the etiologic agent [4]. The treatment of most forms of myocarditis is symptomatic [7]. However, immunohistochemical [1-4, 7-12] and molecular biological analysis of EMB [13] material, as well as serum autoantibody testing, are important for identifying patients in need of specific treatment [1, 4].

**Description of the clinical case**

**Medical history**

On the 3-rd of January 2020, a 30-year-old woman presented to us with complaints of shortness of breath, gradually accelerated to orthopnea, fatigue on minimal physical exertion and pitting edema of the ankles. The complaints were preceded by acute onset of fever up to 38° C accompanied with chills, 6 days before presentation. A cough appeared, which was initially dry but subsequently showed an expectoration of pink foamy phlegm. The patient initially self-treated with Paracetamol, but with the onset orthopnea, she visited her general practitioner. He ordered a chest X-ray and consultation with a pulmonologist. The chest X-ray revealed cardiomegaly and she subsequently was referred to a cardiologist.

In 2013, the patient underwent chemotherapy and subsequent allogeneic bone marrow transplantation for acute myeloid leukemia. Subsequently, she was monitored twice by cardiologist with a transthoracic echocardiographic (TTE). In 2013 the patient had a structurally healthy heart – preserved LV systolic function and
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г. отново е проведена TTE, на която се установява умерено потисната ЛК систолна функция с ФИ на ЛК 43%, нискостепенна митрална инсуфициенция (МИ), дясна камера със запазени размери и систолна функция.

Клинична находка

При настоящия преглед се установи умерено увредено общо състояние, тахи-диспнея с отслабено до липсващо дишане в двете белодробни основи и дребни влажни хрипове, сърдечна честота (СЧ) 94 удара в минута, и артериално налягане 120/60 mm Hg. Аускултира се T3-галоп и систолен шум 2/6 степен на сърдечен връх с аксиална прогащане. Налице са и леки тестовати парамалеларни отоци.

Инструментална находка

При първоначалната TTE оценка се установи ЛК с горногранични размери и обеми: теледиастолен размер (ТДР) 55 mm, телесистолен размер (ТСР) 49 mm, теледиастолен обем (ТДО) 93 ml и телесистолен обем (ТСО) 74 ml; тежка ЛК систолна дисфункция с ФИ 19% глобален лонгитудинален стрейн -4% (фиг. 1). Установени са нискостепенна функционална МИ – вена contracta 0.67 cm, PISA radius 8.7 mm, регургитационен обем 55 ml, ефективен регургитационен отвор 0.55 cm² (фиг. 2A), рестриктив тип диастолна дисфункция E/e' 22. Налице са нискостепенна трикусиплдална инсуфициенция, дясна камера със запазени размери, потисната систолна функция, TAPSE 10 mm. Умерена белодробна хипертония с индиректно измерено налягане в дясната камера 45 mm Hg (фиг. 2B). Дилятирана е долна пълна вена с намален респираторен колапс, има малък хемодинамично незначим парацирден излив пред дясната камера, двустранни малки плеврални изливи. От рентгенографията на белите дробове се установи белодробен застой, двустранни плеврални изливи, дилатирата сърдечна сянка (фиг. 3).

Електрокардиограма

Електрокардиограмата (ЕКГ) при постъпването показва синусов ритъм със СЧ 92 удара в минута, лява електрическа ос, ляв преден фасцикуларен блок, Qr в V₁ и V₂, наличие на волтажни критерии за ЛК хипертрофия (S V₃ + R V₆ > 35 mm) и патоложична прогресия на R-зъбец в прекордилни отвеждания (фиг. 4).

intact valve apparatus. In August 2019 a follow up TTE was performed, which revealed moderately depressed LV systolic function with EF 43%, low-grade mitral insufficiency (MI), right ventricle with preserved systolic function and size.

Physical Examination

The current examination revealed a moderately impaired general condition, tachy-dyspnoea, vesicular breathing with impaired breath sounds in the lung bases accompanied by crackles. The heart rate (HR) was 94 beats per minute, and the arterial blood pressure was 120/60 mmHg. Auscultation revealed a T3 gallop and an apical systolic murmur grade 2/6 with axillary propagation. Mild pitting edema on the ankles.

Instrumental tests

The initial TTE evaluation revealed LV in the upper referent dimensions and volumes: end diastolic diameter (EDD) 55 mm, end systolic diameter (ESD) 49 mm, end diastolic volume (EDV) 93 ml and end systolic volume (ESV) 79 ml; severe LV systolic dysfunction with EF 19% and Global Longitudinal Strain -4% (Figure 1). Sever functional MI with Vena contracta 0.67 cm, PISA radius 8.7 mm, Regurgitant volume 55 ml, Effective regurgitation orifice area 0.55 cm² (Figure 2A) and restrictive type of diastolic dysfunction E/e’ 22. Mild tricuspid insufficiency, right ventricle with preserved dimensions and impaired systolic function TAPSE 10 mm. Moderate pulmonary hypertension with estimated right ventricular systolic pressure of 41 mmHg (Figure 2B). Dilated inferior vena cava with impaired respiratory collapse, small hemodynamically insignificant pericardial effusion in front of the right ventricle, bilateral small pleural effusions. Chest X-ray (supine antero-posterior chest view) revealed pulmonary congestion, bilateral pleural effusions, and dilated cardiac shadow (Figure 3).

Electrocardiogram

The electrocardiogram (ECG) at admission shows a sinus rhythm with HR 92 beats per minute, left axial deviation, left anterior fascicular block, Qr in V₁ and V₂, voltage criteria for LV hypertrophy (S V₃ + R V₆ > 35 mm) and pathological progression of R wave in precordial leads (Figure 4)
Fig. 1. Echocardiography on admission. A–apical 4 chamber view EF 19%; B–M-mod of long-axis view EDD/ESD – 55/49 mm C and D speckle tracking of LV

Fig. 2. Echocardiography on admission. A–apical 4 chamber view and color Doppler with emphasis on mitral insufficiency Vena contracta 0.7 cm, PISA radius 8.7 mm, Regurgitation volume 55 ml Effective regurgitation orifice area 0.55 cm²; B–Continuous-wave Doppler jet of tricuspid insufficiency and estimated measurement of right ventricular pressure 41 mm Hg

Fig. 3. Chest X-ray at admission – supine anteroposterior chest view (description see text)
Laboratory tests

Laboratory tests revealed leukocytosis of about 15 x 10^9/l at the expense of neutrophils 11 x 10^9/l, mild dilution anemia with hemoglobin 110 g/l and hematocrit 32%. Elevated levels of C-reactive protein 20.7 mg/l (norm up to 9 mg/l), high-sensitive Troponin-T 30 ng/l (norm 3-14 ng/l), Pro-BNP 8648 pg/ml (norm up to 130 pg/ml), Elevated transaminases – ALAT 370 U/L (norm up to 59 U/L) and ASAT 89 U/L (norm up to 37 U/L). All other laboratory studies including procalcitonin were within the reference range.

Differential diagnosis

At this stage, on the basis of the carried studies and clinical presentation in the differential diagnosis we considered acute heart failure in the course of respiratory infection, given the previous asymptomatic heart failure or acute myocarditis. Given the persistent of infectious process we sent samples for微生物ological testing those included three blood cultures, sputum, urine, nasal and throat swabs. Also serum was sent for testing for Ebstein-Barr virus, Cytomegalovirus; Adenovirus; Herpes Simplex Virus Type 1; Varicella zoster virus; Enterovirus; Parechovirus; Human herpesvirus 6; B 19 Parvovirus; Hepacivirus C; Hepatitis B virus; Human immunodeficiency viruses; gripp A, gripp B, paragripna virusi; Chlamydia penumonie, Mycoplasma; PCR for Q-fever.

Course of the disease

On the 3-rd of January 2020 given the acute onset of symptoms, poor general condition and high risk of arrhythmia and conduction complication the
Н. Маринов, Я. Симова, И. Петров

пациентката бе хоспитализирана и настанена в реанимационно отделение на постоянно ЕКГ и хемодинамично мониториране. Започна се форсирана диуретична терапия с интравенозен бримков диуретик (furosemide), постепенно титриран според диуретичния отговор и венозен вазодилататор (nitroglycerin) и метаболитна терапия, включваща 4 g креатин, 4 g D-рибоза, 600 mg Coenzyme Q10 и 2 mg витамин Е, събрани в комбинирани капсули, разделена на 3 приема на ден. При хемодинамично стабилно състояние и добър диуретичен отговор, рано в хода на заболяването, успя да се включи в терапията бета-блокер (carvedilol), ACE ингибитор (perindopril) и минералкортикоиден рецепторен блокер (spironolactone). След изпращане на материалите за микробиологично и вирусологично изследване се започна емпирична антибиотична терапия с Ceftriaxone и Azithromycin. В хода на лечението се регистрираха многократни пристъпи на мономорфна непродължителна камерна тахикардия, предвид което в терапията се включи amiodarone. След излизане на микробиологичните и вирусологичните изследвания се установиха IgM антитела срещу парагрипен вирус, като на този етап се прие, че се касае за остър вирусен миокардит. Преустанови се антибиотичното лечение и се започна имуностимулираща терапия с inosine acedoben dimepranol. В хода на лечението се отчете значително подобрение с облекчаване и изчезване на задуха, кашлицата, белодробния застой и периферните отоци, съпровождено от подобрение на функционалния клас. На петия ден от лечението се установи повишаване на ФИ на 41.22% и спад на МИ до тривиална (фиг. 5). След излизане на ФИ и подобрение на клиничното състояние, се преустанови пълен режим и пациентката постепенно бе раздвижена до самообслужване. Пациентката бе изписана на 10-ия ден от лечението, като в деня на изписването от рентгенографията на белите дробове бе отчетена пълна резорбция на двустранните плеврални изливи, значителна редукция на размера на сърдечната сянка и обратно развитие на белодробния застой (фиг. 6). Отчете се задържане на ФИ на 42%, с повишение на глобалния лонгитудинален стрейн до -10.8%, при тривиална МИ (фиг. 7). patient was admitted to intensive care unit for constant ECG and hemodynamic monitoring. Forced diuretic therapy was initiated with intravenous loop diuretic (furosemide) gradually titrated according to diuretic responses, venous vasodilator (nitroglycerin) and metabolic therapy that includes 4 g creatine, 4 g D-ribose, 600 mg Coenzyme Q10, 2 mg of vitamin E in combined capsules, divided into 3 doses per day. Due to the fact that the patient remained in hemodynamically stable condition and with good diuretic response, early in the course of the treatment we were able start therapy with beta-blocker (carvedilol), Angiotensin-converting-enzyme (ACE) inhibitor (perindopril) and mineralocorticoid receptor blocker (spironolactone). After we sent samples for microbial and viral testing, empirical antibiotic therapy with Ceftriaxone and Azithromycin was initiated. In the course of treatment due to multiple episodes of non-sustained monomorphic ventricular tachycardia, therapy with amiodarone was started. The microbial and viral tests showed elevated count of IgM antibodies to Parainfluenza virus. At this stage we discussed as etiology acute viral myocarditis. Antibiotic treatment was discontinued and immunostimulating therapy with inosine acedoben dimepranol was initiated. In the course of treatment a significant improvement was observed: relief and disappearance of dyspnea, cough, pulmonary congestion and peripheral edema, accompanied by improvement of functional class. On the fifth day of treatment, an increase of EF to 41.22% and a decrease in MI to trivial was observed (Figure 5). After taking into account the increase in EF and improvement of the clinical condition, the bed rest was discontinued and the patient was gradually rehabilitated to self-care. The patient was discharged on the tenth day of treatment. On the day of discharge the chest X-ray revealed full resorption of bilateral pleural effusions, significant reduction in heart shadow size, and no pulmonary congestion. (Figure 6). Also the EF remained at 42%, an increase of in the global longitudinal strain to -10.8% was noted and MI remained trivial (Figure 7).
The patient was discharged with medical therapy for heart failure corresponding to the current guideline recommendations of the European Society of Cardiology. It included a beta-blocker (carvedilol 2 x 6.25 mg), ACE inhibitor (perindopril 5 mg), mineral corticoid receptor blocker (spironolactone 37.5 mg), loop diuretic (furosemide 60 mg) and amiodaron 400 mg. Given the growing body of data and our experience with the positive effect of metabolic therapy with creatine, D-ribose and Coenzyme Q10 in patients with heart failure15 we prescribed 4 g creatine, 4 g of D-ribose, 600 mg Coenzyme Q10 and 2 mg vitamin E, mixed in a combined capsule, divided into 3 even doses per day.
Follow-up

At the first follow-up examination on 15 days after discharge, the patient was in good overall clinical condition and NYHA I functional class. No significant change in LV systolic function was detected by TTE, with EF being 38-40% and MI remained trivial (Figure 8). Laboratory test revealed significant reductions of pro-BNP to 628.7 pg/ml (norms of up to 130 pg / ml) and high-sensitive Troponin-T was in the reference range. At the second follow-up examination, on the 25th day after discharge, the patient remained in good general condition, NYHA I functional class without any negative dynamics in laboratory and instrumental tests sines the last visit.

Discussion

We present a patient with acute heart failure hospitalized in severe general condition with severely impaired LV systolic function and severe MI. The patient experienced a rapid improvement in the clinical condition, a significant increase of LV contractility and EF, and reduction of MI to trivial, after initiation of guideline driven therapy for heart failure in combination with immunomodulatory (inosine) and metabolic (creatine, D- ribose and Coenzyme Q10) therapy. Based on the laboratory results (positivation of IgM against parainfluenza virus) we concluded that this was a case of acute myocarditis and in differential diagnosis we discussed acute heart failure in the course of respiratory infection in patient with previously asymptomatic moderate LV systolic dysfunction (EF of 43% on TTE examination from August 2019).

Considering the diagnostic criteria of the European Society of Cardiology for clinically suspected myocarditis [16], our patient fills a criterion of clinical presentation and three diagnostic criteria. These include: newly developed shortness of breath, pathological
Parainfluenza viruses are RNA viruses of the paramyxovirus family causing upper and lower respiratory tract diseases in healthy newborns or children under 6 years of age. The main four antigenic types of parainfluenza viruses infect the airway epithelial
acute myocarditis is a challenging diagnosis with a broad etiology, requiring EMB to confirm it. However, in a favorable clinical course, rapid and good response to treatment, this risky procedure may be avoided. Common seasonal viral diseases can cause cardiovascular complications, among which myocarditis is one of the most severe. Viral myocarditis can lead to severe dilated cardiomyopathy with heart failure symptoms. In these cases, rapid diagnosis and timely treatment can be life-saving.

Conclusion

Acute myocarditis is a challenging diagnosis with a broad etiology, requiring EMB to confirm it. However, in a favorable clinical course, rapid and good response to treatment, this risky procedure may be avoided. Common seasonal viral diseases can cause cardiovascular complications, among which myocarditis is one of the most severe. Viral myocarditis can lead to severe dilated cardiomyopathy with heart failure symptoms. In these cases, rapid diagnosis and timely treatment can be life-saving.

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