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Combination of chronic myocarditis and progressive coronary artery disease: differential diagnosis and stepwise treatment

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Aim. To assess the differential diagnosis in a patient with a combination of coronary artery disease and myocarditis and the results of stepwise treatment (including immunosuppressive therapy (IST), and coronary stenting).

Material and methods. A 56-year-old female patient with hypertension, obesity (body mass index, 31,6 kg/m^2), diabetes and psoriasis developed shortness of breath after a respiratory viral infection. Primary echocardiography revealed left heart dilatation, ejection fraction (EF) of 21%. Coronary angiography revealed anterior descending artery stenosis of 75%, circumflex artery — 80%, right coronary artery (RCA) — 70%. RCA stenting was performed and cardiovascular and diuretic therapy was started. However, shortness of breath and low exercise tolerance persisted.

Results. In the blood test, anti-endothelial cell antibodies were 1:320, anti-cardiomyocyte and anti-smooth muscle antibodies — 1:80, anti-cardiac conduction system fibers — 1:320 (N≤1:40). During myocardial perfusion scintigraphy with computed tomography, an uneven distribution of the indicator was noted. Signs of myocardial scarring and indications for further revascularization were not revealed. Cardiac magnetic resonance imaging confirmed a decrease in left ventricular (LV) contractility (LVEF 37%) and moderate dilatation. Biopsy was not performed due to dual antiplatelet therapy. The condition is regarded as infectious-immune myocarditis. IST was started with azathioprine 150 mg/day. We noted dyspnea relief and a stable increase in LVEF to 50-52%. The clinical course was complicated by sick sinus syndrome with pauses up to 6 seconds and presyncope; a pacemaker was implanted. After 5 years from the onset of IST, dyspnea episodes reappeared without exacerbation of myocarditis. As their cause, ischemia was diagnosed due to the progression of coronary atherosclerosis. Symptoms regressed after repeated coronary stenting.

Conclusion. The presence of moderate coronary atherosclerosis without signs of ischemia and myocardial infarction should not be considered as the only cause of severe systolic myocardial dysfunction. Diagnosis and treatment of myocarditis in combination with coronary artery disease is carried out according to the standard principles and can improve LV systolic function and control the heart failure symptoms.

Key words: coronary artery disease, myocarditis, anticardiac antibodies, heart failure, immunosuppressive therapy.

Relationships and Activities: none.

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In modern cardiology, in recent years, special attention has been paid not only to a comprehensive study of certain diseases, but also to a combination of several disorders. At the same time, the combination of various cardiovascular diseases (CVD) often significantly changes the approach to the diagnosis and treatment of a patient, and also has an important effect on the prognosis. Angina is the most common type of coronary artery disease (CAD). Its prevalence increases in the population with age: from 5-7% among women 45-64 years old to 10-12% among women aged 65-85 years, and from 4-7% among men 45-64 years old to 12-14% among men aged 65-85 [1]. Myocarditis is the most common myocardial disease. According to some estimates, it accounts for up to 10% of patients with CVD in the Russian Federation [2]. Thus, the combination of CAD and myocarditis is quite likely to occur, and it is extremely important to take into account both of these diseases when managing such patients. This will be discussed in the article.

Case report

Female patient, 56 years old, first entered the hospital in December 2013 with complaints of shortness of breath with minimal exercise, pain in the left shoulder with moderate exercise, stopping at rest within 15 minutes, episodes of increased blood pressure (BP) to 170/110 mm Hg, pronounced weakness, and anxiety.

Family history of CVD was negative.

Past history. From childhood to 50 years, the patient suffered from frequent tonsillitis and bronchitis. Since 1986, there has been a wave-like course of psoriasis. In 2007 (at the age of 50), type 2 diabetes (T2D) was diagnosed for the first time, and therefore receives oral hypoglycemic therapy, however, glycated hemoglobin was 9% (with a target range of HbA_{1c} value <7,5%). An architect by profession, currently retired. The patient did not smoke and not abuse alcohol.

Medical history. From about 42 years of age episodes of BP rises to a maximum of 160-170/110 mm Hg was noted. She occasionally took antihypertensive drugs (prestarium, concor) with incomplete effect. Since autumn 2012, for the first time, short episodes of shortness of breath with moderate exercise and left shoulder pain appeared. The patient was not examined. In March 2013, she suffered an acute upper respiratory tract infection with low-grade fever that lasted for 3 weeks. After a course of antibiotic therapy, the temperature returned to normal, but shortness of breath appeared, which then independently regressed within a few weeks. Echocardiography was performed, in which a slight left ventricular (LV) dilation was found; the ejection fraction (EF) was 51%.

There was a worsening since September 22, 2013, when after drinking a large amount of liquid, severe shortness of breath appeared. Chest computed tomography revealed a small amount of fluid in the right pleural cavity, calcification of aorta and coronary arteries. The patient was hospitalized in respiratory medicine unit, the cardiogenic nature of shortness of breath was suspected. Repeated echocardiography revealed EF of 21%, hypoakinetic areas in the anterior septum, left heart dilatation. Coronary angiography revealed 75% stenosis of the anterior descending artery (ADA) throughout, 80% stenosis of left circumflex artery (LCA) orifice, 70% stenosis of the right coronary artery (RCA) in the proximal third. On October 14, 2013, RCA stenting was performed. The patients received furosemide, digoxin, rosuvastatin, ticagrelor, aspirin, perindopril. At discharge, the EF was 33%. After hospitalization, shortness of breath persisted, exercise tolerance remained low, and episodes of left shoulder pain remained unrelated to exercise. The patient turned to cardiology unit for further examination and treatment.

Physical examination. Height was 164 cm, weight — 85 kg, body mass index — 31,6 kg/m^2. Hypersthenic type. Psoriatic plaques located on the elbows and dorsal feet surfaces. There was swollen legs and feet. Respiratory rate of 28 bpm. According to auscultation, breathing was harsh and withoit crackles. Muffled heart tones, no cardiac murmur. Heart rate (HR) of 80 bpm. BP was 150/90 mm Hg. The liver was 1 cm below the costal margin. The spleen was not enlarged.

Parameters of complete blood count, biochemical blood tests, coagulation testing, and urine tests were without findings. Anticardiac antibodies (ACA) were as follows: antinuclear antibody (ANA) — no, antiendothelial cell antibodies — 1:320, anticardiomyocyte antibodies 1:80, anti-smooth muscle antibodies — 1:80, and antibodies to cardiac conduction system fibers — 1:320 (normal range, below 1:40). The genome of cardiotropic viruses (herpes viruses, parvovirus B19) was not detected.

Electrocardiography (ECG) (Figure 1) revealed first-degree atrioventricular block (PQ, 240 ms), signs of left atrial and LV hypertrophy, poor progression of R wave in V_1-V_3. Attention was paid to QS complexes in III and aVF (no negative alteration compared with previous ECGs, including from 1987). Twenty-four hour Holter monitoring revealed a constant first-degree atrioventricular block with a maximum PQ lengthening up to 260 ms, ST segment depression up to 1 mm without diagnostically significant dynamics.

Echocardiography showed a slight left heart dilation (LV end diastolic dimension (EDD), 5,9 cm; LV

end diastolic volume (EDV), 152 ml; left atrial end diastolic volume, 80 ml) and LVEF of 39%. No local contractility disorders were found. According to single-photon emission computed tomography, the indicator inclusion into the LV myocardium with a diffusely uneven distribution was visualized, which is characteristic of non-coronary myocardial damage. Signs of cicatricial myocardial damage were not identified. According to cardiac multislice computed tomography (MSCT), the stent was patient, while in the area of the LV lateral wall, increased trabeculation was determined without myocardial noncompaction. The myocardial enhancement in the arterial phase was uneven, especially in the lateral wall area, while in the delayed phase, there were no areas of contrast accumulation.

To rule out myocardial noncompaction and scarring, contrast-enhanced cardiac magnetic resonance imaging (MRI) was performed: LV moderate dilatation (EDD, 5,8 cm; EDV, 111 ml/m^2 up to 92 ml/m^2) and decreased contractility (EF, 37%) without clear areas of delayed contrasting. No evidence in favor of non-compact myocardium were obtained. There was no myocardial hypertrophy (interventricular septal thickness, 11-12 mm; posterior wall thickness, 10 mm). Myocardial mass was at the upper normal limit.

The previous coronary angiograms were studied by professor V.A. Sulimov: the stenoses were significantly overestimated before; stenosis degree of ADA and LCA did not exceed 50-60% and further revascularization was not required. Moreover, RCA stenosis also did not exceed 50-60%, and therefore the indications for its stenting were dubious, and the procedure did not lead to an improvement in the patient's condition.

Thus, CAD in the presence of significant coronary atherosclerosis was highly probable. Left shoulder pain arising during exercise and stopping at rest was regarded as angina. It was not possible to carry out stress tests due to severe heart failure (HF). According to scintigraphy, echocardiography, MSCT and MRI, there was no evidence in favor of myocardial infarction (MI).

Taking into account the relatively old age for primary cardiomyopathy decompensation, a clear connection between the increase in HF symptoms and the previous upper respiratory tract infection, low immune status (psoriasis), the rapid development of diffuse myocardial dysfunction with a EF decrease to 21%, high titers of antiendothelial antibodies and antibodies to cardiac conduction system, uneven myocardial contrasting in the arterial phase according to cardiac MSCT, diffuse uneven perfusion disorders according to myocardial scintigraphy, the condition was regarded as infectious-immune myocarditis. Due to the need to continue dual antiplatelet therapy until October 2014, myocardial biopsy was associated with a high risk. There was no clear evidence for primary cardiomyopathy (in particular, myocardial non-compaction) with MSCT and MRI. The absence of delayed accumulation did not exclude myocarditis.

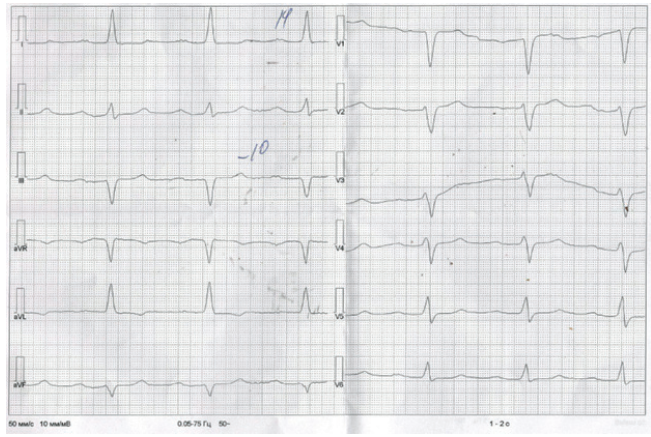

Figure 1. ECG of the patient (description in the article).

Taking into account the moderate degree of myocarditis activity and presence of relative contraindications to steroid therapy (obesity, subcompensated diabetes), azathioprine monotherapy (150 mg/day) was started. Optimal doses of angiotensin-converting enzyme inhibitors and β-blockers (fosinopril 20 mg/day, bisoprolol 2,5 mg/day), diuretics (spironolactone 50 mg/day, furosemide 40 mg/day intravenously with a switch to torasemide 10 mg/day). As a result of treatment, there was a decrease in shortness of breath with a stable positive diuresis, an increase in exercise tolerance, and a significant improvement in general well-being.

Since the beginning of 2014, episodes of dizziness and rare lightheadedness have appeared. In May 2014 she applied to the hospital. There was a clear positive dynamics: a decrease in shortness of breath, an EF increase to 46-48%, a decrease in LV EDD to 5,3 cm, despite an increase in weight of 9 kg. Holter monitoring while taking 2,5 mg of bisoprolol revealed 49 pauses >2 seconds (maximum, 2,3 sec), frequent episodes of postextrasystolic depression of the sinus node. The dose of bisoprolol was reduced to 1,25 mg/day, against the background of which only isolated episodes of sinoatrial block were recorded at night. Signs of moderate myocarditis activity persisted (Table 1) and therapy with azathioprine was continued at the same dose. Doppler ultrasound revealed hemodynamically significant stenosis of the internal carotid arteries (right, 50%; left, 60%). In December 2014, a decrease in antibodies' titers was noted. Therefore, the azathioprine dose was reduced

Table 1

Results of dynamic follow-up of the patient

Parameter	December 2013	May 2014	December 2014	December 2015	May 2016	November 2017	May 2018	May 2019
ANA (no)	нет	нет	нет	1:320	1:80	1:160	1:40	1:40
AECA (1:40)	1:320	1:80	1:80	1:80	1:80	1:160	1:80	1:80
ACA (1:40)	1:80	1:160	1:80	1:160	1:80	1:80	1:80	1:80
ASMA (1:40)	1:80	1:160	1:80	1:160	1:160	1:80	1:80	1:80
CCSA (1:40)	1:320	1:320	1:160	1:160	1:160	1:80	1:80	1:80
Shortness of breath	+++	++	+	++	–	–	–	++
LVEF, %	21→39	47	49	41	52	50	51	41→50
Azathioprine dose (mg/day)	150	150	50	150	150	150	100	150

Abbreviations: ANA — antinuclear antibodies, AECA — antiendothelial cell antibodies, ACA — anticardiomyocyte antibodies, ASMA — antibodies to anti-smooth muscles, CCSA — antibodies to cardiac conduction system fibers, LVEF — left ventricular ejection fraction.

to 50 mg/day. Holter monitoring revealed 195 pauses (maximum, 3,78 sec), in connection with which bisoprolol was completely canceled. The patient felt satisfactory for the next year.

In December 2015, shortness of breath appeared and gradually increased, exercise tolerance decreased, and the patient was hospitalized. Echocardiography revealed a decrease in EF to 41% without LV dilatation. Exercise tests were not performed due to shortness of breath. The patient refused to perform stress transesophageal echocardiography. Holter monitoring without β-blockers' intake revealed episodes of second-degree sinoatrial block with pauses of up to 2,5 seconds in combination with sinus tachycardia. Considering the need for therapy with β-blockers (HF, hypertension, CAD), a maximum pause of 3,78 seconds and a history of syncope, the implantation of a pacemaker was recommended. Taking into account a significant increase in antibodies' titers (Table 1), the deterioration of the condition was regarded as a consequence of myocarditis exacerbation. Therefore, azathioprine dose was again increased to 150 mg/day.

In January 2016, a pacemaker was implanted. Before the implantation, Holter monitoring revealed pauses of up to 6,25 seconds (Figure 2). After implantation of the pacemaker, therapy with bisoprolol 2,5 mg was resumed. The state of health improved: there were no episodes of dizziness, shortness of breath decreased, exercise tolerance increased, and EF stabilized at the level of 50-52%.

The patient's condition remained stable until December 2018 (Table 1), when she noted an increase in shortness of breath, a feeling of "globus behind the breastbone" without a clear connection with physical activity. According to echocardiography in January 2019, LVEF was 41%. In May 2019, she was again hospitalized to rule out an exacerbation of myocarditis. According to the echocardiography performed in the clinic, the EF was 50%. There was no increase in the antibodies' titer, which required the search for other causes of deterioration. Due to the presence of risk factors for CAD and verified coronary atherosclerosis, a stress test was performed (positive results). During the test, a feeling of heaviness behind the sternum appeared, accompanied by ECG changes: horizontal ST segment depression in II, III, aVF, V_5-V_6 up to 0,16 mV). The increase in episodes of shortness of breath is regarded as equivalent to angina.

In November 2019, coronary angiography revealed 75% stenosis of the left coronary artery, 50% stenosis of the proximal third of ADA, 30% stenosis in the proximal third of RCA, while LCA was without significant stenosis. Stent in the middle third was without signs of restenosis. Coronary artery bypass grafting was recommended, which the patient refused, and therefore, in December 2019, bifurcation stenting was successfully performed using the culotte technique. After that, she noted a significant improvement in well-being in the form of a decrease in shortness of breath and the disappearance of discomfort behind the breastbone.

Discussion

In the presented case report, the simultaneous presence of two diseases in the patient was demonstrated: moderate chronic infectious-immune myocarditis and CAD. Both diseases determine the patient's prognosis equally. At the same time, either myocarditis or the progression of CAD played a leading role in the formation of clinical performance at different times.

Initially, the HF symptoms in the patient were regarded precisely as a manifestation of CAD, despite the clear connection between the onset of

symptoms and the previous infection, a rapid EF decrease and left heart dilatation, a moderate coronary artery stenosis and the absence of verified ischemia. The patient underwent RCA stenting, but there was no significant positive dynamics in condition. Only after the start of basic therapy a significant increase in EF (from 21-39% to 52%), normalization of the heart size, and control over HF symptoms were achieved. The restored blood flow through the RCA, a simultaneous decrease in EF and an increase in antibodies' titers make myocarditis a more likely cause of the progression of conduction disorders. In any case, the nature of the pauses did not influence the treatment tactics.

As for the last deterioration in the patient's condition, her long history of myocarditis forced the doctors, who initially diagnosed CAD, to regard the negative dynamics as an increase in the activity of myocarditis. She was again referred to our hospital to determine further management tactics. The stress test revealed myocardial ischemia due to the progression of coronary atherosclerosis in the patient with hypertension, obesity and not fully controlled diabetes. Timely pathogenetic treatment (revascularization) again made it possible to stabilize the condition.

Given the high prevalence of both myocarditis and CAD, a combination of these two diseases is quite likely. However, there is very little data in the literature. There are many publications about the infarct-like acute myocarditis, however, only a few publications were found about the combination of myocarditis and "classical" CAD. A group of Japanese scientists described a patient with a long history of multivessel CAD; this patient had an acute decompensated HF, the cause of which was morphologically verified lymphocytic fulminant myocarditis, first regarded as ACS [3]. The main message of the authors coincides with ours: the presence of a verified CAD in a patient may complicate the timely diagnosis of myocarditis and one should bear in mind the addition of myocarditis as one of the deterioration reasons.

In 1999, Italian researchers described 7 patients with advanced coronary atherosclerosis, biventricular heart failure, and right ventricular and LV dilatation without prior MI. In all of these patients, myocardial biopsy was diagnosed with active lymphocytic myocarditis. In addition, an increase in antibodies' titers was noted in two patients. In addition to the conventional treatment of HF, two patients were prescribed immunosuppressive therapy for myocarditis with a combination of prednisolone and azathioprine, and 8 months after they had a significant increase in LVEF (from 15% to 50% and from 20% to 38%), while in 5 patients without immunosuppressive therapy, EF remained low and one of them died [4].

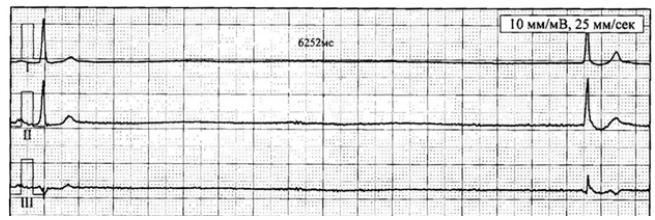

Figure 2. Fragment of 24-hour ECG monitoring (description in the article).

We have repeatedly observed cases of a combination of various types of CAD and myocarditis. When observing more than 600 patients with myocarditis, we identified two variants of infarct-like myocarditis (favorable and unfavorable) and described numerous forms of microvascular ischemia within myocarditis without necrosis [5, 6] and cases of a true combination of CAD with morphologically verified myocarditis, as well as cases of myocarditis after MI [7].

We also repeatedly noted about the ambiguity and often unjustified use of the clinical term "ischemic cardiomyopathy", which, unfortunately, began to be used by pathologists instead of the much more correct and understandable diagnosis of "small focal cardiosclerosis". Today, ischemic cardiomyopathy is most often understood as a pronounced postinfarction LV remodeling with its dilatation and a progressive EF decrease. However, in 1970 this term was proposed to denote the dilated cardiomyopathy in patients with multivessel CAD, regardless of a history of myocardial infarction. At the same time, the reasons for the development of cardiomyopathy in only a small part of patients with CAD remain unclear. Obviously, in addition to chronic ischemia, there must be special factors that are not present in everyone, probably genetic.

In the presented case report, we have no reason to suspect true ischemic cardiomyopathy for a number of reasons: initially there was not only myocardial infarction and severe multivessel lesion, but also verified ischemia. Significant improvement in the condition and increase in LV systolic function were achieved in the absence of complete myocardial revascularization. Before pacemaker implantation, β-blockers were used only in a minimal dose and then were canceled, which does not meet the optimal medical therapy for CAD and HF. Pronounced clinical effect was achieved by use of azathioprine.

Thus, when patients with coronary atherosclerosis develop unexplained biventricular HF without myocardial infarction, one should always remember about the need to actively diagnose and treat myocarditis.

Conclusion

The presence of moderate coronary atherosclerosis without signs of ischemia and myocardial infarction should not be considered as the only cause of severe systolic myocardial dysfunction. In patients with verified CAD, increase in HF symptoms with a significant decrease in EF and cardiac dilatation may be due not only to coronary atherosclerosis progression, but also to the presence of myocarditis. Diagnosis and treatment of myocarditis in combination with CAD is carried out according to the standard principles and can improve LV systolic function and control the heart failure symptoms. Active myocarditis and CAD equally specify the patient's prognosis and equally require treatment. With such a combination, the causes of deterioration and the indications for various types of treatment should be differentially re-evaluated at each stage of the disease.

Relationships and Activities: none.

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