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Differential diagnosis of acute myocardial injury: a case report and discussion

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The article describes a case report of acute myocardial injury developed against the background of systemic inflammatory response in a patient with chronic tonsillitis exacerbation, who had no signs of coronary artery atherosclerosis and pathological changes according to cardiac magnetic resonance imaging. The differential diagnosis and discussion of the problem of acute non-ischemic myocardial injury are presented.

Key words: acute coronary syndrome, acute myocardial injury, magnetic resonance imaging, myocarditis.

Relationships and Activities: none.

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According to the fourth universal definition of myocardial infarction (MI), there are many causes of acute myocardial injury associated both directly with myocardial ischemia and other non-ischemic causes, such as myocarditis, sepsis, chronic kidney disease, and others [1]. It can be quite difficult to establish the cause of myocardial injury. High-tech diagnostic methods are required, which also cannot always give a clear answer to the question of injury cause. We present a case report of acute myocardial injury caused by a systemic inflammatory response syndrome (SIRS), which developed due to chronic tonsillitis exacerbation.

Male patient, 44 years old, was admitted on February 9, 2020 to cardiac intensive care unit with non-ST segment elevation acute coronary syndrome (ACS) and lacunar tonsillitis.

Upon admission, he complained of general weakness, chills, sore throat.

He consider oneself sick since the evening of February 5, 2020, when at about 7 pm he felt a sharp weakness, chills, the body temperature rose to 37,4° C. Two hours later, complaints arose of severe sore throat, aggravated by swallowing, muscle pain; body temperature rose to 40,5° C. The patient receive antiseptics and paracetamol. While taking paracetamol (500 mg), the temperature dropped for several hours to 39,2° C. From February 7, 2020, taking into account the persisting sore throat and an increase in body temperature to 39-40° C, intense knee pain, he independently began to take amoxiclav 500 mg twice a day. On February 9, 2020, he noted a sharp decrease in body temperature to 37,4° C. Then the temperature above 38° C was not noted. On the same day, at about 3 pm, there suddenly appeared a burning pain behind the sternum of moderate intensity, spreading to the left shoulder, left arm and interscapular area. The patient took two Nurofen tablets, after which the pain intensity decreased slightly. At 6 pm, after a daytime sleep and slight exercise, squeezing pain resumed behind the sternum, spreading to the left shoulder and left arm, the interscapular area. An ambulance was called. Electrocardiography did not reveal abnormalities. Repeated intake of sublingual nitrates did not stop the pain syndrome and the patient was admitted to the S. P. Botkin Clinical Infectious Diseases Hospital diagnosed with lacunar tonsillitis. The chest pain had passed by the time of hospitalization and did not recur. The patient was examined by an otorhinolaryngologist. The diagnosis of chronic tonsillitis exacerbation was confirmed. Smears for diphtheria were negative. Considering complaints of chest pain, the patient was examined by a cardiologist. Troponin T was elevated — 750 pg/ml. Therefore, the patient was transferred to the cardiac intensive care unit of the I. I. Mechnikov North-Western State Medical University with non-ST segment elevation ACS lacunar tonsillitis.

Collection of medical history revealed that in the last years 4-5 times a year he had tonsillitis. About 3 years, the patient also had hypertension with maximum blood pressure values of 150/90 mm Hg and did not receive constant antihypertensive therapy. Cardiovascular family history is negative. There were following bad habits: 24-year smoking, 1 pack per day (smoking index — 24), moderate alcohol consumption.

Objectively, the condition was moderate. Clear consciousness. The body temperature was 37,3° C. Hypersthenic type, class 1 obesity (body mass index — 31,6 kg/m^2). Blood pressure of 130/80 mm Hg. Symmetrical regular pulse of 80 bpm. Clear heart tones, no cardiac murmur. Respiratory rate of 16 bpm. According to auscultation, breathing was harsh and without crackles. Pronounced hyperemia of the pharynx was revealed. The tonsils were enlarged and covered with a white lump. Other systems were without findings.

Upon admission to the cardiac intensive care unit, the ECG revealed sinus rhythm, heart rate (HR) of 86 bpm. In I, II, aVL, aVF, V4-6, smoothed T waves were recorded (Figure 1). Troponin T of 903,3 pg/ml was revealed, followed by a natural decrease and normalization by 7 days. According to echocardiography, ejection fraction was 57,6%, left ventricular (LV) end-diastolic dimension — 51 mm, LV end-systolic dimension — 33 mm, LV mass — 140,5 g, left atrial volume — 35 ml, inferior vena cava diameter — 11 mm, pulmonary artery pressure — 22 mm Hg. Areas of impaired local contractility were not identified. The valves were without significant abnormalities. Pericardial effusion was not revealed.

Given the absence of chest pain on admission, typical ECG changes and areas of impaired contractility according to echocardiography, as well as the presence of an acute infectious disease, it was decided not to perform coronary angiography on the day of admission.

Complete blood count revealed neutrophilic leukocytosis: WBC — 12,2*10^9/l, neutrophils — 9,2*10^9/l, Also, attention was drawn to an increase in the following indicators: aspartate aminotransferase — 78 U/L, creatine phosphokinase — 540 U/L, creatine phosphokinase–MB — 55 U/l, C-reactive protein — 138,8 mg/ l. Blood glucose was 6,1 mmol/ l, creatinine — 95 μmol/ l, urea — 5,9 mmol/ l. Lipid profile was as follows: total cholesterol — 4,7 mmol/l, triglycerides — 3 mmol/l, high–density lipoprotein cholesterol — 0,4 mmol/l, low-density lipoprotein cholesterol — 2,92 mmol/l; atherogenic coefficient — 10,7. Chest X-ray was without findings.

According to clinical urine tests, relative density was 1,015, protein — 0,58 g/l, RBC — 87/μl, WBC — 27/μl, transitional epithelium — 6/μl, granular casts — 3 U/ml.

The 44-year-old patient with metabolic syndrome against the background of chronic tonsillitis exacerbation developed a long-term chest pain, similar to anginal, but not accompanied by typical ECG changes and LV contractility disorders, but combined with an increased troponin, studied in dynamics. It is necessary to carry out a differential diagnosis between acute rheumatic fever (ARF) (angina, arthralgia, systemic inflammatory response syndrome, chest pain, which may be a manifestation of myopericarditis, which developed, however, in the first days of the disease, which is not typical for ARF), non-ST elevation ACS and acute myocardial injury against the background of an infectious process. To clarify the nature of kidney injury, additional examination was required.

Oropharyngeal and tonsillar swabs were positive for *Streptococcus viridans* and *Staphylococcus epidermidis*. Antistreptolysin O antibodies were not detected. The level of complement-C3 was 1,3 g/l (normal range, 0,9-1,8 g/l). Venous blood circulating immune complexes level was 14 U (normal range, 50-80 U).

ECG on the second day of hospitalization revealed sinus rhythm with a heart rate of 86 bpm. There were no significant changes in comparison with the ECG from the first day. Repeated echocardiography 3 days after admission were without dynamics.

Repeated urine tests on the third day of hospitalization revealed a relative density of 1,020, protein — 0,3 g/l, RBC — 138/μl, erythrocyte clots — 5/μl, WBC — 19/μl, transitional epithelium — 4/μl, hyaline casts — 2 U/ml. Parameters of urine analysis on the 5th day were normal. According to Nechiporenko's test, WBC was 300 cells/ml, RBC — 675 cells/ml, casts — 10 U/ml. The daily protein loss was 0,95 g/l.

Kidney ultrasound revealed the following data: renal parenchyma was homogeneous, echogenicity was not changed, corticomedullary differentiation was preserved. The pyelocaliceal complex was not expanded. There were no concrements.

Thus, according to the diagnostic tests, data for ARF were not obtained: from the major criteria, the suspicion of myopericarditis was not confirmed, which will be discussed in more detail below; minor criteria — arthralgia, fever, increased C-reactive protein were present, but group A β-hemolytic streptococcus and antistreptococcal antibodies was not detected. There were no evidence in favor of acute glomerulonephritis (no acute nephritic syndrome),

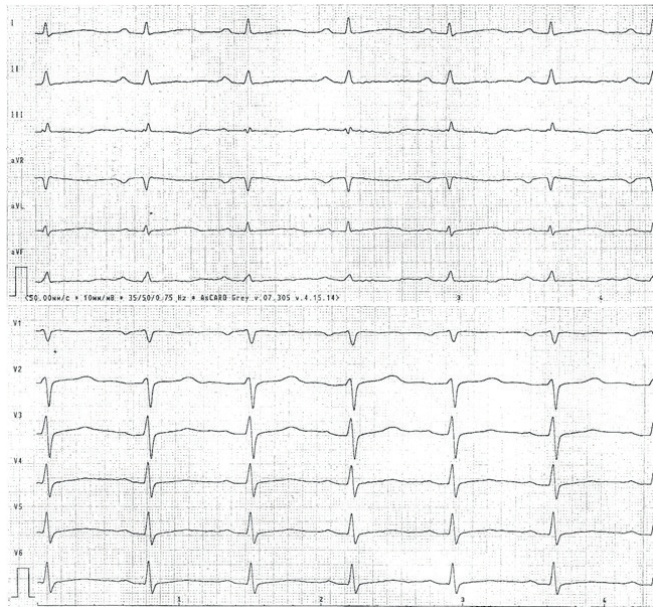


Figure 1. ECG on admission to the cardiac intensive care unit.

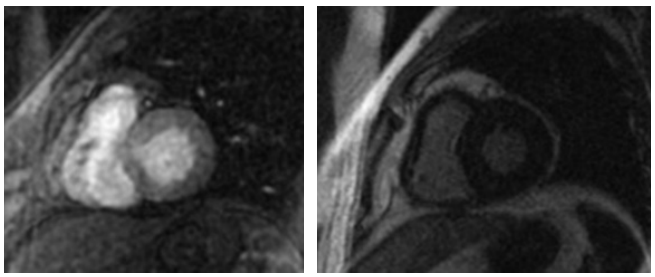
normal complement values, rapid normalization of urine parameters. Evidence in favor acute interstitial nephritis (adequate diuresis, normal relative urine density and creatinine levels, rapid normalization of urinary sediment) was also absent. Transient changes in urine tests fit into the picture of SIRS.

In connection with suspected non-ST-elevation ACS in the patient with signs of metabolic syndrome and cardiovascular risk factors, after normalization of body temperature, coronary angiography was performed, in which no changes were found.

To rule out myocarditis and ischemic myocardial necrosis, on February 17, 2020, contrast-enhanced cardiac magnetic resonance imaging (MRI) was performed: ejection fraction was 69%, heart chambers were not dilated, contractility was preserved, and no local contractility disorders were detected. No MRI signs of myocardial edema were found (Figure 2, 3). On delayed post-contrast images, no pathological accumulation of contrast agent in the LV myocardium was detected. According to conclusion, MRI evidence in favor of LV myocardial edema were not obtained. Inflammatory and postischemic changes were not detected.

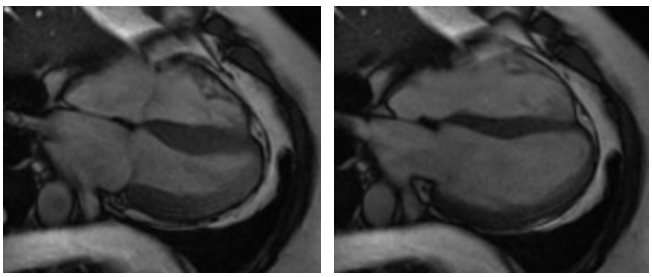
Thus, after rolling out myocarditis and myocardial infarction, the most likely explanation for the increase in troponin was acute reversible myocardial injury due to SIRS in the presence of severe bacterial tonsillitis.

In the hospital, the patient received the following therapy: amoxicillin + clavulanic acid, dual antiplatelet therapy (before coronary angiography), statins, β-blockers, angiotensin-converting enzyme



A **B**

Figure 2. Cardiac MRI, short axis. Myocardial perfusion (**A**), no impaired perfusion areas and delayed contrasting (**B**), no areas of contrast accumulatio.



A **B**

Figure 3. Cardiac MRI, four-chamber view. Systolic (**A**) and diastolic (**B**) phases, no areas of impaired contractility.

inhibitors. With treatment, the patient's condition improved: there was no fever, chest pain did not recur; shortness of breath, heart failure, and weakness wan not established. Tonsillitis was resolving. Complete blood count, C-reactive protein, and transaminases returned to normal value by the 5th day of hospitalization. At discharge, the patient was recommended an additional examination for steatohepatitis, control of urine tests against a background of fever to rule out Berger's disease, and intake of statins and antihypertensive drugs, as well as modification of cardiovascular risk factors.

Discussion

The patient with severe chronic tonsillitis exacerbation was admitted to the cardiac intensive care unit with a diagnosis of non-ST-segment elevation ACS due to chest pain and elevated troponin. The pain developed against the background of pronounced arthralgia and intoxication, responded to non-steroidal anti-inflammatory drugs, not nitrates. It also lasted a long time (about 6 hours) and there were no typical ECG changes and echocardiographic local contractility disorders. Coronary angiography showed no signs of atherosclerosis. According to the results of cardiac MRI, no evidence was obtained in favor of MI.

The assumption of ARF with myopericarditis was not very convincing from the very beginning due to the early pain onset (on the 3rd day of illness) and subsequently was not confirmed by laboratory data. There were no pericardial friction rub and no ECG changes specific to pericarditis. Finally, no myocarditis was detected by contrast-enhanced cardiac MRI. Thus, the pain could be explained by muscle pain against the background of fever and an acute infectious process.

Then the question remains, what was the reason for the troponin turn observed in the patient? In our opinion, this phenomenon can be explained by acute myocardial injury against the background of SIRS, which developed as a result of bacterial infection. The severity of SIRS, in addition to long-term fever, neutrophilic leukocytosis and high C-reactive protein, was also evidenced by urine changes and increased transaminases upon admission.

As follows from recent European and Russian literature, an increase in troponin levels does not always indicate ACS and, in the absence of other ischemia signs, may reflect acute or chronic myocardial injury, which, in turn, develops for various reasons [1].

Differential diagnosis of acute myocardial injury and ACS can be difficult. In addition to troponins, first of all, the presence of acute myocardial ischemia signs should be taken into account: clinical performance, ECG alterations, areas of impaired local myocardial contractility, and, of course, coronary angiography data. In the case of coronary artery thrombosis with pronounced atherosclerotic changes according to angiography, as a rule, there are no diagnostic problems, and type 1 MI is diagnosed.

In the absence of significant (>50%) coronary artery changes and acute thrombosis, but with *ischemia signs and increased troponin*, myocardial infarction with nonobstructive coronary arteries (MINOCA) is suspected. MINOCA is a working diagnosis that requires a search for the cause of myocardial infarction or disorders masking it: myocarditis, takotsubo syndrome, etc. [2].

It should be borne in mind that one of MINOCA causes may be a small plaque damage with the development of thrombosis, the signs of which, according to coronary angiography, may be absent due to spontaneous thrombolysis. In this case, the diagnosis is confirmed by intracoronary imaging methods. With this data, a working diagnosis of MINOCA should be transformed into a type 1 MI. Another variant of MINOCA occurs when there are no significant atherosclerotic changes and/or signs of thrombosis in the suspected infarct-related artery, but ischemia can be explained by an acute discrepancy between myocardial oxygen demand and its delivery, arising, for example, due to coronary artery spasm, arrhythmias,

severe hypertensive crisis, etc. In this situation, the final diagnosis will be type 2 MI [1].

It is far from always possible to immediately establish the cause of MINOCA, given insufficiently available intracoronary imaging methods. In this case, the key diagnostic method is cardiac MRI, which allows visualizing the area of ischemic necrosis in MI, including hemodynamically insignificant atherosclerotic plaque, and also to rule out myocarditis and other causes of myocardial injury, for example, Takotsubo syndrome, amyloidosis, sarcoidosis, etc. [1, 2].

If there are no clinical symptoms of ACS and no signs of ischemic injury according to ECG and echocardiography, an increased troponins can be explained by acute or chronic myocardial injury that can occur with sepsis, end-stage chronic kidney disease, severe respiratory failure, etc. [1]. Also, in patients with COVID-19 and severe lung injury, cases of acute myocardial injury have been described, aggravating the prognosis of the disease [3].

In presented case, the patient had a bacterial infection accompanied by SIRS. According to experts, such a body response with sepsis and other infectious processes can be an independent cause of myocardial injury. As is known, the main mediators of inflammation with a direct cytotoxic effect are tumor necrosis factor alpha, interleukins 1 and 6, which are present in large quantities in the blood of patients with sepsis and other severe infections [4]. Increased blood troponin may be associated not only with cardiomyocyte necrosis, accompanied by myofilament rupture, but also with the leakage of cytosolic troponin due to an increase in the sarcolemma permeability associated with an action of endotoxins, cytokines, and also reactive oxygen species [5].

The issue of ischemic and non-ischemic myocardial injury is relatively new for modern cardiology and not all questions have been resolved by now. So, for example, how sensitive is the MRI in detecting acute ischemic myocardial injuries and their differential diagnosis with myocarditis? So, according to a number of authors, in 10-20% of patients with MINOCA, no changes were found on cardiac MRI [6]. Perhaps the timing of MRI is important [6].

Even less studied is the question of whether it is possible to visualize myocardial injury in sepsis and SIRS with the help of cardiac MRI? When is troponin elevated? What is the nature of this injury? In the study by Siddiqui Y, et al. (2013), group of patients with elevated troponin I on the background of sepsis or SIRS was studied, authors found an increased T2 relaxation time of the epicardium, which indicates a nonischemic reversible mechanism of myocardial injury due to inflammation or the development of tissue acidosis [7]. Similar results were obtained by Takasu O, et al. (2013) during analysis of the hearts of deceased patients with sepsis. The authors found that “septic hearts” did not have signs of irreversible acute injury and cell death, i.e., signs of necrosis, but there was focal potentially reversible damage to cardiomyocyte mitochondria [8].

Thus, the issues of differential diagnosis of ACS and acute myocardial injury, as well as the mechanisms of the latter, including with a SIRS, require further study.

Relationships and Activities: none.

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