

Case report

Heart failure in a young woman due to toxoplasmic myocarditis

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Summary

The article presents a case of heart failure (HF) in a young immunocompetent parturient woman. She was admitted to Vilnius University Hospital Santariškių Klinikos with cardiogenic shock and pulmonary edema. An initial 2 days' treatment with normal human immunoglobulin and a 10 days' mechanical circulatory support – intra-aortic balloon contrapulsation – were applied. New markers of inflammation and myocardial dysfunction were investigated. The diagnosis of the cause of HF was differentiated between peripartum cardiomyopathy and myocarditis. The diagnosis of toxoplasmic myocarditis was confirmed by a serial endomyocardial biopsy. Specific therapy was administered.

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Heart failure in young patients without previous cardiac pathology is usually caused by systolic left ventricular (LV) dysfunction. The reason for this may be cardiomyopathy or more seldom – myocarditis. It is rather difficult to differentiate the diagnosis between these two entities. We report the case of acute overt heart failure, which developed suddenly during the last weeks of pregnancy in a young immunocompetent woman.

Case presentation

Status on admission

A 30-year-old woman (56 kg, 146 cm, body surface area 1.47 m²) was admitted to the Depart-

ment of Obstetrics and Pathology of Pregnancy in Panevėžys (Lithuania) on the 24th of September 2004 because of cough and shortness of breath that appeared a few days ago. She was in the 38th week of her first pregnancy which was absolutely normal until then. She never had any complaints before.

In two days she acutely deteriorated and was transferred to the Intensive Care Unit due to progressive pulmonary insufficiency. On admission to the Intensive Care Unit she presented pronounced tachypnoea – 40 r/min, tachycardia up to 120 b/min and decreased oxygen saturation – Sp O₂ 84%. She was intubated and artificial ventilation was started. On the same day the foetus was delivered through Caesarean section; the newborn was evaluated by Apgar score of 6–7 points. Chest X-ray showed signs of pulmonary distress and edema, the suspicion of pneumonia of the lower lobe of the right lung. On the 29th of September she was transferred to the Intensive

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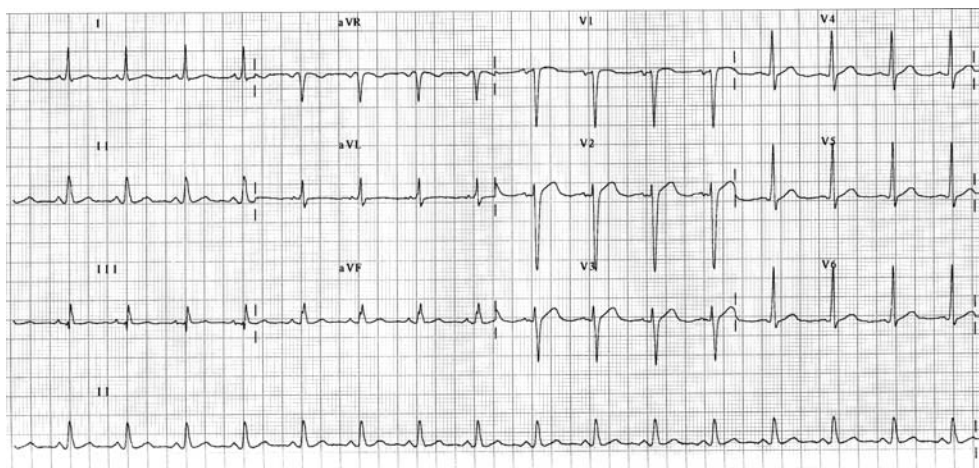


Figure 1. Electrocardiogram shows sinus tachycardia and ST elevation in the precordial leads.

Care Unit of the Centre of Cardiac Surgery of Vilnius University Hospital Santariškių Klinikos.

At admission she was conscious, ventilated (oxygenation index – 132 mm Hg), with stable hemodynamics and good peripheral circulation (blood pressure – 90/70 mm Hg); body temperature was 37.8°C, sinus tachycardia was present (120 b/min). Her chest X-ray examination showed signs of pulmonary edema. Electrocardiogram (ECG) findings included sinus tachycardia and ST elevation in the precordial leads (Figure 1).

A complete blood count assay showed leucocytosis ($10.3 \times 10^9/l$, young forms 2%), C-reactive protein was 68.8 mg/l. The sepsis marker procalcitonin [1] (BRAHMS PCT-Q assay) <0.5 ng/ml did not show any systemic bacterial infection. Interleukin-6 was markedly elevated – 48 pg/ml. Troponin I was at the borderline – 0.47–0.52 $\mu\text{g/ml}$, aspartate aminotransferase (ASAT) – 84 U/l, alanine aminotransferase (ALAT) – 65 U/l. N-terminal pro-brain natriuretic peptide (NT-proBNP) was 1217 pg/ml, indicating severe cardiac involvement [2]. The patient's condition evaluated using the APACHE II score [3] (a scoring system developed for quantifying the severity of illness in intensive care patients), was 9 points (the predicted death rate – 7.9%).

Echocardiogram

The global systolic function of the left ventricle (LV) was severely depressed (Table 1, Figure 2) with concomitant local differences in contractility, as the basal part of the interventricular septum and the inferior wall were dyskinetic comparing to other walls. The left ventricle (LV index 3.5 cm/m^2) and the left atrium (5.5×5.0 cm) were slightly dilated, with moderate mitral regurgitation (I–II°). The reduced values of the cardiac output and cardiac index, calculated by the modified Simpson method, are presented in Table 1. The filling of the LV showed a restric-

tive pattern of diastolic dysfunction. Using tissue Doppler echocardiography, pulmonary capillary wedge pressure (PCWP) was calculated from the equation suggested by Nagueh [4] ($\text{PCWP} = 1.24(E/E') + 1.9$, E – the wave of early left ventricular filling, E' – the wave of early diastolic motion of the mitral valve, see Table 1). The interrogation of the myocardium using tissue Doppler technique revealed reduced systolic myocardial velocities (6–8 cm/s) and a restrictive pattern of regional diastolic function [5]. The right ventricle was normal, no pericardial effusion was observed.

The course of the disease

On the second day after admission, the patient's hemodynamics deteriorated. The dobutamine infusion at 7 $\mu\text{g/kg/min}$ and intra-aortic balloon contrapulsation were started. The implantation of a LV assisting device (Berlin Heart, ExCor) was considered. As the diagnosis was differentiated between peripartum cardiomyopathy and myocarditis of unclear etiology, on the 1st of October endomyocardial biopsy was performed (6 samples were taken). During the right heart catheterisation mean pulmonary artery pressure was 47 mm Hg, mean pulmonary capillary wedge pressure was 34 mm Hg. After that, the infusion of nitroglycerine was administered. Without having results of the biopsy and in the setting of markedly elevated IL-6 and NT-proBNP, acute myocarditis was highly suspected, and the infusion of human normal immunoglobulin IgG (“Endobulin”, Baxter) was started. The total dose of 120 g was administered within 2 consecutive days since the 1st of October. Gradually the patient's condition improved. On the 4th of October, dobutamine dose decreased from 7 $\mu\text{g/kg/min}$ to 3.4 $\mu\text{g/kg/min}$, oxygenation index increased from 132 to 212 mm Hg and the patient was successfully weaned from artificial lung ventilation (duration: 8 days). C-reactive protein decreased from

Table 1.
Dynamics of selected laboratory, invasive hemodynamic and echocardiographic parameters

	September 30	October 4	October 20	November 26
Laboratory parameters				
NT-proBNP, pg/ml	1217	1455	618	1043
IL-6, pg/ml	48		3.4	
CRP, mg/l	68.8	20.5	0.99	
ESR, mm/h	65	106	26	11
CPK, U/l	39		20	
CK-MB, μ g/l	0.1		1.1	
Troponin I, μ g/l	0.47	0.52	0.01	
Heart catheterisation				
RA pressure, mm Hg	25/12		9/4	
RV pressure, mm Hg	70/0		60/0	
PCWP, mmHg	42/28 (34)			
Echocardiography:				
LV diastolic diameter, cm	5.2	5.1	5.5	5.7
LV EF, %	20	31	22	22
LV diastolic volume, ml	102	108	105	91
dP/dt, mmHg/ms	969	1142	681	618
calculated PCWP, mm Hg	14	11	16.8	13.5
cardiac output, l/min	3.2	4.7	3.9	4.0
cardiac index, l/min/m ²	2.2	2.8	2.5	2.7

CK-MB – creatine phosphokinase MB fraction; CPK – creatine phosphokinase; CRP – C-reactive protein; EF – ejection fraction; ESR – erythrocyte sedimentation rate; IL-6 – interleukin 6; LV – left ventricle; NT-proBNP – N-terminal-pro-brain natriuretic peptide; PCWP – pulmonary capillary wedge pressure; calculated PCWP = $1.24(E/E') + 1.9$, E – the wave of early left ventricle filling, E' – the wave of early diastolic motion of the mitral valve; dP/dt – contractility index, derived from the spectrum of mitral regurgitation (normal > 1200 mmHg/ms); RA – right atrium; RV – right ventricle.

66.8 to 20.5 mg/l, leucocytosis – from $10.3 \times 10^9/l$ to $7.2 \times 10^9/l$. Further, the levels of IL-6 and NT-proBNP reduced from 48 to 3.4 pg/ml and from 1455 to 618 pg/ml, respectively (see the dynamics of other parameters in Table 1).

The patient was examined for the presence of immune deficiency on the second day after the admittance to our hospital and four days after the Caesarean section. The investigation of the immune state included determination of lymphocyte subtypes, as CD3⁺ (T lymphocytes), CD3⁺CD4⁺ (T lymphocytes helpers/inductors), CD3⁺CD8⁺ (T cytotoxic/suppressor lymphocytes), CD3⁻CD16⁺/56 (NK cells), CD19⁺ (B lymphocytes), as well as activation markers, as HLA-DR expression on T lymphocytes and CD57 – on T cytotoxic/suppressor cells. Lymphocyte subsets were found to be normal, with no signs of activation. Nevertheless, the absolute lymphocyte count was far below the age-related standard. To ascertain the cause of immunodeficiency, lymphocyte immunophenotyping was repeated two weeks later; immunological analyses were found to be normal.

From the 5th of October, the patient was treated in the Intensive Care Unit of the Centre of Cardiology. The intra-aortic balloon pump

was withdrawn on the 9th of October (duration: 10 days), dobutamine infusion was stopped on the 10th of October (duration: 11 days).

Repeated laboratory and echocardiographic examinations showed biphasic response to treatment: the value of BNP decreased and cardiac performance improved during the first 2–3 weeks of treatment with slight subsequent deterioration (Table 1). However, clinically the patient was stable and felt progressively better during 30 days of hospitalisation.

Results of endomyocardial biopsy

All samples underwent immunohistochemical analysis to characterise inflammatory cell infiltration by using the following antibodies: CD45RO (Dako 1 : 100), CD43 (Dako 1 : 40), CD68 (Dako 1 : 50). The type and severity of the infiltrate were assessed.

Haematoxylin and eosin staining of the first samples (obtained on the 1st of October) showed the absence of myocardial necrosis or marked fibrosis, and a few (10–15 cells/mm²) inflammatory cell infiltrates (Figure 3). Immunohistochemical staining for CD43 (T leucocytes) (Figure 4), CD45RO (leucocytes) and CD68 (macrophages) showed the presence of inflammatory cells within the myocardium. Haematoxylin and eosin stain-

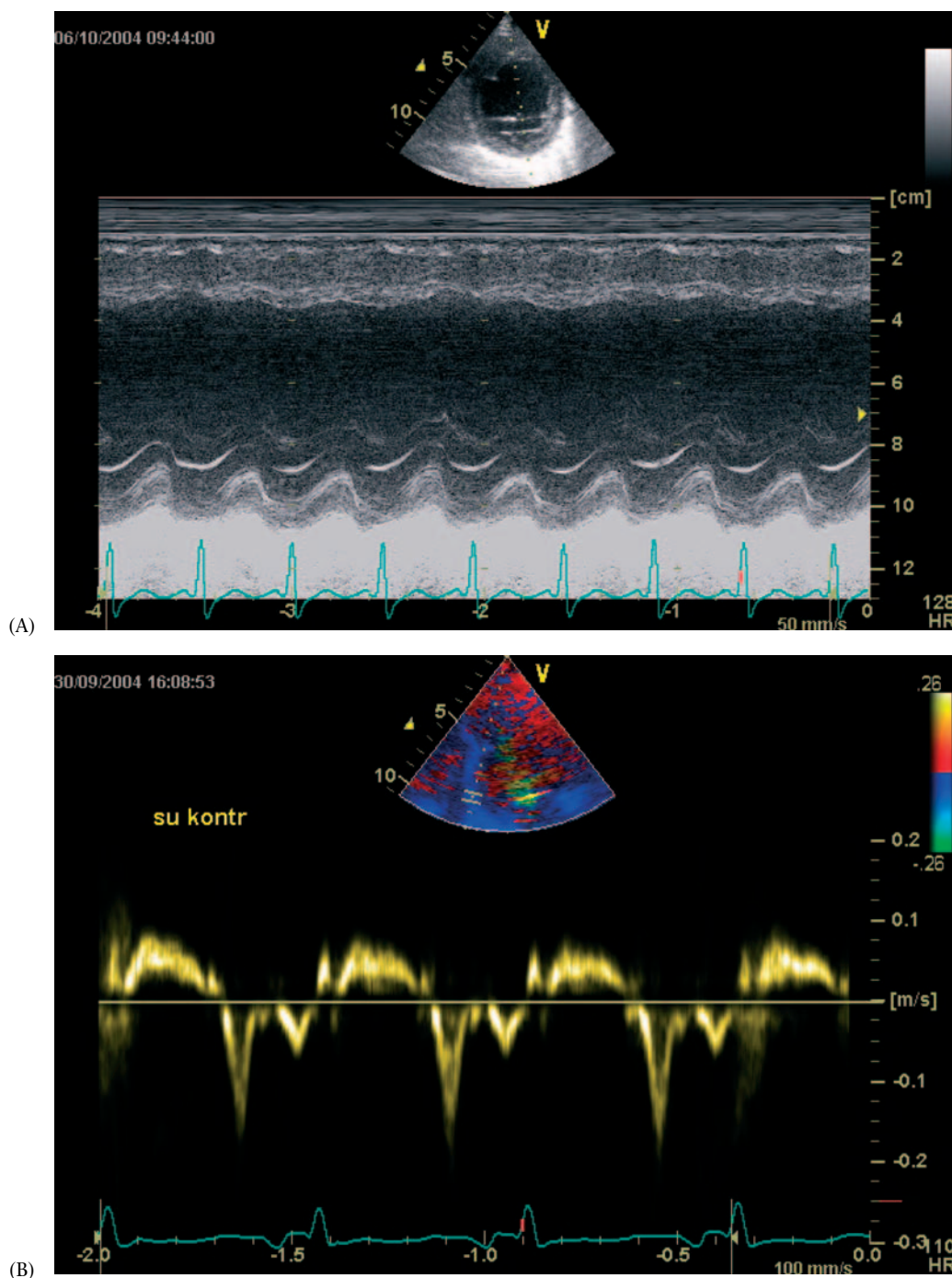


Figure 2. (A) M-mode imaging of the left ventricle in a parasternal axis shows severely depressed global contraction, left ventricular dilatation and almost akinetic interventricular septum. (B) Tissue Doppler imaging shows reduced systolic myocardial velocity and restrictive pattern of regional diastolic function.

ing showed pseudocysts containing tachyzoites of *Toxoplasma gondii* in the heart muscle (Figure 5).

According to the Dallas histopathological criteria myocarditis was classified as a borderline, because necrosis and degeneration were absent [6,7]. The specimens were sent to Prof. K. Geboes, Pathologische Ontleedkunde, Leuven, who also confirmed the diagnosis of toxoplasmic myocarditis.

The repeated endomyocardial biopsy (on the 21st of October) revealed the subsequent progression of the disease: the focus of myocardial necrosis with collagen fibers and myocyte degeneration were seen. The degree of inflammatory cells infiltration increased: >15 cells/mm². According to the Dallas criteria, the diagnosis became definite: active myocarditis. Pseudocysts containing tachyzoites of *Toxoplasma gondii* again were present in the heart muscle.

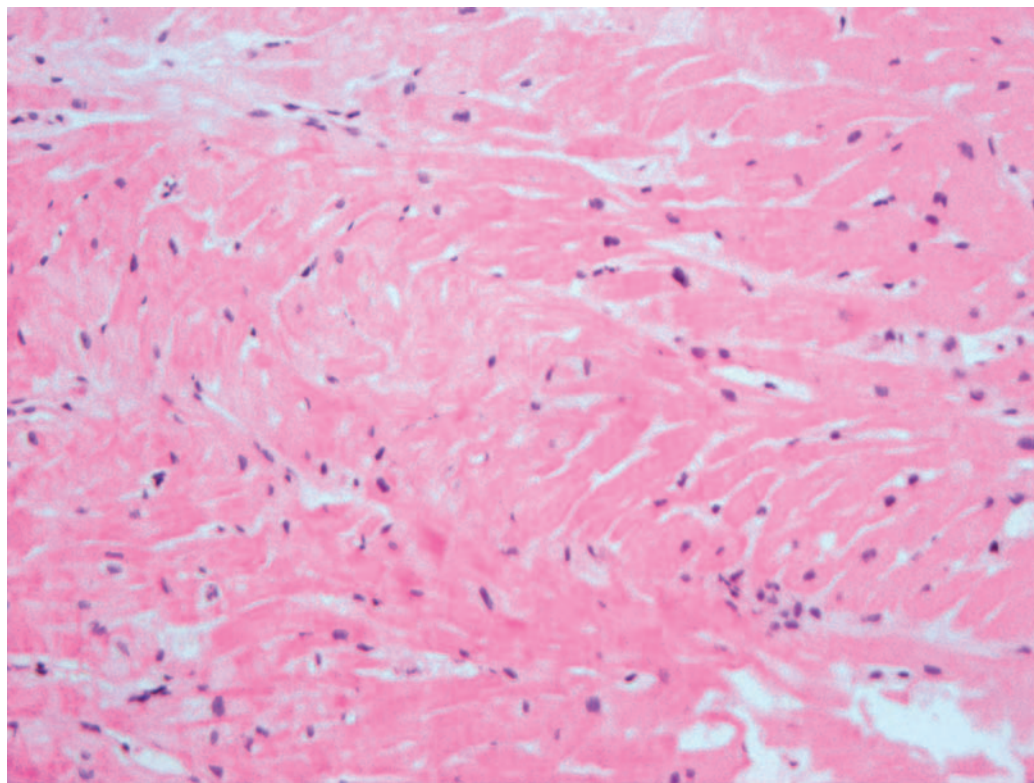


Figure 3. Haematoxylin and eosin staining shows few inflammatory cells. Original magnification $\times 200$.

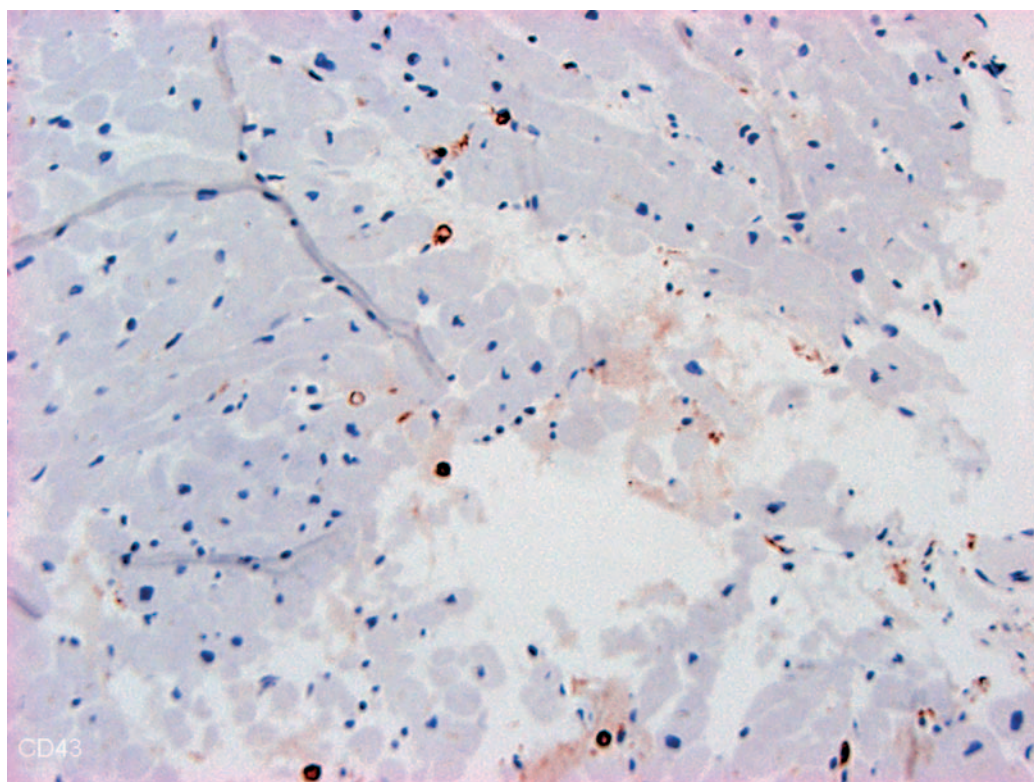


Figure 4. Immunohistochemical staining for CD43 (T lymphocytes) confirms the presence of inflammatory cells within the myocardium. Original magnification $\times 200$.

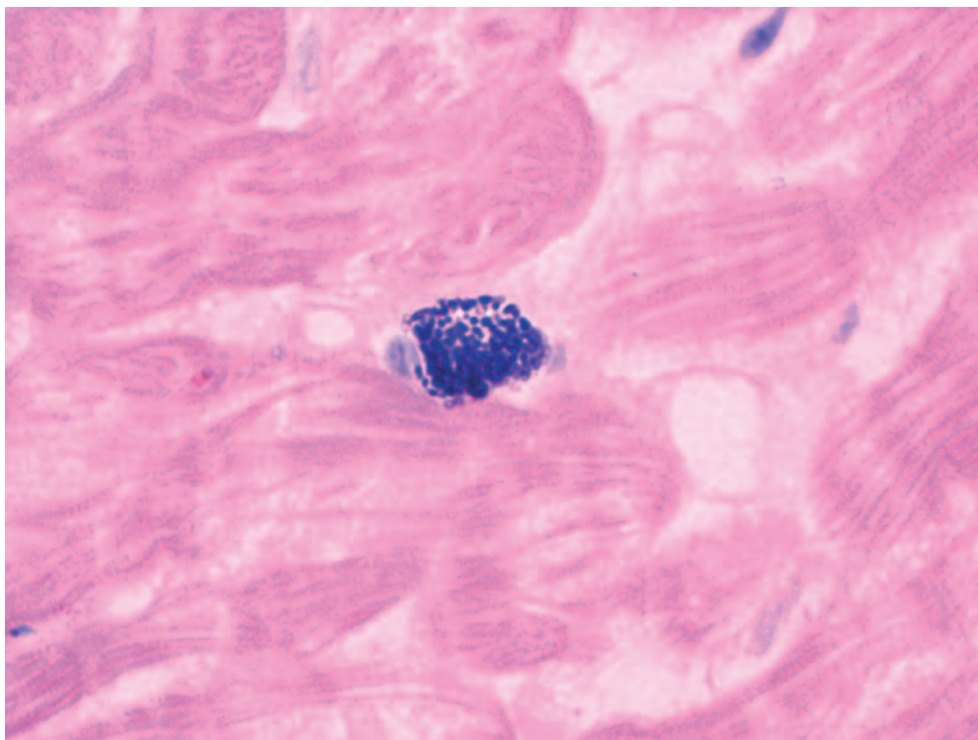


Figure 5. Giemsa staining shows pseudocysts containing tachyzoites of *Toxoplasma gondii*. Original magnification $\times 200$.

After the detection of toxoplasmosis the brain computed tomography (CT) was performed, no pathological changes were found. Abdominal sonoscopy did not reveal any abnormal findings as well. Anti-HIV antibodies were negative. Toxo IgG antibodies were positive, 18.9 IU/ml, IgA and IgM were negative (the MEJA method, ABBOTT). The newborn was tested, no signs of toxoplasmosis were found.

Treatment

Until the diagnosis of toxoplasmic myocarditis was confirmed, the patient received the treatment with human IgG and conventional treatment with diuretics, ACE inhibitors, beta-blockers, digoxin, spironolactone. After the confirmation of the diagnosis of toxoplasmic myocarditis by the second endomiocardial biopsy specific treatment with pyrimethamine (50 mg twice daily for 10 days), clindamycin (600 mg 4 times per day for 2 weeks) and methylprednisolone (32 mg + 16 mg for 2 weeks) was started. Later pyrimethamine was continued for 6 weeks.

After the discharge, the patient's condition remained stable at 1 month follow-up, she had mild symptoms of heart failure, however, tachycardia 100 b/min was present, and no improvement on echocardiography was seen, as well as in the level of NT-proBNP (Table 1). The specific therapy is going on. If further there is no improvement in myocardial function and the level

of NT-proBNP, the patient will be included into the list of recipients for heart transplantation.

Discussion

Primary *T. gondii* infection in any host often goes unrecognised [8]. Lymphadenopathy and fatigue with or without fever are the most frequently observed clinical manifestations. Other manifestations including chorioretinitis, myocarditis, and polymyositis are very rare. Cardiac involvement may result in arrhythmia, pseudo-infarction and more frequently – in acute congestive heart failure due to myocarditis [9,10].

Among immunologically impaired individuals, toxoplasmosis most often occurs in those with defects in T-cell-mediated immunity. It is widely accepted, that infection concomitant with HIV or immunosuppression administered to control transplant rejection or malignancies may result in active toxoplasmosis [11,12]. Disseminated toxoplasmosis during acute infections, or local toxoplasmic infections has rarely been observed in immunocompetent patients. We report a histologically confirmed case of toxoplasmic myocarditis in an immunocompetent patient. The acute myocardial damage coincided with the peripartum period in this patient. The absolute lymphocyte count in the first immunology test of our patient was decreased presumably due to the recent surgery. It is described, that patients who have

experienced trauma or a major surgical intervention have temporary immunodeficiency, related to anaesthesia and tissue injury [13,14]. The number of lymphocytes is significantly decreased only on the first post-operative day and parameters are back to the normal range at the end of the first post-operative week, as it occurred in our patient.

The diagnosis of toxoplasmosis in the presented case was confirmed by positive serology and biopsy. The detection of *T. gondii* DNA in peripheral blood using polymerase chain reaction (PCR) was not available at that time. Antibody levels to the *T. gondii* were positive for anti-toxoplasmic IgG in moderate titers, anti-toxoplasmic IgM and IgA were negative. Serological tests for toxoplasmosis were repeated in the course of treatment, antibody levels were stable. Generally, IgA and IgM are seen to increase in the first few weeks after infection, reaching a peak after about 1 month and subsiding to non-detectable levels after 6–9 months [15]. IgG starts to increase only 1–2 months after infection, reaching a peak after 6–9 months, then steadily decreases without ever completely disappearing. Obviously, our case represents a rare situation with the onset of cardiac complications long after primary toxoplasma infection. Few similar cases of toxoplasmic myocarditis in immunocompetent patients were described previously [15]. Authors pointed that the results of immunoglobulin binding and differential agglutination tests implied that seroconversion had occurred 6–12 months before the acute cardiac problems [16, 17]. The mechanism linking high or persistent raised levels of the antibody to the onset of cardiac complications is not clearly understood. Re-infection may play a role [15]. It is important to determine whether a patient has been exposed to a parasite. Our patient's history revealed that she had had indirect contact with kittens in the village and three months prior to hospitalisation touched raw pork in her native Katinų village.

There were no typical changes for toxoplasmosis on the brain CT scan. After the first biopsy it was even debated that only a few toxoplasma pseudocysts found could not be the reason of the patient's deterioration. Peripartum cardiomyopathy was still considered as a possible cause of acute heart failure.

The present case confirms the statement that a serial endomyocardial biopsy remains the gold standard in the diagnosis of myocarditis [18]. The borderline was a result of the first biopsy. According to the recommendations of the expert group [19], the repeated endomyocardial biopsy was performed. It permitted to estimate a definitive diagnosis: histological examination revealed the characteristic morphology of active infection –

a parasite in tissues with the presence of tachyzoites and multiple cysts.

Regarding other diagnostic features, the regional abnormalities of myocardial contraction on the background of global depression of inotropy are described in the literature in case of toxoplasmic myocarditis [15]. It is hard to explain the absence of elevation of cardiac enzymes in our case. However, similar findings – normal cardiac enzymes and slightly elevated levels of transaminases (ALAT and ASAT) – are reported in the literature [15]. The dynamics of inflammatory markers (CRP, IL-6, erythrocyte sedimentation rate) indicated the inflammatory nature of myocardial damage and correlated with the improvement in clinical status. An innovative sepsis marker PCT allowed to exclude systemic bacterial infection in the early stage of the disease. The favourable short-term clinical outcome implies the value of immunomodulatory treatment with Endobulin in the early stage of the disease [20].

The biochemical marker of cardiac dysfunction NT-proBNP after the initial decrease in 2–3 weeks showed the subsequent tendency of repeated elevation, what is in accordance with persisting poor echo findings. By other reports, complete recovery of cardiac function was observed in 6 months after the acute episode [15].

Every case of myocarditis with a history of touched raw pork in Lithuania should be investigated for toxoplasmosis. Appropriate antitoxoplasmic therapy may provide clinical improvement and predict better outcome.

Conclusions

Well-timed transfer of a patient with progressing cardiogenic shock to the tertiary university centres of cardiology and cardiac surgery is relevant. A short-term clinical result of immunomodulatory treatment in the early stage of acute myocarditis is favourable. A serial endomyocardial biopsy yields crucial diagnostic information and impacts the treatment in case of acute heart failure and suspected myocarditis. A new biochemical marker NT-proBNP is helpful in the suspicion of myocardial damage and the monitoring of treatment. Every case of acute myocarditis and the history of touched raw pork should be investigated for toxoplasmosis.

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