Could it have been better? A patient with peripartum cardiomyopathy treated with conventional therapy

Da li je moglo biti bolje? Prikaz bolesnice sa peripartalnom kardiomiopatijom koja je lečena konvencionalnom terapijom

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Abstract

Introduction. Peripartum cardiomyopathy is a life threatening condition of unknown cause that occurs in previously healthy women. It is characterized by symptoms of heart failure due to left ventricular dysfunction that occurs in the last month of pregnancy or the first five months after delivery. Case report. We presented woman who underwent caesarean section due to preeclampsia. Two weeks after delivery first signs of heart failure appeared and only after six weeks following the onset of symptoms peripartal cardiomyopathy was recognized. A conventional treatment with diuretics, ACE inhibitor and beta blocker along with anticoagulant therapy was applied, which resulted in a complete recovery of the left ventricular function four months after.

Conclusion. Timely detection and initiation of treatment are an important precondition for the complete or partial recovery.

Key words: pregnancy complications, cardiovascular; cardiomyopathies; diagnosis; drug therapy; treatment outcome.

Introduction

Peripartum cardiomyopathy (PPCM) is clinically defined as the occurrence of heart failure due to left ventricular dysfunction of unknown reasons, in late pregnancy or within the first five months after delivery

Despite the low prevalence (approximately 1 out of 2,000 to 4,000 deliveries), this disease associated with pregnancy arises attention due to unexplained etiology and concerns about treatment.

We reported a patient with unrecognized PPCM who recovered entirely with conventional drug therapy including complete recovery of left ventricular systolic function. In this context we have considered a place of new modalities in the treatment of this disease.

Case report

Arterial hypertension was diagnosed in the third trimester of the first gravidity in a 33-year-old woman. The treatment with alpha-methyldopa resulted in a reduction but not normalization of blood pressure. Because of the development of preeclampsia – proteinuria and grade 3 arterial hypertension, pregnancy was terminated by cesarean section two weeks before the term. Two weeks after the delivery dyspnea appeared. Six weeks later the patient was admitted
to the regional hospital because of dyspnea, paroxysmal nocturnal dyspnea and leg edema. Differential diagnosis was postpartum cardiomyopathy and the patient was sent to a tertiary institution.

On admission the patient was pale, respiratory rate was 24/min, heart rate > 120/min and blood pressure 120/80 mmHg. Her Body Mass Index (BMI) was 21 kg/m². Jugular veins were discretely distended. Auscultation of the lugs revealed normal breathing sound with late inspiratory crackles basally and bilaterally. Cardiac apex was palpable in the fifth intercostal space, 2 cm to the left of the medioclavicular line. Auscultation of the heart revealed systolic gallop rhythm with regurgitation murmur on the apex. The liver was palpable 3 cm below the rib. Bilateral pretibial edema was also detected.

The patient was free of previous cardiovascular disease or infection during pregnancy. During pregnancy the patient did not receive tocolytics. She did not use alcohol, cocaine and cigarettes.

Laboratory analyses at admission found sideropenic anemia (Hb 109 g/L, Ht 0.33, Fe 4 umol/L and transferrin saturation 5%), hypoproteinemia (54 g/L) with hipoalbuminemia (30 g/L), increased levels of uric acid (488 umol/L), ALT (110 U/L), LDH (727 U/L), and CRP (17 mg/dL). The brain natriuretic peptide (BNP) level was 3556 pg/mL. Other findings were within normal range, including prolactin levels and cardiac enzymes (CK-MB, troponin). The patient reported to have bronchopulmonary infection with bilateral pleural effusion and small pericardial effusion five years before pregnancy, which had resolved after three months. Because of this information we made basic immunological analyses (ANA, ANCA, immunoglobulin and complement components) which were all in referent ranges.

The first chest X-ray revealed enlarged heart and signs of lungs congestion. Sinus tachycardia was detected in ECG. Initial echocardiographic examination showed the dilated left ventricle with thin walls and septum and reduced systolic contractility (Figure 1), the dilated left atrium and the right ventricle, and Doppler ultrasound found mitral 2+ and tricuspid 3+ regurgitation. The right ventricular systolic pressure was estimated at 80 mmHg. Small pericardial effusion was also detected.

Table 1 shows the echocardiographic parameters of four consecutive examinations (on admission, after four, eight and 16 weeks of the start of the treatment).

Magnetic resonance (MR) imaging with gadolinium showed the enlarged left ventricle echocardiographic end-diastolic diameter (EDD) 64 mm, end-systolic diameter (ESD) 53 mm) with ejection fraction (EF) 23%, end-diastolic volume (EDV) 145 mL, end-systolic volume (ESV) 114 mL, CO 2.3 L/min. Mitral regurgitation 2+ was also found. The right ventricular EF was estimated at 24% EDV 109 mL, ESV 83 mL, CO 1.81 L/min. There was a severe tricuspid regurgitation 3+. MR confirmed the existence of pericardial effusion. At the early stage after contrast application there were no signs to indicate the presence of intraluminal mass. In the late phase, 10 and 15 min after the application of contrast, the areas of delayed myocardial enhancement on MR images were not seen.

The treatment with the loop diuretics, aldosterone antagonist, ACE inhibitor, beta blocker and digoxin (only the first seven days, with control of serum concentrations) was started. The anticoagulant therapy with low molecular weight heparin was added shortly and it was replaced with warfarin after two weeks. Subjective improvement with the withdrawal of heart failure signs occurred after two weeks. The BNP level was reduced by > 80% after four weeks of the treatment, and decreased by > 90% after two months. However, it remained insignificantly increased even after four months (Table 1).

**Table 1**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>On admission</th>
<th>After 4 weeks</th>
<th>After 8 weeks</th>
<th>After 16 weeks</th>
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<td>LVEDD (cm)</td>
<td>5.7</td>
<td>5.7</td>
<td>5.4</td>
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<td>4.5</td>
<td>4.2</td>
<td>3.4</td>
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<td>EF (%)</td>
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<td>35</td>
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<td>FS (%)</td>
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<tr>
<td>LA (cm)</td>
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<td>3.4</td>
<td>3.2</td>
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<tr>
<td>RV (cm)</td>
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<td>BNP (pg/ml)</td>
<td>3556</td>
<td>650</td>
<td>290</td>
<td>145</td>
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</table>

**Table 1**

**Table 1.** The echocardiographic findings and brain natriuretic peptide (BNP) level from admission to the hospital to the last control (16 weeks).

LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; EF – ejection fraction of the left ventricle; FS – left ventricular shortening fraction; LA – left atrial diameter; RV – right ventricular diameter; RVSP – right ventricular systolic pressure.
Controlled chest X-ray was performed after four weeks and it showed the decreased heart and the absence of congestion signs in the lungs. Eight weeks after the beginning of conventional treatment, significant improvement of systolic left ventricular function was registered (EF increased from 22% to 38%) with its normalization after 16 weeks (Table 1 and Figure 2).

Discussion

The etiology and pathogenesis of PPCM are unknown. There are many speculations about its etiopathogenesis.

During pregnancy intravascular volume and cardiac output increase while vascular resistance decreases. These changes could induce the left ventricular remodeling – eccentric hypertrophy with a mild reduction of systolic function. The theory that abnormal hemodynamic changes during pregnancy are responsible for PPCM is not convincing enough.

Based on the absence of differences in pathological findings between PPCM and idiopathic cardiomyopathy it was assumed that PPCM was a type of idiopathic dilated cardiomyopathy induced by hemodynamic stress in pregnancy. This hypothesis was called into question because, in this case, the incidence of PPCM would be higher, and it would be manifested in the second trimester when hemodynamic changes characteristic for pregnancy are most present and not in the third trimester or the postpartum period. Complete recovery in 30% and partial in about 50% of patients distinguish this form of cardiomyopathy from idiopathic dilated cardiomyopathy in which recovery is extremely rare.

The theory that myocarditis is the reason of PPCM was accepted for a long time. It was based on the fact that during pregnancy there is a decrease in both cellular and humoral immunity, with an increased level of corticosteroids and "blocking antibodies". This hypothesis was challenged because myocarditis was confirmed in 0% to 100% of patients, according to different authors.

A possible reason for PPCM could be an abnormal immune response to pregnancy and within it the reduced possibility of “cleaning” of antigens which enter the circulation of the mother. It was assumed, thus, that fetal cells, which remained unrecognized and unrejected from maternal circulation, could remain in cardiac tissue and could cause an abnormal autoimmune response in the postpartum period. Also, rapid degeneration of the uterus after delivery may result in fragmentation of tropocollagen and release of actin and myosin into the circulation which could result in cross-reactions with myocardial proteins. Detection of antibodies to β1 receptors in conjunction with increased adrenergic tone due to emotional and physical stress characteristic for pregnancy might represent another possible mechanism in the development of PPCM.

Apoptosis of cardiomyocytes is another possible reason for PPCM development. Also, it was found that increased levels of CRP and tumor necrosis factor alpha, found in patients with PPCM, correlated with the increased left ventricular dimensions.

Prolonged tocolytic therapy also could be a possible cause of PPCM but it is not determined whether it directly affects its manifestation or unmasks preexisting subclinical disease. Genetic predisposition was shown in the series of cases in families but there is still no confirmation of this hypothesis.

Interest in determination of the role of prolactin in the pathogenesis of PPCM has increased in the recent years. Prolactin exists in at least two biologically active forms with the opposite effects. A 23kDa form promotes angiogenesis and has a protective effect on endothelial cells in contrast to 16kDa that induces cellular apoptosis and disconnection of capillary structures, disturbs the metabolism of cardiomyocytes and influences negatively contractility. It is assumed that the 16kDa form of prolactin which occurs under the influence of oxidative stress has a role in the development of PPCM.

Numerous factors increase the risk of PPCM: higher maternal age, multiple gravity, twin gravity, poor socioeconomic status and arterial hypertension. The presented patient had a history of preeclampsia. Arterial hypertension (pregnancy-induced hypertension, preeclampsia and postpartum hypertension) was detected as a risk factor in 22% to 43% of patients with PPCM. The fact that in preeclampsia there are no significant changes in the left ventricular function classified hypertension as a risk factor and not as a cause.

The diagnosis of PPCM is echocardiographic. Magnetic resonance imaging is a complementary method of diagnosing PPCM. In addition to determination of segmental and global left ventricular function, the finding of the delayed contrast enhancement (with gadolinium) can help in differentiating the inflammatory from noninflammatory form of PPCM. Subepicardial nonvascular nodular or linear distribution of contrast is characteristic of the inflammatory form of PPCM. The absence of delayed contrast enhancement, as in our patient, is typical of noninflammatory origin of PPCM. Based on this evidence we assumed that malnutrition, genetics, prolactin production excess, abnormal hor-
mone function and increased adrenergic tone caused PPCM in our patient. MR findings and the result of endomyocardial biopsy can influence the decision on the treatment modality.

The treatment of PPCM is empirically limited to a standard therapy of heart failure with ACE inhibitors/AT1 receptor blockers, beta blockers, diuretics and aldosterone antagonist. Because of the relationship between impaired left ventricular function and prothrombotic state, characteristic for pregnancy, and the increased risk of thromboembolic complications indicated a need for additional anticoagulant therapy.

There are attempts to use different modalities of treatment based on some of these possible mechanisms of PPCM. One of those was the idea to use intravenous immunoglobulin with immunomodulatory properties based on the hypothesis of abnormal maternal immunoglobulin response. The evidences of this modality of treatment are limited by a small number of included patients.

Based on the theory of inflammation, mediated by cytokines, in the development of PPCM, there was an attempt in pentoxifylline treatment that inhibits the production of tumor necrosis factor and prevents apoptosis. Sliwa et al. showed that patients who receive conventional therapy and pentoxifylline, six months after PPCM diagnosing, are significantly better in recovery of systolic left ventricular function. But the absence of recent confirmation of this treatment did not make this treatment modality widely accepted.

The treatment of PPCM with bromocriptine was based on the concept that oxidative stress-mediated cleavage of prolactin in antiangiogenic and proapoptotic 16kDa form is responsible for the development of PPCM. Individual case reports about the application of bromocriptine in the treatment of PPCM showed faster recovery of the left ventricular function. Last year Sliwa et al. published the results of a pilot study in which they applied bromocriptine to 10 patients (2 × 2.5 mg two weeks and 2.5 mg for six more weeks). Significantly better recovery of left ventricular function and mortality reduction was reported in a group of patients who received bromocriptine in comparison to patients treated with empirical therapy. The limitation of this study was the small number of patients and African origin of the patients which could imply phenotypic differences and may be the reason for inapplicability of the obtained results to patients from other regions.

Our patient was treated with conventional therapy. In adjusting intensity of the treatment, we were not guided primarily by subjective and objective improvement of the patients and by the recovery of heart systolic function (EF), but mostly by the BNP level (Table 1). Namely, the subjective and objective improvement occurred after two weeks. The BNP level in this period was significantly, but not satisfactorily reduced and we decided to continue intensive treatment in the hospital. A slow reduction of the BNP level corresponded to a slow recovery of left ventricular function that is characteristic for this form of cardiomyopathy.

During a prolonged recovery, there was a concern about whether conventional therapy would lead to a full recovery and if it was still necessary to apply a modern treatment modality. Among the previously mentioned modern therapy modalities, we preferred bromocriptine more than pentoxifylline primarily due to the results of gadolinium MR examination.

The reason for conventional therapy application was the lack of family consent for bromocriptine treatment. It is possible that the lack of agreement came after introduction of a patient and family members to numerous potential side effects of bromocriptine, which include increasing incidence of arterial hypertension, stroke, epilepsy, myocardial infarction, arterial thrombosis or intracardiac thrombus formation.

We were extremely satisfied when detected that application of conventional therapy led to a complete recovery of left ventricular function. It remains controversial whether the use of bromocriptine would lead to earlier recovery. This doubt still remains in the shadow of the fact that all “modern” treatment modalities are used in addition to conventional therapy, and the question of actual profit from its application remains to be open.

Conclusion

Anyway, timely detection and initiation of treatment are an important precondition for complete or partial recovery of patients with PPCM.

REFERENCES


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