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Peripartum cardiomyopathy in a patient treated for acute myeloid leukemia

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SUMMARY

Introduction Peripartum cardiomyopathy usually presents with systolic heart failure during the last months of pregnancy and up to five months postpartum. The disease is rare and can be fatal.

Case Outline We report a 30-year-old female who was diagnosed with acute myeloid leukemia, with maturation and cytogenetic finding of t(8;21)(q22;q22),del(9)(q22) in January 2004. She was treated with chemotherapy and achieved complete remission that lasts to date. She became pregnant and delivered a healthy newborn with caesarean section in 2009. Seven months later, she again became pregnant and delivered the second child with caesarean section in January 2011. Seven days after delivery she developed symptoms and signs of heart failure. Electrocardiogram showed sinus rhythm, low voltage and negative T-waves in inferior and lateral leads. Echocardiography revealed global left ventricular dysfunction with ejection fraction of 15%, with mobile thrombotic mass of 12 mm attached to the left ventricle wall. She was treated with both unfractionated and low-molecular heparin, diuretics, cardiotonics, and beta-blockers. Within six following weeks left ventricle systolic function improved up to 25–30%. The full clinical recovery was achieved in September 2013, resulting in absence of heart failure and left ventricular ejection fraction of 54%.

Conclusion Peripartum cardiomyopathy is a rare condition. The cause of cardiomyopathy is unknown, but it is believed that it could be triggered by various conditions and risk factors. Although the patient was treated with cardiotoxic drugs (doxorubicin and mitoxantrone) in permitted doses, they could have been contributory factors of myocardial damage. Close monitoring of cardiac function in the peripartal period might be beneficial in patients treated with cardiotoxic drugs.

Keywords: peripartum; cardiomyopathy; acute myeloid leukemia

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a rare cardiovascular disease of unknown cause which develops in otherwise healthy women in the last month of pregnancy or within five months after delivery. The incidence of PPCM varies and ranges between 0.2% and 3% [1, 2]. Diagnosis of PPCM is based on symptoms and signs of heart failure during pregnancy or in postpartum period with echocardiography criteria (impairment of left ventricle systolic function below 45% and end-diastolic dimension index >2.7 cm/m^2) [3, 4]. We report a rare case of reversible PPCM in a woman seven years after chemotherapy treatment for acute myeloid leukemia (AML) with which a complete remission of AML had been achieved, lasting to date.

CASE REPORT

A 30-year-old female was diagnosed with AML in January 2004. At that time laboratory data were as follows: hemoglobin (Hb) 97 g/l, platelets 29×10^9/l, white blood cell count (WBC) 17.9×10^9/l, with 74% of myeloblasts in differential leukocyte formula. Liver function tests showed elevated values for aspartate transaminase 55 U/l, alanine transaminase 59 U/l, and lactate dehydrogenase (LDH-3) 451 U/l. Other biochemical findings were within normal limits. Myocardial function, electrocardiogram (ECG) and chest X-ray were normal. The bone marrow aspirate showed hypercellularity with 74% of myeloblasts, which were myeloperoxidase-positive, with oval, cleaved nuclei, so that the cytology was in full correlation with AML with maturation. Flow immunocytometry of bone marrow mononuclear cells detected the following immunophenotype: (HLA-DR, CD117, CD33, CD13, CD15, and CD64) + that was also in accordance with the diagnosis of AML with maturation. Cytogenetic analysis: 45X, -X, t (8; 21) (q22; q22), del (9) (q22) [14]/46,XX[6]. The patient was submitted to the induction cycle of ADE scheme of chemotherapy according to AML MRC 12 regimen in the following doses: doxorubicin 60 mg on D1 (D-day), D3 and D5 iv, cytarabine 2×140 mg iv from D1 to D8 in bolus, and etoposide 140 mg in one-hour infusion from D1 to D5. After the induction therapy the patient achieved a complete remission. In May 2004 the patient was submitted to consolidation chemotherapy, and developed hepatosplenic candidiasis after-

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wards. A full recovery was achieved after six months of antimycotic treatment with fluconazole, amphotericin B, voriconazole and itraconazole. In September 2004 she was submitted to the second consolidation cycle (regimen MACE – composed of amsacrine 15 mg iv from D1 to D5, cytarabine 2×150 mg iv continuous infusion from D1 to D5, and etoposide 150 mg iv from D1 to D5). During the treatment she was given fluconazole. In November 2004 she received the MiDAC regimen (mitoxantrone 15 mg iv from D1 to D4, and cytarabine 3 g iv from D1 to D3). Thus, she received a total dose of 360 mg of doxorubicin and 60 mg of mitoxantrone. She achieved a complete remission and stayed in remission ever since.

Five years after the diagnosis of AML she was well and became pregnant. In 2009 she successfully delivered a healthy child by caesarean section. After delivery she was without complaints and hematological laboratory data were within normal limits. Seven months later, she again became pregnant and delivered a healthy child in January 2011, again by caesarean section. Seven days later she became febrile and experienced first signs of heart failure (shortness of breath, legs edema, and cough). She was hypotensive (85/60 mmHg), with sinus tachycardia (105 beats per minute), and as a consequence she was admitted to the emergency cardiac unit. Physical finding also included gallop rhythm and enlarged liver. X-rays showed enlarged heart and small pleural effusion. ECG revealed sinus rhythm, low voltage, negative T in V4–6, D2, D3, aVF (Figure 1). As the patient was in life-threatening condition, she was immediately transferred to the tertiary institution (Department of Cardiology of the Clinical Center of Serbia) for evaluation and treatment. Echocardiography showed hypokinetic left ventricle 52/42 mm with movable thrombotic mass 12 mm in diameter attached to the lateral wall. Mitral insufficiency was estimated to 3+, into the enlarged left atrium (44×50×40 mm). Tricuspid insufficiency 2+ gave systolic pressure in the right ventricle of 47–50 mmHg. Laboratory data were as follows: Hb 152 g/l, platelets 190×10^9/l, WBC 8.1×10^9/l, urea 15.2 mmol/l, creatinine 131 umol/l, aspartate transaminase 234 raised to 571 U/l, glutamic pyruvic transaminase 193, which raised to 1,904 U/l, alkaline phosphatase 432 U/l, gamma-glutamyl transpeptidase 120 U/l, C-reactive protein 13.2 mg/l, fibrinogen 4.6 g/l, D-dimer 27 ug/l. Brain natriuretic peptide reached level of 3,196 pg/ml with further decrease to 1,388 pg/ml (upper reference value 100 pg/ml). The patient was treated with dobutamine, unfractionated and low-molecular-weight heparin, diuretics, cardiotonics, beta-blockers and antiplatelet therapy. She was also treated with bromocriptine, which had to be discontinued because the patient developed very serious side effects such as nausea, vomiting and somnolence. After six weeks of treatment, her clinical condition improved, resulting in left ventricular ejection fraction of 25–30% at discharge. In September 2013, clinical findings showed the patient in complete remission of leukemia without signs of heart failure, normal findings on chest radiography, in sinus rhythm and echocardiography showing left ventricular ejection fraction of 54%. At present she is symptom-free and in complete remission of AML.

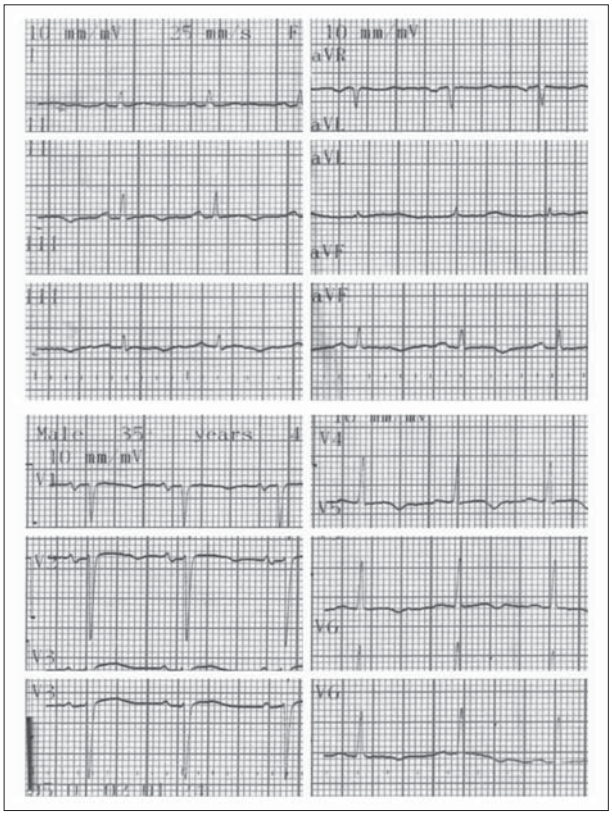

Figure 1. Electrocardiogram showing sinus rhythm, low voltage, negative T in V4–6, D2, D3, aVF

DISCUSSION

PPCM is a rare form of heart failure in a previously heart-healthy peripartum patient with mortality rate between 5% and 23% [5]. It usually presents with symptoms and signs of heart failure with enlargement of left ventricle on echocardiography, often accompanied by mitral and tricuspidal regurgitation [1, 2, 5]. The initial severity of left ventricular dysfunction is not always predictive for long-term outcome [6, 7]. PPCM may occur at any age but it is more frequent in women older than 30 years [6, 7].

The etiology of PPCM is still unknown. A number of possible etiopathogenic and contributing factors have been mentioned in literature such as viral myocarditis, abnormal immune response to pregnancy, multiparity, hemodynamic stress to pregnancy caused by increased blood volume, stress activated cytokines, especially tumor necrosis factor α, C-reactive protein, apoptotic marker Fas/Apo-1, familial predisposition to PPCM, and unbalanced peripartum and postpartum oxidative stress which induces proteolytic cleavage of hormone prolactin into fragment of 16kDa, which is known to have proapoptotic and angiostatic features [8-13]. Other possible causes of PPCM such as thyroid disease, alcohol abuse, hypophosphatemia, hypocalcaemia, cocaine abuse and chronic uncontrolled tachycardia, and excessive prolactin production which causes increased blood volume and changes to the levels of water, sodium and potassium, have also been considered [9-12]. In the presented case, the risk factors for PPCM could be the treatment of AML with cardiotoxic drugs

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doxorubicin and mitoxantrone, although these were given in allowed doses, long treatment of hepatosplenic candidiasis with antimycotics, as well as the second pregnancy that came soon after the end of the first one.

Our patient presented with fever and cough, followed by symptoms and signs of heart failure, dyspnea, orthopnea, edema of legs, and palpitations after second delivery. At first a suspicion of pulmonary embolism was raised, which could have been a pregnancy associated comorbidity, but after performing echocardiography, diagnosis of PPCM became clear, fulfilling all four criteria for the diagnosis of PPCM: 1) the development of cardiac failure in the last month of pregnancy or within five months of delivery; 2) the absence of an identifiable other cause for the cardiac failure; 3) the absence of recognizable heart disease before the last month of pregnancy, and 4) left ventricular dysfunction – ejection fraction of less than 45% [3, 4]. The following therapy was applied: anticoagulation therapy for the treatment of intracardiac thrombosis, heart failure treatment included dobutamine, diuretics and beta-blockers in further course, as well as conventional therapy, sodium restriction, diuretics, vasodilators, cardiotonics and beta-blockers. In spite of the fact that therapy of peripartum cardiomyopathy with bromocriptine (as suggested by the European Society of Cardiology Working Group), had to be discontinued due to serious side effects, the patient recovered completely [13]. Angiotensin-converting enzyme inhibitors (ACEI), spironolactone, angiotensin receptor blockers, may also be used in case of ACEI intolerance, but they are not recommended during pregnancy or conception and can only be given after the delivery. The anticoagulation therapy should be given in case of predisposition to thrombus formation and when left ventricular ejection fraction is low, especially in peripartum period. Currently it is accepted that anticoagulation therapy may be given only when left ventricular function is less than 35% [3, 4, 9, 13]. Very severe systolic dysfunction during the development or at diagnosis of PPCM with cardiogenic shock requires management with inotropes [13].

For the success of treatment of PPCM it is extremely important to establish the exact diagnosis as early as possible and to start immediate treatment, including anticoagulation therapy. High parity, age greater than 30 years, twin gestation, and late onset of symptoms after a delivery are regarded as poor prognostic factors for the outcome of PPCM [10, 13]. With this management, good results can be achieved in up to two thirds of patients [14]. The return of the left ventricle size and function to normal during the next six months of postpartum period is regarded as a good prognostic sign. However, the recovery may be slow and prolonged, up to 12 months, and in some rare cases even up to two or three years [1].

In conclusion, PPCM is a rare but serious disease. In a majority of cases, in whom a prompt diagnosis and adequate treatment were established, the condition is frequently reversible and prognosis is good. The risk factor to PPCM in the presented case could have been the treatment of acute leukemia with cardiotoxic drugs doxorubicin and mitoxantrone, long treatment of hepatosplenic candidiasis with antimycotics, and the second pregnancy, which came soon after the end of the first one.

As in some patients PPCM can progress to irreversible heart failure requiring heart transplantation or it can even terminate with sudden death, patients that recover should be strongly advised to avoid further pregnancies.

NOTE

The study was approved by the Institutional Ethical Board.

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Перипартална миокардиопатија код болеснице лечене од акутне мијелоидне леукемије

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КРАТАК САДРЖАЈ

Увод Перипартална кардиомиопатија је редак, али тежак поремећај срчане функције који се јавља последњег месеца трудноће или у првих пет месеци након порођаја. Болест је ретка и може бити фатална.

Приказ болесника Приказана је тридесетогодишња жена код које је јануара 2004. године постављена дијагноза акутне мијелоидне леукемије (АМЛ), *M2*, с кариотипом *t(8;21)(q22;q22),del(9)(q22)* и код које је хемиотерапијом постигнута ремисија. Током ремисије болесница је први пут затруднела и породила се царским резом 2009. Потом је седам месеци касније поново затруднела и порођена је јануара 2011. Седам дана након другог царског реза развили су се типични симптоми и знаци инсуфицијенције срца. На електрокардиограму утврђени су ниска волтажа, нормалан синусни ритам, негативни Т-таласи у *V4-6*, *D2*, *D3*, *AvF*. На ехокардиограму ејекциона фракција леве коморе била је само 15%, а у њој је виђена призидна, покретна тромботичка маса од 12 *mm*. Болесница је лечена инфузијама хепарина, нискомолекуларним хепарином, диуретицима, кардиотоницима, бета-блокаторима и антигрегационом терапијом. После шест недеља лечења почео је постепени опоравак и ејекциона фракција се повећала на 25–30%. Опоравак се полако наставио, тако да је у септембру 2013, тј. две и по године од почетка болести, болесница била без знакова кардијалне дисфункције, с ејекционом фракцијом леве коморе од 54% и у комплетној ремисији АМЛ.

Закључак Перипартална миокардиопатија је ретко стање које се најчешће јавља крајем трудноће или првих месеци после порођаја. Сматра се да постоје бројни фактори који могу допринети настанку обољења. Иако је АМЛ код приказане болеснице лечена (кардиотоксичним) цитостатицима у дозвољеним дозама, могуће је да су уз дуготрајну терапију антимикотицима и релативно брзу следећу трудноћу они ипак били важни фактори који су допринели настанку перипарталне миокардиопатије. Зато је код болесница код којих се постигне потпуна ремисија неопходно пажљиво праћење срчане функције, нарочито током трудноће и у првих неколико месеци постпартално. Правовременом дијагнозом и одговарајућим лечењем повољан исход може се постићи код две трећине болесника. За успех је најчешће потребно неколико месеци лечења, иако понекад опоравак може бити спор и трајати две-три године.

Кључне речи: перипартум; кардиомиопатија; акутна мијелоидна леукемија

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