

## **Peripartum cardiomyopathy with a history of doxorubicin therapy: case report & review of literature**

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Keywords: Peripartum cardiomyopathy, doxorubicin, osteosarcoma

### **Abstract**

*Background: Peripartum cardiomyopathy and doxorubicin-induced cardiomyopathy are well described conditions but there is little description in the literature of both occurring together.*

*Case: A 29 year old G1P0 with a remote history of childhood chondroblastic osteosarcoma treated with high-dose doxorubicin therapy who developed minimally symptomatic cardiomyopathy during her pregnancy with ejection fraction reaching as low as 20-30%. She delivered via primary low-transverse cesarean section at 37 weeks complicated by uterine atony with an unremarkable recovery. Cardiomyopathy was treated with metoprolol and enalapril and she achieved ejection fraction of 44% at one year follow-up with complete return to baseline activity.*

*Discussion: We present a woman with a history of doxorubicin therapy who developed peripartum cardiomyopathy and recovered symptomatically after one year. Although treatment of peripartum cardiomyopathy regardless of etiology is well-defined, there are few reports and no standard guidelines for special considerations in pregnant women with a history of doxorubicin therapy, a topic that may warrant further investigation.*

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### **Introduction**

Peripartum cardiomyopathy and doxorubicin-induced cardiomyopathy are well-described conditions, but the pathophysiology of both is uncertain. Current management strategies for patients with cardiomyopathy who are contemplating pregnancy are based on the type of cardiomyopathy and not necessarily the etiology. To this end, there exists a plethora of literature on the management of heart failure with reduced ejection fraction in pregnancy. Recent data indicates peripartum cardiomyopathy affects roughly 1 in 1000 pregnancies worldwide with lower incidences in the United States.<sup>1</sup> Meanwhile, the incidence of doxorubicin-induced cardiotoxicity is 3-

4% in patients who received a cumulative dose of 450 mg/m<sup>2</sup> or greater.<sup>2</sup> However, there is minimal literature and no standard guidelines addressing pregnancy considerations for patients with a history of doxorubicin therapy. We report a case of cardiomyopathy in the peripartum period in a patient with a remote history of doxorubicin therapy for childhood chondroblastic osteosarcoma.

### **Case Report**

A 29 year-old G1P0 white female presented to University of Iowa Hospitals & Clinics (UIHC) at 12 weeks gestation for an obstetric consultation regarding her history of osteosarcoma of the hip. In 1995, at age seven, she underwent a right hip disarticulation with complete removal of her right lower extremity to treat chondroblastic osteosarcoma and received doxorubicin chemotherapy (total dose 364 mg/m<sup>2</sup>). She achieved full remission after this treatment with no subsequent recurrences and demonstrated sufficient mobility after her disarticulation with the use of crutches.

At the time of her initial obstetric consultation, she underwent an echocardiogram which showed a normal ejection fraction (EF) of 55%. She continued care at an outside hospital until 31 weeks gestation when her local physician noted changes on a repeat echocardiogram and transferred her obstetric care to UIHC, a tertiary care center. The patient was evaluated by the cardiology service; the echocardiogram performed as part of this consultation showed an EF of 50%. At this time she endorsed shortness of breath though this symptom was

attributed to pregnancy as she was able to move up four flights of stairs without discomfort. Other symptoms of heart failure were denied.

At 37 weeks gestation, the patient presented to UIHC for routine cardiology and obstetric care visits; lower extremity edema was documented, but also noted to be “stable” suggesting it had been present previously. She denied any exertional shortness of breath, orthopnea, or paroxysmal nocturnal dyspnea. She remained active at full term, still utilizing stairs without change in symptoms. Vital signs during these visits included mild tachycardia (107 beats per minute) and a blood pressure 135/95, slightly higher than her baseline of 110s/60s. On physical exam, cardiovascular, respiratory and abdominal examinations were benign. Her left leg showed 2+ non-pitting edema with good peripheral pulses. Hemoglobin was 11.8, white blood cell count was 9.9k and urinalysis was normal. Differential diagnoses considered included preeclampsia, peripartum cardiomyopathy likely compounded by a history of doxorubicin therapy, acute myocardial infarction, and pulmonary edema. At this time, an echocardiogram suggested an EF of 20-30% by visualization; these EF measurements were confirmed by transthoracic echocardiogram (TTE). There was evidence of left ventricular global hypokinesis and the ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/E') was 15, which predicts an elevated left ventricular (LV) filling pressure. Left ventricular internal diameter (LVID) measured to 3.9 cm. Given this rapid decline in left ventricular function, the

team opted to proceed with induction of labor within 24 hours.

The patient was admitted to UIHC Labor & Delivery; in addition to routine labor monitoring, maternal telemetry was utilized during induction until 24 hours postpartum. Efforts to minimize excess fluid overload were employed including strict measurement of fluid intake and output. Induction of labor was prolonged; regional anesthesia was a spinal block in an effort to minimize blood pressure alterations. Due to the duration of induction and maternal exhaustion in the second stage of labor, a vacuum-assisted vaginal delivery was unsuccessful, and she underwent a primary low transverse cesarean section. The surgery was complicated by uterine atony treated with rectal misoprostol 1000 mcg, intramuscular (IM) carboprost and IM intrauterine oxytocin. The patient did well and was transferred to the cardiovascular intensive care unit (CVICU) for 48 hours of monitoring after delivery. Her recovery was unremarkable during this time. Medical management of heart failure had been initiated with metoprolol 12.5 mg twice daily and enalapril 2.5 mg once daily. She was subsequently transferred to the mother-baby care unit and was discharged home on post-operative day four meeting all post-operative goals.

The patient returned to clinic one week after discharge with no symptoms of heart failure and an improving EF of 35%. Her heart failure medications were titrated up and she was instructed to monitor her blood pressures at home. The patient was also counseled about the significant risks of future pregnancy. She agreed to consider use of an

intrauterine device for contraception in follow-up with her local provider and planned to use condoms in the interim.

Subsequent follow-up at three months postpartum included a TTE demonstrating an EF of 35% based on visual estimate and no regional wall abnormalities. One year follow-up TTE showed an EF of 40-45% based on visual estimate. Cardiac MRI at that time showed an EF of 44% and no evidence of regional wall motion abnormalities, cardiac ischemia, infiltration, or scarring. Her medications were changed to metoprolol 25 mg daily and enalapril 2.5 mg daily. The patient did not have a documented form of contraception at that visit, but she denied symptoms of cardiomyopathy and her baby was noted to be healthy.

## **Discussion**

Defined as cardiac failure in the last month of pregnancy or within five months of delivery without pre-existing cardiac dysfunction and no recognized cause of cardiomyopathy, peripartum cardiomyopathy (PPCM) is a well described pathophysiologic condition associated with pregnancy. The incidence of PPCM is estimated to be one in 3,186 live births; risk factors include advanced maternal age, preeclampsia, gestational hypertension, multiparity, and African American race.<sup>3</sup> Doxorubicin is a potent and efficacious chemotherapeutic agent used in the treatment of multiple forms of cancer, including osteosarcoma. Use of doxorubicin is often limited by cardiotoxic side effects.

Doxorubicin cardiotoxicity in the peripartum period is described in only a

few case reports. This may be due in part to the effects of chemotherapeutic agents on fertility in general. Systemic chemotherapy with multiple agents is used for patients with high-grade sarcoma and carries a risk of delayed fertility issues, although this is more common in males than females.<sup>4</sup>

Doxorubicin has been included in the chemotherapeutic combination for osteosarcoma since the 1970's and contributed to a dramatic improvement in prognosis for patients with localized osteosarcoma. Long-term survival rates improved from 20% to 65%.<sup>5</sup> Doxorubicin cardiotoxicity is dose dependent and mechanistically related to protein processing, hyper-activated immune responses, impaired cardiac repair and decreased vasculogenesis.<sup>6</sup> The standard cumulative doxorubicin dose used in the United States to treat osteosarcoma is up to 450 mg/m<sup>2</sup>. This dose is associated with acute cardiomyopathy during chemotherapy, late cardiomyopathy sometimes delayed by decades as well as death. After 300 to 450 mg/m<sup>2</sup> of doxorubicin therapy, more than 25% of patients experience left ventricular systolic dysfunction beyond 15 years of follow-up and remain at risk for cardiac deterioration for the rest of their lives.<sup>4</sup>

There have been a few other case reports published on peripartum cardiomyopathy associated with doxorubicin therapy. A 1997 case report narrates the case of a 28 year old primigravid woman who developed congestive heart failure 3 months after delivery with a history of doxorubicin therapy 10 years previously. The authors discuss the significance of the cumulative dose of doxorubicin.<sup>7</sup>

Similarly, in a 2016 case report from Belgrade, Serbia, a 30-year-old woman with a history of doxorubicin chemotherapy for acute myelogenous leukemia became pregnant five years after achieving remission. This patient had an uneventful first pregnancy and vaginal delivery. She became pregnant again seven months after her prior delivery and developed heart failure one week after delivery by cesarean with an EF of 15%. She was treated with dobutamine, unfractionated and low-molecular-weight heparin, diuretics, cardiotonics, beta-blockers and antiplatelet therapy for six weeks. Her EF improved to 25-30% by the time of discharge. Two years later, she continued to be asymptomatic considering her history of heart failure with an EF of 54%.<sup>8</sup> This patient's presentation of cardiomyopathy after two pregnancies in close proximity supports the hypothesis that pregnancy and doxorubicin cardiotoxicity cause a synergistically toxic effect on cardiac function.

Prior to pregnancy, our patient had normal cardiac functioning with no symptoms of cardiac failure. In fact, throughout her pregnancy, the only definite sign of her deteriorating cardiac function was a declining EF. Her symptoms included mild shortness of breath and lower extremity edema which could also have been routinely attributed to pregnancy. It is possible that the increased cardiovascular load attributable to normal physiologic alterations in pregnancy further exacerbated an underlying left ventricular dysfunction caused by her remote therapy with cardiotoxic doxorubicin.

A retrospective cohort study of female cancer survivors was published in the *Journal of Cancer Survivorship* in 2016. The study included 847 female cancer survivors treated at St. Jude Children's Research Hospital from 1963 to 2006 to see how many developed cardiomyopathy and whether there was an association with pregnancy. In this study, only three of the 847 female cancer survivors who achieved a cumulative 1554 live-birth pregnancies developed pregnancy-associated cardiomyopathy. Forty of these female cancer survivors developed non-pregnancy associated cardiomyopathy. Overall, only 5% of 847 patients developed any form of cardiomyopathy. Of these 40 patients, only eight had deteriorated cardiac function during pregnancy.<sup>9</sup>

In this group of eight, one patient received doxorubicin therapy at seven years of age with full remission and normal cardiac function. Similar to our patient, this patient developed cardiomyopathy in the third trimester of pregnancy and subsequently had a normal delivery with full recovery from the cardiomyopathy in 6 months. The study also found patients who developed cardiomyopathy had received higher doses of anthracyclines, including doxorubicin and daunorubicin, than those who did not develop cardiomyopathy.<sup>9</sup> Patients in the study who developed cardiomyopathy had median dose of anthracyclines of 321 mg/m<sup>2</sup>. Our patient followed this trend with a total dose of 364 mg/m<sup>2</sup> of doxorubicin therapy.

Regardless of the etiology of our patient's cardiomyopathy, the management of PPCM is usually similar

to standard treatment for heart failure of other etiologies, although no randomized clinical trials have been done to evaluate this treatment approach in PPCM.<sup>10</sup> The goals of treating heart failure are to improve hemodynamic status, minimize signs and symptoms, and optimize long-term outcomes. Therapeutic emphasis is on reducing preload and afterload while increasing cardiac inotropy. Vasodilators like hydralazine and nitrates, which are safe during pregnancy, are used to achieve preload reduction. In the postpartum period, angiotensin-converting enzyme inhibitors (ACE-I) are the mainstay of treatment for afterload reduction but are teratogenic and therefore contraindicated during pregnancy.<sup>11,12</sup> Beta adrenergic antagonists such as extended release metoprolol and carvedilol are recommended in the postpartum period for women who continue to have signs of heart failure as well as echocardiographic evidence of ventricular compromise after more than two weeks of therapy.<sup>13</sup> In the peripartum setting, additional considerations must be made for fetal safety as well as excretion of drugs or metabolites during breastfeeding.<sup>13</sup>

The National Institutes of Health recommendations for peripartum cardiomyopathy stress the importance of interprofessional collaboration among providers including obstetricians, cardiologists, and neonatologists.<sup>13</sup> Conventional non-pharmaceutical therapies include limiting dietary sodium two grams per day and restricting fluid intake to two liters per day. Participation in daily light activity, such as walking, is encouraged.<sup>11</sup>

Our patient had been following recommendations for regular activity and was receiving care at a tertiary care facility with coordination between the Obstetric and Cardiology Departments. The patient's blood pressure was in the normal obstetric range and she did not complain of symptoms of heart failure, therefore medications were not initiated in the antepartum period. She was started on metoprolol and enalapril postpartum for a persistently low EF. Following cesarean delivery, care was taken to minimize fluid shifts including use of intramuscular, instead of intravenous, oxytocin. She was monitored in the CVICU after delivery because the first 24 hours postpartum carry the most risk to develop complications of cardiomyopathy. Digoxin and anticoagulation are other common therapies for PPCM, but were not given to our patient because she did not demonstrate an arrhythmia as a symptom of heart failure and her EF improved after delivery. Currently, anticoagulation therapy is only indicated when left ventricular function is less than 35%. Furthermore, patients who develop any degree of PPCM should be strongly advised to avoid future pregnancy as mortality risk is approximately 55%.<sup>14</sup>

## **Conclusion**

In conclusion, PPCM is a rare, serious complication of pregnancy. Although the pathophysiology is unknown, it is important to remain vigilant for signs and symptoms and to employ an especially low threshold of suspicion in patients with a history of doxorubicin chemotherapy. With early recognition and therapy, prognosis for PPCM is generally good in the majority of cases.

The first three months postpartum is an initial high risk period with 25-50% of women dying; meticulous surveillance is necessary during this time.<sup>15</sup> However, in a 2005 study of 123 women with cardiomyopathy during or after pregnancy, 54% of patients achieved normalization of left ventricular systolic function at two years, an outcome that was more likely if the EF at diagnosis was more than 30%.<sup>16</sup> Patients who receive doxorubicin therapy should receive counseling regarding cardiotoxic effects that could manifest during pregnancy. While there is minimal literature on the pregnancy considerations for patients with a history of doxorubicin therapy, the treatment recommendations for any cardiomyopathy, regardless of etiology, in pregnancy is clear and well-studied.

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