JACC: CASE REPORTS VOL. 2, NO. 7, 2020


CASE REPORT

ADVANCED

HEART CARE TEAM/MULTIDISCIPLINARY TEAM LIVE

# Successful Triplet Pregnancy Post-Allogeneic Stem Cell Transplant in a Patient With Doxorubicin-Induced Cardiomyopathy

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## ABSTRACT

We report the unique case of a patient who recovered cardiac function despite a history of doxorubicin-induced cardiomyopathy, chest radiation therapy, high dose chemotherapy post-allogeneic stem cell transplant, and triplet pregnancy. Data are sparse on doxorubicin-induced cardiomyopathy in pregnant patients, calling for further studies to help formulate management or surveillance recommendations. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2020;2:987–90) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 27-year-old Hispanic female with a past medical history of natural killer (NK)/T-cell lymphoma, nasal type, presented in 2014 after 12 years of achieving complete remission, with complaints of fever, cough, shortness of breath, and a 20-lb weight loss over 2 to 3 months. For her lymphoma, she had received treatment with 8 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and radiation therapy (XRT); total doxorubicin dose ~320 mg/m$^2$. She had otherwise been active and in relatively good health before these symptoms developed. She denied complaints of chest discomfort, dizziness, syncope, palpitations, lower extremity edema, or claudication symptoms. She had an unremarkable physical examination with no jugular venous distention, normal apical impulse, no S3 or S4; she had clear lungs bilaterally, and no lower extremity edema. Her vital signs were stable with blood pressure of 108/57 mm Hg, pulse rate of 86 beats/min, respiratory rate of 20 cycles/min, and oxygen saturation of 100%. Initial laboratory values were within normal limits.

Upon evaluation, she was found to have moderate bilateral pleural effusions for which she underwent thoracentesis with flow cytometry revealing NK lymphocytosis and confirming disease relapse. Further workup included a pre-treatment echocardiogram that demonstrated a left ventricular ejection fraction (LVEF) of 37% (Videos 1A and 1B), confirmed by cardiac magnetic resonance imaging.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received January 29, 2020; revised manuscript received April 3, 2020, accepted April 9, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.04.020

**ABBREVIATIONS AND ACRONYMS**

**ASCT** = allogeneic stem cell transplant

**CHF** = congestive heart failure

**GDMT** = guideline-directed medical therapy

**LVEF** = left ventricular ejection fraction

**RIC** = reduced intensity conditioning

**SCT** = stem cell transplant

**XRT** = radiation therapy

## QUESTION 1: WHAT IS THE DIFFERENTIAL DIAGNOSIS IN OUR PATIENT?

**ANSWER 1.** The results of our initial work up did not support a diagnosis of myocarditis, infiltrative cardiomyopathy, or ischemia/infarction. Further investigation into this new-onset cardiomyopathy yielded normal cardiac enzyme, B-type natriuretic peptide, and thyroid-stimulating hormone levels, and normal iron saturation; the electrocardiogram revealed no ischemic changes.

This 27-year-old patient with normal cardiac biomarker levels and no cardiac risk factors, presenting with overt symptoms of heart failure 12 years after receiving combination chemotherapy has cardiomyopathy likely secondary to the combined effects of her prior doxorubicin-based chemotherapy and mediastinal radiation therapy.

Doxorubicin cardiotoxicity is cumulative, and a pooled analysis of 630 patients who underwent conventional doxorubicin treatment in 3 controlled trials reported a congestive heart failure (CHF) incidence of 5% at a cumulative dose of 400 mg/m$^2$, rising to 16% at a dose of 500 mg/m$^2$, 26% at a dose of 550 mg/m$^2$, and 48% at a dose of 700 mg/m$^2$ (1). However, a study of 141 patients who received conventional doxorubicin for lymphoma by Hequet et al. (2), showed that CHF occurred in 25% of patients who received a cumulative dose of 300 mg/m$^2$. Our patient received 320 mg/m$^2$ of doxorubicin, which is above the 250 to 300 mg/m$^2$ threshold where the lifetime risk of cardiomyopathy starts to increase (1).

XRT has been associated with significant cardiovascular toxicity, particularly ischemic heart disease. Cardiovascular disease incidence was assessed in 1,474 survivors of Hodgkin's lymphoma by Aleman et al. (3) in 2006 with a median follow-up of 18.7 years. Multivariable Cox regression and competing risk analyses were used to quantify treatment effects on cardiovascular disease risk. The risks of CHF significantly increased when mediastinal radiotherapy was combined with anthracycline-containing chemotherapy (hazard ratio: 2.81; 95% confidence interval: 1.44 to 5.49) (3).

## QUESTION 2: HOW DID WE MANAGE THIS PATIENT?

**ANSWER 2.** The patient was subsequently initiated on guideline-directed medical therapy (GDMT) for heart failure with carvedilol 3.125 mg and lisinopril 2.5 mg daily. For her recurrent lymphoma, she received 4 cycles of steroid (dexamethasone), methotrexate (with leucovorin), ifosfamide (with mesna), L-asparaginase, and etoposide (SMILE) chemotherapy. She was followed closely by cardio-oncology throughout her treatment, and there were no heart failure exacerbations through that time. She was then referred for evaluation for stem cell transplant (SCT) as a potentially curative option. A 10/10 match was found in her older brother, and she successfully underwent fludarabine/melphalan conditioning followed by a matched related donor allogeneic stem cell transplant (ASCT).

One year after ASCT with continued GDMT for heart failure, she remained clinically stable and was noted to have a near-normal LVEF of 55% on follow-up echocardiogram (Video 2).

The patient subsequently presented with a positive pregnancy test, and her pregnancy was confirmed by gynecologic ultrasound to be triplets (spontaneous trichorionic triamniotic gestation). The patient had been counseled against pregnancy for the first 2 years post-transplant but got pregnant while on immunosuppressive therapy post-SCT and GDMT for heart failure.

## QUESTION 3: WHAT ARE THE CHALLENGES TO PREGNANCY IN A CANCER PATIENT POST-ASCT AND WITH A HISTORY OF HEART FAILURE?

**ANSWER 3.** The patient conceived while she was receiving immunosuppressive therapy and GDMT for heart failure, which included lisinopril, a known teratogenic. Additionally, continuation of pregnancy in our patient warranted discontinuation of these drugs. She also had a history of aggressive lymphoma, relapse, and was post-ASCT. She was therefore considered a patient at high risk for both lymphoma relapse and worsened heart failure during her pregnancy.

Pregnancy is high risk in women with LVEF below 45% (World Health Organization functional class III) and is contraindicated if LVEF is below 30% (World Health Organization functional class IV) (4). Pregnancy should also be avoided during the first 2 years post-transplant due to the risk of relapse and management of other post-transplant complications (5). Therefore, effective contraception is crucial for those patients in whom pregnancy is contraindicated.

Furthermore, women with multiple gestation are known to have an increased risk of maternal and perinatal morbidity and mortality. Maternal risks of multifetal pregnancies include hypertension, preeclampsia, gestational diabetes, postpartum hemorrhage, and peripartum cardiomyopathy. Perinatal complications include preterm delivery, small for gestational age, intrauterine fetal death. The risks of perinatal morbidity and mortality increase with the presence of each additional fetus (6). For example, the risk of spontaneous loss of the entire pregnancy is 25% for quadruplets, 15% for triplets, and 8% for twins.

Our patient received intense counseling as a high-risk obstetrics patient. She was offered the choice of abortion and also multifetal pregnancy reduction. She was also educated regarding her risk of lymphoma relapse and heart failure. However, the patient opted to keep her pregnancy.

## QUESTION 4: HOW WAS THE PATIENT MANAGED DURING HER PREGNANCY?

**ANSWER 4.** The management of pregnancy in the concurrence of heart failure and cancer presents an enormous challenge to health care providers. A multidisciplinary team, which included cardio-oncology, SCT hematology, and high-risk obstetrics/maternal fetal medicine, were involved in providing care during the pregnancy. Many of her medications were discontinued, including her immunosuppressive therapy and lisinopril. She remained on carvedilol and prenatal vitamins, and was followed very closely by the involved teams, with initial monthly visits and monthly echocardiograms.

During the third trimester, the patient began bimonthly visits with the teams. Her LVEF remained stable until about 32 weeks of gestation when she began to have worsening dyspnea. Her echocardiogram showed decreasing LVEF of ~45% (Video 3), moderate tricuspid regurgitation, and borderline pulmonary hypertension (right ventricular systolic pressure ~35 mm Hg). She had baseline tachycardia (heart rate 120 to 130 beats/min), and was therefore followed and managed weekly. Her carvedilol was switched to metoprolol succinate to allow improvement in her relative hypotension during pregnancy.

At 36 weeks of gestation, the patient delivered via cesarean section. Her C-section was complicated by bleeding from an atonic uterus, which required blood transfusion support and eventually a total hysterectomy. She was discharged on post-op day 4. The 3 neonates did very well (APGAR [appearance, pulse, grimace, activity, and respiration] scores of 9 each) and were discharged with their mother. The patient opted out of breastfeeding; lisinopril was reinitiated, and she remained on GDMT for her heart failure. She had initial close follow-up and remained clinically stable in the postpartum period. Two years later, she continues to follow with our SCT team, without evidence of graft versus host disease or recurrence of her lymphoma. Her LVEF has recovered to 45% to 50% and has remained stable throughout her follow-up visits/testing.

## QUESTION 5: WHAT ARE THE LEARNING POINTS FROM THIS CASE?

**ANSWER 5.** This is an unprecedented case of a patient who recovered well despite a history of doxorubicin-induced cardiomyopathy, chest radiation therapy, followed by ASCT, and a triplet pregnancy.

Long-term cancer survivors are increasing in number with increased success of chemotherapeutic regimens and improved transplant-related outcomes. However, there is still a high burden of late morbidity and mortality. One of the most distressing consequences of SCT is the high incidence of infertility, particularly with myeloablative conditioning regimens (7) with 2 or more alkylating agents. In recent years, a considerable number of young patients have received SCT with less toxic, more tolerable reduced intensity conditioning (RIC) regimens. Although recovery of ovarian function and preservation of fertility have been studied in patients receiving RIC regimens (8), there are only a few case reports of successful pregnancies in this cohort. Our case report is one of the few to report a successful pregnancy using a RIC regimen consisting of fludarabine/melphalan.

Although doxorubicin is a well-known cause of cardiotoxicity, the normal physiological changes that occur during a normal pregnancy, peaking in the second trimester, are stressful to the cardiovascular system. During pregnancy, blood volume increases by 45% to 50%, and cardiac output rises 30% to 50% above baseline. These changes are tolerated well by normal healthy adults. However, patients with anthracycline exposure such as our patient, are at increased risk of developing heart failure exacerbation during pregnancy.

Doxorubicin cardiotoxicity in the peripartum period has been described in very few case reports.

JACC: CASE REPORTS, VOL. 2, NO. 7, 2020
JUNE 17, 2020:987–90

Overall, the clinical manifestations and response to GDMT for heart failure and the outcomes of late doxorubicin-induced cardiomyopathy are variable (9). One of the studies by MD Anderson Cancer Center evaluated cardiac outcomes of childhood cancer survivors who had pregnancies and were previously exposed to anthracyclines and/or chest XRT (10). The study compared 58 patients who had pregnancies to a control group of 80 women without pregnancies from the same population with mean anthracycline dose of 272 mg/m$^2$ and median follow-up time of 20 years. Pregnancy was associated with 2.35-fold increase in risk of cardiotoxicity in the overall study population (95% confidence interval: 1.02 to 5.41; p = 0.045). From this study, younger age at the time of cancer diagnosis, longer time from cancer treatment to first pregnancy, and higher total anthracycline dose were some of the high-risk factors identified.

A multidisciplinary approach was paramount to the successful management of this patient's cardiovascular health during pregnancy. With collaborative efforts and early intervention, a successful outcome is possible as documented in our case. There are sparse data on doxorubicin-induced cardiomyopathy in pregnant patients; and although management guidelines for peripartum cardiomyopathy are well defined regardless of etiology, there are only a few reports and no standard guidelines for special considerations in pregnant women perichemotherapy or transplant. Further studies are paramount to help formulate management or surveillance recommendations in this patient population.

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## PERSPECTIVES

**A UNIQUE CASE:** This is an unprecedented report of a patient who recovered well despite a history of doxorubicin-induced cardiomyopathy, chest radiation therapy, followed by ASCT, and a triplet pregnancy.

**COMPETENCY IN PATIENT CARE:** Since management of pregnancy in cancer patients is based on limited evidence, a collaborative effort of a multidisciplinary team is indispensable. Each patient might present with a different challenge, so an individualized approach is needed to manage the various stages of pregnancy and perinatal care.

**COMPETENCY IN INTERPERSONAL AND COMMUNICATION SKILLS:** Specialists might be the only source of health information for these patients. So, all patients should be counseled regarding contraception and educated about the risks and challenges in pregnancy and symptoms of heart failure to ensure early intervention or refer them to appropriate specialists.

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**KEY WORDS** cancer, cardiomyopathy, doxorubicin, stem cell transplant, triplet pregnancy

**APPENDIX** For supplemental videos, please see the online version of this paper.


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