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Treatment of Recurrent Metastatic Breast Cancer in Pregnancy: A Case Report and Literature Review

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Abstract

Background: We present the case of a woman previously treated with surgery, adjuvant chemotherapy and radiation who was diagnosed with recurrent metastatic breast cancer during pregnancy.

Case: A 25-year-old woman was diagnosed with recurrent metastatic breast cancer during the second trimester of pregnancy. Tamoxifen was initially tried, however she had progression of her tumor markers, so was switched to a continuous infusion of 5-flurouracil (5-FU). She achieved a partial response and delivered a viable infant without congenital malformations.

Conclusion: Many complex medical decisions occur when treating pregnant women with cancer. Infusional 5-FU was used successfully in this patient with no effect noted in the fetus. This regimen has not been previously described as treatment for recurrent breast cancer in pregnancy and should be considered.

Keywords: Recurrent breast cancer; Pregnancy; Tamoxifen; 5-Flurouracil

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Introduction

The incidence of cancer during pregnancy is approximately 1 in 1,000 [1]. The most common cancers in pregnancy are breast, cervical, leukemia, lymphoma, and melanoma, similar to those found in non-pregnant women of reproductive age [1]. The incidence of breast cancer during pregnancy is approximately 1 in 3,000 [1]. Little data exists regarding the optimal treatment of pregnancy-associated breast cancer, and even less so for recurrent breast cancer during pregnancy [2]. We present the case of a 25-year-old woman who was diagnosed with recurrent metastatic breast cancer during the second trimester of pregnancy. We will review her treatment course and discuss the literature regarding treatment options.

Case Presentation

A 25-year-old African-American Gravida 3 Para 1 was diagnosed with recurrent metastatic breast cancer during the second trimester of pregnancy. In addition to her history of breast cancer, her medical history was significant for obesity (body mass index of 30), glucose-6-phosphate-dehydrogenase deficiency, and angioedema of unknown etiology. She was initially referred to hematology/oncology for evaluation of angioedema with suspicion for systemic mastocytosis, after having two episodes of hives and facial swelling that required intubation and intensive care unit admission for several days. A bone marrow biopsy at that time was suboptimal, but showed a small population of mast cells (3%) by flow cytometry. During the evaluation of angioedema, the patient noted a grape-sized mass in the upper outer quadrant of the left breast. A breast ultrasound revealed a 1 centimeter (cm) mass; a core biopsy revealed invasive ductal carcinoma. She underwent a left breast mastectomy with sentinel node biopsy, which showed a 4 cm tumor with 3 of 3 sentinel nodes positive for carcinoma, and was ultimately diagnosed with Stage IIb invasive ductal carcinoma of the breast (T2N1aMx, grade 2, estrogen and progesterone receptor positive [ER/PR+], HER-2 negative). Further staging with a positron emission tomography and computed tomography (PET/CT) did not reveal any distant disease. She desired future fertility and underwent oocyte retrieval before starting adjuvant chemotherapy with doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 intravenously (IV) every 2 weeks for 4 cycles followed by paclitaxel 175 mg/m2 IV every 2 weeks for 4 cycles. After her course of adjuvant chemotherapy, a completion axillary dissection was performed. No residual disease was seen and this was followed by chest wall and axillary radiation

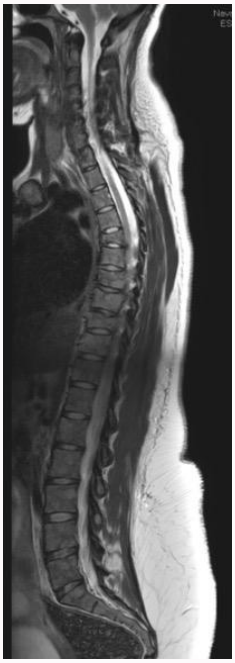

Figure 1: Spinal MRI at 21wks showing diffuse lytic lesions.

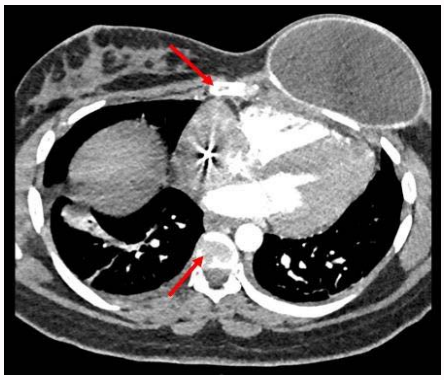

Figure 2: Chest CT at 21wks showing diffuse lytic lesions in vertebral bodies and sternum.

(50 gray in 25 fractions to the chest wall and axilla with an additional 10 gray in 5 fractions as a scar boost). Shortly after finishing radiation therapy, she became pregnant and subsequently miscarried in the first trimester. At that time, the recommendation was made to postpone future pregnancies and start endocrine therapy with tamoxifen (20mg orally daily) and goserelin (3.6mg subcutaneously every 28 days). However, she strongly desired pregnancy and declined endocrine therapy.

Several months later, she became pregnant again. At 14 weeks gestation she presented to the emergency department with acute onset of severe low back pain. She was admitted to the hospital for pain control for 3 days. An X ray of the lumbar spine showed no osseous lesions. Nine days later she was readmitted for uncontrolled pain. A magnetic resonance image (MRI) of the spine showed multiple foci of heterogeneous bright T2 signal and dark T1 signal within the vertebral bodies, suspicious for metastatic breast cancer (Figure 1). A chest CT scan performed around the same time also showed diffuse lytic lesions throughout her spine (Figure 2). This was confirmed with an image guided biopsy of the L3 vertebra. A multidisciplinary team

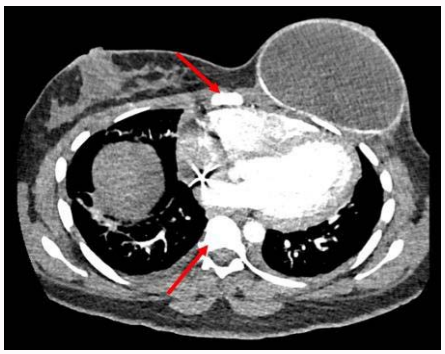

Figure 3: Chest CT at 3wks postpartum showing interval resolution of lytic lesions in vertebral bodies.

consisting of oncology, neonatology, and maternal-fetal medicine physicians reviewed the case and recommended treatment with tamoxifen. Tamoxifen was started at 16 weeks gestation. Serial CA 15-3 measurements were obtained and increased from 83.5 to 126.9 over the course of 4 weeks. Additionally, she developed worsening pain, anemia and thrombocytopenia within the first month of treatment with tamoxifen. A follow-up MRI of the spine showed progressive metastatic disease involving nearly every bone, which was thought to account for her significant cytopenias. A second multidisciplinary meeting was held and the recommendation was for her to switch treatment to a continuous infusion of 5-fluorouracil (5-FU) (250 mg/m2/day by continuous IV infusion for 21 days, followed by 7 days of no treatment). This was started at 21 weeks gestation and was continued until delivery for a total of 3 cycles. For the remainder of her pregnancy, despite incrementally increasing high dose narcotics, she was repeatedly admitted for control of pain, nausea, and constipation. Her CA 15-3 improved from 126.9 to 41.3 while on 5-FU.

Due to concerns for preterm labor, she received a course of betamethasone (12.5 mg intramuscular, 2 doses 24 hours apart) for fetal lung maturation at 27 weeks. A rescue course was completed 24 hours prior to her planned delivery at 34 weeks gestation. She was not a candidate for neuraxial anesthesia due to her spinal metastases, so the recommendation was made for delivery via primary cesarean with bilateral salpingo-oophorectomy (due to ER/PR+ tumor) under general anesthesia or induction of labor with Remifentanil patient-controlled analgesia. The patient elected for induction of labor and underwent an uncomplicated spontaneous vaginal delivery with post-placental placement of a Paraguard intrauterine device for contraception. A 1740 gram male infant was born without obvious congenital malformations. Due to the high doses of narcotic medications necessary to control pain during pregnancy, the infant was treated for neonatal abstinence syndrome in the neonatal intensive care unit and was discharged home in good condition on day of life 45. The patient's postpartum course was significant for hospital readmission on postpartum day 6 for endomyometritis that was treated with antibiotics until resolution of fever and fundal tenderness.

After delivery, PET/CT scan showed no evidence of solid organ metastases, with diffuse bony sclerosis, consistent with a partial response to 5-FU (Figure 3). At 3 weeks postpartum, she was started on capecitabine (2000 mg orally, every 3 weeks) and denosumab (120 mg subcutaneously monthly). Denosumab was stopped due to hypocalcemia. At 17 weeks postpartum she

underwent an uncomplicated laparoscopic bilateral salpingo-oophorectomy. Pathology showed malignancy on pelvic washings with micrometastases on the bilateral ovaries. Follow-up CT at that time showed diffuse bony sclerosis, without obvious other areas of involvement. After surgery capecitabine was stopped due to progressive increase in CA15-3 levels and fulvestrant was initiated.

Discussion

Breast cancer is most commonly treated with a multi-modality approach including chemotherapy, radiation, and surgery. However, radiation is contraindicated in pregnancy and surgery is not useful in patients with recurrent multi-focal metastatic disease.

The initial treatment for our patient was tamoxifen, a non-steroidal, anti-estrogen medication that is used to treat ER+ breast cancers. The effects of tamoxifen on pregnancy are not well understood, and most information comes from animal studies and case reports. The majority of information regarding fetal effects of tamoxifen exposure comes from case reports and the AstraZeneca Safety Database. A review article of this database by Braems et al [3], describes 15 cases of fetal tamoxifen exposure after the first trimester, 3 resulting in fetuses with congenital anomalies. In general, the recommendation is to stop tamoxifen prior to pregnancy and delay conception for 2 months due to the long half-life of the drug [3]. In this case, the fetus was exposed to tamoxifen from 16 weeks to 22 weeks gestation and to date, no congenital anomalies have been noted. Unfortunately, our patient did not respond to this treatment, likely due to the very high levels of estrogen during pregnancy. Estradiol levels of a non-pregnant premenopausal woman can reach up to 400 pg/mL, depending on the time in her menstrual cycle. During pregnancy, estradiol levels can be greater than 7,000 pg/mL [4]. There is little data discussing the efficacy of tamoxifen during pregnancy, given the high estradiol levels. Our experience would suggest tamoxifen is of little benefit in this setting.

Traditionally, chemotherapy is avoided in the first trimester due to the 14% risk of major malformations versus the baseline risk of 3% in the general population in the United States [5]. Treatment with cytotoxic chemotherapy in the second or third trimester appears to be safer with a risk of major fetal malformation similar to baseline, although the rate of stillbirth is higher (2% versus 0.3%) [5]. Choosing treatment for a pregnant patient with recurrent metastatic breast cancer who has been previously treated is challenging. In the case of this patient, the challenge was selecting a chemotherapy regimen that did not include agents that she had previously been exposed to (doxorubicin, cyclophosphamide, and paclitaxel). Berry published a standardized protocol for breast cancer during pregnancy that utilizes a multidisciplinary team approach, including surgery for those women with operable disease and systemic chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil (FAC regimen). In their study of 22 women, no unusual neonatal complications were seen. [2]. Our patient had previously been treated in the adjuvant setting with doxorubicin and cyclophosphamide, but not with fluorouracil. According to Lambertini et al, fetal exposure to 5-FU in the first trimester can cause spontaneous abortion and major malformations including skeletal defects. However, second trimester exposure has not been associated with birth defects [5]. In a non-pregnant patient, a reasonable alternative to 5-FU may have been capecitabine, an oral 5-FU prodrug, although this medication has been linked to teratogenicity in animal studies. Continuous infusion of 5-FU as treatment for advanced breast cancer was first described by Huan et al in 1989 [6]. Later, Regazzoni et al [7]. described it as a well-tolerated and effective treatment for metastatic breast cancer that could be infused in the outpatient setting. 5-FU was chosen in our patient because of its relative safety in pregnancy and it was not a medication to which she had been previously exposed. To our knowledge, this is the first reported case where the continuous infusion of 5-FU was used to treat recurrent metastatic breast cancer in a pregnant patient. Our patient responded well to 5-FU as noted by the decrease in the CA 15-3 level from 126.9 to 41.3 as well as improvements in pain, anemia and thrombocytopenia. Additionally, no effects have been noted in the infant thus far.

Many complex medical decisions occur when treating pregnant women with cancer including treatment choice, symptom control and timing and route of delivery. 5-FU was used with success in this patient. This medication has not been previously described as a treatment option for recurrent breast cancer in pregnancy and should be considered.

Teaching Points

1. Cancer recurrence and metastasis should be part of the differential for all pregnant patients presenting with pain and a history of cancer.

2. Continuous infusion of 5-fluorouracil should be considered for pregnant patients with recurrent breast cancer.

3. Tamoxifen is generally not effective during pregnancy due to high estrogen levels.

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