

Breast cancer with brain metastases in pregnancy

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Breast cancer during pregnancy is a therapeutic challenge. Evidence to guide management in metastatic breast cancer during pregnancy is limited, mainly because of a lack of randomized trials. Care needs to be individualized with interdisciplinary collaboration. Various case reports and case series in the literature have shown the safety of some chemotherapeutic agents during the second and third trimesters of pregnancy. Surgery is also safe after the first trimester. Brain metastasis from breast cancer during pregnancy is an especially challenging clinical situation and has been reported only in one other case. We present the case of a young woman with HER2/neu over-expressed inflammatory breast cancer who became pregnant while on treatment, refused termination of pregnancy, and developed brain metastasis during the second trimester of pregnancy, posing a management dilemma.

Case presentation

A 24-year-old obese woman, gravida 3 para 3, who was 7 months post partum, presented with a 2-month history of an enlarging left breast mass with intermittent pain requiring acetaminophen. She had no significant past medical history. Her family history was significant for breast cancer in her mother and sister. A physical exam was significant for a 12 x 10-cm hard, nontender, fixed left-inner, lower-quadrant breast mass with erythema and peau de orange appearance. There was 3-cm fixed left axillary lymphadenopathy and a 3-cm hard left supraclavicular lymph node.

The results of a biopsy were consistent with infiltrating ductal carcinoma, grade 3. The tumor was ER/PR negative (estrogen receptor/progesterone receptor negative) and HER2/neu-positive by FISH (fluorescence in situ hybridization; ratio, 3.02). Her genetic testing was positive for BRCA1 gene mutation. The results of a computed-tomography (CT)

scan of the chest showed a large left breast mass fixed to the chest wall with left axillary, left supraclavicular, and mediastinal lymphadenopathy. There was a 9-mm noncalcified nodule in the right lower lobe of the lung. A CT scan of the abdomen showed a mildly enlarged left ovary of 40 x 25 mm. An ultrasound of the abdomen showed leuteal and simple cysts in the right ovary and a normal left ovary.

The patient was staged T4N3cMx because of concern about the lung findings. She was started on dose-dense doxorubicin and cyclophosphamide (AC) for 4 cycles. Cycle 3 was delayed owing to the patient's noncompliance. She received 4 cycles of paclitaxel every 2 weeks, with weekly trastuzumab for 8 weeks. During the same time, she was seen by staff in the gynecology clinic for contraception counseling and she was offered insertion of an intrauterine device (IUD). She did not go for the IUD insertion despite repeated counseling.

A repeat ultrasound of the pelvis showed resolution of the ovarian cysts. She had an excellent clinical response, and the breast mass decreased to 1.5 x 1.5 cm in size and the axillary and supraclavicular lymphadenopathy resolved. She was evaluated by physicians in the breast oncology surgery service to discuss surgical options and continued on trastuzumab every 3 weeks. The patient underwent lumpectomy for local control of her disease, after consensus at the multidisciplinary meeting. The pathological stage was pT1bNx. Trastuzumab was continued after the surgery. She was started on radiation therapy (RT) to the breast, which she finished uneventfully. After completion of the RT, while on she was on trastuzumab, a CT scan showed resolution of the lung nodule but the re-emergence of left supraclavicular lymphadenopathy. She presented 2 weeks later for continuation of therapy.

At that time, her urine pregnancy test was positive. Trastuzumab was held. An ultrasound showed a 12-week normally developing fetus. The calculated

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total dose of radiation she received while she was pregnant (including the last few days of RT and a CT scan) was 50 milligrays (mGy). She was informed of the risk to the fetus secondary to in utero exposure to radiation as well as the potential risk to herself because of progression of the disease. She refused termination of pregnancy and became more noncompliant with clinic visits. She underwent neuropsychiatric testing and was deemed competent for medical decision making.

At 22 weeks gestation, the patient presented with headaches for 1 week. An MRI scan of the brain showed 2 brain metastatic lesions in the left thalamic and left parietal areas measuring 14 x 12 x 12 mm and 24 x 16 x 20 mm, respectively, with surrounding edema and localizing mass effect on the third ventricle (Figure 1 and 2). The edema extended into the posterior limb of the left internal capsule, remaining portion of left basal ganglia and into the left cerebral peduncle. After discussion with the patient, gynecologist, and radiation oncologist, the patient was started on dexamethasone and whole brain RT with external shielding. During that time, the left supraclavicular adenopathy worsened and she developed new posterior cervical lymph nodes. After completing RT to the brain, she was restarted on trastuzumab after an extensive multidisciplinary team discussion and her consent.

The patient was monitored closely with serial ultrasounds, which showed normal fetal development. After 2 cycles, the left supraclavicular adenopathy worsened. Weekly paclitaxel was added to the regimen. After discussion with the anesthesiologist and gynecologist about delivery in the presence of treated brain metastasis, an elective cesarean section was planned for. A repeat MRI scan before delivery showed a reduction in the size of the brain metastatic lesions, with resolution of brain edema and mass effect. At 38 weeks, the patient underwent an elective caesarian section. The baby had normal APGAR scores of 9 and 9. At 6 weeks postpartum, the patient's MUGA (multigated acquisition) scan showed mildly reduced ejection fraction and trastuzumab was held.

At that time, the patient also had new onset headache and severe pain in the left posterior neck. A CT scan showed mild increase in the size of the left parietal lobe metastatic lesion with no mass effect and new leptomeningeal spread. She refused a lumbar puncture. She was switched to oral capecitabine and lapatinib but she was noncompliant with therapy and died 6 months post partum and 23 months after the initial diagnosis of cancer. The baby, last seen at age 6 months, continues to do well.

Discussion

Breast cancers are the most common invasive cancers to be diagnosed during pregnancy.¹ These often carry a worse prognosis compared with nonpregnant patients.²

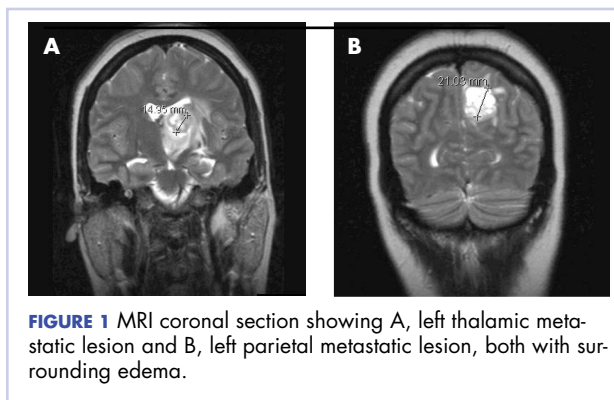


FIGURE 1 MRI coronal section showing A, left thalamic metastatic lesion and B, left parietal metastatic lesion, both with surrounding edema.

Pregnancy may be an independent, worse prognostic risk factor for breast cancer,³ but carefully controlled studies are lacking. Findings in a study with one of the largest-reported cohorts of breast cancer in pregnant patients showed that only 3.7% of them were metastatic and 25% were HER2/neu overexpressed. There is a paucity of data on management of metastatic breast cancer that occurs during pregnancy.⁴ Our patient presented with locally advanced stage IIIC breast cancer before she became pregnant and wanted to continue the pregnancy while the cancer progressed clinically.

Brain tumors in pregnancy are rare, with an estimated incidence of 15 per 100,000 population.⁵ Most of them are primary brain neoplasms, with gliomas being the most common, followed by meningiomas.⁶ Brain metastasis from a systemic primary is extremely rare during pregnancy in young women. Choriocarcinoma is the most commonly reported primary cancer with brain metastasis during pregnancy.⁶ To our knowledge, breast cancer with brain metastasis during pregnancy had been reported in the literature only once before our report.⁷

MRI is the modality of choice for brain imaging in a pregnant patient because it is better than the CT scan at distinguishing between soft tissues and between normal and abnormal tissues, and it avoids the ionizing radiation one gets from a CT scan, which requires lead shielding. The dose of radiation exposure from a CT scan has been shown not to have any deleterious effects on the fetus. However, the intravenous contrast media for a CT scan which is iodine based can cause hypothyroidism in the fetus as opposed to the gadolinium contrast used in MRI, which is not iodine based.⁶

Mazonakis and colleagues have shown that while giving radiation therapy to the brain during pregnancy, the radiation dose to the fetus corresponding to an isocentric dose of 65 Gy never exceeded 100 mGy without shield.⁸ According to Stovall and colleagues, 100 mGy is considered the cut-off point, below which the risks for biological effects of radiation to the fetus are substantially lowered, with mini-

mal risk of damage to the fetus when exposed to less than 50 mGy.⁹ Breast irradiation during pregnancy exposes the fetus to 0.1%-0.3% of the total dose of radiation and lead shielding during pregnancy can decrease the dose exposure by 26%-71% depending on the gestational age, field size, and distance from the isocentre.¹⁰ Our patient received 50 mGy radiation unshielded in the first trimester (centered at the chest, and 1 CT scan of the pelvis), which made the exposure of the fetus minimal.

Use of trastuzumab during pregnancy has been reported in case reports with a 53% incidence of oligohydramnios or anhydramnios (mostly reversible).⁷ Taxanes on the other hand may be relatively safe during the second and third trimesters of pregnancy, based on a systematic review done on case studies.¹¹ Our patient received trastuzumab and paclitaxel in the third trimester, with weekly serial fetal ultrasound and did not develop any maternal complications. She was able to carry the pregnancy to term at which time she had an elective cesarean section to deliver a healthy baby boy.

Palliative and supportive care should be offered to all patients with metastatic cancer during pregnancy, and supportive care can be extremely helpful for the patient in making decisions about pregnancy continuation and treatment during pregnancy.¹²

Our case emphasizes the importance of being aware of treatment options for a pregnant patient with metastatic breast cancer. Brain metastasis occurs at a higher frequency in HER2/neu overexpressed breast cancers, and because a quarter of pregnant patients with breast cancer are HER2/neu overexpressed, physicians may expect to see more brain metastases.⁴ Radiation therapy to the brain can be relatively safe for the fetus in the second and third trimesters. Intravenous paclitaxel may be safe after the first trimester, based on other case reports.¹¹ Despite reports of oligohydramnios and anhydramnios, our patient did not have any adverse outcomes as a result of the trastuzumab. However, more studies are needed to clearly define the pharmacokinetics of these chemotherapeutic agents during pregnancy to confirm their safety.

In conclusion, pregnancy in the setting of metastatic breast cancer is an especially challenging problem. If the pregnancy is not terminated, both maternal and fetal outcomes must be considered when formulating a treatment plan, which requires collaboration of a multidisciplinary team. In addition to potential toxicity to the fetus from anticancer therapy, maternal life expectancy may influence whether the fetus will be able to reach maturity for delivery.

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