

Ewing Sarcoma in Pregnancy: A Rare Case Report

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ABSTRACT

This is a case of 34-year-old female Gravida 1 Para 1 37 weeks age of gestation and has been diagnosed as a case of Extraskkeletal Ewing Sarcoma, Right Axillary Mass Grade 3 during the first trimester. Patient had received 4 cycles of Doxorubicin as part of the “Bridging Therapy” and Chemotherapeutic regimen. Chemotherapy has been pursued to this patient, initiated on the 21st week of gestation with hopes to decrease the size of the mass and alleviate the pain during the course of pregnancy. The ethical and therapeutic concerns for both the patient and the physician remains to be a challenge up to this course. A multidisciplinary approach was instigated to weigh risks versus benefit for the expecting mother and the unborn child.

Keywords: Chemotherapy, Cancer, Ewing Sarcoma, Doxorubicin, Pregnancy, Neoadjuvant

INTRODUCTION

Cancer diagnosis and treatment in pregnant women is a challenging situation. A multidisciplinary network of experts is vital to monitor both, the pregnant mother and the fetus through the diagnostic workup and the cytotoxic therapy, by considering the respective risks and benefits. Tumor entity, stage, biology and

gestational week at diagnosis determine the applicable approach. As premature delivery transpired as one of the core risk factors for unfavorable long-term effect of the progeny, it should be avoided, if reasonable from the oncological perspective.

The concurrent incidence of cancer and pregnancy is a rare occurrence and is projected for only 1 to 2 cases per 1000 pregnancies.¹ The numbers have increased in recent years because of the increase in maternal age at the time of the 1st pregnancy.

Chemotherapy during the first trimester of pregnancy is preferably avoided owing to the hazard of several congenital malformations. Conversely, the particular gestational age at which chemotherapy can be introduced safely rests unclear.

Because chemotherapy attacks rapidly multiplying cells and is plainly selective, it also puts the developing fetus at risk of teratogenic effects. Harmful dealings during the periconceptional phase may assume early embryogenesis and end in a miscarriage, though ensuing toxic coverage might hinder with the development of organs,

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with the most critical periods being the 2nd and 8th week after conception.² There is a comprehensive consensus that chemotherapy should be given until after organogenesis is completed. But since the precise time of conception is undetermined, the crucial question of when to safely administer chemotherapy to pregnant patients to avoid congenital malformations remains an enigma.

9 months prior to consult, patient was noted to have developed a 3 centimeter sized hematoma associated with swelling and palpable mass formation on the right axilla which was tender and warm on palpation after a bicycle accident. A few weeks later, the said hematoma and swelling eventually subsided, however the mass persisted and noted to be increasing in size with noted limitations with range of motion. No numbness, no skin changes, no weight loss, no pins and needles sensation noted. Patient sought consult with a General Physician and was advised to undergo Ultrasound of the Right axilla revealing a well defined, lobular, homogenous, hypoechoic avascular solid mass measuring 5.4 x 6.0 x 4.0 centimeters. Patient underwent Axillary lymphadenectomy as advised by Surgery with additional tests for Immunohistochemical stains due to suspicions of lymphoma. The findings yielded a Fibrocollagenous to Fibroadipose tissues with CD99 Positive Round Cell Malignancy. At this juncture, patient was also noted to be on the first trimester of her first pregnancy specifically at 9 weeks AOG based on Ultrasound. Closer monitoring and surveillance was observed with this patient during the course of the first trimester of pregnancy with aims to treat the said malignancy at a later period.

An MRI of the breast and chest was performed because of the growing size of the said right axillary mass which revealed BIRADS 4: Suspicious for malignancy. Review of slides were then reconducted as recommended which

reviewed Extraskkeletal Ewing Sarcoma FNCLCC Grade 3. The Right axillary lymph node was noted to be negative for metastases.

However, during the interim, patient was noted to have worsening of symptoms such as increased intensity of pain with pins and needles sensation and limitations on ranges of motion. Patient was then referred to a Pain Specialist and was prescribed with Morphine 10mg tab every 12 hours which would provided minimal to no relief.

In line with the persistence of the above mentioned signs and symptoms, patient was then advised to proceed with the planned Chemotherapy even at 21 weeks Age of gestation. Patient was then referred to a Perinatologist and advised to proceed with Chemotherapy after the 24th week of gestation (Age of viability).

A multi disciplinary conference was conducted and a consensus decision was made to begin the Chemotherapy regimen at an earlier week of gestation.

DISCUSSION

Ewing sarcoma (ES) is a rare malignancy that most frequently presents as an undifferentiated primary bone tumor; less commonly, it arises in soft tissue (Extraosseous Ewing Sarcoma). It is an ultra-orphan disease (2/1,000,000/year) which requires a multimodal therapy approach in high-volume centers.

A minority of ES arise in soft tissue. Patients with EES are more often older, likely to be female and arise more often within the axial rather than the appendicular skeleton

Ewing's sarcoma is a highly malignant bone tumor that rapidly metastasizes at an early stage. These tumors have rapid growth and recurrent distant metastasis and individuals present with

chief complaint of persistent pain. Treatment selections include radiation, chemotherapy, and surgery. The combination of chemotherapy with both surgery and radiotherapy increases the survival rate as compared to chemotherapy alone. Prognosis has been developed in recent years. Due to modern-day managements, long-term survival up to 70%-80% can be reached among patients without metastases. Ewing's tumor is favorably chemosensitive and hence treatment of choice is chemotherapy, but sometimes radiotherapy is also given. During pregnancy, chemotherapy is very crucial. In most of the cases, detrimental outcomes were perceived when chemotherapy was given during the 1st trimester have an increased chance of fetal congenital malformations, intrauterine growth restriction (IUGR), or intrauterine fetal death (IUD). When chemotherapy is administered in the 2nd trimester maternal survival rate is much better than delaying the treatment to until after delivery.

Lysyj and Bergquist reported the first case of Ewing's sarcoma in pregnancy in 1963.³ Their patient was at 32nd week of gestation manifested with pain in the right leg.⁴ Cesarean section was performed on the 36th week of gestation but patient did not receive any radiotherapy nor chemotherapy.

Just like Patient MV, patients typically would present with restricted pain or swelling for a few weeks' or months' duration. Trauma, often minor, may be the initiating event that calls attention to the lesion. The pain may be mild at first but intensifies fairly rapidly. A distinct soft tissue mass can sometimes be appreciated.

The diagnostic work-up is usually instigated with a plain radiograph of the affected area. CT scan delineates the extent of the cortical destruction and soft tissue disease better however; MV cannot perform such imaging due to current status. Metastatic work-up is advised including PET

which has a greater utility for surveying the response to chemotherapy and or radiation therapy (particularly neoadjuvant chemotherapy) but all cannot be performed for this patient.

A CT-guided core needle biopsy is also warranted. Adequate amounts of tissue are vital in order to postulate sufficient diagnostic material. The analysis of ES is confirmed using histopathologic evaluation and molecular assessment of malignant tissue obtained via tumor biopsy.⁵

ES seems to advance rapidly during pregnancy. Treatment should consist of therapeutic abortion followed by chemotherapy, radiation therapy, and surgery if discovered early in pregnancy. Controversy exists as to the treatment late in pregnancy. Treatment requires a multimodal therapy approach consisting of pre-operative therapy which patient MV is receiving and post-operative combination of chemo-radiotherapy.

Any pregnant woman suspected with Sarcoma, are mostly subjected with neoadjuvant therapy which are widely accepted and must be started whenever possible during gestation. Radiation therapy is harmful because of the toxic ionizing agents that might scatter to the fetus.

Patient MV received a total of 4 cycles of Doxorubicin 90mg in 200ml PNSS for 30 minutes. Patient stopped chemotherapy sessions on her 32nd week AOG with aims to free her from the side effects of Chemotherapy. Patient gave birth via Cesarean Section due to Breech presentation at 37 weeks AOG to a Term, Appropriate Age of Gestation, Live female neonate with a birth weight of 2.268 kgs (5lbs) with no noted congenital malformations. Patient is set to undergo clearance prior to resuming full doses of Chemotherapy regimen and for metastatic work-up.

Table 1.1 IMAGING

Ultrasound of Right Axilla	<u>05/05/2022</u> - Scanning of the clinically palpable mass in the right axilla shows well defined, lobular, homogenous, hypoechic, avascular solid mass measuring approximately 5.4 x 6.0 x 4.0 cm (l x w x ap). No perilesional hypervascularity. - In light of patient's history, consider hematoma. Neoplastic process not ruled out. Tissue correlation suggested
2D Breast Ultrasound	<u>09/13/2022</u> INTERPRETATION AND FINDINGS Breast ultrasound revealed the following: RIGHT BREAST - Cyst at the 10C position measuring 0.4 x 0.3 x 0.4 cm. LEFT BREAST - Complex nodule at the 2B position measuring 1.2 x 1.0 x 1.0 cm. SHORT INTERVAL FOLLOW-UP is recommended IMPRESSION: SHORT INTERVAL FOLLOW-UP is recommended for the complex nodule in the left breast. Right breast nodule with benign features.
	AXILLARY AREAS: Enlarged lymph node with heterogenous echogenicities at the right axillary area measuring 6.0 x 4.6 x 8.3 cm. TISSUE CORRELATION is recommended.
Second and Third Trimester Ultrasound	<u>10/17/2022</u> IMPRESSION: - Pregnancy uterine 16 weeks 3 days by composite sonar age, live, singleton fetus in cephalic presentation with good cardiac and somatic activities - Placenta anterior, grade 1 - Normohydramnios - Long and closed cervix <u>11/29/2022</u> IMPRESSION: - Pregnancy uterine 21 weeks and 3 days by fetal biometry, live, singleton in CEPHALIC presentation with good cardiac and somatic activities - Right anterior, grade 1 high lying. - Adequate amniotic fluid volume. - EDD by ultrasound: April 08 2023
MRI of the Breast and Chest	<u>10/22/2022</u> IMPRESSION: - Axillary mass, RIGHT, as detailed above. Tissue correlation is suggested. - Irregularly shaped T1W hypointense/SPAIR hyperintense focus, left breast. Due to lack of contrast imaging, enhancement pattern of this focus is not available. A malignant neoplastic process cannot be entirely ruled out. - Breast cysts, bilateral. - No distinct pulmonary or mediastinal mass noted. BIRADS 4: SUSPICIOUS FOR MALIGNANCY Tissue correlation is suggested for the right axillary mass.
Congenital Anomaly Scan	<u>11/18/2022</u> IMPRESSIONS: - Pregnancy uterine 20 weeks and 5 days by average fetal biometry, live, singleton in CEPHALIC presentation, - Placenta anterior, Grade II, High lying, with visualization of subplacental sonolucency adequate amniotic fluid by deepest vertical pocket. - No gross congenital anomalies noted at the time of scan

Pelvic Ultrasound	<u>12/02/2022</u> IMPRESSIONS: • Pregnancy uterine 21 weeks and 4 days age of gestation by average fetal biometry • Live singleton in cephalic presentation with good cardiac and somatic activities. • Placenta anterior, GRADE II, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket <u>12/21/2022</u> IMPRESSIONS: • Pregnancy uterine 24 weeks and 5 days age of gestation by average fetal biometry live singleton in BREECH presentation with good cardiac and somatic activities. • Placenta anterior, GRADE II, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket/Normohydramnios • Estimated fetal weight is appropriate for gestational age <u>01/06/2023</u> IMPRESSIONS: • Pregnancy 25 weeks and 5 days age of gestation by average fetal biometry • Live singleton in breech presentation with good cardiac and somatic activities • Placenta anterior, grade II, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket/Normohydramnios • Estimated fetal weight is below the 10th percentile for gestational age (at 27 weeks: 850-1450 grams) <u>01/20/2023</u> IMPRESSIONS: • Pregnancy 28 weeks and 1 day age of gestation by average fetal biometry • Live singleton in breech presentation with good cardiac and somatic activities • Placenta anterior, prematurely aged, grade III, high lying, with visualization of subplacental sonolucency • Adequate amniotic fluid by deepest vertical pocket/Normohydramnios • Estimated fetal weight is below the 10th percentile for gestational age (at 29 weeks: 1050-1625 grams)
OB DOPPLER Ultrasound	<u>01/20/2023</u> IMPRESSIONS: • Maternal Doppler study reveal presence of unilateral uterine artery notching suggestive of abnormal trophoblast space invasion of the spiral arterioles, predictive of the development of hypertension later in pregnancy. • Maternal Doppler studies of the uterine arteries reveal unilateral elevation of the indices, suggestive of suboptimal uteroplacental flow • However, all Fetal Doppler indices are within normal limits suggestive of good fetoplacental flow

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	<u>07/13/2022</u> Immunohistochemical Stain Result: OCT2- NEGATIVE REMARK/S: The diagnosis and comments remain unchanged. Dr. Raymundo W. Lo concurs. <u>10/27/2022 (Report date: 11/14/2022)</u> HISTOPATH REVIEW OF SLIDES (SGD22-685 A1-A4 AND B, S-22-0369) (A) RIGHT AXILLARY MASS: EXTRASKELETAL EWING SARCOMA • FNCLCC GRADE 3 ➢ Differentiate score: 3 ➢ Mitotic Score: 3 (25-30/10HPF) ➢ Necrosis Score: 1 (<5%) • TUMOR IS PRESENT ALONG CAUTERIZED EDGE OF SPECIMEN • LYMPHOVASCULAR INVASION IS NO IDENTIFIED • PERINEURAL INVASION IS NOT IDENTIFIED (B) RIGHT AUXILLARY LYMPH NODE: • LYMPHNODE WITH REACTIVE LYMPHOID HYPERLASIA • NEGATIVE FOR METASTASES REMARKS: Correlation with previous histopathology report and radiologic findings is recommended for the tumor size GROSS AND MICROSCOPIC DESCRIPTION Received for review are five H and E slides (labeled SGD22-685 A1-A4 and B) three immunohistochemistry slide (labeled SR-22-0369 for CD99, S100 and cyclin D1 from St. Luke's medical center) and five paraffin blocks stated to be from (A) right axillary mass and (B) right axillary lymph node Immunohistochemical staining was performed on paraffin block A3 with the following results): <table><tr><td>SMA</td><td>- Negative</td><td>Synaptophysic</td><td>- Negative</td></tr><tr><td>Desmin</td><td>- Negative</td><td>Pan-CK</td><td>- Negative</td></tr><tr><td>HMB45</td><td>- Negative</td><td>Desmin</td><td>- Negative</td></tr><tr><td>LCA</td><td>- Negative</td><td>ER</td><td>- Negative</td></tr><tr><td>GATA3</td><td>- Negative</td><td>EMA</td><td>- Negative</td></tr></table>	SMA	- Negative	Synaptophysic	- Negative	Desmin	- Negative	Pan-CK	- Negative	HMB45	- Negative	Desmin	- Negative	LCA	- Negative	ER	- Negative	GATA3	- Negative	EMA	- Negative
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Immunohistochemistry	<u>10/27/2022 (Report date: 11/14/2022)</u> Chromogranin – negative Review of the immunohistochemical slides done in St. Luke's Medical Center (S-22-0369, done on July 5, 2022) performed on block A1 showed the following results: • CD99 – Positive, strong diffuse membranous • Cyclin D1 – Positive • S100 – Focal Positive The histopathology report form St. Luke's Medical Center (S-22-0369, done on July 5, 2022) also showed the following IHC results: • CD78A – Negative (as per histopathology report) • CD20 - Negative (as per histopathology report) • CD3 - Negative (as per histopathology report) • CD30 - Negative (as per histopathology report) • CD34 - Negative (as per histopathology report) • MPO - Negative (as per histopathology report) • SALL4 - Negative (as per histopathology report) • CD68 - Negative (as per histopathology report) • Ki67 – Positive, 70-80% (as poer histopathology report) • CD5 - Negative (as per histopathology report) • CD10 - Negative (as per histopathology report) • Bcl2 - Negative (as per histopathology report) • SOX11 - Negative (as per histopathology report) • EBERish - Negative (as per histopathology report) Paraffin block A3 was sent to St. Luke's Medical Center for EWSR (22q12) Break Apart by FISH, and showed positive for EWSR break apart by FISH (GC22-FISH-0111F, November 11, 2022) Microscopic examination done.																				

CONCLUSION

The main goal of therapy is to weigh risk and benefit between the mother and the developing fetus. Although there is a very limited guideline and knowledge with ES as of this moment, the diagnosis of a malignant disease during pregnancy remains to be a serious medical as well as ethical, emotional, religious and philosophical questions.

The mother's health and safety as well as the fetal well-being is of equal essence and value. Thus, in favorable prognosis, multi-agent chemotherapy should be administered early in the course of malignant sarcomas since the risk of metastasis occurrence is high.

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