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A rare case of Extraskeletal Ewing's sarcoma of the axilla in a primigravida

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Abstract:

Ewing's sarcoma is a rare cancerous tumor of bone or soft tissue that usually occurs mostly in young adults. The diagnosis of Ewing's sarcoma in pregnancy, most especially the subtype extraskeletal Ewing's Sarcoma, is very rare with only few cases published in the literature worldwide. We present a case of a primigravida diagnosed with extraskeletal Ewing's sarcoma at 6 weeks age of gestation. Currently, because of the rarity of this condition, there is lack of a universal consensus on the recommended therapeutic approach. A multidisciplinary management involving the generalist obstetrician, perinatologist, medical oncologist, and neonatologist was initiated at the outset to provide timely balance between optimal maternal treatment and fetal well-being. The maternal and fetal condition was stable all throughout the course of the chemotherapy using doxorubicin during pregnancy. Close interdisciplinary coordination regarding the treatment plans across these subspecialists resulted in a successful pregnancy outcome.

Keywords:

Doxorubicin in pregnancy, Ewing's sarcoma, extraskeletal Ewing's

Introduction

Ewing's tumor is part of the Ewing's Sarcoma Family of Tumors (ESFT), which includes Askin's disease of the chest wall, primary neuroectodermal tumor of bone or soft tissue, and extraskeletal Ewing's sarcoma.[1] After osteosarcoma, it is the second most prevalent bone cancer in adolescents, reaching its peak in the second decade of life. It favors flat bones and typically affects the diaphyseal region of long bones. A typical "onion skin" periosteal reaction with a liberal soft tissue mass, as seen most frequently by computed tomography or magnetic resonance imaging, may be visible on plain radiographs. This mass resembles small cell cancer, fetal rhabdomyosarcoma, and lymphoma histologically due to its flat, small, spherical, blue cell layers.[2] This disease is very aggressive and is therefore considered a systemic disease. The most common sites of metastasis are the lungs, bones, and bone marrow. Occurrence at unusual sites can lead to the consideration of alternative clinical diagnoses and make the evaluation process more challenging.

Currently, breast cancer remains to be the most common cancer treated during pregnancy, followed by ovarian cancer, cervical cancer, leukemia, lymphoma, and lung cancer. Conversely, bone and soft tissue sarcomas are rare tumors that are not often seen during pregnancy. There are only three reported cases with the diagnosis of primary axillary soft tissue extraskeletal Ewing based on an extensive worldwide literature search for this condition. Murphey *et al*. in 2013 reported the first case of extraskeletal Ewing's sarcoma in an 11-year-old boy with an enlarging axillary soft tissue mass in his left axilla.[3] In 2017, Chatterjee *et al*. documented the second known case as part of a review of 50 adult patients with ESFT,

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highlighting the imaging features observed in these tumors. Only one from that case series of ESFT presented with an axillary mass.[4] Most recently, Albasri *et al*. in 2022 reported the third case in Saudi Arabia involving a 29-year-old female patient who presented with a lump in her left axilla.[5]

Review of the literature on pregnancy-related cases of Ewing's sarcoma showed only a few reported cases worldwide. The first was documented in 1963 by Lysyj and Bergquist. The patient, at 32 weeks age of gestation, complained of pain in the right leg and was diagnosed with Ewing's sarcoma of the pubic ramus. However, radiation and chemotherapy were not performed during the course of her pregnancy. She delivered by cesarean section at 36th week age of gestation. In another case, a 21-year-old female patient at 25th week age of gestation was diagnosed with left iliac wing Ewing's sarcoma. This patient was given a single round of multiagent chemotherapy that included actinomycin D, cyclophosphamide, bleomycin, vincristine, and doxorubicin before a planned cesarean section at 34 weeks age of gestation and delivered a healthy baby. The third case reported by Merimsky *et al*. involved a case of right sacroiliac bone Ewing's sarcoma. The patient received three cycles of 3 weekly doses of doxorubicin plus ifosfamide and mesna. Cesarean section was planned in advance after completion of the 3 cycles of chemotherapy and after fetal lung maturity was achieved. The outcome was a small baby, but with normal development.[6] Nakajima *et al*. report the case of a 17-year-old female with extraskeletal Ewing's sarcoma of the upper left leg treated with doxorubicin and ifosfamide between the 25th and 30th week of pregnancy. The fetus developed intrauterine growth restriction after three cycles of chemotherapy, leading to an elective cesarean delivery at 32 weeks. Subsequently, she delivered to a small-for-gestational-age baby who required intubation due to respiratory distress. The infant also had hyperbilirubinemia, low reticulocyte, and hemoglobin levels and received phototherapy and erythropoietin, respectively. Nevertheless, the baby's growth and development were adequate and exhibited no abnormalities on follow-up at 8 months of age.[7] Another reported case described an ovarian primary neuroectodermal tumor discovered at 24 weeks' gestation. Doxorubicin, cyclophosphamide, and vincristine were used in two cycles of chemotherapy beginning at 30 weeks' gestation. Subsequently, a healthy baby was delivered via cesarean section at 37 weeks of pregnancy. Unfortunately, 13 months after the mother's first diagnosis during pregnancy, the mother succumbed to the disease's progression to metastasis.

Systemic chemotherapy prior to surgery is the backbone of treatment for Ewing's sarcoma. Doxorubicin, cyclophosphamide or ifosfamide, etoposide, vincristine, and dactinomycin are active agents used in this condition.[8] While topotecan and irinotecan with an alkylating drug are frequently used in relapsed patients. Surgery to remove the original tumor is one form of local treatment, frequently combined with radiation therapy or limb preservation. With proper therapy, patients with lesions below the elbow and below the mid-calf have an 80% 5-year survival rate. Even in the midst of evident metastatic disease, Ewing's sarcoma is treatable when it first manifests, especially in children under the age of 11.

The management of Ewing's sarcoma in a pregnant patient is similar to that in a nonpregnant patient. However, due to the rarity of such case, currently, there is no universal consensus on the recommended therapeutic approach. Treatment is determined through a multidisciplinary approach to ensure that both mother and child will be able to avoid serious toxicity with adequate treatment of the mother. Pretreatment chemotherapy is given to the majority of pregnant patients with Ewing's sarcoma. Chemotherapy administered during the third trimester is generally considered safe even if low birth weight infants have been reported following the chemotherapy. Nonetheless, there were no late consequences or immediate hazardous effects reported on the 6th month of follow-up. The preferred method of delivery in patients with pelvic sarcoma and probably other tumors is a cesarean section. However, individualized management might be necessary in all situations of pregnant women with bone or soft tissue sarcoma.

Case Report

This is a case of a 34-year-old, primigravid, diagnosed with Ewing's Sarcoma at 6 weeks age of gestation. The patient is a family physician, nonsmoker with a body mass index of 27 kg/m^2. Her past medical and social histories are non-contributory. She has family history of breast, colon, and prostate cancer.

The condition started at 6 weeks' gestational age as a rapidly enlarging right axillary mass with associated paresthesia on the affected arm [Figure 1]. Magnetic Resonance Imaging of the breast and chest demonstrated a *"large lobulated mass, measuring approximately 8.8 cm × 10.1 cm × 7.9 cm, centered on the right axillary region extending inferiorly into the lateral chest wall, medially into the anterior chest* wall/breast *region and right supraclavicular region where a malignant neoplastic process cannot be entirely ruled out"* [Figure 2]. An excision biopsy was done revealing a right axillary mass with extraskeletal Ewing's sarcoma, Grade 3, with no nodal involvement nor metastasis to other organs. Further immunohistochemical analysis [Figure 3] was recommended, revealing positive for CD99, cyclin D1,

and a more specific marker for Ewing's sarcoma, the Ewing's sarcoma breakpoint region 1 (EWSR) break-apart by fluorescence *in situ* hybridization (FISH). She was referred to a medical oncologist who then referred her to the attending obstetrician. Subsequent referral was made by the attending obstetrician to a perinatologist and neonatologist. All obstetrical examinations and fetal parameters were within normal.

Neoadjuvant chemotherapy with doxorubicin at 21 weeks' gestational age was initiated after extensive family conference with all the subspecialists involved in the management of the patient regarding maternal as well as fetal prognosis.

Doxorubicin 90 mg in 200 ml of plain normal saline solution for 30 min was started. This regimen is recommended to be safer for pregnant patients with lesser fetal complications. At 24th week gestational age, betamethasone 12 mg intramuscularly every 24 h for 2 doses was given to enhance fetal lung maturity. Magnesium sulfate 20 g in 1 L of 5% dextrose water was also started at 1 g/h through an infusion pump for 24 h for fetal neuroprotection. She received her second cycle of doxorubicin chemotherapy at 25 weeks gestational age, her 3rd cycle at 28 weeks gestational age, and her 4th cycle at 31 weeks gestational age with a notable significant decrease in the right axillary mass size and slight resolution of symptoms [Figure 4].

The chemotherapy was well tolerated by the patient using adequate antiemetic prophylaxis and bone marrow support. Regular antenatal care and close maternal and fetal monitoring were done [Table 1]. During her routine scan at 29 weeks' gestational age, the fetus is appropriate for gestational age with good diastolic flow on umbilical artery Doppler scan. However, the placenta was noted to be prematurely aged at Grade 3. Hence, aspirin 80 mg tablet once a day was started. At 34 weeks' gestational age, a rescue course of betamethasone 12 mg intramuscularly every 24 h for 2 doses was administered in anticipation of a premature delivery. Aspirin was discontinued at this time. At 36 weeks' gestational age, a repeat scan revealed a fetus in breech presentation, with biophysical profile score of 8/8 and a reactive nonstress test. The fetal weight and amniotic fluid volume, however, were below the 10th percentile and the 5th percentile for age, respectively. Maternal and fetal Doppler studies at this time both demonstrated suboptimal uteroplacental flow. Fortunately, the middle cerebral artery pulsatility index was still within normal limits, suggestive of the absence of preferential blood flow to the brain. Close antepartum surveillance was done. She delivered by cesarean section at 37 weeks gestational age to a live, term baby girl with a birth weight of 2268 g that is appropriate for gestational age. The maternal postoperative course as well as that of the infant was uncomplicated. The baby was roomed in with the mother and was discharged on the second postoperative day.

Discussion

The presentation of extraskeletal Ewing's sarcoma in this case–palpable mass and persistent pain–was typical of extraskeletal Ewing's sarcoma, which facilitated timely

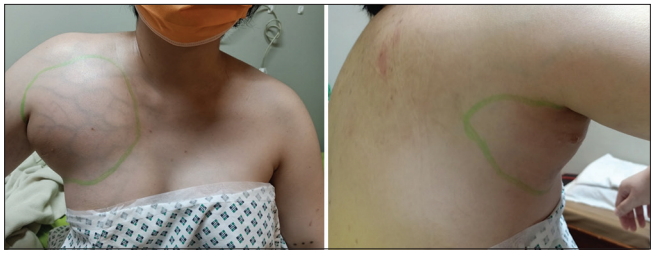

Figure 1: Right axillary mass. 32 x 30 cm vascularized mass, tender on deep palpation, non-movable, non-erythematous on the right axilla

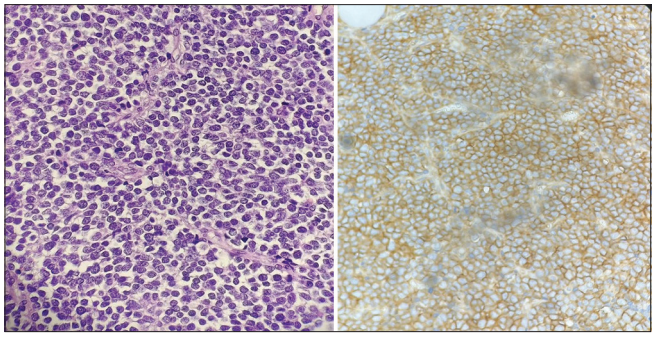

Figure 3: Histologic slide. Immunohistochemistry yielded CD99-positive Extraskeletal Ewing Sarcoma FNCLCC Grade 3

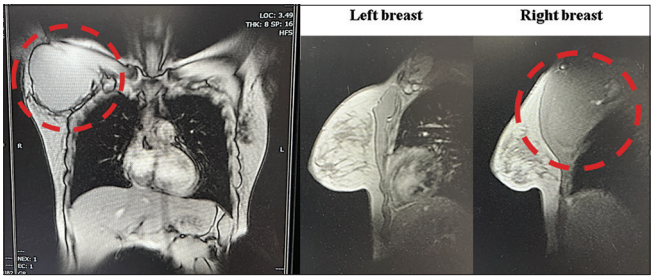

Figure 2: MRI of the breast and chest. A large lobulated mass, measuring approximately 8.8 x 10.1 x 7.9cm, centered on the right axillary region

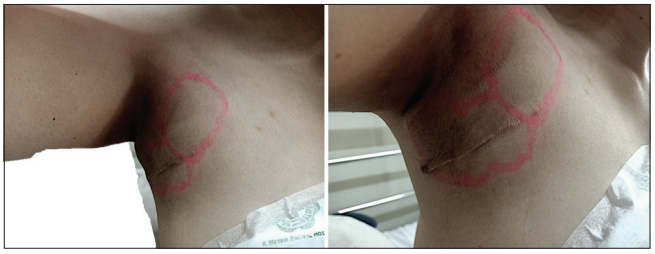

Figure 4: Right axillary mass after 4th cycle of doxorubicin at 31 weeks' gestational age. 10 x 5cm non vascularized mass, non-tender on deep palpation, non-movable, non-erythematous on the right axilla

Table 1: Ultrasound results

AOG	EFW (g)	AGA/ SGA	Weight difference from previous (g)	AFI/SVP	Doppler studies	Other
20 weeks 4 days	364±53		-	Adequate	-	No gross congenital anomaly
22 weeks 1 day	441		77	Adequate	-	-
25 weeks 2 days	766	AGA	332	Adequate	-	-
27 weeks 4 days	840	SGA	74	Adequate	-	-
29 weeks 4 days	1129	AGA	289	Adequate	Normal right UA elevated left UA (+) notching normal UMA normal MCA	Placenta anterior prematurely aged, grade III high lying
32 weeks 5 days	1450	AGA	321	Adequate	-	Breech placenta anterior prematurely aged, grade III high lying
34 weeks 4 days	1836	AGA	386	Adequate	Normal right UA elevated left UA (–) notching normal UMA normal MCA	Breech placenta anterior prematurely aged, grade III high lying
36 weeks 4 days	1955	SGA	119	Below 5th percentile for AOG	Normal right UA elevated left UA (+) occasional notching elevated UMA normal MCA	Breech placenta anterior prematurely aged, grade III high lying

AOG: Age of gestation, AGA: Appropriate for gestational age, SGA: Small for gestational Age, EFW: Estimated fetal weight, AFI: Amniotic fluid index, SVP: Single vertical pocket, UA: Uterine artery, UMA: Umbilical artery, MCA: Middle cerebral artery

diagnosis and initiation of treatment. This rare cancerous tumor of bone or soft tissue is fast-growing and often metastasizes to distant organs that an early diagnosis and initiation of treatment is imperative. It comprises the surrounding soft tissue as well as the skeletal muscles. Typically, the diaphyseal portion of the bone is where Ewing's sarcoma develops.[9] Not commonly, they may occur at unusual sites and can lead to consideration of alternative clinical diagnoses and make the evaluation process more challenging. The availability of good imaging studies and immunohistochemistry stains clinched the diagnosis in this case. There are only three reported diagnosed cases of primary axillary soft tissue extraskeletal Ewing's sarcoma worldwide. This case may represent the 4th reported case.

The diagnosis of Ewing's sarcoma in pregnancy is very rare. Osteomyelitis may be one of the differentials due to the clinical manifestation of the inflammatory reaction surrounding the tumor. Hence, a biopsy or fine needle aspiration tissue sampling subjected to appropriate staining, as in this case, is the diagnostic procedure of choice. Magnetic resonance imaging, as has been done in this case, was able to evaluate the amount of tumor invasion and was utilized to gauge the effectiveness of the therapy. Since magnetic resonance imaging done in this case did not demonstrate metastasis to the lungs, no other diagnostic tests were requested like a chest computed tomography scan or a positron emission tomography scan. Various studies have also looked into the hormonal effects of pregnancy on this illness. By examining the expression of estrogen and progesterone receptors in the tumor, it was reported negative immunohistochemistry staining for such. On the other hand, Ewing's sarcoma cells almost always exhibit insulin-like growth factor-1 receptors. Research shows that rising levels of insulin-like growth factor-1 during pregnancy have been linked to the formation, development, growth, and spread of the disease in Ewing's sarcoma. However, evidence supporting this finding remains limited.[10] In this case, these tests were not requested since the patient appeared to have responded to the chemotherapy.

The management of Ewing's sarcoma in this case followed that of a regimen for a nonpregnant patient. Recently, with the improvement in diagnostic techniques, the long-term survival rates of up to 80% were seen among those who have not developed metastases. In this case, the lack of evidences for a metastatic process may allow good prognosis and survival rate for this patient. The multidisciplinary approach in this patient ensured that both mother and child were able to avoid the possibility of serious toxicity brought about by the chemotherapy. Options include radiation therapy, chemotherapy, and surgery. In some literature, combining chemotherapy with surgery and radiotherapy increases survival compared with chemotherapy alone. In the case, surgery could not be offered because of the rapid progression of tumor size and because the mass was situated in a highly vascularized region.

Currently, the treatment of choice during pregnancy is chemotherapy, which is deemed safe throughout the third trimester. However, this can result in abnormalities, intrauterine growth restriction, and even intrauterine fetal death when given during the first trimester of pregnancy. As has been mentioned, because of its rarity, there is no universal consensus on the management of this case. Nevertheless, it has been reported that administering chemotherapy during the second trimester of pregnancy considerably increases the likelihood of maternal survival compared with delaying treatment

until after delivery. Most published cases of Ewing's sarcoma in pregnancy use chemotherapy as the main treatment, and most chemotherapy regimens have been doxorubicin-based. These were the guidelines utilized and agreed upon by the multidisciplinary team to institute in this case that resulted to a successful outcome. Doxorubicin, cyclophosphamide, vincristine, and dactinomycin have been the foundation of almost every chemotherapy regimen for Ewing's sarcoma, and they have been alternated with ifosfamide and etoposide. In our case, instead of giving multichemotherapeutic agents, monotherapy with doxorubicin was used as it is safer for pregnant patients and with lesser demonstrable fetal complications. Nonetheless, doxorubicin is categorized as pregnancy category D wherein there is a demonstrated risk to the fetus following the use of the medication. Hence, the risks of fetal prematurity, neutropenia, and anemia were all explained to the patient. The potential fetal growth restriction that places neonates at risk for both short- and long-term adverse outcomes prompted prenatal monitoring of fetal growth and Doppler measurements during chemotherapy in this case. Subsequently, concerns regarding fetal growth restriction were addressed at the outset. Similarly, during the family conferences for this case, it was emphasized that psychological support should be an integral part of the management plan, as a cancer diagnosis during pregnancy presents both psychological and biological challenges. A multidisciplinary counseling approach helped alleviate the distress experienced by the patient and her family. Active participation in the decision-making process empowered the patient, fostering confidence and providing emotional support. Consent for the proposed treatment plan was carefully obtained during these discussions, ensuring that both the patient and her family were fully informed of the potential risks, benefits, and uncertainties involved. This collaborative process also involved addressing any concerns and ensuring that their preferences were respected. The patient and her family were given ample time to ask questions and reflect before providing their consent to proceed.

This case underscores the importance of shared decision-making between the patient, her family, and the medical team when navigating complex conditions during pregnancy. Ethical dilemmas, especially when balancing the health of the mother with the well-being of the fetus, require transparent, compassionate communication. The patient's autonomy must be respected, while her emotional and psychological needs are met throughout the treatment process. Given the complexity, there is no one-size-fits-all solution, but a thoughtful, patient-centered approach ensures that key ethical principles, such as autonomy, beneficence, and nonmaleficence, are upheld.

Summary

Extraskeletal Ewing's sarcoma during pregnancy is extremely rare. However, the early diagnosis and prompt treatment through a multidisciplinary approach involving also the patient and her family resulted in a successful outcome in this case.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authorship contributions

Adiong, Annabilah A. - Involved in conceptualization, methodology, writing of the original draft, review and editing.

Umipig-Guevarra, Zoraida - Involved in supervision, and writing- review and editing.

Ursua, Joanna Pauline - Involved in writing- review and editing.

Cuya, Ruzabeth - Involved in supervision.

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Conflicts of interest

There are no conflicts of interest.

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