Management of cancer in pregnancy: A case of Ewing's sarcoma of the pelvis in the third trimester


Unit of Bone and Soft Tissue Sarcoma, Institut Gustave Roussy, Villejuif, France

Summary

Ewing's sarcoma of the pelvic bones was diagnosed in a 21-year childbearing woman, raising major medical and ethical problems. The diagnostic and therapeutic approaches during the sixth month of gestation were tailored in order to cure the patient and avoid unnecessary toxicity to the fetus. Ancillary tests included ultrasound and MRI studies of the pelvis. Ifosfamide and adriamycin, premedicated by granisetron, were administered during gestation, and were found to be safe. Cesarean section was the preferred way of delivery since the tumor involved the pelvic bones. The outcome was a disease-free patient and a small healthy baby who is now two years of age.

Key words: chemotherapy, Ewing's sarcoma, pregnancy

Introduction

The occurrence of cancer in a pregnant woman is a relatively low-probability event. Epidemiological data suggest that the incidence of cancer during pregnancy is 0.07% to 0.1% of all malignant tumors [1, 2]. Quite infrequently, bone and soft tissue sarcomas arising in limbs or other organs have been reported during gestation in HIV negative patients [3, 4]. To our knowledge, only two cases of Ewing's sarcoma developing during gestation has been described [5, 6]. We herewith report the third case of Ewing's sarcoma in a childbearing woman, in whom the diagnostic and therapeutic approaches were tailored in order to cure the patient and avoid unnecessary toxicity to the fetus.

Case report

A 21-year-old Caucasian woman complained of a progressive right sciatic pain that appeared during the first month of her first pregnancy, and unsuccessfully treated by rest and mild analgesics. Ultrasound and MRI studies of the pelvis were performed during the sixth month of gestation following aggravation of the pain, finding of impaired tendon reflexes in the right leg, and paraesthesia along the right thigh.

A 12 cm heterogeneous polylobulated mass was observed at the vicinity of the right sacro-iliac joint, infiltrating the sacrum and the adjacent soft tissues including the psoas muscle, side by side to a fetus-harboring uterus (Figure 1). The patient was premedicated by oral morphine, and an ultrasound-guided biopsy from the mass was performed, yielding small round cells compatible with Ewing's sarcoma. Thorough staging evaluation revealed no other involved sites. An intravenous access device was implanted, and three courses of three-weekly doxorubicin (50 mg/m²) plus ifosfamide and mesna (each 5 g/m²) (ADR-IFX) were delivered. Three courses were given in the 27th, 30th, and 33rd week of gestation. Nausea and vomiting were controlled by i.v. granisetron 3 mg/day. No prophylactic bone marrow support was planned. Complete pain relief was achieved following the second course of ADR-IFX. Only one episode of grade 3 myelotoxicity, i.e., neutropenia without fever, was observed following the third course on a routine blood count, requiring no antibiotic treatment, nor hospitalization. Fetal monitoring and repeated ultrasonographic evaluations showed mild intrauterine growth...
retardation without fetal stress. MRI evaluation performed after the three cycles of chemotherapy revealed partial regression of the tumor (Figure 2). A Cesarean section was planned and performed at the beginning of the 36th gestation week. The newborn was a 42 cm length and 1300 g weight female. A fourth course of ADR-IFX was administered two weeks later, followed by definitive surgery, consisting of a large resection of the iliac bone and hemisacrectomy sacrificing the S1, S2 and S3 roots. Pathologic evaluation of the surgical specimen documented complete resection and 80% necrosis of the tumor. Planned adjuvant chemotherapy consisted of ifosfamide (12 g/m² given by continuous infusion over three days) plus etoposide (100 mg/m²/day i.v. for three days) according to our adult Ewing's sarcoma protocol was started. Etoposide was rapidly aborted due to severe allergic reaction to the drug observed within the first minutes of infusion. Despite prophylactic administration of granulocyte colony stimulating factor (GCSF) the patient experienced neutropenic fever after each of the two ifosfamide courses. The chemotherapy was discontinued. A dose of 46 Gy (four MV photons, 2 Gy ×5/week, isocentric AP-PA fields) was subsequently delivered to the tumor bed and the right hemipelvis after ovarian transpositioning. The patient is disease-free for 24 months now, and her daughter shows no chemotherapy-related late effects.

Discussion

Ewing's sarcoma during pregnancy

Our case represents the third of pregnancy-associated pelvic Ewing's sarcoma. It points to the rare occurrence of Ewing's sarcomas in a pregnant woman, to the possibility of performing MRI and biopsy without morbidity, to the feasibility of giving repeated curative courses of doxorubicin, ifosfamide, mesna and granisetron during gestation without hurting the fetus, nor causing any immediate deleterious toxicity to the normal development of the pregnancy.

Interestingly, the two previous published cases of Ewing's sarcoma developing during pregnancy involved the pelvic bones [5, 6]. The first case was reported by Lysyj and Bergquist in 1963 [6] in a pregnant woman during the 32nd week of gestation. Cesarean section was indicated one month later since the tumor destroyed the pubic ramus and was large enough to preclude vaginal delivery. The baby was normal. No chemotherapy nor radiation therapy were given during the period of gestation. No follow up data are available.

The second case, published 22 years later, in 1985, by Haerr and Pratt [5] was diagnosed in a 21-year-old woman during the 25th week of gestation, following complaints of pain in the hip. Evaluation included plain X-rays and ultrasound of the pelvis, which revealed the mass and an intrauterine pregnancy, followed by a tomogram and an isotope bone scan. A histologic diagnosis was obtained from an open surgical biopsy. The patient chose to carry on the pregnancy and to receive chemotherapy combination of daunomycin, cyclophosphamide, bleomycin, vincristine, and doxorubicin, without methotrexate, according to the T6 protocol [7]. The tumor responded by shrinkage, but then progressed. Pregnancy was interrupted by a Cesarean section performed on the 34th week. The baby was normal, apart from a low weight. Following delivery, the mother received another cycle of chemotherapy, and underwent en-bloc resection of the iliac wing, radiation therapy to the tumor bed and remaining iliac bone, and 10 months of multidrug chemotherapy. Within a follow-up of four years, the patient was disease-free and the child was developing normally without evidence for late chemotherapy-related toxicity.

Management of Ewing's sarcoma should include aggressive chemotherapy, extended surgery and radiation therapy, to maximally control the disease. However, only chemotherapy was given during gestation in our case, and the other treatments were delayed. There is no evidence in the literature that combining the three modalities is superior to any combination of two modalities in treating pelvic Ewing's sarcoma, but it is accepted that the prognosis of pelvic Ewing's tumor in young adults is usually grim. In our case of Ewing's sarcoma occurring in a pregnant woman, chemotherapy consisting of doxorubicin (50 mg/m²), ifosfamide (5 g/m²), and mesna, supported by intravenous granisetron (3 mg/day), was safely administered during the third trimester. Our data point to the relative feasibility and efficacy of this combination of adriamycin and ifosfamide during pregnancy. The neo-adjuvant treatment yielded a 80% necrosis, while the baby remained normal, although small in size and weight. The long-term effects on mental and physical development of the baby, together with the possible risk of future malignancy need to be monitored.

Other malignancies during pregnancy

Several types of malignancy that have been reported during pregnancy and may deserve special considerations...
are breast cancer, uterine cervical cancer, lymphoma and sarcoma.

Reports of the incidence of invasive cervical cancer during pregnancy vary between 0.02% and 0.9%. [8, 9]. Diagnosis is often delayed because bleeding is usually attributed to pregnancy-related complications. Any suspicious lesion should be biopsied. If the Pap smear is positive for malignant cells and the diagnosis of invasive cancer cannot be made with colposcopy and biopsy, a diagnostic conization may be necessary. Because conization subjects the mother and fetus to complications, it should be performed only in the second trimester and only in patients with an inadequate colposcopy and strong cytological evidence of invasive cancer. Conization in the first trimester of pregnancy is associated with an abortion rate of up to 33%. [8, 10]. It appears to be safe to delay definitive treatment of patients with carcinoma in situ or stage IA disease until the fetus has matured. The infant may be delivered by a cesarean section that is followed immediately by modified radical hysterectomy and pelvic lymph node dissection [8, 9, 11]. In more advanced stages, treatment depends on the stage of gestation and the wishes of the patient. Since modern neonatal care affords a 75% survival rate for infants delivered at 28 weeks of gestation age and 90% for those delivered at 32 weeks, labor can be induced and treatment can be introduced in order to save the mother’s life. There should be a thorough discussion of the risks and options with both parents before any treatment is undertaken.

Breast cancer occurring during pregnancy is relatively uncommon. The incidence of breast cancer during pregnancy is 2.2 breast cancers per 10,000 pregnancies [12].

Breast biopsy under local anesthesia is safe at any time during pregnancy and should be done for any suspicious mass [13–15]. As in other cases of malignancy during pregnancy, the options for the local treatment of breast cancer during pregnancy are limited for the woman who wishes to continue her pregnancy. The use of radiation therapy during pregnancy is contraindicated because of the inability to shield the fetus from internal scatter. If cancer is diagnosed in the third trimester, breast conserving surgery can be performed and radiation therapy delayed until after delivery. Delays for longer periods to allow this approach may be detrimental. Immediate reconstruction is also contraindicated during pregnancy because the risk to the fetus of a more prolonged anesthesia and increased blood loss is not warranted. Therapeutic abortion does not appear to play a role in the treatment of nonmetastatic breast carcinoma. [16, 17]. The use of chemotherapeutic agents in pregnant patients with breast cancer is controversial as with other cancers. Tamoxifen should not be used in pregnant women, but may be initiated after delivery.

Non-Hodgkin’s lymphoma is uncommon in young women, and its association with pregnancy is infrequent [18–22]. The primary sites of NHL in association with pregnancy were bone, gastrointestinal tract, breast, peripheral lymph nodes, genital tract, mediastinum, tonsil and skin [18, 21, 23]. Signs and symptoms can be present before conception [18]. Post partum acceleration of tumor growth has been reported [18, 23]. Staging procedures are limited, though abdominal ultrasound or MRI are safe. The therapeutic approach is based on the histological type of the lymphoma, as well as other factors such as the fetal maturation and the patient’s will [18]. Pregnant women with indolent lymphoma can be observed until after delivery. Localized indolent lymphoma can be cured by radiation therapy to the involved field, even during pregnancy [21, 22]. Stage I or II supradiaphragmatic disease was treated by radiation therapy during pregnancy [22], although this approach is highly controversial. Therapeutic abortion in the first trimester is indicated in cases with widespread disease, rapidly progressive disease, and unfavorable histology. Patients who refuse abortion, may be offered chemotherapy [22]. Patients presenting close to full-term pregnancy can be observed until after delivery, as long as the disease is more or less stable.

Sarcoma in association with pregnancy is an extremely rare situation. Several types of soft tissue sarcomas and bone sarcomas, occurring anywhere in the body, have been reported in the literature in association with pregnancy [24–26]. In this context, although theoretically applicable in our patient, the administration of regional chemotherapy by using the isolated limb perfusion technique should be considered in cases of soft tissue sarcomas. Since the vast majority of soft tissue sarcomas occur in the limbs, in sites that permit limb sparing surgery, a reasonable attempt for local control of the disease may include this highly-selective chemotherapy, followed by surgery. The need for adjuvant chemotherapy is still debated in any case of high grade soft tissue sarcoma, and thus may not be given during gestation nor after labor. In cases of osteosarcoma and Ewing’s sarcoma, as in our case, pre-operative chemotherapy is well-accepted, and should be started whenever possible during pregnancy. Postoperative chemotherapy may be delayed till after delivery or given during the third trimester. In the third trimester, chemotherapy can usually be postponed until fetal maturity, when delivery can be induced.

The possibility of delivering effective radiation therapy whilst avoiding exposure of the fetus to ionizing radiation should be evaluated. Radiation therapy is regarded as harmful to the fetus, and is usually avoided during childbearing [4, 27]. However, brachytherapy by using remote after loading technique may be a good way to deliver tumoricidal dose to the tumor bed, especially in distally located primaries.

The dilemma of therapeutic approach

Three partners share the dilemma of what the therapeutic approach should be. It should be stressed, early in the discussion, that a best approach does not exist, but should be tailored to each case. From the mother’s point-of-view, it is necessary to estimate the risk to the
mother's life and health in carrying on the pregnancy without any intervention versus the risk of losing the fetus in favor of saving the mother's life. The growth dynamics of the mother's tumor (e.g., Ewing's sarcoma in our case), the related signs and symptoms, and the possible jeopardy to her longevity of life contribute to the assessment of this risk. This is especially important if the prognosis of the mother's disease is favorable and the chances for cure are high. The feasibility of curative surgery, either limb-sparing or amputation, under general or segmental anesthesia, should also be assessed [28]. However, if the planned treatment is only palliative, or there is no effective treatment (particularly metastatic chondrosarcoma) the effect of therapy on the fetus may be more important. Cesarean section should be performed when pregnancy is to be terminated urgently or in order to administer chemotherapy, as also noted elsewhere [5], or when the tumor involves the pubic bone, the uterus and cervix [6].

From the aspect of fetus and continuing pregnancy, it is necessary to estimate the immediate risk to the fetal life, health and expected post-natal growth, physical and mental maturation, and genetic aberrations leading to future malignant transformation (late sequels), in performing diagnostic procedures such as ancillary tests, biopsy and oncological treatments. In this context it is intriguing to mention the case of Haerr and Pratt [5] where plain films of the pelvis and chest, radionuclide bone scan and lung tomograms were performed, without having any deleterious effects on the fetus and newborn, seen within up to four years of follow-up. The age of the fetus, the state of the organogenesis, the fetal lung maturity, and the time needed to complete the pregnancy and having a mature baby may determine the degree of risk.

An additional factor that may play a role in diagnostic and therapeutic decisions is the possibility of delivering effective anti-cancer chemotherapy with effective supportive care. It is important to avoid increased toxicity due to drug-accumulation within the pregnancy-related third space, or due to effects of anti-emetics or colony-stimulating factors on the fetus. Moreover, the risk of developing chemotherapy-related toxicity, such as neutropenic fever and septic shock, should be assessed for the mother and fetus.

In this very complicated issue, the patient's will should be taken into consideration. Every therapeutic option should be clearly discussed with the patient. However, the final decision should be made by the patient supported by her physicians.

**Staging studies during pregnancy**

Several important management considerations should be made on the basis of the limited world-wide experience in this combination of events. In general, workup and treatment options of patients malignant tumors diagnosed during gestation are quite limited. The diagnostic and therapeutic approaches should be tailored specifically in every pregnant woman in whom malignancy, and especially sarcoma, is suspected. Open biopsy or resection of tumor and limb sparing surgery may be relatively safe during pregnancy, while prolonged manipulations might be hazardous to the normal propagation of pregnancy. Ancillary tests should be limited to those associated with the lowest exposure to ionizing radiation. In our case ancillary tests included ultrasound and MRI of the pelvis, compared with plain films, tomograms and radionuclide bone scan reported in the second case.

**Chemotherapy and supportive care during pregnancy**

The use of chemotherapy during pregnancy may be associated with harmful effects on the intra-uterine fetal organogenesis and development, and on the post-natal growth and maturation. The reported rate of chemotherapy-related fetal malformation are 12.7%-17% [29, 30], and that of low-birth weight was 40% [31]. The usual rate of malformations in non-chemotherapy related pregnancies is 3%-9% [29]. Other immediate or late adverse effects of chemotherapy on the fetus and newborn include teratogenesis, organ toxicity, carcinogenesis, sterility, retarded development, mutations, teratogenesis in second generations and spontaneous abortion [29].

The timing of chemotherapy during gestation is crucial. In most cases toxicity was observed when chemotherapy was given during the first trimester and less often during the other trimesters. The first-trimester chemotherapy induced malformation rate is 17% while the rate in the other trimesters is only 1.7% [29]. On the other hand, aggressive chemotherapy given for cancer during the first trimester of gestation does not prevent normal births [29, 32].

Different pregnancy-associated pharmacological factors may affect drug-metabolism in a pregnant woman. These include decreased gastrointestinal motility, increased total amount of total body water and plasma content, decreased albumin concentration, increased distribution volume and decreased peak concentration of the drug following bolus administration, increased pharmacological third space (the amniotic fluid), increased hepatic oxidation of drugs by the mixed-function hepatic oxidation system [29].

Various drugs have been delivered during pregnancies in order to treat different malignant tumors. The scarcity of experience and literature data exclude the possibility of reaching a solid conclusion regarding the safety of chemotherapy during pregnancy. The data presented on the following drugs refer only to the risk of development of congenital malformations and not to late organ toxicity or carcinogenesis after administration during the first trimester.

In any case of chemotherapy during pregnancy, attention should be paid to the mother's blood counts, in order to avoid delivery-related complications such as hemorrhage or infection during the nadir. Moreover,
immediate post-chemotherapy delivery or cesarean section should be avoided, due to the possible presence of as yet uneliminated drugs in the placenta and fetal blood. These drugs might lead to unnecessary toxicity to the newborn [8].

There are several reports on chemotherapeutic agents that were given during pregnancy.

Doll et al. [29] reviewed cases in which chemotherapy was given to pregnant women. Alkylation agents were given to pregnant women with various diseases during the first trimester, and were associated with 15% rate of fetal malformations. The most dangerous drug in this list was cyclophosphamide [29]. Cyclophosphamide early in pregnancy is known to cause fetal abnormalities [33]. Antimetabolites, i.e. aminopterin, methotrexate, 6-mercaptopurine (6-MP), cytarabine, 5-fluorouracil (5-FU), were associated with 19% rate of fetal malformation, when given during the first trimester. The most toxic drug was methotrexate, responsible for three out of three cases of fetal malformations, followed by aminopterin, causing a malformation rate of 20%. MTX also tends to accumulate in third spaces and cause delayed toxicity during its late elimination. These agents should be avoided in pregnant women. 5-FU was given safely to three women with breast cancer, during the 24th to 29th week of gestation, causing no fetal malformations [34]. Antibiotics, such as daunorubicin, were given in one case during the first trimester, and in our case later in the gestation, and may be considered safe, causing no malformations. The available evidence suggests that doxorubicin is safe during the second and third trimesters [35]. Vinblastine was repeatedly administered in patients with Hodgkin's lymphoma, causing no teratogenicity [36]. In a second report, the rate of fetal malformations was found to be 7% [29]. Recently, it was reported that vinorelbine had been given safely during 24th to 29th week of gestation, together with 5-FU, causing no fetal dysmorphic syndrome [34]. Cisplatin was administered in one case and was not associated with malformations. MOPP combination (mustard, vincristine, prednisone and procarbazine) given to patients with Hodgkin's lymphoma was associated with a statistically non-significant increase in the rate of spontaneous abortion [37]. The rate of congenital malformations after treatment with combination chemotherapy was reported to be 16% [29]. A combination chemotherapy of daunorubicin, cyclophosphamide, bleomycin, vincristine, and doxorubicin, given for Ewing's sarcoma during the 30–33rd week of gestation, was not associated with any malformations or four-year late toxicity [5]. Combination of adriamycin, ifosfamide and mesna, which was premedicated by granisetron was given in our case.

Supportive care during and after chemotherapy has a major role in maintaining the patient's quality of life and for optimal administration of the treatment. Antimetabolites such as metoclopamide, chlorpromazine, or the modern serotonin-receptor antagonists, colony stimulating factors as G-CSF or GM-CSF, pain killers and antibiotics may be hazardous to the developing and growing fetus. While the pain killers might depress the respiratory drive, and while the older classes of antimetics might affect the fetal brain cortex, the possible effects of serotonin-receptor antagonists and the CSF's remain unknown. In our experience, intravenous administration of granisetron during pregnancy controlled the emesis and was not associated with toxicity to the newborn. The risk of late effects is of course unclear.

Cesarean section

The relationship between the developing fetus and the developing tumor in cases of pelvic tumors represents two processes competing for the same limited space. The tumor may not arrest its growth because of the adjacent uterus, and might penetrate any soft tissue or bony component in its vicinity. The uterus and fetus might be compressed by the tumor, and a premature birth of a low-birth weight baby is to be expected. The second reason for low-birth weight is of course the chemotherapy, as observed in two cases of Ewing's sarcoma. Cesarean section may be the preferred way of delivery when the primary tumor involves the pelvic bones and structures. In the first case the tumor size and involvement of the pubic bone excluded the option of vaginal delivery. In the second case the disease re-grew during the course of chemotherapy, endangering the mother's life, and required Cesarean section. In our case Cesarean section was pre-planned after having completed three courses, and achieving fetal lung maturation.

Conclusions

Ewing's sarcoma during pregnancy is extremely rare. The influence of pregnancy on the initiation, promotion and development of Ewing's sarcoma cannot be explained according to these cases. Chemotherapy during the third trimester is relatively safe, and apart from low-birth weight, there were no immediate toxic effects, and no late effects within 1.5–4 years of follow-up have been reported. Cesarean section is the preferred way of delivery in cases of pelvic sarcoma and possibly other tumors. Attention should be made to the mother's blood counts in order to avoid severe bleeding or sepsis during and following the surgery. The major medical and ethical problem is the workup and management procedures required for the treatment of the pregnant woman presenting with Ewing's sarcoma, as well as other tumors, and the possible influences of the procedures on the developing fetus. There are no strict guidelines for the best medical decision in cases of pregnancy-associated sarcoma. In each case of a pregnant woman with bone or soft tissue sarcoma a specific approach should be tailored. The most important clue is, in our opinion, the curability of the mother's disease. Where cure is feasible the treatment should be given as early as possible.
References


Received 4 February 1998; accepted 24 March 1998.

Correspondence to: A. Le Cesne, MD
Departement de Medecine
Institut Gustave Roussy
39, rue Camille Desmoulins
94800 Villejuif
France