The Complexity of Management of Pregnancy-Associated Malignant Soft Tissue and Bone Tumors

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Key Words
Pregnancy • Soft tissue sarcoma • Bone sarcoma

Abstract
Objective: The incidence of musculoskeletal tumors during pregnancy is very low. The aim of this study was to summarize our experience in treating a large cohort of pregnant patients diagnosed with these rare tumors. Methods: Women diagnosed with musculoskeletal tumors during pregnancy or immediately after delivery were identified retrospectively in our database between 1996 and 2006. Relevant maternal and neonatal data were collected. Results: Twenty patients, 8 with bone sarcomas (BS) and 12 with soft tissue sarcomas (STS) were identified. Two women were treated by wide excision of mass during pregnancy. In all other cases oncological treatment was delayed until delivery or termination of pregnancy. Vaginal delivery was possible in 9 patients, cesarean section was performed in 7, spontaneous abortion occurred in 1, and 3 underwent termination of pregnancy. Three newborns were premature, but normal growth and development were observed. Different techniques of fertility preservation were used in our patients. Five patients with BS and 5 patients with STS received preoperative chemotherapy, with different grades of toxicity. The degree of tumor necrosis tended to correlate with dose-intensity of chemotherapy. Seven patients with BS received adjuvant chemotherapy. Two patients with STS received adjuvant chemotherapy, two – radiotherapy, and four – both modalities. Median disease-free survival was 15.1 months, median overall survival – 25.4 months. Conclusions: Musculoskeletal tumors diagnosed during pregnancy, or after delivery, do not appear to have a significant impact on the prognosis. A multidisciplinary team should tailor the oncological approach individually.

Introduction

The incidence of cancer in general, and in particular musculoskeletal tumors, is very low during pregnancy. The mechanism by which gestation initiates or accelerates the malignant process is still not understood. Is it a change in a hormonal profile of a pregnant woman? Is there modification of immune system activity? And if so, will abortion be necessarily a part of a therapeutic approach? There are additional questions that arise while
determining our management, especially because it involves two persons, the mother and the fetus. The stage of the pregnancy at which the diagnosis is made will influence the choice of primary therapeutic option. The type of the tumor, its primary site, extent of the tumor and its growth rate, the associated symptoms – are all important determinants for our approach to the patient. Does a woman diagnosed with bone or soft tissue sarcoma have a worse prognosis than anyone else with the same diagnosis?

The present report summarizes our experience in treating 20 women with malignant soft tissue and bone tumors diagnosed at pregnancy during the last decade.

**Patients and Methods**

The study is based on a retrospective analysis of 20 patients treated in our institution between January 1996 and February 2006. The patients were diagnosed with either soft tissue sarcoma (STS) or bone sarcoma (BS) or other malignant musculoskeletal tumors that developed or progressed during pregnancy or immediately after delivery. STS and BS staging was based on the system of the American Joint Committee on Cancer [1].

**Results**

The median age of our patients was 28 years (range 22–38). Their medical histories were variable (table 1): total thyroidectomy and treatment with radioactive iodine, NF-1-related neurofibrosarcoma, industrial exposure to nitrous oxide gas, previous germ cell tumor (malignant teratoma) treated by chemotherapy (data could not be retrieved), treatment with gonadotropin for an infertility problem. One patient who already had a history of metastatic bone sarcoma that was treated entered a disease-free state and developed pulmonary metastases during pregnancy. One patient developed a desmoid tumor during her fourth pregnancy; the tumor was completely resected and re-appeared during the fifth pregnancy. One patient underwent an excision of low-grade paraosteal bone sarcoma 9 years previously (at the age of 23), and actually developed a local recurrence during her first pregnancy.

In half of the patients the malignancy was diagnosed during their first pregnancy, while in the others it was associated with second to ninth gestation. The usual clinical presentation was a growing mass and/or increasing pain. Fifteen percent of the patients started seeking help during the first trimester of pregnancy, 40% during the second trimester and the rest during the third trimester or immediately after delivery. Nonetheless, it was hard to determine the exact date of appearance of the first symptom or sign. Most of the masses were located in the lower part of the body.

Systemic work-up required for diagnosis and staging of bone or soft tissue sarcomas was rather limited during pregnancy. Ultrasound and MRI studies were the only initial radiological studies permitted until the decision regarding the clinical approach was made. Staging studies such as isotope scans, plain films or CT were completed after delivery or after termination of pregnancy. Figure 1 depicts the case of a 28-year-old patient with a

![Fig. 1. Patient D.L., 28 years old. MRIs showing a huge right pelvic-inguinal and proximal thigh soft tissue sarcoma pushing the uterus.](image-url)
huge right thigh-inguinal-pelvic soft tissue mass pushing the uterus.

Pretreatment tissue diagnosis was made in all cases. There were eight bone sarcomas: four osteogenic, one chondroblastic, two fibroblastic and one giant cell rich sarcoma. There were 12 malignant soft tissue tumors: two synovial sarcomas, two myxoid liposarcomas, two leiomyosarcomas, two malignant peripheral nerve sheath tumors (MPNST), one small blue round cell skin tumor (Merkel cell tumor), one dermatofibrosarcoma protuberans (DFSP) and one unclassified soft tissue sarcoma. There was an additional patient with desmoid tumor: primary and recurrence during and following two consecutive gestations. Two of our patients presented with metastatic disease.

Vaginal delivery was possible in nine patients with no complications, cesarean section was performed in 7, spontaneous abortion occurred in 1 and 3 patients underwent termination of pregnancy. Indications for cesarean delivery were clearly obstetric and unrelated to the location or clinical symptoms of the tumor in 3 of the cases. There are no available data regarding the indications in the other cases. All but 3 babies were healthy. Three newborns were iatrogenically premature.

All placentas were macroscopically normal; therefore, no microscopic evaluation for the presence of micro-me-

**Table 1. Medical history and clinical picture: previously reported cases are marked by their reference number**

<table>
<thead>
<tr>
<th>Name</th>
<th>Ref.</th>
<th>Age</th>
<th>History</th>
<th>Pregnancy</th>
<th>Week</th>
<th>Symptoms</th>
<th>Effect of pregnancy</th>
<th>Location</th>
<th>Size</th>
<th>Diagnosis</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>F.E.</td>
<td>16</td>
<td>27</td>
<td></td>
<td>2</td>
<td>16</td>
<td>painful mass</td>
<td>increasing pain and mass</td>
<td>thigh</td>
<td>7 × 4.5</td>
<td>OS osteoblastic paraosteal</td>
<td>4</td>
</tr>
<tr>
<td>B.A.R.</td>
<td>16</td>
<td>36</td>
<td></td>
<td>4</td>
<td>17</td>
<td>LBP</td>
<td>progressive pain; spcc</td>
<td>back</td>
<td>3</td>
<td>OS fibroblastic</td>
<td>3</td>
</tr>
<tr>
<td>E.L.</td>
<td>16</td>
<td>36</td>
<td>11/1991; OS; 99-ILP TNF; 2000-thoracotomy</td>
<td>1</td>
<td>45</td>
<td>no</td>
<td>development of lung metastasis</td>
<td>lung 2 masses</td>
<td>OS fibroblastic</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Z.F.</td>
<td>16</td>
<td>22</td>
<td></td>
<td>1</td>
<td>24</td>
<td>LBP</td>
<td>increasing mass pain</td>
<td>pelvis</td>
<td>20 × 15 × 15</td>
<td>OS chondroblastic paraosteal</td>
<td>4</td>
</tr>
<tr>
<td>V.R.</td>
<td>16</td>
<td>26</td>
<td>hypothyroid-131I, hypothyroidism</td>
<td>1</td>
<td>30</td>
<td>mass</td>
<td>increasing mass</td>
<td>pubis</td>
<td>24 × 17 × 10</td>
<td>OS</td>
<td>3</td>
</tr>
<tr>
<td>L.A.</td>
<td>16</td>
<td>25</td>
<td>NF, giant nevus</td>
<td>1</td>
<td>40</td>
<td>painful mass</td>
<td>after pregnancy</td>
<td>hip, gluteus</td>
<td>20 × 20 × 20</td>
<td>MPNST</td>
<td>3</td>
</tr>
<tr>
<td>A.R.</td>
<td>16</td>
<td>35</td>
<td>pergontal</td>
<td>4</td>
<td>34</td>
<td>mass</td>
<td>increasing mass</td>
<td>gluteus</td>
<td>8.5 × 12.5 × 13.5</td>
<td>Merckel</td>
<td>4</td>
</tr>
<tr>
<td>Z.I.</td>
<td>16</td>
<td>29</td>
<td>nitrous oxide</td>
<td>2</td>
<td>17</td>
<td>mass</td>
<td>increasing mass</td>
<td>thigh</td>
<td>10 × 7 × 3</td>
<td>lipomyxoid</td>
<td>3</td>
</tr>
<tr>
<td>R.M.</td>
<td>16</td>
<td>24</td>
<td></td>
<td>1</td>
<td>22</td>
<td>mass</td>
<td>increasing mass</td>
<td>thigh</td>
<td>3 × 3 × 3</td>
<td>lipomyxoid</td>
<td>1</td>
</tr>
<tr>
<td>M.L.</td>
<td>16</td>
<td>27</td>
<td>teratoma, ChT</td>
<td>1</td>
<td>36</td>
<td>mass</td>
<td>mass developed</td>
<td>leg</td>
<td>1 × 1 × 1</td>
<td>leiomyosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>H.A.</td>
<td>16</td>
<td>35</td>
<td></td>
<td>4</td>
<td>NA</td>
<td>pain</td>
<td>painful mass developed</td>
<td>sole</td>
<td>3 × 4 × 2</td>
<td>desmoid</td>
<td>1</td>
</tr>
<tr>
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<td>35</td>
<td>s/p pregnancy-desmoid</td>
<td>5</td>
<td>NA</td>
<td>pain</td>
<td>painful mass developed</td>
<td>sole</td>
<td>4 × 3 × 2</td>
<td>desmoid</td>
<td>1</td>
</tr>
<tr>
<td>L.E.</td>
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<td>25</td>
<td></td>
<td>3</td>
<td>14</td>
<td>mass</td>
<td>mass pain</td>
<td>axilla</td>
<td>6 × 8 × 5</td>
<td>unclassified STS</td>
<td>1</td>
</tr>
<tr>
<td>L.B.</td>
<td>new</td>
<td>37</td>
<td></td>
<td>9</td>
<td>8</td>
<td>mass</td>
<td>increasing+bleeding mass</td>
<td>back</td>
<td>DFSP</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>C.I.</td>
<td>new</td>
<td>35</td>
<td></td>
<td>2</td>
<td>15</td>
<td>pain</td>
<td>progressing pain</td>
<td>knee</td>
<td>giant cell rich OS vascular invasion</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>B.A.D.</td>
<td>new</td>
<td>30</td>
<td>pulmonary trunk&gt;&gt;thrombectomy –</td>
<td>2</td>
<td>29</td>
<td>dyspnea</td>
<td>worsening dyspnea</td>
<td>pulmonary trunk</td>
<td>7 × 1.5 × 1.8</td>
<td>Intimal leiomyosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>B.N.</td>
<td>new</td>
<td>27</td>
<td></td>
<td>1</td>
<td>8</td>
<td>painful mass</td>
<td>operated before pregnancy</td>
<td>leg</td>
<td>3.5 × 4 × 3</td>
<td>synovial</td>
<td>3</td>
</tr>
<tr>
<td>I.G.</td>
<td>new</td>
<td>24</td>
<td></td>
<td>1</td>
<td>29</td>
<td>knee pain</td>
<td>progressing pain</td>
<td>knee</td>
<td>20 × 3+5.5 × 3.5</td>
<td>OS</td>
<td>3</td>
</tr>
<tr>
<td>S.A.</td>
<td>new</td>
<td>23</td>
<td></td>
<td>1</td>
<td>NA</td>
<td>mass</td>
<td>increasing mass</td>
<td>thigh</td>
<td>NA</td>
<td>MPNST</td>
<td>3</td>
</tr>
<tr>
<td>D.L.</td>
<td>new</td>
<td>28</td>
<td></td>
<td>2</td>
<td>21</td>
<td>painful mass</td>
<td>increasing mass and pain</td>
<td>pelvis</td>
<td>10 × 11 × 6</td>
<td>synovial</td>
<td>3</td>
</tr>
<tr>
<td>R.A.K.</td>
<td>new</td>
<td>32</td>
<td>paraosteal LG OS of right distal femur age 21 excision only, hypothyroidism, depression</td>
<td>1</td>
<td>20</td>
<td>knee pain</td>
<td>progressing pain</td>
<td>knee</td>
<td>NA</td>
<td>HG OS – local recurrence</td>
<td>3</td>
</tr>
</tbody>
</table>

NA = Not available; OS = osteosarcoma; MPNST = malignant peripheral nerve sheath tumors; STS = soft tissue sarcoma; DFSP = dermatofibrosarcoma protuberans; HG = high grade; AJCC = American Joint Committee on Cancer; APIAI = doxorubicin-cisplatinum-ifosfamide in alteration with doxorubicin ifosfamide; ILP TNF = isolated limb perfusion with tumor necrosis factor-α; AI = doxorubicin ifosfamide.
Discussion

Cancer is the second most common cause of death during the reproductive years, complicating approximately 0.07–0.1% of pregnancies [2]. Breast cancer, cervical cancer, Hodgkin’s disease, malignant melanoma and
leukemias are the most frequently diagnosed malignancies during gestation, comprising more than a half of the cases [3, 4]. There is no evidence for an increased incidence of sarcoma in pregnancy.

A number of studies showed that pregnancy-associated malignancies do not predict worse prognosis or different maternal and neonatal outcomes for the patient compared to those diagnosed in nonpregnant women. This is true regarding patients with ovarian cancer [5], thyroid cancer [6], and melanoma [7, 8]. The picture is less certain regarding other malignancies, especially breast cancer, mostly because the stage of the disease is more advanced when it is discovered and also due to delay in therapy [9–11]. On the other hand, stage-controlled studies show similar survival rates [12, 13]. In the case of sarcomas, we can also find several studies on bone sarcomas concluding that the outcomes in pregnant patients does not differ significantly from the matched, nonpregnant control subjects [14, 15]. There are no specific data about soft-tissue tumors and according to our impression, based on accumulated experience, the prognosis seems to be comparable.

A general and overruling treatment strategy for pregnant patients with musculoskeletal malignancies cannot be outlined. The diagnostic and therapeutic approaches should be tailored specifically for each patient, considering the stage of pregnancy at the time of tumor diagnosis, the site of the tumor and the tumor stage and grade. Radiological ancillary tests such as ultrasound and magnetic resonance imaging (MRI) are considered safe in a pregnant woman, while tests applying X-rays or γ-rays (isotope scans) should be avoided. Shielding the pelvis during a CT scan of an extremity may not be perfect, and damage to the fetus might occur due to scattered photons. Each case should be discussed by the treatment team, which should comprise an oncologist, radiologist, pathologist, gynecologist, neonatologist, orthopedic or surgical oncologist, anesthesiologist, social worker, oncologic nurse and psychologist, and the decision should be presented and explained in detail to the patient and the family [16].

With a diagnosis of sarcoma in a pregnant woman, there are no data justifying termination of pregnancy as a therapeutic intervention to improve survival, as in the cases of pregnancy-associated breast cancer [17, 18]. The issue of possible acceleration of sarcoma growth during pregnancy remains unresolved. In spite of the fact that in all of our patients there was clear evidence of tumor growth and development, there are no sufficient data in the literature that pregnancy aggravates the progression of tumors. Although certain types of sarcomas have been shown to express estrogen and progesterone receptors, the implication of such receptor status in tumors associated with pregnancy is unknown [19]. However, pregnancy status limits and postpones the treatment options; this is sometimes after delayed diagnosis. Radiological examinations applying mutagenic technologies are prohibited in pregnant women. Extensive surgery is not always possible because of the tumor location, although there is much experience with surgical intervention and general anesthesia in pregnant women. Radiotherapy is contraindicated during pregnancy; the use of chemotherapy is usually avoided because of the potential for teratogenicity in the first trimester and risk of fetal growth retardation throughout gestation. In the case of osteosarcomas that are highly responsive to chemotherapy, a delay in treatment may affect the prognosis; the caring team and the patient should discuss preterm delivery or termination of pregnancy.

The rate of tumor necrosis is considered one of the most important determinants of outcome in sarcoma patients [20, 21], hence factors that influence the histologic response were investigated intensively. Bacci et al. [22] suggested that the dose intensity of chemotherapy in a neoadjuvant setting of BS is crucial for the outcome – continuous disease-free survival resulted significantly higher for those patients who received 90% or more of the scheduled dose intensity than for those who had less than 90% of the scheduled dose intensity (76.5% vs. 57.3%; p < 0.02). The conclusion of the European Osteosarcoma Intergroup [23] on this question was less decisive, at least in the context of a two-drug regimen. Several studies suggested that dose intensity of specific drugs, particularly doxorubicin [24–26] and methotrexate [25] in preoperative treatment is an important determinant of outcome. It is not clear if dose intensity directly impacts the histologic response of the tumor and hence the prognosis, or poor histologic response to preoperative chemotherapy reflects inherent biologic resistance of the tumor to chemotherapy unrelated to dose intensity [27]. Bacci et al. [28] suggested in another study that the histologic response significantly and independently correlated with the number of drugs administered before surgery and with the histologic subtype of the tumor, which supports the former statement regarding the inherent biologic behavior of the tumors. An additional report from this group [29], which investigated the possible factors influencing histologic response to primary chemotherapy, also showed that patients with metastatic osteosarcoma and localized chondroblastic osteosarcoma have a re-
duced chemosensitivity to primary chemotherapy with methotrexate, cisplatin and doxorubicin. They concluded that methotrexate serum peak level (≥ 700 μmol/l) and histologic subtype significantly predicted histologic response.

In our series of BS during pregnancy, because of the small sample, we could only demonstrate that the higher dose intensity was associated with the higher rate of tumor necrosis. The association is less clear in the case of STS in the current series. The follow-up is too short to determine the impact of dose intensity on disease-free or overall survival of our patients.

We could find no data in the literature suggesting that women with pregnancy-associated malignancies are prone to more complications or adverse events of chemotherapy. Although there was a substantial rate of bone marrow toxicity in our series, particularly in more advanced cycles, it does not seem to be higher than in other treated patients. Unfortunately, we could not find enough matched (by sex and age and histology and chemotherapy protocol) nonpregnant control subjects to investigate this issue.

Along with the improved survival of sarcoma patients due to advances in chemotherapy during the past two decades, there have been concerns of gonadal toxicity and fertility. Embryo cryopreservation is an established technique that is available for fertility preservation, but the protocols require a delay in implementing chemotherapy [30]. Additional techniques that could be offered after counseling the patient about their experimental nature include oocyte cryopreservation, ovarian cryopreservation, and gonadotropin-releasing hormone agonist co-treatment with chemotherapy, which is the only available medical protection means for gonadotoxic chemotherapy. A few reports [31–33] on fertility outcomes with chemotherapy for bone sarcomas showed that chemotherapy does not significantly alter neither the reproductive function of the patients nor the health of their newborns. Although counseling should include the possibility of infertility, patients should also be reminded of the high rate of success of having a normal conception and childbirth.

In summary, pregnant women with bone and soft tissue tumors tend to have maternal and fetal outcomes similar to their nonpregnant counterparts if they receive appropriate local and systemic treatment. As noted earlier, diagnostic and therapeutic approaches should be tailored specifically for every pregnant woman. Surgical resections may be performed safely during all 3 trimesters of pregnancy. Uncompromised oncological treatment and full systemic work-up should be postponed until delivery or termination of pregnancy. Concerns of gonadal toxicity and fertility should be discussed. A multidisciplinary approach is crucial in managing these complex cases.

References