Gestation-Related Malignant Musculoskeletal Tumors

Ofer Merimsky MD[1], Moshe Inbar MD[1], Josephine Issakov MD[3], Yehuda Kollender MD[2], Gideon Flusser MD[4], Isaac Meller MD[2] and Jacob Bickels MD[2]

[1]Unit of Bone and Soft Tissue Oncology, [2]National Unit of Orthopedic Oncology, [3]Unit of Bone and Soft Tissue Pathology and [4]Service of Bone and Soft Tissue Radiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: sarcoma, musculoskeletal tumor, gestation, pregnancy

Abstract

Background: The incidence of malignant musculoskeletal tumors during pregnancy is very low. The paucity of data precludes the drawing of solid conclusions regarding a standard approach.

Objectives: To summarize our experience treating 13 pregnant women with malignant soft tissue or bone tumors.

Methods: We conducted a retrospective analysis of 13 cases of patients with either soft tissue or bone sarcoma that developed or progressed during pregnancy or immediately after delivery.

Results: The clinical presentation of the tumors was a growing mass and/or increasing pain and disability. Most of the masses were located in the lower part of the body and were of considerable size. Treatment given during gestation was limited to wide excision of the mass in the 28th week of gestation in one patient. All the patients reported disease progression during gestation. Vaginal delivery was possible in eight patients with no complications, cesarean section was carried out in three women, spontaneous miscarriage occurred in one and termination of pregnancy was performed in one patient.

Conclusions: The diagnostic and therapeutic approaches should be tailored specifically in every pregnant woman in whom sarcoma is suspected.

IMAJ 2003;5:264–267

The occurrence of cancer in a pregnant woman is a relatively infrequent event. The influence of pregnancy on the initiation and development of sarcomas is yet unclear. The medical approach is strongly influenced by the type and site of the primary tumor, its growth rate and associated symptoms, and by the need to treat the woman while minimizing fetal toxicity. Several issues remain unresolved. What is the effect of gestation and hormones on the development of sarcoma? Is therapeutic abortion justified? What factors influence the oncologic approach? What is considered safe or deleterious when treating a pregnant woman with sarcoma? The present study summarizes our experience in treating 13 cases of malignant soft tissue or bone tumors in pregnancy.

Patients and Methods

The study is based on a retrospective analysis of 13 cases of patients with either soft tissue or bone sarcoma that developed or progressed during pregnancy or immediately after giving birth. STS and BS staging was based on the system of the American Joint Committee on Cancer [1].

STS = soft tissue sarcoma
BS = bone sarcoma

Results

The patients' age ranged between 22 and 36 years (median 28 years). Their medical histories were variable: 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), and treatment with gonadotrophin 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.

The clinical presentation of the tumors was a growing mass and/or increasing pain and disability. In 50% of the patients the tumor was associated with the first gestation, while it occurred during the second to fifth gestation in the others. The patients started to complain of a mass and/or pain during the 14th to 36th week of gestation (median 22nd week). Most of the masses were located in the lower part of the body and were of considerable size [Table 1].

Pre-treatment tissue diagnosis was mandatory in all cases. Histologically there were five bone sarcomas: two were fibroblastic, two osteogenic, and one chondroblastic. There were seven soft tissue tumors: two myxoid liposarcoma, one malignant peripheral nerve sheath tumor, one small blue round cell skin tumor (Merkel cell tumor), one leiomyosarcoma, one patient with desmoid (primary and recurrence during and following two consecutive gestations), and one unclassified soft tissue sarcoma. The bone sarcoma was confined within the cortex in one patient, invaded beyond the cortex in three patients, and metastatic to the lung in one patient. The STS were greater than 5 cm (T2) in four patients, and deeply seated (T1b/T2b) in seven patients.

Vaginal delivery was possible in eight patients with no complications, cesarean section was carried out in three, spontaneous miscarriage occurred in one and termination of pregnancy was performed in one patient. In all but two cases, the newborns were healthy, and two newborn babies were premature. In all the newborns, normal growth and development was reported by the mothers on their follow-up visits.

The spectrum of treatments given during gestation was limited to wide excision of the mass in the 28th week of gestation in one patient. In all other cases treatment was delayed until delivery. Neither chemotherapy nor radiation therapy was administered

Table 1. Medical history and clinical picture

Patient	Age (yrs)	History	Pregnancy	Week	Symptoms	Effect of gestation	Site	Tumor Size (cm)	Histology	AJCC stage (BS or STS)
FE	27		2nd	16	Painful mass	Increasing pain and mass	Thigh	7x4.5	OS osteogenic	T2G4N0M0
BAR	36		4th	17	Back pain	Progressive pain, spinal cord compression	T-spine	2–3	OS fibroblastic	T1G3N0M0
EL	36	November 1991: osteosarcoma. June 1999: local recurrence, ILP TNF2. March 2000: lung metastases, thoracotomy	1st	Post-partum	None	Development of lung metastases	Lung: 2 nodules		OS fibroblastic	M1
ZF	22		1st	24	Low back pain	Increasing pain, growth of mass	Pelvis	20x15x15	OS chondroblastic	T2G4N0M0
VR	26	Thyroid carcinoma, I131 therapy, hypothyroidism,	1st	30	Mass	Growth of mass	Pubis	24x17x10	OS osteogenic	T2G3N0M0
LA	25	NF3	1st	36	Painful mass	Growth of mass	Hip, gluteus	20x20x20	MPNST	T2bG3N0M0
AR	35	Gonadotropin use	4th	34	Mass	Growth of mass	Gluteus	8.5x12.5 x13.5	SBRC tumor in skin (Merkel tumor)	T2bG4N0M0
ZI	29	Industrial exposure to nitrous oxide	2nd	17	Mass	Growth of mass	Thigh	10x7x3	Liposarcoma myxoid	T2bG3N0M0
RM	24		1st	22	Mass	Growth of mass	Thigh	3x3x3	Liposarcoma myxoid	T2bG1N0M0
ML	27	Malignant teratoma (age 12), ChT5	1st	36	Mass	Mass developed	Leg	1x1x1	Leiomyosarcoma	T1aG1N0M0
HA	33		4th	~20	Painful mass	Painful mass developed	Sole*	3x4x2	Desmoid	T1bG1N0M0
HA	35	s/p pregnancy related-desmoid 6	5th	~20	Painful mass	Painful mass developed	Sole*	4x3x2	Recurrent desmoid	T1bG1N0M0
LE	25		3rd	14	Painful mass	Increasing pain, growth of mass	Axilla	6x8x5	Unclassified STS	T1bG1N0M0

OS = osteosarcoma, MPNST = malignant peripheral nerve sheath tumor, SBRC = small blue round cell tumor
* Two separate desmoid tumors during two consecutive pregnancies.

during gestation. Preoperative and adjuvant chemotherapy or radiation therapies were given according to the current protocols for BS and STS. Most of the patients are alive without evidence for disease at the time of this report [Table 2].

Discussion

The occurrence of cancer in a pregnant woman is a relatively infrequent event, with an incidence of 0.07–0.1% of all pregnancies [2,3]. The influence of pregnancy on the initiation and development of sarcomas is highly controversial and unclear. Several authors have pointed to a pregnancy-related marked aggressiveness of malignancy [4–8]. However, there is still no solid evidence of an increased incidence of cancers in pregnant women, neither are there data showing that pregnancy itself adversely affects the course of the disease [9]. Similarly, there is no evidence for an increased incidence of sarcoma in pregnancy.

In the present series, there was a clear evidence for tumor growth and development during gestation in all patients. The clinical picture varied between overt growth of a mass and increasing pain to progression of back pain and the development of spinal cord compression up to the appearance of pulmonary metastases. There were no special gestation-related symptoms of sarcoma in our patients. Clinical and radiologic features of sarcomas were similar to those in the general population.

The exact date of the first symptom or sign could not be retrieved. The timing of seeking help was the 14th to 36th week of gestation, and in one patient pulmonary metastases were diagnosed soon after delivery. A delay in seeking help occurs because early symptoms might be attributed to gestation or are ignored by the mother; more so when the sarcomas are located in the region of the lumbosacral spine or pelvis. The initial work-up included physical examination, ultrasonography or magnetic resonance imaging of the affected organ, and core-needle biopsy in case of extremity tumor. Imaging studies based on ionizing radiation (plain X-rays, computed tomography and radionuclide scans) were avoided. In most of the cases, after establishment of

Table 2. Oncologic approach

Patient	Obstetric procedure	Newborn status	Preoperative treatment*	Timing of definitive treatment	% necrosif	Adjuvant treatment	Patient's status**	Disease-free survival (mos)
FE	Buero	Dead	API-AI	After delivery	98	API-AI	awod	9+
BAR	Delivery	Normal		After delivery	NA	API-AI	awod	8+
EL	Delivery	Normal	None	After delivery	NA	None	awod	4+
ZF	Cesarean	Premature	API-AI	After delivery			awod	1+
VR	Cesarean	Normal	CDDP+ADR+IFX	After delivery	25	CIS-ADR-MTX	dwd	8
LA	Cesarean	Normal	AI	After delivery		AI+XRT	awd	11
AR	Delivery	Premature		After delivery		RT	awod	23+
ZI	Spontaneous abortion	Dead	AI	After abortion	95	AI+XRT	awod	40+
RM	Delivery	Normal	None	Week 28	NA	None	awod	45+
ML	Delivery	Normal twins	None	After delivery			awod	3+
HA	Delivery	Normal	ILP / TNF***	After delivery	100		Recurrence	28
HA	Delivery	Normal		After delivery		RT 50Gy	awod	11+
LE	Delivery	Normal	None	After delivery	NA	no	awod	32+

* API AI: ADR-CDDP-IFX in alternation with ADR-IFX

** awod = alive without disease, awd = alive with disease, dwd = died with disease

*** Isolated limb perfusion with tumor necrosis factor-alpha.

the clinical diagnosis of a mass, patients were referred to our center for further evaluation including core needle biopsy.

The sarcomas involved the lower limb or lower hemibody in the majority of cases. It remains unclear whether the location of the primary mass was related to the possible impaired blood flow and lymph drainage in the lower hemibody due to gestational changes. Lymphedema may indeed contribute to the development of STS and especially of lymphangiosarcoma, but should be chronic and longstanding, in contrast to the short and temporary gestational edema [10]. It seems that any type of sarcoma might develop during pregnancy and not a specific gestation-related type of sarcoma.

The influence of hormones on the natural process of bone and soft tissue sarcomas is controversial. *In vitro* studies suggested that osteosarcoma cell lines may be affected by sex steroids, but the effect was not related to the gender of the cell line [11]. Ovariectomy and tamoxifen in sarcoma-bearing animals resulted in tumor growth suppression and prolonged survival by protection against the lethal tumor. On the other hand, estrogen treatment exerted an adverse effect, leading to faster growth of the tumors and a marked decrease in survival [12]. In human surgical specimens, estrogen receptors and progesterone receptors were expressed in all leiomyomas but was markedly reduced in leiomyosarcoma [13,14].

Data regarding human use of hormone show that tamoxifen has a negligible effect on the development of sarcoma [15]. Hormone replacement therapy is probably not associated with evolution of uterine leiomyosarcoma [16–18]. It has been suggested that the hormonal, physiologic and mechanical changes that are present within the body during or after pregnancy and labor might induce or promote the process of malignancy and metastasis [19]. Thus, there is no justification to use hormonal therapy for gestational sarcomas, or to perform therapeutic abortion in order to control tumor growth or shrink the tumor.

The issue of possible acceleration of sarcoma growth during pregnancy remains unresolved. In the present series, tumor progression during gestation was evident. However, it is still unclear whether this progression was accelerated due to gestational factors in comparison with similar tumors in non-pregnant women or in men. In a previous report from Institut Gustav Roussy [20] enhancement of tumor growth was evident in several cases. The literature supports this observation [4,6,7].

Certain types of sarcoma warrant further comment. Desmoid tumor has been reported in pregnant women. It has been suggested that hormonal effects, trauma, and pregnancy contribute to the growth behavior of the tumor [21].

The combination of pregnancy and osteosarcoma does not predict a worse prognosis compared to osteosarcoma occurring in non-pregnant women. A survival analysis of 18 pregnant patients yielded a 1 year survival rate of 78% and a 5 year survival rate of 37.5%. This survival was comparable to that of non-pregnant women with bone sarcomas, matched by age, site, and histologic type [22]. Ewing's sarcoma has been rarely reported in pregnant women. Chemotherapy during pregnancy has been suggested but remains controversial [23,24].

In the present series, as in most case reports in the literature, chemotherapy was not given during gestation. The management of sarcoma in a pregnant woman is based on several factors. The stage of pregnancy at the time of tumor diagnosis, the site of the tumor, and the tumor stage and grade should be considered in a multidisciplinary approach. Each case should be discussed by the treatment team, comprised of an oncologist, gynecologist, neonatologist, orthopedic or surgical oncologist, anesthesiologist, social worker, oncologic nurse and psychologist, and the decision should be presented in detail to the patient and the patient's family [9,20].

A general treatment strategy for pregnant women with sarcoma cannot be outlined since the event of sarcoma in gestation is rare.

The diagnostic and therapeutic approaches should be tailored specifically for every pregnant woman in whom sarcoma is suspected. Radiologic ancillary tests such as ultrasound and MRI are considered safe in a pregnant woman, while tests applying X-rays (plain films, CT scan) or gamma-rays (isotope scans) should be avoided. Core needle, incisional or excisional biopsy may be safe procedures for obtaining tissue for diagnosis. Surgical removal of the primary tumor is permitted at all stages of gestation, provided that the mass is not located in the vicinity of the uterus. Chemotherapy (doxorubicin and ifosfamide) may be administered during the third trimester but should be avoided in the first and second trimesters [7]. Other drugs such as cyclophosphamide and methotrexate [9] should be avoided unequivocally during gestation. The paucity of data on the safety of vincristine, etoposide, dactinomycin, vinblastine and bleomycin in pregnant women precludes any evidence-based conclusion.

References

1. AJCC Cancer Staging Manual. 5th edn. Philadelphia: Lippincott-Raven Publishing, 1997.
2. Potter JF, Schoeneman M. Metastasis of maternal cancer to the placenta and fetus. *Cancer* 1970;25:380–8.
3. Nieminen V, Remes N. Malignancy during pregnancy. *Acta Obstet Gynecol Scand* 1970;49:315–18.
4. Aterman K, Fraser GM, Lea RH. Disseminated peritoneal leiomyomatosis. *Virchows Arch (Pathol Anat)* 1977;374:13–26.
5. Taylor HB, Helwig EB. Dermatofibrosarcoma protuberans: a study of 115 cases. *Cancer* 1962;15:717–25.
6. Weiss SW, Enzinger FM. Myxoid variance of malignant fibrous histiocytoma. *Cancer* 1977;39:1672–85.
7. Spittle MF, Newton KA, Mackenzie DF. Liposarcoma: a review of 60 cases. *Br J Cancer* 1970;24:696–704.
8. Bickerstaff ER, Small JM, Guest IA. The relapsing course of certain meningiomas in relation to pregnancy and menstruation. *J Neurol Neurosurg Psychiatry* 1968;21:89–91.
9. Doll DC, Scott Ringenberg Q, Yarbro JW. Antineoplastic agents and pregnancy. *Semin Oncol* 1989;16:337–46.
10. Murray F, Brennan MF, Alektiar KM, Maki RG. Sarcomas of the soft tissue and bone. In: DeVita VT, Hellman S, Rosenberg S, eds. Cancer: Principles and Practice of Oncology. 6th edn. St. Louis, USA: Lippincott Williams & Wilkins, 2001:Chapt. 39.1: Soft Tissue Sarcoma.
11. Remmelink M, Decaestecker C, Darro F, et al. The in vitro influence of eight hormones and growth factors on the proliferation of eight sarcoma cell lines. *J Cancer Res Clin Oncol* 1998;124:155–64.
12. Remedi MM, Demarchi M, Hliba E, Depiante-Depaoli M. Effect of estrogen and antiestrogen therapy in rats bearing mesenchymal tumors. *Tumor Biol* 1999;20:242–50.
13. Zhai YL, Kobayashi Y, Mori A, et al. Expression of steroid receptors, Ki-67, and p53 in uterine leiomyosarcomas. *Int J Gynecol Pathol* 1999;18:20–8.
14. Reich O, Regauer S, Urdl W, Lahousen M, Winter R. Expression of oestrogen and progesterone receptors in low-grade endometrial stromal sarcomas. *Br J Cancer* 2000;82:1030–4.
15. Kennedy MM, Baigrie CF, Manek S. Tamoxifen and the endometrium: review of 102 cases and comparison with HRT-related and non-HRT-related endometrial pathology. *Int J Gynecol Pathol* 1999;18:130–7.
16. Schwartz SM, Weiss NS, Daling JR, et al. Exogenous sex hormone use, correlates of endogenous hormone levels, and the incidence of histologic types of sarcoma of the uterus. *Cancer* 1996;77:717–24.
17. Goldschmidt PR, Goldschmidt JD, Lieblich SE, Eisenberg E. Leiomyosarcoma presenting as a mandibular gingival swelling: a case report. *J Periodontol* 1999;70:84–9.
18. Zacharin M, Waters K, Chow CW, Crock P, McKelvie P. Recurrent rhabdomyosarcoma after 25 years: a possible association with estrogen and progestogen therapy. *J Pediatr Hematol Oncol* 1997;19:477–81.
19. Albrektsen G, Heuch E, Tretli S, Kvale G. Is the risk of cancer of the corpus uteri reduced by a recent pregnancy? *Int J Cancer* 1995;61:485–90.
20. Merimsky O, LeCesne A. Soft tissue and bone sarcomas in association with pregnancy. *Acta Oncol* 1998;37:721–7.
21. Hayry P, Reitamo JJ, Totterman S, Hopfner-Hallikainen D, Sivula A. The desmoid tumor. II: Analysis of factors possibly contributing to the etiology and growth behavior. *Am J Clin Pathol* 1982;77:674–80.
22. Huvos AG, Butler A, Bretsky S. Osteogenic sarcoma in pregnant women. *Cancer* 1985;56:2326–31.
23. Loguidice V, Tehranzadeh J, Jones E. Ewing's sarcoma and pregnancy. A case report and review of the literature. *Clin Orthop* 1986;210:132–6.
24. Merimsky O, LeChevallier T, Missenard G, et al. Management of cancer in pregnancy: a case of Ewing's sarcoma of the pelvis in the third trimester. *Ann Oncol* 1999;10:345–50.

Correspondence: Dr. O. Merimsky, Unit of Bone and Soft Tissue Pathology, Dept. of Oncology, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel.
Phone: (972-3) 697-3057
Fax: (972-3) 697-4828
email: merimsky@zahav.net.il

Capsule

DNA methylation as tumor suppressor

Many human cancers show reduced levels of genome-wide DNA methylation, and this epigenetic alteration appears to play a causal role. Gaudet et al. (*Science* 2003:300:489) generated genetically altered mice with severely reduced levels of DNA methylation. Within 4 to 8 months of birth, the mutant mice developed aggressive T cell lymphomas that exhibited a high frequency of trisomy (the presence of extra chromosomes in cells). In a related study of a mouse model genetically predisposed to develop sarcomas, Eden et al. (p. 455) showed that reduced genomic methylation accelerates tumor development and that hypomethylated cells from these mice have a higher rate of chromosome loss than do normally methylated controls. Thus, genome-wide hypomethylation promotes cancer development, most likely by enhancing chromosomal instability.