Uterine Sarcoma – A Challenging Entity

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Uterine sarcomas are characterized by rapid clinical progression and poor prognosis. They are rare tumors, accounting for only 3%–7% of malignant tumors of the uterine corpus and for only 1% of all female genital tract malignancies [1,2]. Their incidence (number of newly diagnosed cases per 100,000 women per year) has been accepted generally to be less than one [1,2]. Arrastia et al. [3], however, reported an incidence of 1.7 in white women and 3.3 in black women residing in New York City and Brooklyn. Because of their rarity and histopathological diversity, very few individuals or even referral centers can accumulate adequate experience in handling uterine sarcomas. Current knowledge related to uterine sarcomas is largely based on the experience of authors who have reported large series of patients; however, patient accrual occurred over prolonged periods during which treatment approaches and modalities changed. Thus, the understanding of the variable biological behavior and treatment alternatives of this condition is still limited and poses a challenge [4].

Ober and Tovel [5] introduced a histological classification of uterine sarcomas in 1959. However, application of this histological classification has presented a problem for clinicians due to its excessive detail. Consequently, a simplified histological classification based on the three main histological types of uterine sarcoma has been established and widely accepted – namely leiomyosarcoma, endometrial stromal sarcoma, and carcinosarcoma [1]. Until recently all histological types of uterine sarcoma were surgically staged according to the 1988 International Federation of Gynecology and Obstetrics criteria for endometrial adenocarcinoma, despite the different biological behavior between endometrial adenocarcinoma and uterine sarcoma and regardless of the fact that uterine sarcomas constitute a heterogeneous group of malignancies from both a pathological and clinical perspective [6]. Most problematic has been the staging of leiomyosarcomas because, unlike ESS and carcinosarcomas that arise from the endometrium, leiomyosarcomas originate in the myometrium and thus cannot be subdivided according to myometrial invasion. Consequently, Berchuck et al. [7] simplified the FIGO staging of endometrial adenocarcinoma and accommodated it for uterine sarcomas by omitting the substages as follows: stage I – tumor confined to the uterine body, stage II – tumor confined to the uterine body and cervix, stage III – tumor spread outside the uterus but confined to the true pelvis, and stage IV – tumor spread outside the true pelvis.

In Israel, uterine sarcoma is the fourth most common female genital tract malignancy after endometrial adenocarcinoma, ovarian carcinoma and cervical carcinoma [1,8]. Only three large series of uterine sarcomas were previously reported from Israel [1,8,9]. In their study of 104 cases of uterine sarcomas diagnosed in Israel during the 7-year period 1969–1975, Schwartz et al. [8] reported that the incidence in Israel is 1.55 and thus speculated that since the incidence in Israel is higher than that reported in the literature (0.67) [10], the disease is presumably more prevalent among Jewish women (especially Ashkenazi*) than non-Jewish women.

In this issue of *IMAJ*, Naaman and colleagues [11] from the Department of Obstetrics and Gynecology at Hadassah-Hebrew University Medical Center, Jerusalem, report a large series of 40 patients with uterine sarcomas managed in their institution. Patient accrual occurred over 25 years during which, obviously, treatment approaches and modalities changed. An increase over the years was noted in the number of newly diagnosed uterine sarcoma patients, especially carcinosarcoma patients. Overall, leiomyosarcomas predominated in this series (55% of the patients). All patients were staged according to the simplified staging system for uterine sarcomas suggested by Berchuck and colleagues [7]. None of the patients had a history of prior pelvic radiotherapy, one-fourth had a family history of cancer, and one-tenth had received tamoxifen for breast cancer. Like others [1,8,9,12], the authors demonstrated that patients with leiomyosarcoma tend to be younger than patients with ESS or carcinosarcoma. The issue of "fast-growing uterus" (defined as an increase in uterine size by more than 6 cm over one year) is not addressed; yet, one should remember that the incidence of uterine sarcomas among patients operated on for presumed uterine leiomyoma and even among patients having surgery

ESS = endometrial stromal sarcomas
FIGO = International Federation of Gynecologists and Obstetricians

*Ashkenazi refers to Jews of European descent, in contrast to Sephardic which denotes Jews of Middle Eastern or North African origin

for "fast-growing" leiomyoma is extremely low (0.23% and 0.27%, respectively) [13]. The authors do not relate to the absence or presence of heterologuous elements (rhabdomyosarcoma, chondrosarcoma, osteosarcoma, liposarcoma) in the tumors. They noted a trend for a better 5-year survival rate for ESS (80%) as compared with leiomyosarcoma (50%) and carcinosarcoma (67%). Overall, the 5-year survival rate was 60%. Like others [1], the authors observed that the majority of patients with uterine sarcoma are diagnosed in stage I. Stage of disease was the only significant prognostic factor; 5-year survival rate for stages I-II combined was 73.1% and stages III-IV combined was 22.2% (P = 0.011). The authors conclude that despite improvement in means of diagnosis and treatment, the survival of patients with uterine sarcoma has not improved over the last 25 years.

Management of uterine sarcomas has traditionally followed that of endometrial adenocarcinoma, with total abdominal hysterectomy and bilateral salpingo-oophorectomy being the mainstay of treatment [1,2,14,15]. Removal of the ovaries during primary surgery is justified since these tumors have a tendency for spreading to the ovaries (ovarian metastases have been seen in about 10% of patients with early stage), and a possible stimulating effect of estrogen from the preserved ovaries on the tumor cells has been suggested. Although lymph node involvement was observed in 15–45% of patients with uterine sarcoma, the practical value of staging with lymphadenectomy has been debatable [1]. Postoperative adjuvant pelvic radiotherapy may reduce the risk of local recurrence in patients with early-stage disease (stage I and II); nevertheless, it cannot prevent the development of recurrent disease in distant sites [1]. The validity of chemotherapy for uterine sarcoma has remained uncertain. Several studies have demonstrated the superiority of the combination of doxorubicin and ifosfamide over other chemotherapy regimens in the treatment of advanced/recurrent uterine sarcomas. The toxicity is of much concern and the results of treatment in terms of response duration and patient survival are poor [14,16].

In 2009, the FIGO Committee on Gynecologic Oncology recognized that the old staging for uterine sarcomas was no longer sufficient and a new FIGO classification and staging system was specifically designed for uterine sarcomas in an attempt to reflect their different biologic behavior [17]. In summary, three new classifications were developed: a) staging for leiomyosarcoma, b) staging for ESS and adenosarcoma, and c) staging for carcinosarcoma [17]. In leiomyosarcoma, stage I is subdivided according to tumor size (< 5 cm vs. > 5 cm) and cervical involvement does not upgrade to stage II. In ESS + adenosarcoma, stage I is subdivided according to degree of myometrial invasion, and cervical involvement does not upgrade to stage II. In both leiomyosarcoma and ESS + adenosarcoma, involvement of uterine serosa and cytology of peritoneal washing are not taken into account. Carcinosarcoma, whose sarcomatous (mesenchymal) component has been recognized to arise from the epithelial component via a metaplastic process, will continue to be staged as endometrial adenocarcinoma [6,17]. After the publication of the 2009 FIGO staging for uterine sarcoma in the March 2009 issue of the *International Journal of Gynecology and Obstetrics* [17,18], a correction appeared in the September 2009 issue of the same journal placing ESS together with leiomysarcoma in one classification that subdivides stage I according to tumor size and not according to degree of myometrial invasion [19]. In my opinion, however, the original 2009 FIGO staging for uterine sarcoma as appeared in the March 2009 issue [17,18] is the most appropriate staging for uterine sarcomas since it subdivides rightfully stage I ESS (a tumor that originates in the endometrium) according to the degree of myometrial invasion and not according to tumor size.

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