Gynecologic sarcoma: a clinico-pathological review

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Summary

Most of the cases showing good prognosis in literature are probably intermediate tumors between benign and malignant of undetermined malignant potential (UMP) and other tumors with intermediate features which are currently not considered among sarcomas. Misdiagnosis of a malignant lesion as a benign one has a tragic outcome for the patient. Best therapic choice for sarcomas remains surgery, while chemotherapy (CTX) and radiation therapy (RT) could be used in adjuvant settings. A major effort should be played in the understanding of biological features and behavior of the disease to address a better clinical practice. Uterine sarcomas are rare gynecological tumors; their incidence has been increasing during the last few years.

Key words: Endometrial Stromal Sarcoma; Malignant MixedMullerian Tumors; Leiomyosarcoma; Radiation Therapy; Chemotherapy; Lymphadenectomy

Introduction

Uterine sarcomas are a rare gynecologic malignancy. Recently, some authors have reported some increase in their incidence [1]. FIGO has also published a revised staging in 2009. Some authors reported a good prognosis for some tumors, even when a fertility-sparing approach was used for young women in some cases. The authors analyzed all cases that occurred in the present centre and reviewed the literature available to date. The challenging management of mesenchymal cancer of corpus uteri (CU) requires experienced equipes and multidisciplinary approach. A pivotal role is played by the pathologist, which should have a specific experience for mesenchymal diseases to make a correct diagnosis.

Epidemiology and risk factors

The incidence per year in 1995 among American women was 17 per million, accounting for two to five percent among all uterine malignancies [2].

Investigating the Surveillance, Epidemiology, and End Results (SEER) database for women with invasive uterine neoplasm diagnosed in the period 1988-2004, 76,953 women were stratified by histology into endometrioid, sarcoma and clear cell type. Sarcomas rates were nine percent in whites and 26% in blacks [3].

In 1989-1999, 2,677 women underwent a uterine sarcoma diagnosis. White women were significantly older at the time of diagnosis compared to blacks (64.2 vs 62.7, $p < 0.05$). The age-adjusted incidence rate of uterine sarcoma in black women was nearly twofold greater than that of white women (7.0/105 vs 3.6/105, $p < 0.05$) [4].

Tamoxifen adjuvant therapy has been associated to an increased risk of sarcomas. Role of tamoxifen as an agent promoting the development of endometrial carcinomas is well-established, based on evidences from different studies. According to literature, women with long-term use of tamoxifen are more likely than non-users to develop a uterine sarcoma, with sarcomas making up more than ten percent of all uterine malignancies in this group of patients [5].

One study evaluated the association between tamoxifen use and the risk of developing uterine sarcomas and endometrial carcinomas in a cohort of Israeli women diagnosed with breast cancer from 1987-1988. There were four uterine sarcomas among the tamoxifen users but none among non-users [6]. Risk of corpus uteri (CU) cancer after breast cancer was 2.5 (CI: 1.1-4.7) for adenocarcinomas and 29 (CI: 3.5-104.9) for malignant mixed Müllerian tumor (MMMT) in women treated with tamoxifen. The strongly increased risk for developing MMMTs among these women does make close surveillance mandatory [7].

In conclusion, from a population-based evidence, use of tamoxifen appears to be associated with an overall fourfold relative risk for MMMTs, which increased to eightfold among long-term breast cancer survivors, compared with the twofold risk for endometrial adenocarcinomas [8].

A history of breast cancer can be found in many patients with sarcomas. Among 52,109 women diagnosed with CU cancer, 1922 had a history of breast cancer in a large, multicenter study [9].

The proportional incidence of uterine papillary serous cancer (UPSC) and sarcoma was significantly higher in women with a breast cancer history. These findings highlight the association of breast cancer with high-risk corpus cancer subtypes.

Pelvic radiation is found in the natural history of 10%-25% of women with a sarcoma of the uterus [10]. Relative risk after radiation is estimated to be 5.38 with an interval of usually 10 to 20 years [11].

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Classification

According to World Health Organization (WHO) classification, uterine sarcomas are divided into non-epithelial and epithelial non-epithelial tumors. Non-epithelial tumors could be homologous or heterologous whether they express tissues that are native to the uterus or not. Homologous tumors are endometrial stromal sarcoma (ESS) (low-grade-LG and high-grade-HG) and such smooth muscle tumors as leiomyosarcoma (LMS) and leiomyoma (LM) variants and benign metastasizing smooth muscle cell (SMC) tumors. Heterologous tumors show extra-uterine tissues in their context, which could be bone, cartilage or striated muscle. Epithelial/non-epithelial tumors include mixed Müllerian tumors (MMT) (homologous also known as carcinosarcomas (CS) and heterologous) and adenosarcoma.

Current opinion is that tumors with epithelial composition-like carcinosarcomas should not be included among sarcomas but should rather be considered as carcinomas [12]. CS is better thought as an aggressive metaplastic adenocarcinoma of the endometrium. Evidences supporting this view refer to their behavior resembling a carcinoma rather than a sarcoma. They show a lymphatic spread rather than diffusion via blood stream (typical of sarcomas). Furthermore they respond to chemotherapy agents that are effective in treating adenocarcinomas (paclitaxel, cisplatin, carboplatin) but are not active on sarcomas. The sarcomatous component is thought to be secondary to a dedifferentiation suggesting a common clonal endometrial origin of both carcinomatous and sarcomatous elements. Although CS cases were included in this study, WHO still classifies them as sarcomas.

Staging

FIGO 2009 revised staging for uterine cancer. CU cancer includes MMT. Uterine sarcomas have two different substagings for LMS/ESS and adenosarcomas (Figure 1).

LMS

LMS shows cells with a smooth muscle differentiation. It accounts for the 25%-36% of uterine sarcomas and one percent of all uterine malignancies [13]. Smooth muscle tumors of uncertain malignant potential (STUMP) are considered intermediate between benign leiomyomata and LMS. They show an unpredictable behavior, from highly lethal to relapse at 25 years.

Pathologic and biologic features

To define a LMS on its morphological ground, criteria adopted should include the number of mitosis per field (that was the main previous criteria), but even coagulative tumor cells necrosis and cytological atypia need to be included. The previous criteria were raising confusion regarding the histology of this tumor, since the peculiarity of the disease is a varying clinical presentation. It could show a very aggressive outcome in terms of spread and aspect, whether it underlies a benign pathology and falsely subtlety in malignancies.

Necrosis, atypia, and mitotic index define the Broders four-level system, which is a prognostic model for LMS. Level 1 is considered LG; 2, 3, and 4 as HG [14]. Grade 1 tumors show diffuse, mild cytological atypia, abundant eosinophilic cytoplasm, and a fascicular growth pattern. Grade 2 tumors possess more nuclear irregularity with a greater degree of nuclear variation in size and shape. Grade 3 and 4 tumors demonstrate moderate to marked nuclear irregularity.

Typical LMS is positive for actin, desmin, and caldesmon but even for such epithelial markers as CAM 5.2 and AE1/AE2. c-Kit proto-oncogene expression was found in all histological types of uterine sarcomas in one series published in 2004 and it was suggested that further investigation on c-kit tyrosine kinase inhibitor as imatinib mesylate role in these mesenchymal tumors should be done [15]. c-Kit is also mandatory to differentiate LMS from gastrointestinal stromal tumors (GIST). Estrogen receptor (ER) and progesterone receptor (PR) expression were reported in 57% of LMS [16] and in 57% [17] and 43% of cases [18]; microarray tissue analysis, showed immunoexpression of ER and PR in 40% and 48% of LMS and in 78% and 88% of leiomyomata [19, 20]. Many studies agree in reporting an increased expression of MIB-1 (Ki-67) [21, 22], overexpression of p53 (16; 23; 24) and loss of PR expression [16]. MIB-1, p53 and steroid receptors can be useful in differentiate LMS from cellular leiomyomas and STUMP [25].

LMS typically have complex cytogenetic abnormalities. Karyotypes show both numerical and structural aberrations. These aberrations are often unstable, resulting in significant variation from metaphase to metaphase. Quade *et al.* examined archival materials from 16 LMS and 13 benign LMS by polymerase chain reaction (PCR) for 26 microsatellite polymorphisms. Interestingly, eight of 14 (57.2%) informative LMS had loss of heterozygosity (LOH) for at least one marker on chromosome 10 and involved both chromosomal arms in 45.5% (5 of 11). In contrast to LMSs, LOH for chromosome 10 was not found in 13 benign LMs. Microsatellite instability was found infrequently in LMSs and not detected in LM. Clinico-pathological features (e.g.: atypia, necrosis and clinical outcome) did not appear to correlate with LOH for chromosome 10. In contrast to other chromosomes studied, LOH on chromosome 10 was frequent in LMS and absent in benign LM [26].

LMS arises de novo. Many studies confirmed that LM would not turn malignant. Despite this support, rapidly growing myomas are quite common indications for such surgeries as myomectomy or hysterectomy. Still, the incidence of sarcomas in a series of hysterectomy performed for LM was very low (0.5%) [27].

In contrast, a useful tool, as hierarchical cluster analysis, applied in the study by Hodge and Morton [28], raised the fascinating idea that LMS do indeed derive from LM, and that the discrepancy in their frequency lies in the fact that only rare histologic and karyotypic variants of LM are amenable of malignant progression. Mittal and Joutovsky (GO 2007) [29] investigated LM subsets, suggesting that the ability to progress into LMS could be more likely with cellular and symplastic LM.

Macroscopically, a LMS shows as a single mass, soft, fleshy, yellow-brownish in the context of a uterus that could often present as fibromatous (Viereck *et al.* 2002) [30]. Usually, the malignant mass is rather a single lesion than multiple, other lesions being benign fibroids. Some studies have focused on the diverse histological patterns that these tumors could display. They could show, in fact, either as such a "classic" form [31, 32] or LMS variants. Variants include epithelioid, differentiated, myxoid, intravenous, osteoclast-like giant cells in SMT, LMS with a clear cell component, and LMS with liposarcomatous differentiation [33].

Clinical presentation

The clinical presentation of LMS resembles that of fibroids. In one series, the most common presentation symptom was abnormal uterine bleeding (AUB) in the 45%-86% of cases [34]. Pelvic pain was found to be relevant in 20% to 50% of cases in another series [35]. Some authors recommend regularly checking the largest myoma in a polimyomatous uterus [36]. In 95% of cases LMS appeared, in fact, to be the largest or the unique mass of the uterus.

Imaging techniques for LMS seem not to discriminate from benign to malignant lesions at the state of the art. A prospective study among 298 women, who had a uterine smooth muscle tumor (SMT) diagnosis during the decade 1990-2000, evaluated the role of combining dynamic magnetic resonance imaging (MRI) with serum markers, as lactate dehydrogenase (LDH) isoenzymes. The authors reported 100% specificity, 100% positive predictive value, 100% negative predictive value, and 100% diagnostic accuracy for LMS. This study shows the feasibility of a preoperative diagnosis for LMS. One of the latest techniques for fibroids care is MRI-guided ultrasound (US), which does not allow obtaining samples of the tissue lesion after treatment. That is one additional reason to promote the search for a preoperative diagnosis of the lesion.

Treatment and prognostic features

LMS are confined to the uterus in the majority of cases. Ovarian and lymphatic spread is uncommon in patients without extra-uterine disease [14]. Thus, oophorectomy and lymph node resection in patients with disease limited to the uterus should not be a standard procedure. In one series only five out of 101 women with uterine LMS had lymph node involvement and ovarian metastases were present in four out of 108 [37]. In pre-menopausal patients with LG of LMS the ovaries can be preserved [38].

Another series of 208 women showed lymph node metastasis in four out of 36 patients who had a lymph node biopsy [39]. When LMS is localized out of the uterus, it usually extends to the pelvic cavity.

Lymph node invasion does not predict whether or not there are or there will be distant metastases. The tumor may spread via blood stream and show a negative lymph node sampling.

Most common localization for metastases is lung, followed by liver, kidney, brain, and bone [40].

Thyroid is considered an uncommon site of metastasis; the most recent report to date cites only three previous cases [41].

The reported five-year survival rates range from 4% to 74% [42, 43] for all Stages together and as high as 81% for Stage I disease. This wide variation relates to the use of small samples, failure to use standard pathologic criteria, lack of a standardized staging, various proportion of low- and high-stage patients in different series, and long periods accumulating patients with different treatment approaches during these intervals. A retrospective study of 1,396 patients (1988-2003) found a five-year survival rate of 65.7%, similar to the rates found in the most recent series published [44]. Disease stage is a strong prognostic factor in nearly all multivariate analyses, with better survival rates for Stages I and II [39, 43, 45-47]. Patient age has been identified as a strong, independent prognostic factor in favor of younger patients attaining a better prognosis. Earlier studies indicated that premenopausal patients had better outcomes than postmenopausal patients. However, more recent analyses have not identified an independent prognostic benefit associated with menopausal status when patient age is taken into account. Tumor grade is considered as a prognostic factor in several studies, but other series do not consider it as influent on the outcome. Probably, it reflects the lack of using unique grading criteria in earlier studies. Race is also an independent prognostic factor. Various series showed a higher incidence in Afro-American women [48, 49]. Brooks *et al.* in 2004 [4] reported a threefold higher risk among black women. Silverberg *et al.* (1971) [50] in a series of 34 patients reported that 11 out of 21 Afro-American patients died from the disease while only one out of nine white women deceased. The importance of primary surgical management of LMS were confirmed in multivariate analyses [44] Sagae *et al.* also reported that the presence of known residual disease after initial surgery was associated significantly with the risk of recurrence or death [45]. In a series of 46 patients with uterine sarcomas that included 14 patients with LMS, Marchese et al. noted that complete surgical resection was essential for long-term survival surgery for LMS [51].

The role of adjuvant pelvic RT has become intriguing. In a case-control study of 31 cases and 31 controls performed

at Mayo Clinic, there was no statistically significant improved survival between cases and controls, but it significantly reduced the rate of pelvic recurrence [39].

Yoney *et al.* (2008) [52] in a retrospective analysis of 105 patients favor a treatment that includes radical surgery and adjuvant RT alone at 54 Gray or with chemotherapy. Adjuvant CTX would be mandatory if we consider that LMS have a very high-rate of early metastases, still there are no proven benefits in literature.

Endometrial stromal sarcoma (ESS)

ESSs are most commonly seen in pre-menopausal women, but age at presentation may range from 20 to 80 year. It accounts for 0.2% of all uterine malignancies, 15% of uterine sarcomas, with a prevalence of 0.19/100000 women (> 20 years) [3, 4]. Median age at diagnosis is 47 years. In the series by Brooks, race disparity was not really significant as in LMS (a incidence rate of 0.623 in whites and 0.583 in blacks) [4].

Pathologic and biologic features

ESS may possibly arise from uterine stroma, adenomyosis or endometriosis. It resembles cells from the endometrial stroma during the proliferative phase of the menstrual cycle, showing small round or elongated, often hyperchromatic cells exhibiting varying degrees of atypia. Immunochemistry shows reactions for vimentin, inhibin, CD99 (MIC2) [53], and keratins [54]. The most reliable tool to distinguish ESS from SMT is CD10 [55] in contrast to the h-caldesmon, CD44 positivity, and widespread actin positivity in smooth muscle lesions. ER and PR positivity reflects the response to progestagens typical of normal stromal cells, identifying LG lesions [56-60].

ESSs are divided into three entities: stromal nodule, LGESS and the undifferentiated ESS, formerly known as HGESS (WHO). An infiltrating margin and vascular space invasion separates ESS from benign stromal nodule [61]. The mitotic rate alone cannot indicate whether a ESS is HG or LG and therefore has no chance to suggest a poor outcome or a more aggressive behavior [62-64]. Some years ago ESSs included diverse entities, LG, HG, stromatosis, and endolymphatic stromal myosis (SESM). The LGESS includes nowadays many tumors that would have been considered once as HG. LG is, nowadays, a tumor that shows morphologic aspects of endometrial stroma, while the HG or undifferentiated are anaplastic tumors without endometrial differentiation.

Grossly, ESS resembles pale yellow rubbery growths extending through the myometrium into lymphatic and venous channels. Therefore, evaluating an hysterectomy specimen, close attention should be given to vessels to the broad ligaments and adnexa [65].

Treatment and prognostic features.

The surgical approach for ESS consists of primary surgery and surgery for restaging or recurrences. Another option is fertility-sparing surgery in younger women that expressed the wish for an offspring. Primary surgery consists of a total hysterectomy, bilateral salpingo-oophorectomy (BSO), and lymphadenectomy (LND). Surgical options may be different, considering the stage and the grade. The surgical plans for LGESS confined to the uterus, Stages I-II, should include BSO, but literature shows different results in affecting survival. Li *et al.* [66] argue that progestins have no defined value in adjuvant settings and no in vitro studies confirmed the hormonal induced proliferation in LGESS. Furthermore, there is a wide variation in recurrences if the ovaries are retained (0%-100%), and these series include all stages, all ages, and HG [67-70]. If we consider the data extrapolated from other hormonal responsive gynecologic cancers, BSO is very unlikely to affect survival [71]. Nevertheless there is some authors [70, 72] that still recommend performing BSO. Progestins (GnRH analogs, aromatase inhibitors) cause regression/stabilization of recurrent LGESS [73] and the expression of ER/PR in LGESS suggests hormonal responsiveness [74]. In the multicenter case-control study 1976-2002 by Li *et al.* [66] there were no differences in the pattern of recurrence among patients where BSO was not performed, and eventually no disease recurred in the ovaries. The only independent risk factor was an older age at diagnosis. Immunohistochemistry was positive for ER and PR in all cases. All recurrences were ER and PR positive. Gadducci *et al.* [75] considered 12 patients younger than 50 years with LGESS Stage I who underwent total abdominal hysterectomy (TAH). The rates of recurrent disease were 33.3% with BSO and 16.7% without BSO. Amant *et al.* [76] included 18 premenopausal patients Stage I-II LGESS with TAH in their study. Their rates of recurrence were 25% with BSO and 17% without BSO; these results overlap. While BSO should always be performed in primary surgery for HGESS, it could be discussed for LG. Young women could retain their ovaries when a diagnosis of LGESS is made as an incidental finding on a hysterectomy for a benign indication. The decision to perform a BSO should then be taken on an individual basis and discussed with the patient.

ESS was first designed as endolymphatic stromal myosis (ESM), underlining its strong tendency to invade lymphatic tissue. The benefit for LND is first in a more accurate staging; Reich *et al.* [77] recommend to perform it while Riopel *et al.* [78] found 33% (5/15) of nodal metastases at some point in ESS evolution. On the other hand, Chang *et al.* [68], Gadducci *et al.* [75], Amant *et al.* [76] argue as ESS has tendency to recur at different sites. Amant *et al.* [76] found only three percent (1/31) of retroperitoneal recurrences. In the series by Li *et al.* [79] 2/3 ESS with node negative after radical hysterectomy had distant metastases at 12/39 months.

Considering the multi-institutional review 1972-2004 by Leath III *et al.* [80], 72 patients with LG and 31 with HG, LND was performed in 16 patients at all stages. The rates of positive pelvic nodes were nine percent in LG, and 18% in HG ($p = 0.44$). Aortic nodes were involved in 0% of cases for LG and 15% for HG ($p = 0.12$). The series 1972-2003 by Geller *et al.* [81] presented 19 LG and nine HG, 13 of which underwent complete LND. Survival rates favored the LND, but as a retrospective study, cases with extrauterine disease had no LND. As with BSO, LND in early stages should then be taken on an individual basis and discussed with the patient.

Surgery for restaging means performing BSO and/or LND in patients who had a previous hysterectomy. BSO for LGESS in patients approaching menopause is of less concern, if it was not performed, primarily they may not need it. Lymph node sampling is rarely performed, since ESS is often diagnosed after surgery for benign condition. Prognostic significance of nodal metastases in LGESS is still unknown [82]. In advanced or recurrent ESS, the most common option for salvage therapy is surgery [79]. A secondary or tertiary debulking surgery is often required [76]. If primary surgery was suboptimal, a secondary debulking surgery is mandatory [52]. The strongest independent prognostic factor in the series by Nordal *et al.* [48] pts 1976-1985 71% Stage I; 46 pts TAH and BSO) [83] was positive resection margins. Evidences in literature about fertility-sparing surgery are few. Lissoni *et al.* [84] present six nulliparous women, median age 27 years, median follow-up 51 months in the period 1982-1996 who underwent laparotomic myomectomy for ESS. There were three pregnancies (37%) with two spontaneous deliveries. Two patients underwent a second surgical procedure: a resection of a pedunculated lesion seen during first surgery and a myomectomy 31 months after first procedure. They reported that all patients were alive and well and had no recurrences.

For HG it should be considered that it could be strongly residual disease after removal of the mass. A possible conservative strategy for ESS surgery should be guided by some criteria, as: a tumor completely resected (free margins > two mm), a woman who strongly desires fertility, accepts risk of recurrence-related mortality, attends close follow-up procedures, and accepts radical surgery after reproduction.

In the classic series by Salazar *et al.,* 1980, the five-year survival for ESS was 55% among Stage I, 12% for Stages II-IV [85].

MMT (CS and AS)

CS account for 1.5% of all gynecologic malignancies. CS shows a prevalence of 0.82/100000 women (> 20 years). Mean age at diagnosis is 65 years. Race seems to play a major role in CS etiology, with a fourfold higher incidence among Afro-American women when compared to Caucasians [3, 4].

Biology and pathology

CS is a biphasic mixture of malignant epithelial, usually endometrioid adenocarcinoma, and malignant stromal component [86, 87]. The latter can be undifferentiated or resemble a differentiated stromal sarcoma with a heterologous component, with, either benign or malignant, rhabdoid, cartilage, bone or adipose elements [88].

Epithelial and stromal elements can merge but in most cases they are separated. Many present with a HG stroma but a LG stromal component can be seen in the 16% of cases [86, 88, 89]. The apparent fusion of epithelial and stromal components brought to studies that showed how stroma had an epithelial immunohistochemical profile and a similar reactivity to p53 [90]. It is widely accepted that the tumor represents a metaplastic change of a carcinoma in a sarcomatous malignant component in 85%-95% of cases [86, 89, 91, 92]. The epithelial Müllerian component plays a major role in survival. Recurrences are more often carcinomatous, endometrioid or serous papillary subtype; nevertheless, they could show a sarcomatous or mixed histology.

CA125 is a marker that results preoperatively elevated and seems to have a prognostic value during follow-up [93].

Therapy

Recurrence rate for Stages I and II is 50%. Distant metastases constitute the 50%-80% of all. The most common sites of metastases are the omentum and the lungs. Risk factors associated to a worst prognosis are adnexal involvement, lymph node metastases, and HG tumor. Five-year survival rate is lower than 20%.

Primary surgery in carcinosarcomas should include an exploratory laparotomy, pelvic washing, whole peritoneal cavity surgical staging, omentectomy, multiple lesion biopsies, mass debulking, para-aortic lymphadenectomy (PALA), and pelvic lymphadenectomy (PLND).

Sixty-two patients, consecutively treated in 1974-1995 with Stages I-II showed extra-uterine spread in 61% of cases. Among them, 81% underwent a gynecologic oncology referral; PLND and PALA were performed in 89% and 42% of cases, respectively [94].

LND, even in early Stages (I-II), is currently recommended. Fronting a higher morbidity (age-related, obesity, and hypertension) [95, 96], there are still benefits derived from LND. Undoubtedly, 15%-20% of patients show node metastases at the time of diagnosis [97], six percent will have the first recurrence at the para-aortic lymph nodes [98] and it showed to be a prognostic factor on multivariate analysis [99].

One hundred thirty-three out of 206 consecutively treated patients (1991-2000) underwent LND: an average of 19 nodes were dissected [9-74]. Higher rates of complications occurred when more than 14 nodes were removed [95].

Conclusion

The management of uterine sarcomas requires a multidisciplinary approach or tumor board before commencing the treatment. Until last decade, these tumors had been grouped together with other tumors generally described under the name of uterine sarcomas. This has been limiting current knowledge considering that the latter are different tumors in terms of etio-pathology, genetics, behavior, and treatment. Old studies are therefore of limited use for meta-analysis. Gynecologists instead of a soft-tissue sarcomas expert have classically treated these tumors. Current views suggest to consider LMS as the only "true" sarcoma of the uterus and the worst histotype in terms of prognosis.

It is of paramount importance to ensure expertise management of the disease. Rarity and pauciness of data are some reasons for a very poor prognosis and render them very good candidates for international multicentric studies.

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