International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Diagnostic Criteria for Uterine Sarcoma: Review of the Literature

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Abstract.
Uterine leiomyosarcomas are rare and have a poor prognosis, particularly at the metastatic stage. The rarity of this tumor justifie that patients be referred to referral centers afin order to have optimal diagnostic and therapeutic management. Anatomopathologic diagnosis is based on the demonstration of three features: necrosis, cytologic atypia, and mitoses within a smooth muscle proliferation. Chemotherapy probably has a place in the adjuvant management. In locally advanced or metastatic forms, the prognosis is poor, with an overall survival of about 12-14 months despite first-line polychymic therapy that gives response rates of about 30%. Anti-angiogenic drugs and hormone therapy have their place in the therapeutic arsenal. Multimodal management can improve the prognosis of some patients

Keywords: uterine leiomyosarcoma, rare disease, chemotherapy, multidisciplinarity

Introduction

Leiomyoma is the most common mesenchymal tumor of the uterus (50% of women at menopause). Malignant mesenchymal tumors are much rarer. Thus, sarcomas represent 1% of gynecological cancers and only 5.2% of uterine cancers. Their prognosis is poor, with a 5-year survival rate of 15 to 25% for leiomyosarcoma, and is conditional on adequate surgical resection without preoperative rupture.

Uterine cancers are divided into two major classes according to their embryological origin: carcinomes, of epithelial origin, and sarcomas, of mesenchymal origin. Uterine sarcomas include mesenchymal tumors of the myometrium (leiomyosarcomas), mesenchymal tumors of the endometrium (low-grade endometrial stromal sarcomas, undifferentiated sarcomas and adenosarcomas) and other rarer mesenchymal tumors (rhabdomyosarcoma, liposarcoma, etc.) [1]. Uterine car- cinosarcomas were excluded from the classification of uterine sarcomas when last updated in 2009. They are currently considered highly undifferentiated car- cinomas and treated as such. Leiomyosarcomas (LMS) account for 1% of uterine tumors, 40% of uterine sarcomas, and 40% of LMS at all sites combined [2].

Anatomopathology

The macroscopic appearance of SML is in 90% of cases that of a single nodule forming an intramyometrial mass with a well defined growth boundary [3]. On cross-section, the tumor is pink to pale

gray in color with necrotic and hemorrhagic areas. If there is a gelatinous appearance, a myxoid form should be suspected.

The diagnosis of uterine leiomyosarcoma (UML) is difficult to make. In front of a smooth muscle tumor, the diagnosis of malignancy is based on three characteristics: necrosis, moderate to severe cytological atypia and mitotic activity [4]. The cells are arranged in long bundles intersecting at right angles. They have abundant, eosinophilic cytoplasm, often fibrillar, possibly containing a vacuole notching the nucleus. There are three histological forms: the typical form of SML and two variants: epithe- lioid and myxoid [5].

In immunohistochemistry, 50% of SMLs are positive with an antidesmin antibody that has good specificity. Other expressed markers are global muscle actin (HHF35), smooth muscle actin, and h-caldesmone, which has good spe- cificity and is expressed by 85% of SMLs. Enfin, hormone receptors (HR) are also frequently expressed in uterine SMLs [6], which may point to a uterine origin when diagnosed with a metastasis and may also be a potential therapeutic target.
The differential diagnosis between SML and smooth muscle tumors of uncertain malignancy (STUMP) is difficult. Indeed, STUMPs are at the border between benignity and malignancy and pose prognostic and therapeutic management problems [7]).

Clinic

- **Clinical presentation:**

Age at diagnosis
The median age at diagnosis is 52 years [8], with extremes ranging from 18 to 95 years. LMSU occurs preferentially in premenopausal women, whereas carcinosarcomas and carcinomas tend to occur postmenopausally: 41% of patients were postmenopausal at diagnosis in a Mayo Clinic series [9].

Clinical signs
The most frequent clinical signs are metroradia (56%), a palpable pelvic mass (54%) and/or pelvic pain (22%) [10]. The clinical symp- toms and signs are those of the much more common fibroma, and the distinction between these two tumor types is difficult on the basis of clinical don- ations alone. The incidence of LMS in patients with clinical signs of leiomyoma is less than 1% but increases with age [11]. Sometimes the clinical signs are related to tumor rupture (e.g., hemoperitoneum), ectopic extension (e.g., obstructive renal insuffisance), or metastases. Any symptomatic fibroma after menopause in an unsubstituted woman should raise the possibility of uterine sarcoma.

Diagnostic workup
The positive diagnosis is made by the anatomopathologist following a hysteroscopic biopsy in the case of preoperative suspicion, a metastasis biopsy in the case of advanced disease, or on a myomectomy or hysterectomy specimen in the case of incidental discovery during a hysterectomy for suspected leiomy. In a franc¸aise retrospective study, out of 1,297 hysterectomies performed between 1996 and 2005 for leiomyoma, three (0.23%) revealed an LMSU [12]. Similar rates are reported in the literature this
Clinical prognostic factors

Prognostic factors are: young age (better prognosis), ethnicity (worse prognosis in black women), initial surgery and adjuvant treatment (better prognosis) [8]. These factors are found in several retrospective studies in which stage and age are the two most frequently found clinical prognostic factors.

- **Biological prognostic factors:**

The FNCLCC grading of soft tissue sarcomas does not apply to uterine sarcomas [13]. While the prognostic character of grade has been clearly demonstrated in soft tissue tumors [14], for LMSU, the mitotic index is a more accurate prognostic marker. Indeed, the anato- mopathological criteria used to make the diagnosis of LMSU (necrosis, atypia, mitoses) already imply a high grade in themselves. In a retrospective study of 157 uterine sarcomas, including 78 UMSLs, the only two prognostic factors in the entire population were age (> or < 60 years) and stage. In the SML subpopulation, multivariate analysis showed a prognostic role for stage and mitotic index [13]. This was found in another French study in which multivariate analysis showed a prognostic role for mitotic index on the metastasis-free interval. The mitotic index was subdivided into three scores 1, 2, and 3 (<10 mitoses/10 large fields [GC], 10-20 mitoses/10 GC, and >20 mitoses/10 GC, respectively). The prognostic difference was significative between scores 1 and 2. Furthermore, vascular invasion was also prognostic in multivariate analysis [15]. Overexpression of p53 on immunohistochemistry (if mutated) involves about 50% of tumors and is a poor prognostic factor for OS in most studies [16].

Pelvic ultrasound

Pelvic ultrasound is the first line imaging technique for the detection of myometrial tumors and the exploration of metrorrhagia. It has shown its usefulness for the diagnosis of typical endometrial or leiomyomatous pathology. Nevertheless, it is rapidly limited for large tumors (Fig. 1) and has little potential for tissue characterization, with an overlap between degenerating myomas and malignant lesions.

Uterine sarcomas are classically described on ultrasound as single, heterogeneous tumors with hypervascularization [17] . In cou- leur Doppler, the distribution of vessels in the tumor is reported in the literature as irregular, with low resistance indices and elevated systolic velocities. However, this analysis is difficile because Doppler findings fluctuate with menopausal status, mass size and position, and the presence of cystic degeneration.

Sarcomas also represent a differential diagnosis of malignant endometrial lesions, taking the form of diffuse hypervascularized endometrial thickening.

In the same study [18] carried out in our center on 108 patients (84 leiomyomas and 24 sarcomas), the preoperative ultrasound descriptions were retrospectively analyzed: 3 categories of findings were listed: classic leiomyoma, atypical leiomyoma or mass that could not be characterized on ultrasound.
In this study, sarcomas appeared most often as single masses (81% or 18/22). While the myometrial origin of leiomyomas was almost always (94%, or 80/85) noted by the sonographer, the latter could not determine the origin of the tumor in 43% of sarcomas (9/21) ($p < 0.001$). In sarcomas, attenuation of the ultrasound beam was described in only 28% (2/7) whereas it was noted in 82% of leiomyomas (19/23)

(p = 0.01). Enfin, endometrial thickening was also more often found in malignant pathology, with 52% (9/16) thickening versus 8% (6/71) in leiomyomas (p < 0.001).

Pelvic MRI

Magnetic resonance imaging (MRI) is the second-line examination that allows better tissue characterization.

Morphological study:

-T2-weighted sequences

In the literature, uterine sarcomas are most often reported as a bulky mass with an intermediate or high T2 signal intensity, heterogeneous [19] (Fig. 3). However, the T2 signal of leiomyomas may also be high in case of edema or cystic remodeling or if the histological subtype is myxoid or cellular. It is therefore essential to rely on the other sequences.

Another mode of presentation is a mass appearing centered on the endometrium [20] (36% in the study by Sahdev et al.). The differential diagnosis is more likely to be that of an endometrial adenocarcinoma. The orienting elements are the ratio between the tumor volume (high) and which highlights the difficulty of diagnosing LMS before hysterectomy and the rarity of its discovery on the hysterectomy specimen.

myometrial invasion (low). In the same study, ascites was associated in 20% of cases.
Using the population analysed in our center on ultrasound data, we carried out a study [21] targeting the MRI aspect of uterine mesenchymaltumours, with the aim of evaluating the diagnostic performance of the combination of functional and conventional sequences for the discrimination of malignant and benign tumours.

-T1-weighted sequences

Without injection:
On morphological sequences, intratumoral hemorrhagic remodeling is also classically described in the literature in sarcomas, but it is not constant (50%) [22]. Moreover, such remodeling can occur in remodeled leiomyomas [23].

After injection:
Sarcomas classically show intense and heterogeneous enhancement after injection, with unenhanced areas related to necrosis in more than 50% of cases [19].

Nuclear imaging:
The PET-scanner is promising because it provides both morphological and anatomical information. It has not been studied for the discrimination of malignant and benign mesenchymal lesions. It has been shown to be useful in the assessment of extension and the search for recurrence [24]. However, it may miss small uterine leiomyosarcomas, including small low-grade metastases.

Conclusion

LMSU are rare diseases with a poor prognosis, whose diagnostic and therapeutic management must be ensured in a multidisciplinary manner by reference centers with systematic review by an expert anatomopathologist. Initial management should be surgical whenever possible. Adjuvant chemotherapy and pelvic radiotherapy should be discussed in the PCR. There is currently no therapy targeting a "driver" oncogenic mechanism of this disease and chi- miotherapy is therefore the treatment of choice at the metastatic stage, as part of a multi-modal management whenever possible.

Infin, it is essential to maintain clinical research activity for these rare diseases. Clinical trials are made possible by the collaborative network work in France within the French sarcoma group.

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- Patient Management: Allaeeddine BOUCHAIB*
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- Manuscript writing :Allaeeddine BOUCHAIB*
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- All authors have approved the final version of the manuscript

Figures

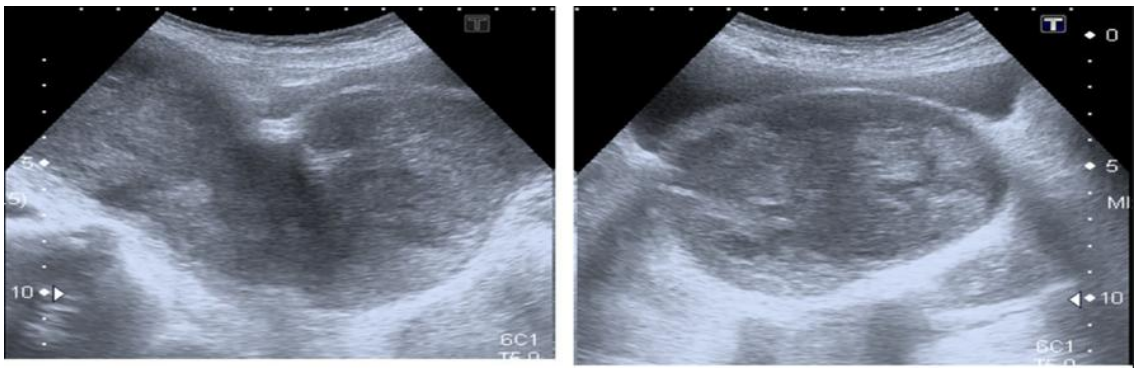

Figure 1: aspect échographique du sarcome utérin

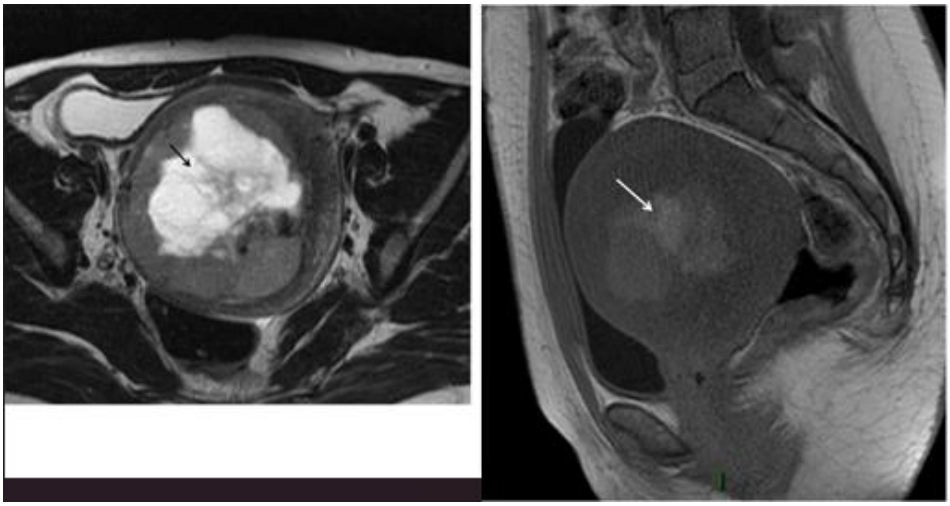

Figure 2: aspect du sarcome utérin montre l'aspect typique des sarcomes utérins à l'IRM : masse unique relativement bien limitée de signal principalement intermédiaire, très hétérogène avec portions liquidiennes sur les séquences en pondération T2 dans le plan axial ; remaniements hémorragiques sur la séquence T1 sans saturation de la graisse

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