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Sarcoma do estroma endometrial de baixo grau: relato de caso

| Low-grade endometrial stromal sarcoma: case report

RESUMO | Introdução: *O sarcoma estromal endometrial é um tumor raro que corresponde a aproximadamente 1% dos tumores uterinos. Seu diagnóstico é desafiador devido à semelhança com tumores benignos tanto nas características da lesão nos exames de imagem quanto nos sintomas, o que só é obtido a partir da análise histopatológica.* **Relato de caso:** *No caso relatado, para a obtenção do diagnóstico foram necessárias várias tentativas e métodos, e a paciente encontrava-se em estágio avançado, com metástase à distância, prejudicando seu prognóstico. Este artigo discute formas de diagnóstico, estadiamento, prognóstico e manejo dessa rara neoplasia.*

Palavras-chave | *Hemorragia Uterina; Neoplasias; Sarcoma.*

ABSTRACT | Introduction: Endometrial stromal sarcoma is a rare tumor that corresponds to approximately 1% of uterine tumors. Its diagnosis is challenging to make due to the similarity with benign tumors both in the characteristics of the lesion in imaging exams and about the symptoms, which is only obtained from the histopathological analysis. **Case report:** In the case reported, to obtain the diagnosis was necessary several attempts and methods, and the patient was in an advanced stage, with distant metastasis, impairing her prognosis. This article discusses ways to diagnose, staging, prognosis, and management of this rare neoplasm.

Keywords | Uterine Hemorrhage; Neoplasms; Sarcoma.

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INTRODUCTION |

Uterine sarcomas are rare mesenchymal neoplasms, corresponding to 3-5% of malignant neoplasms of the uterine body[1]. These tumors are divided into two groups: homologous and heterologous tumors. The homologous sarcomas are those formed by tissues normaly found in uterine tissues, and this group include endometrial stromal sarcoma and leiomyosarcomas. Heterologous tumours are those compounds of histological elements that are not themselves the uterus; for example, skeletal muscle and adipose tissue, being included in this group of tumors, the rhabdomyosarcoma, and uterine liposarcoma.

Clinically, uterine sarcomas manifest with abnormal uterine bleeding, post- menopausal bleeding, pelvic pain or abdominal pain, or patients could be asymptomatics[2].

The focus of this article will be endometrial stromal sarcoma, which represents only about 0.2% of all uterine tumors, and, considering only uterine sarcomas, the prevalence is 7-25%[3]. These tumors, in turn, are classified, according to the World Health Organization (WHO), into five categories: endometrial stromal nodule, low-grade endometrial stromal sarcoma, high-grade endometrial stromal sarcoma, undifferentiated uterine sarcoma, and uterine tumor resembling ovarian sex cord tumor[4].The difference between these subtypes is on degree of cell differentiation and degree of invasion to the myometrium. The nodule of the endometrial stroma is a well-defined benign tumor, and the others are malignant tumors.

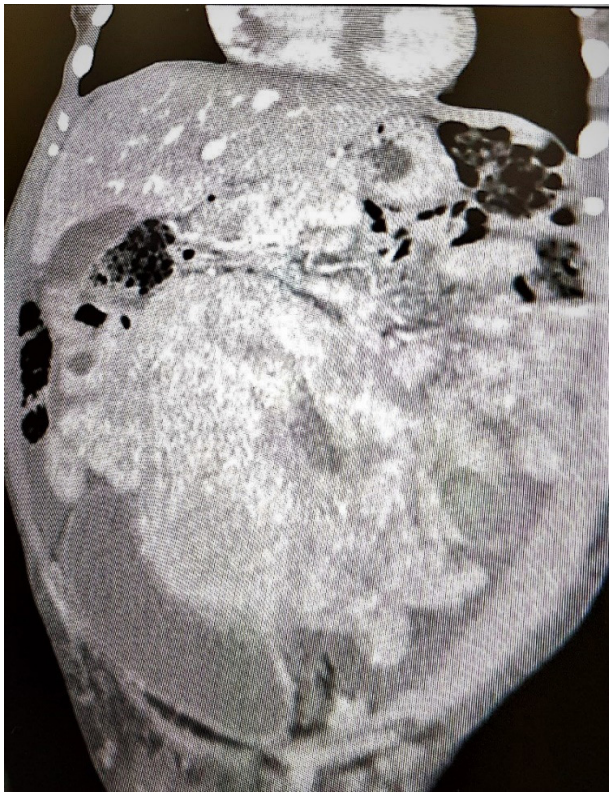
This article aims to alert the possibility of malignancy in patients with abnormal uterine bleeding at menacme, discussing differential diagnoses, including endometrial stromal sarcoma. In addition, this report emphasizes the importance of valuing the patient's complaint and carrying out an adequate diagnostic investigation on time to ensure a good prognosis.

CASE REPORT |

Patient female, 49 years old, G4P3(3C)A1, hypertensive in irregular use of captopril with abnormal uterine bleeding history and abdominal mass with progressive growth. The patient does not know how long it takes for symptoms to evolve. In April / 2020, there was a worsening of the bleeding condition when she was admitted to a hospital in the municipality of origin, being subjected to transfusion of 07 red blood cell concentrates and drug therapy without bleeding control.

Patient was transferred to University Hospital Cassiano Antonio Moraes (HUCAM) on 04.26.2020, which was subjected to the tomography of the abdomen and pelvis, which showed an increased volume of the uterus (1569 cm^3) with multiple nodules myometrial poorly defined, thick endometrium, and heterogeneous (Figure 1), in addition to a large thrombus extending from the inferior vena cava to the right atrium and another thrombus in the left external iliac vein (Figure 2).

Figure 1 - Tomography of the abdomen and pelvis with an enlarged and irregular uterus

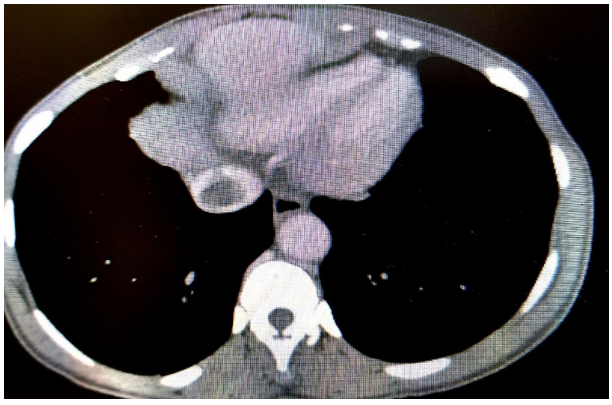


Source: Authors.

Subsequently, also held magnetic resonance of the abdomen and pelvis that could better define the uterine lesions and the largest with intermediate signal intensity on T2 and restriction on diffusion, hinting and filling almost for complete the uterine cavity, which is presented extended without cleavage planes with your component myometrial previous body, probable neoplastic nature. Ovaries of

increased dimensions were observed with intermediate signal intensity, which may be secondary neoplastic involvement. In the chest resonance was described a sparse nodular lesions in bilateral pulmonary parenchyma irregular outline, probably secondary injuries.

Figure 2 - Chest tomography showing thrombus in the vena cava



Source: Authors.

Adding the high surgical risk due to the presence of extensive thrombus and large bleeding without control, it was decided the holding Novak curette in April 28 to obtain a sample of the endometrium and tentative of diagnosis. However, anatomopathological was inconclusive, obtaining only necrotic tissue and blood clots.

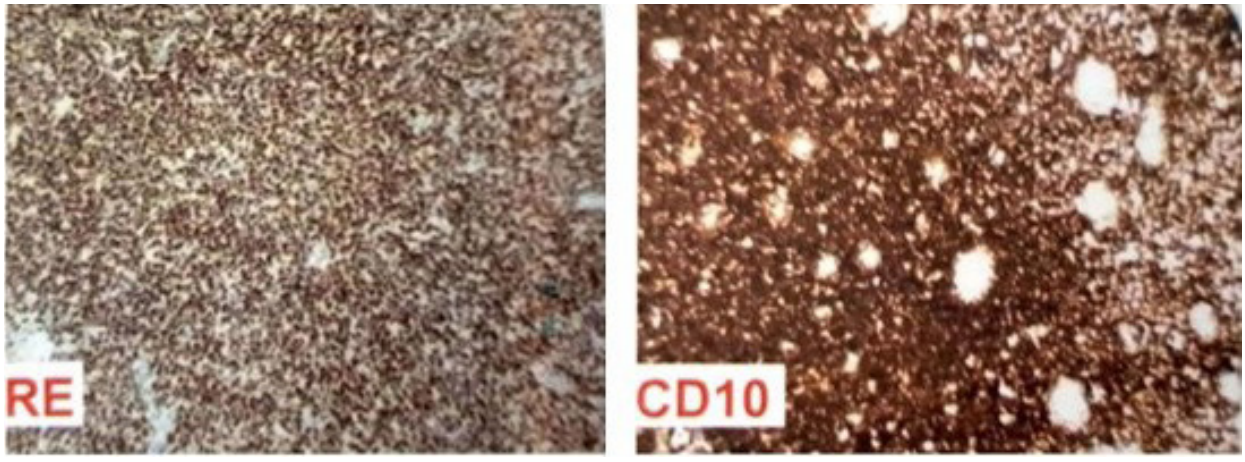
The patient maintained heavy bleeding, unresponsive to medication, with the need for transfusion of more 03 red blood cell concentrates. Therefore, it was decided in conjunction with the vascular surgery team for embolization of uterine arteries to control bleeding and clinical stabilization of the patient. Procedure performed on May 06, with embolization of the left uterine artery with microspheres. Upon angiographic study of the right internal iliac artery, no arterial branch was observed in the usual uterine topography, and the right side was not embolized.

After the embolization procedure, the patient stopped vaginal bleeding, and a second attempt was made to collect the endometrium sample using semiotic uterine curettage on May 12. During the procedure, the patient returns with significant bleeding. Histopathology was inconclusive again, obtained only material with necro-hemorrhagic fibrin.

On May 21, she was then submitted to diagnostic hysteroscopy, which showed an endometrium with no changes and masses of myometrial origin in the anterior wall of the uterus, bulging the endometrium and deforming the entire uterine cavity. A deep biopsy of the lesion was performed, and a histopathological study diagnosed low-grade endometrial stromal sarcoma. In immunohistochemical was the expression of CD10 and estrogen receptors, confirming the diagnosis (Figure 3).

Patient with advanced disease, with distant metastasis and high surgical risk due to extensive thrombus in the vena cava, being opted for palliative treatment. She was forwarded to a clinical oncologist and opted for hormone therapy with megestrol acetate 160 mg/day. The patient remains clinically stable, without further episodes of vaginal bleeding.

Figure 3 - Immunohistochemistry with expression of estrogen and CD10 receptors



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DISCUSSION |

Uterine sarcoma is a rare malignant tumor and usually affects young women between 42 and 58 years old, and in 10 to 25% of the time, it affects pre-menopausal women[5]. The most common clinical manifestations are pelvic pain and abnormal uterine bleeding, which are also the same symptoms as leiomyomas, the most common benign tumors in the uterus[2].

Low-grade endometrial stromal sarcoma can manifest as intramural or submucosal tumors with undefined margins. They may also have a polypoid shape or growing and deforming the uterine cavity[6].

In imaging studies, sarcomas are also similar to leiomyomas. Both are focal nodules in the uterus. Furthermore, although some ultrasound signals such as echogenicity mixed, central necrosis, irregular distribution of vessels, and the Doppler peak systolic velocity high, may be suggestive of sarcomas, none of that are pathognomonic, could also being found in fibroids[7]. Therefore, the diagnosis is not easy to perform, is based on the histological analysis of the tumor.

The histopathological study of the lesion can be done by obtaining a sample of endometrial tissue or after a hysterectomy or myomectomy of a mass that presumably was a leiomyoma. In patients with uterine sarcoma, the diagnosis is obtained from an endometrial sample in 33 to 68% of cases. There is no difference in the sensitivity of the diagnosis between the different techniques for obtaining an endometrial sample: curettage or direct biopsy of the endometrium using hysteroscopy[8].

In the case exposed, the patient is in the most prevalent age group of the disease and presented the most common clinical manifestation of abnormal uterine bleeding. The diagnostic difficulty is evident from the delay in seeking care, being diagnosed at an advanced stage of the disease, and the need for numerous surgical approaches and methods of investigation to obtain a satisfactory sample for histological study and diagnostic definition.

Histologically, low-grade endometrial sarcoma is characterized by densely uniform stromal cells with minimal cellular pleomorphism, mild nuclear atypia, and variable mitotic figures[9]. Generally, myometrial invasion and blood and lymph vessels are observed. The number of mitoses is variable, but it is usually low[6].

For a better diagnostic definition and differentiation between the subtypes of endometrial stromal sarcomas, an immunohistochemical study and analysis of molecular pathology are generally used, and this analysis is also important for adjuvant therapeutic definition. Most tumors express CD10 and WT1 receptors[10]. Tumors may also have gonadotropin-releasing hormone (GnRH), estrogen, and progesterone receptor expression, as observed in the case-patient. Cyclin D1 has heterogeneous and variable nuclear expression in less than 10% of tumor cells, being important in the distinction between these lesions and high-grade endometrial stromal sarcomas[6,10].

The staging of endometrial stromal sarcoma is the same as leiomyosarcoma and follows the FIGO and TNM classification (Table 1), and is the main prognostic factor of low-grade tumors[10]. Tumor lesions can develop in places other than the uterus, such as ovaries, pelvis, abdominal cavity, and also vulva and vagina[11].

Table 1 - FIGO / TNM stage for leiomyosarcomas and low-grade endometrial stromal sarcoma

TNN stage	FIGO stage	Definition
T1	I	Tumor limited to the uterus
T1a	IA	Tumor 5 cm or less in the larger diameter
T1b	IB	Tumor more than 5 cm
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III	Tumor infiltrates abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
N1	IIIC	Regional lymph node metastasis
T4	IVA	Tumor invades bladder or rectum
M1	IVB	Distant metastasis

Source: Authors.

In patients diagnosed with endometrial stromal sarcoma, chest, abdomen, and pelvic imaging exams are recommended for the stage and diagnosis of metastases. The most common site of metastasis is the ovaries[12].

The stagings FIGO I and II are the most prevalent in diagnosis in 65% of cases. Patients with these stagings have a 5-year survival of more than 90%; however, the patient

in whom the diagnosis is stage FIGO III or stage IV have a survival by 50% at 05 years[3].

Wu *et al.* proposes the creation of a nomogram in which he uses the combination of independent variables to estimate patient survival. The variables used were age, tumor size, marital status, radiotherapy, chemotherapy, lymphadenectomy and FIGO tumor staging. Scores are applied depending on the importance of each factor, and the sum of this score will determine whether the patient is at low risk (<325), medium risk (325-359) and high risk (≥ 360). The article concludes that the nomogram have increased accuracy, good clinical utility, and more need prognosis prediction compared with conventional staging system[13].

The case-patient already had metastasis to ovaries and lungs, she was already classified as stage IV and have a reserved prognosis.

The treatment of choice is total hysterectomy with bilateral annexectomy[10,14]. The ovaries are removed since most tumors have many steroid receptors and because most metastases are from the uterus to the ovary[3]. If extrauterine tumors are diagnosed on imaging or intraoperative exams, the resection of metastatic implants should be evaluated[14]. If the diagnosis of endometrial stromal sarcoma was made following hysterectomy for a presumed benign condition, it could be reoperated to perform bilateral salpingoophorectomy, particularly if positive tumor to ovarian hormone receptors[14]. The involvement of pelvic and para-aortic lymph nodes does not influence the prognosis; therefore, lymphadenectomy is not routinely recommended[3]. Shah *et al.* Found that there were no statistically significant differences in the 5-year survival rate between node positive and node-negative (86% vs. 95%)[15]. It is indicated only in case of lymph node involvement in imaging exams or lymphadenopathy seen during the surgery[16]. The recent literature reports that the lymph node metastasis rate is between the 7% and 9.9%, more frequent locally within the pelvis[17].

There is no consistent data to prove that adjuvant chemotherapy has benefits. In a large observational study conducted by the National Cancer Database, patients with low-grade endometrial stromal sarcoma who underwent adjuvant chemotherapy did not experience increased survival, only those with the high-grade variant[18].

The expression of estrogen, progesterone, and aromatase receptors suggests that adjuvant therapy with progestogens, GnRH analogs, or aromatase inhibitors may be effective, but the studies have not been conclusive. For tumors that have not been safely removed, adjuvant hormone therapy is a therapeutic possibility. In the study by Dahhan *et al.*, a remission rate of 82% was demonstrated in 10 years[14].

In patients on stage 1, the guideline of the National Comprehensive Cancer Network (NCCN), considered ideal for surgical treatment and monitoring without adjuvant therapy. The endocrino therapy should be indicated from stage II, associated with radiotherapy, which reduces local recurrence risk[14]. The drugs available for hormone therapy are medroxyprogesterone acetate or megestrol acetate or aromatase inhibitors, such as letrozole or anastrozole[10]. There is also no consensus regarding the duration of endocrine therapy, but there is a preference to remain for 05 years[14].

Follow-up will include physical examination every three months for the first 02 years and, subsequently, every 6 to 12 months. It should also take imaging, prefers abdomen and pelvis tomography every 6 to 12 months in the first 05 years of the disease. Also, lifestyle changes should be guided, with weight loss in obese individuals, encouraging physical activity, nutritional monitoring, and smoking cessation[14].

The recurrence risk in low-grade endometrial sarcoma corresponds to about 10-20%, being common in this disease appearance onset of the late, in more than 10-30 years[20]. Despite this, follow-up with imaging tests is not recommended for more than 05 years due to the increased risk of exposure to radiation[14]. The sites more commonly affected are vagina and lower pelvis but could have distant metastases to the lung and abdominal wall[20].

In patients with metastasis naive of treatmente should consider hormone therapy as the primary treatment. However, patients previously submitted to treatment presenting recurrence should perform second-line chemotherapy-associated hormone therapy, and the doxorubicin is the drug of choice. The surgical treatment should always be considered, and mainly in case of a single tumor mass[14]. Only complete resection surgery of tumors presents a cure rate of excellent and prolonged survival[21].

CONCLUSION |

The endometrial stromal sarcoma are rare malignant tumors, that manifest with abnormal uterine bleeding, pelvic mass, and pelvic pain and must be listed as the differential diagnosis in patients who have those signals and symptoms.

Diagnosis is challenging once initial disease is difficult to differentiate in imaging tests of leiomyomas, benign condition, and more prevalent. Thus, it is essential that if differentiated findings are observed on ultrasound, or if the patient has an atypical clinical evolution, with exacerbated symptoms or evolve in unexpected ways, be done complement research action with magnetic resonance and study of the endometrium.

Clinical suspicion, adequate investigation, and early diagnosis are fundamental for this neoplasia to be discovered early, thus guaranteeing a better prognosis and survival for the patient.

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