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Epithelial-mesenchymal transition in uterine carcinosarcoma from a dedifferentiated papillary serous carcinoma to a sarcoma: case report

Transição epitelial-mesenquimal em carcinossarcoma uterino oriundo de carcinoma seroso papilífero desdiferenciado para sarcoma: relato de caso

Yago Eloy Souza Barbosa[1], Ana Camila Xavier Lopes[1], Camila Delfino Chaves[1], Régis Ponte Conrado[1], Marcelo Leite Vieira Costa[2], Renato Mazon Lima Verde Leal[2]

ABSTRACT

Carcinosarcomas are endometrial neoplasms with malignant epithelial and mesenchymal components. These are rare tumors, corresponding to <5% of uterine cancers. The average age at diagnosis is 65 years and the most characteristic symptom is transvaginal bleeding, common to other uterine tumors. The definitive diagnosis of the lesion is done by analyzing the surgical specimen and the first-line treatment is surgery with adjuvant chemotherapy and radiotherapy. The authors report a case of a 59-year-old female diagnosed with a uterine carcinosarcoma, whose epithelial component underwent an epithelial-mesenchymal transition. The outstanding aspects of this report are the aggressiveness of this tumor and the presence of a lymph node metastasis by the sarcomatous component, which represents an unusual biological behavior.

Keywords: Carcinosarcoma; Mixed tumor, Mullerian; Epithelial-mesenchymal transition; Gynecology; Surgical oncology.

1. Federal University of Ceará (UFC), Medical School - Fortaleza - CE - Brazil.
2. Walter Cantídio Universitary Hospital (HUWC), Surgical Oncology Service - Fortaleza - CE - Brazil.

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Correspondence author: Yago Eloy Souza Barbosa.
E-mail: yago.eloy30@gmail.com

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RESUMO

Os carcinossarcomas são neoplasias endometriais com componentes epiteliais e mesenquimais malignos. São tumores raros, correspondendo a <5% dos cânceres uterinos. A idade média ao diagnóstico é de 65 anos e o sintoma mais característico é o sangramento transvaginal, comum a outros tumores uterinos. O diagnóstico definitivo da lesão é feito pela análise da peça cirúrgica e o tratamento de primeira linha é a cirurgia com quimioterapia e radioterapia adjuvantes. Os autores relatam o caso de uma mulher de 59 anos com diagnóstico de carcinossarcoma uterino, cujo componente epitelial sofreu transição epitelial-mesenquimal. Os aspectos marcantes deste relato são a agressividade desse tumor e a presença de metástase linfonodal pelo componente sarcomatoso, o que representa um comportamento biológico incomum.

Descritores: Carcinossarcoma; Tumor misto mulleriano; Transição epitelial-mesenquimal; Ginecologia; Oncologia cirúrgica.

INTRODUCTION

Uterine carcinosarcoma is a type of malignant neoplasm consisting of mixed histology, with epithelial and mesenchymal components.[1,2] It corresponds to <5% of uterine tumors,[2,3] has an aggressive character, with mortality of up to 30% among malignant neoplasms of uterus.[2] Due to the mixed character of carcinosarcomas, several theories about their histogenesis[3] are proposed and recent evidence indicates that most of these neoplasms have monoclonal origin, with differentiation of carcinoma in sarcomatous elements.[2,4] This transformation is a process known as epithelial-mesenchymal transition, in which epithelial cells obtain mesenchymal cell phenotype.[5] Immunohistochemistry is fundamental for the identification of its components and for definitive diagnosis.[3]

Most women affected by this neoplasm have a mean age of 65 years, and the clinical presentation is similar to that of uterine body tumors, with transvaginal bleeding. In general, they have a low overall survival rate due to late diagnosis and tumor aggressiveness. They often experience locally advanced disease or distant metastases at diagnosis. Metastases occur more frequently by the epithelial component that tends to spread initially lymphatically, as opposed to the sarcomatous component that tends to spread hematogenously. Despite curative treatment, there is a high risk of locoregional and distant recurrences, demanding stricter surveillance.[6] The main objective of this work is to present the differential points of the study, which are related to the fact that the patient in the case is a little younger than the average age and the lymph node metastasis was caused by sarcoma, a very rare situation in the literature and little documented.

Another interesting aspect is that the histology of the tumor apparently revealed that there were two lesions without any connection, something that was later refuted by immunohistochemistry, which revealed, however, that it was the same lesion and that it underwent a transformation called epithelial-mesenchymal transition, a complex phenomenon also described in this article.

CASE REPORT

Female patient, white, 59 years old, menarche at 10 years, sexarche at 27 years, menopause at 52 years, G0P0A0, overweight, with hypertension, was admitted to the surgical oncology service with mild pain in the mesogastrium and daily metrorrhagia for six months, interrupted with tranexamic acid. After 2 months of using the medication, she reported pain intensification, from mild to moderate and transvaginal bleeding of small intensity. On physical examination, the uterus was palpable at the level of the umbilical scar and, on the specular examination, a large vegetative lesion was evidenced in the external orifice of the cervical canal and affecting the vaginal wall, friable and foul odor. Pelvic ultrasound detected an endometrial thickening of 25mm, an increased volume of uterus (178cm²) and a heterogeneous echotexture of the cervix (Figure 1).

Surgical hysteroscopy showed multiple, voluminous, cystic, friable and tubular vaginal canal lesions. However, there were technical difficulties to overcome the lesion, excising fragments of a polypoid-configuration neoplasm. Histopathological analysis of the fragments showed atypical oval and fusiform cells, some pleomorphic, with round nuclei, evident nucleolus, presence of mitosis, eosinophilic cytoplasm, involving typical endometrial glands, amid loose stroma with areas of recent hemorrhage and necrosis; suggestive of Müllerian adenosarcoma. Pelvis CT reinforced the ultrasound findings. She was then submitted to the surgical procedure, with intraoperative findings of ascitic fluid in moderate amount, topical uterus with the presence of a large mass exceeding the uterine cervix, but without adhesions to the vaginal walls. Total hysterectomy, bilateral adnexectomy and pelvic lymphadenectomy

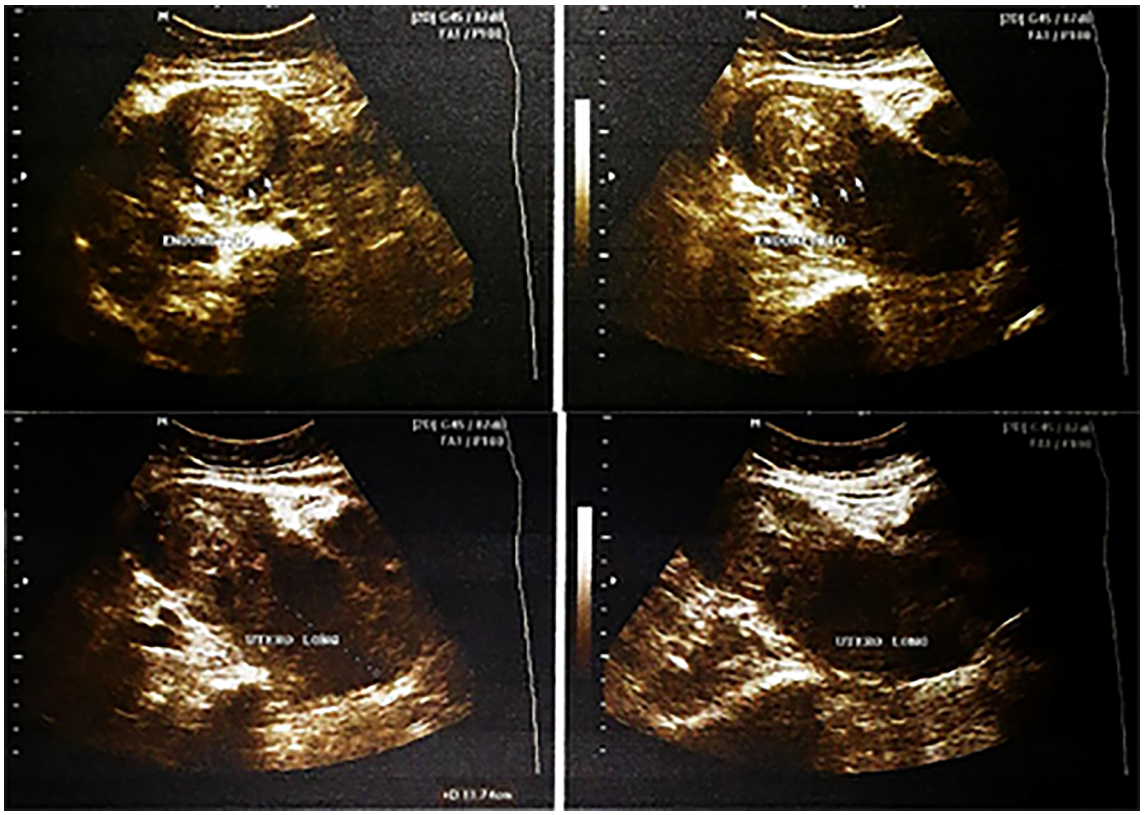

Figure 1. Pelvic ultrasound showing uterus of regular pear-shaped appearance and surface. Increased volume = 178.6cm³, heterogeneous myometrial echotexture, heterogeneous thickening of the cervix, and the sonographic appearance of the endometrium is irregular (25mm, normal = 5mm). Nonvisualized ovaries. Full bladder, regular surface, shape and normal volumes, in ecostructures inside.

were performed, *en bloc* resection of the lesion. The patient progressed well, being discharged without complications.

The ascitic fluid revealed a suspicious cytological aspect of neoplastic cells and the pathological study of the material identified two distinct tumors, with no connection between them (Figure 2). The major vegetative lesion measuring 11.5 x 9.5 x 7.5cm was diagnosed as a high-grade stromal endometrial sarcoma, with invasion of more than 50% of the myometrium with the presence of lymphatic invasion, without evidence of apparent perineural invasion and without detection of glandular focus of differentiation (Figure 3). The other minor lesion measuring 9.5 x 8.5 x 6.5cm was diagnosed as a high-grade serous adenocarcinoma with uterine serous infiltration and vascular invasion present (Figure 3). Due to the large deformity of the surgical specimen, neither the *cervix* nor *adnexa uteri* were identified. In the product of pelvic lymphadenectomy, there was one compromised lymph node of nine by sarcoma of the endometrial stroma of high degree (1/9). By FIGO classification, the lesions were staged as IIIC1 for sarcoma and IIIA for adenocarcinoma. The immunohistochemistry of the sample resulting from the total hysterectomy was performed with the antibodies actin smooth muscle (alpha), anti-cytokeratin, CD10, CD99, CD117, cyclin D1, cytokeratin, CK7, CK20, desmin, EMA, PAX8, RE, RP and WT-1, and the profile revealed positivity only for CD10 antibody in rare cells and for desmin antibody (Table 1); profile compatible with papillary serous carcinoma of high-grade dedifferentiated for sarcoma (epithelial-mesenchymal transition). She was referred to clinical oncology for adjuvant treatment.

DISCUSSION

Carcinosarcomas, also called malignant mixed Müllerian tumors, are endometrial carcinomas with a malignant sarcomatous component, which can assume homologous or heterologous elements.[7,8] Apparently, the epithelial and mesenchymal components derive from the same cell lineage, since apparently the epithelium undergoes an epithelial-mesenchymal transition, in view of the sharing of genetic changes in both parts of the tumor.[9-11] The report deals with a carcinosarcoma of the uterine body, whose primary lesion consisted of high-grade endometrial papillary serous carcinoma that suffered a sarcomatous dedifferentiation. Some interesting aspects of the present report are the fact that it is a very rare and aggressive type of tumor, as well as the presence of lymph node metastasis by sarcoma, which does not correspond to common situations, since most metastases of carcinosarcomas are usually due to the epithelial component.[12-14] Sarcoma comes from

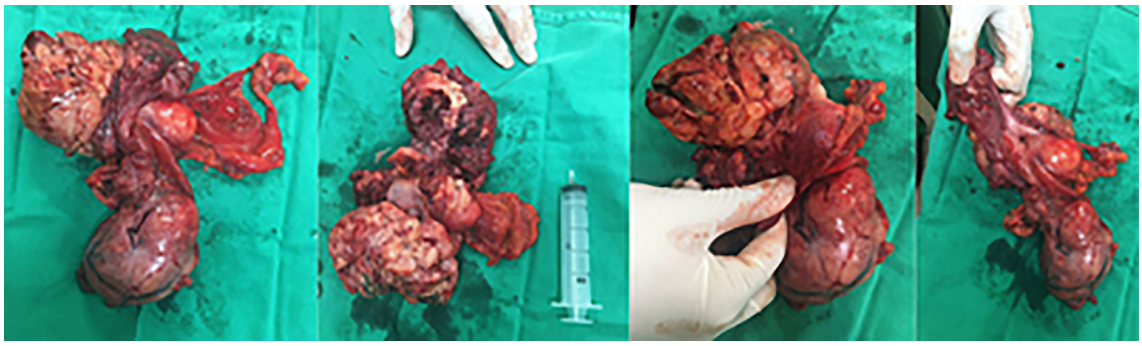

Figure 2. Images of the product of total hysterectomy, weighing 575g, measuring 17.0 x 8.0 x 7.5cm, with smooth serosa and evident vessels. The larger lesion measured 11.5 x 9.5 x 7.5cm, with 0.1cm thickness, the surface is white, externally vegetative and friable. The smaller lesion measured 9.5 x 8.5 x 6.5cm, with a white and friable surface.

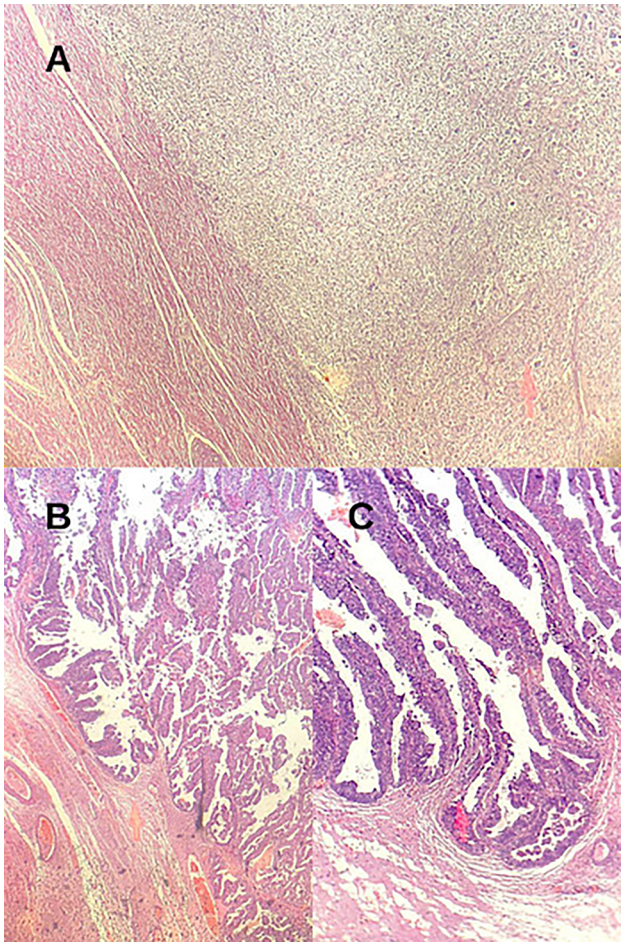

Figure 3. A. Histological sections stained in HE shows endometrial neoplasm with atypical round cell component, with inconspicuous cytoplasmic limits, large nuclei, sparse chromatin, arranged incohesively, with stretches of myxoid stroma. In a smaller increase, neoplastic tissue intersecting with normal myometrium on the right; B. Presence of neoplasia of epithelial origin, forming primitive glands that invade the myometrium, with cells of pleomorphic, hyperchromatic nuclei, conspicuous nucleoli, in addition to mitoses; C. Epithelial tissue invading the myometrium, with cells of distinctly neoplastic characteristics. In greater increase than the anterior image.

the dedifferentiation of carcinoma by means of epithelial-mesenchymal transition, characterized by the immunohistochemical study of the case.[15-19]

The incidence of carcinosarcomas is less than 5% of malignant neoplasms of the uterus.[6,16,17] Despite its rarity, this type of cancer is responsible for more than 15% of all deaths related to malignant neoplasms of the uterus.[13-18] The highest incidence is in afrodescendant and postmenopausal women, between 62 and 67 years, peaking at 65 years of age.[2,6,18] However, our case report presents a patient aged slightly younger than the age of peak incidence.

The reported patient is nulliparous and overweight, which are considered risk factors because they allude to states of chronic hyperestrogenism. The association of tamoxifen, metabolic syndrome, early menarche, late menopause, and exogenous estrogen exposure isolated with endometrial hyperplasia, proliferative endometrial lesions and endometrial adenocarcinoma is also well established.[3-6]

The epithelial-mesenchymal transition is a process in which epithelial cells lose intercellular support and adopt a phenotype similar to that of the mesenchymal, through cytoskeletal remodeling and alteration of migratory activity (increasing the ability to generate metastases).[5,9,20] Epithelial cells have an arrangement that preserves the apical and basal polarity, through cell adhesion proteins, while mesenchymal cells are separated from each other by an extracellular matrix without this type of histological organization. This phenomenon, in the context of neoplasms, occurs with the loss of cell adhesion proteins, with the replacement of epithelial markers (downregulation of E-cadherin, catenins and claudins, for example) by mesenchymal markers (upregulation of smooth-muscle actin, fibronectin, and vimentin, for example).[15] This process occurs physiologically in embryogenesis (type 1) and tissue repair, due to regeneration, fibrosis, and inflammation (type 2). Type 3 corresponds to carcinogenesis, a process in which there is a local invasion and distant metastasis and, unlike other types of transition, it is a dysregulated process that gives the tumor an infiltrative property with metastatic potential. Initially, transcriptional repression of genes associated with epithelial cell junctions occurs, the apical-basal polarity of the epithelium is lost, leading to detachment of cells from the basal membrane due to changes in interactions

Table 1. Immunohistochemistry of the surgical specimen from total hysterectomy.

Immunohistochemistry		
Antibody	**Clone**	**Result**
Actin smooth muscle (alpha)	1 to 4	Negative
Anticytokeratin	5.2 CAM	Negative
CD10	56C6	Positive in rare cells
CD99	12e7	Negative
CD117	Polyclonal	Negative
Cyclin D1	SP4	Negative
Cytokeratin	AE1/AE3	Negative
CK7	OV-TL 12/30	Negative
CK20	Ks 20.8	Negative
Desmin	D33	Positive
RHEA	E29	Negative
PAX8	MRQ-50	Negative
RE	SP1	Negative
RP	1e2	Negative
WT-1	6F-H2	Nuclear negative

with the extracellular matrix (degradation of basement membrane through the release of metalloproteinases). In summary, this epithelial plasticity contributes to the transdifferentiation of the epithelium to the mesenchyme, characterizing this mixed cancer composed of epithelial and spindle cells. It is noteworthy that inflammation is a process implicated in the epithelial-mesenchymal transition through the induction of adhering molecules and transcription factors. An example of chronic inflammatory status is obesity, considered a risk factor for some neoplasms.[2,4,15,16,18,21]

Four theories concerning the histogenesis of carcinosarcomas are reported. They are theories of collision, combination, conversion, and composition.[7,19,22] The collision theory predicts that the epithelial and mesenchymal components have distinct genesis; the combination theory describes that carcinosarcoma comes from two histological presentations that overlap but have a stem cell in common in tumorigenesis; the composition theory is described as one in which the fusiform component in histopathological findings is actually a presentation of a stromal pseudosarcomatous reaction.[7,8,11] And finally, the conversion theory is that the epithelial component undergoes a type 3 epithelial-mesenchymal transition, and this theory is mainly supported by the idea that the epithelial tissue appears as a high-grade epithelium, which has undergone successive epigenetic changes in microRNAs and histones, amplifications, in particular c-myc in the epithelial component.[8,14] The two most accepted theories are conversion and collision theories, which are not mutually exclusive.[7,18,19] Therefore, this theory of epithelial-mesenchymal dedifferentiation is the one that currently best explains the histogenesis of carcinosarcomas.[20]

The monoclonal origin of carcinosarcoma is well established, so that immunohistochemistry shows great agreement between both components. However, some studies still cite the collision of the two biclonal lineages of different progenitor cells as a possible genesis of these tumors. The characterization of mutations and the genetic profile of carcinosarcomas has been improved with sequencing methods. The most common mutations are those of the genes *PTEN*, *PARP1*, *TP53*, *PIK3/AKT/MTOR*, *FBXW7*, *CCNE1*, *CHD4*, *HER2*, *ARID1A* among others; and the *TP53* mutation is the most present. Other genetic associations include mutations in *KRAS*, *PPP2R1A* and *BCOR*, as well as abnormalities in the expression of H2A/H2B histones.[4,6,14,19] Cytokines are related to the development of carcinosarcomas, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and interleukin-10 (IL-10) which they stimulate the growth of the epithelium and cause immunosuppression in the tumor microenvironment, favoring metastasis. A plausible explanation for the aggressiveness of this tumor, especially the epithelial component, is given by analyzing the vascular pattern of both components, so that studies have shown that carcinoma has higher microvascular density and higher expression of VEGF than sarcoma (this is associated with reduction of E-cadherin and others epithelial proteins). The presence of circulating tumor cells (CTC) may also help explain the higher proportion of epithelial cells with metastasis, since CTCs are made up of epithelial cells with

incomplete epithelial-mesenchymal transition that infiltrate blood vessels and are considered precursors of hematogenous metastasis. Clinically, this can be verified by evaluating the pattern of metastases which are most commonly derived from carcinoma.[3,4,8,15,17,20,23]

The most prevalent symptom is postmenopausal transvaginal bleeding or premenopausal intermenstrual transvaginal bleeding. Other less common symptoms are palpable mass, pelvic pain, and urinary and fecal changes.[6,20,21] The patient in the report presented the triad of transvaginal bleeding, pelvic pain and palpable mass.[19,22] About 10% of patients already present distant metastases at diagnosis and 30-40% of cases with extrauterine involvement at the first presentation.[6] Commonly, the tumor presents as a polypoid lesion that can protrude from the cervix,[6,19] similar to the description of this report.

The diagnosis usually occurs after the pathological study of the entire surgical specimen, since, macroscopically, a carcinosarcoma is indistinguishable from an endometrial carcinoma.[15] Imaging exams play an important role in diagnosis, staging, and therapeutic planning. Ultrasound may show hyperechoic masses compared to the endometrium and show a thickening and/or heterogeneity of the endometrial range, similar to the ultrasound description of this report (Figure 1). Although CT plays a role in assessing local disease and distant metastasis, MRI has greater sensitivity in describing local boundaries and assessing metastatic disease. It is an excellent study method, allowing more accurate staging and risk stratification, such as percentage of myometrial invasion, local extension, invasion of adjacent organs and lymph node involvement. The MRI study also assists in surgical planning, regarding the need or not for pelvic and/or paraaortic lymphadenectomy and adds details to the biopsy data. The anatomy of the healthy tissue is well demonstrated in T2-weighted images, which usually depict a hypersignal of the endometrium surrounded by a hyposignal of the junctional zone and a myometrium of intermediate signal intensity. Endometrial carcinoma usually has T1-weighted isosignal and T2-weighted hyposignal when compared to healthy endometrium.[18,24] One finding is that sarcomatous differentiation can be identified by the early enhancement, distinguishing the carcinosarcoma of the uterus from tissues of exclusive epithelial origin. With the use of gadolinium, the epithelial component shows subtle homogeneous enhancement, obtained more slowly than the surrounding myometrium on dynamic T1-weighted images.[18,19]

Among the markers researched in immunohistochemistry from the total hysterectomy, only desmin and CD10 antibodies were positive in rare cells. The other ones were negative and, considering these results and the study of the surgical specimen, the most compatible diagnosis was high-grade papillary serous carcinoma with dedifferentiation to high-grade sarcoma through epithelial-mesenchymal transition (Figure 3). It is worth mentioning that pathologists consider carcinosarcoma as a high-grade endometrial carcinoma, both the pattern of recurrence and metastasis is very similar to that of carcinoma and not to sarcoma.[21] In this case, initially, due to technical limitations in obtaining the first sample in hysteroscopy, the tumor was initially confused with a Müllerian adenosarcoma, a predominantly mesenchymal tumor, but with a malignant stromal pattern, which is usually of low degree, and also with a benign glandular epithelial component, sometimes with atypical findings.[25] Müllerian adenosarcoma should be part of the list of differential diagnoses of uterine carcinosarcoma because it is also a biphasic tumor and with more subtle differences in relation to malignant mixed Müllerian tumors for a less experienced examiner.

Treatment is multimodal, with adjuvant surgery and chemotherapy and/or radiotherapy. Surgery is the main modality of initial treatment and has as objective complete cytoreduction (without macroscopic residual disease) or optimal cytoreduction (residual disease <1cm) and consists of total hysterectomy with bilateral salpingo-oophorectomy, omentectomy, pelvic lymphadenectomy and retroperitoneal, and can be performed openly or minimally invasively (laparoscopic or robotic). According to the guidelines of the European Society for Medical Oncology (ESMO) in the clinical practice guideline, concomitant or sequential chemotherapy and EBRT (external beam radiotherapy) are recommended even in the initial cases.[26] Chemotherapy or radiotherapy alone may be considered. Chemotherapy is platinum-based and taxanes (usually carboplatin and paclitaxel) for 6 cycles every 21 days, whose purpose is the treatment of micrometastatic disease. Adjuvant pelvic radiotherapy consists of external radiotherapy and/or vaginal brachytherapy, with the role of reducing the risk of locoregional recurrence, as well as being an option to treat patients with locoregional recurrent disease or treatment of recurrence without prior use of radiotherapy. In resectable metastatic disease, chemotherapy should be considered alongside surgical cytoreduction.[19,21] In unresectable disease, we should consider exclusive chemotherapy and/or immunotherapy.[14]

The metastases are more derived from the epithelial component, and may, however, present metastasis of the sarcomatous component, or both. The epithelial component is initially disseminated lymphatically, while the mesenchymal component spreads loco-regionally or it is hematogenously disseminated, affecting lung, liver and bone.[7,8,11] Although the epithelial component metastasize more than the mesenchymal component; interestingly, this report illustrates that one of the nine lymph nodes presented a metastasis by high-grade endometrial

sarcoma, which does not represent the most common situation for this type of tumor, and this type of metastasis pattern, more common due to the epithelial component, has statistical support in the literature. Some authors speculate that the presence of a lymph node affected purely by a metastasis of sarcoma, without evidence of carcinoma, signals to a lesion whose carcinogenesis arose from the collision of two lines, soon coming from a biclonal lesion.[7,27]

This study is interesting, in this perspective, because, considering these data, the present report would not be in accordance with the speculation that the lesions with metastases due to sarcomas were, in fact, due to the collision of two different tumors, according to the histological report that initially revealed to be distinct lesions with no connection to each other. However, the immunohistochemical study of the piece clarified that it was a monoclonal lesion, which had undergone metaplastic transdifferentiation from carcinoma to sarcoma, contrary to the collision theory presented by those authors.

Previous studies have indicated that the indications of aggressiveness came mainly from the epithelial component, since a serous or clear cell component is more associated with metastases, with greater lymphovascular invasion, greater depth of myometrial invasion and isthmic and cervical involvement, which are markers of worse prognosis of the disease.[7,12,13]

Other prognostic factors to be considered are myometrial involvement >50% of its thickness, presence of heterologous components, incomplete cytoreduction (residual disease >1cm), proportional predominance of the sarcomatous component in the tumor and presence of compromised pelvic and/or retroperitoneal lymph nodes.[12,13] Regarding prognosis, the overall survival in five years is about 30%, varying according to staging: I - II: 59%, III: 25%, and IV: 9%. There is also a correlation between overall 5-year survival and the histological degree of endometrial carcinoma.[7,18,19]

The neoplasm of this report was staged as IIIC1 because it presented pelvic lymph node metastasis by the sarcomatous component, according to the staging of the FIGO. It is noteworthy that, macroscopically, the lesion consisted mainly of sarcoma.

The overall survival rate is very low and prognosis is more reserved than in other gynecological tumors with a similar high degree of carcinogenesis,[12,18,19] and most patients die of local recurrence.[7] Patients should be followed up with greater surveillance, regardless of the stage of the disease, as recurrence may occur in more than 50% despite standard treatment.[12-19] As carcinosarcoma is considered as part of the group of high-risk endometrial carcinomas due to their aggressiveness, the European Society for Medical Oncology (ESMO), in the clinical practice guideline, recommends that physical and gynecological examination be taken in the first 3 years, every 3 months, during this surveillance period and then, every 6 months, until the end of 5 years if no residual or recurrent disease is detected.[26]

CONCLUSION

This paper presents a case of uterine carcinosarcoma, a biphasic tumor whose behavior is still little known in a 59-year-old patient with risk factors for the development of uterine cancer.[2,6,18] The report presents differential aspects because it is a very rare malignant tumor, whose immunohistochemical study reinforced the hypothesis of the epithelial-mesenchymal transition, proposed to explain the histogenesis of carcinosarcomas, as well as the fact that the sarcomatous component of this mixed tumor had metastasized to one of the pelvic lymph nodes.[7,19,27] The work illustrates correspondences of this case with the scientific literature, differential aspects of the case and also reveals the importance of the diagnostic approach with immunohistochemistry for the definitive diagnosis and the multimodal therapeutic approach of this cancer by surgery and adjuvant treatment with chemotherapy.[8,9,18,19]

AUTHORS' CONTRIBUTIONS

YESB	Collection and assembly of data, Conception and design, Data analysis and interpretation, Manuscript writing
ACXL	Collection and assembly of data, Conception and design, Manuscript writing
CDC	Conception and design, Manuscript writing
RPC	Manuscript writing
MLVC	Conception and design, Final approval of manuscript, Manuscript writing
RMLVL	Conception and design, Final approval of manuscript, Manuscript writing

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