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CASE REPORT

Carcinosarcoma of the Uterine Corpus - a Case Report and Brief Review of the Literature

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Abstract

Uterine carcinosarcomas or Malignant Mixed Müllerian Tumors are exceptionally rare and extremely aggressive tumors of the uterine corpus, accounting for less than 1% of all gynecologic malignancies and 2-5% of all uterine malignancies, being responsible for more than 15% of all uterine cancer associated deaths. In this report we present the case of a 66 years old woman with no personal history of gynecologic malignancy, addressing the Department of Obstetrics-Gynecology of the University Emergency Hospital in Bucharest Romania for postmenopausal vaginal bleeding. Ultrasonography and CT scan of the pelvis revealed an endocavitary mass limited to the uterine corpus. As a result, a radical hysterectomy with bilateral salpingo-oophorectomy was carried out under general anesthesia. Microscopic evaluation revealed an admixture of malignant epithelial and mesenchymal components with small foci of clear cell carcinoma and scattered heterologous elements. These features, as well as the gross aspect and immunohistochemical results were consistent with the diagnosis of carcinosarcoma of the uterine corpus. In conclusion, due to the severe outcome and reduced survival rate of these extremely aggressive tumors, we emphasize the importance of awareness, early detection, treatment and proper surgical staging for all females with uterine carcinosarcoma.

Keywords: carcinosarcoma, malignant mixed müllerian tumor, immunohistochemistry

Rezumat

Carcinosarcoamele uterine sau tumorile mülleriene mixte sunt neoplasme excepțional de rare și extrem de agresive ale corpului uterin, ce reprezintă mai puțin de 1% dintre toate cancerele din sfera ginecologică și 2-5% dintre cancerele corpului uterin, fiind responsabile de mai mult de 15% dintre toate decesele asociate cancerelor uterine. În acest raport prezentăm cazul unei paciente în vârstă de 66 ani care se prezintă în cadrul Secției de Obstetrică-Ginecologie a Spitalului Universitar de Urgență București din România pentru metroragie în climax. Investigațiile imagistice ultrasonografice și CT relevă o masă tumorală limitată la corpul uterin. Drept urmare, se efectuează o histerectomie radicală cu anexectomie bilaterală sub anestezie generală. Evaluarea histopatologică utilizând colorația clasică, precum și testele imunohistochimice relevă un amestec de componente epiteliale și mezenchimale cu mici focare de carcinom cu celule clare și rare elemente heterogene. Toate aceste caracteristici corelate cu aspectul macroscopic și rezultatele testelor imunohistochimice susțin diagnosticul de carcinosarcom al corpului uterin. În concluzie, datorită prognosticului nefavorabil indus de această patologie, accentuăm importanța diagnosticării precoce, a diagnosticului diferențial precum și a tratamentului și stadializării corecte în vederea sporirii duratei și a calității vieții pacientelor cu carcinosarcom de corp uterin.

Cuvinte cheie: carcinosarcom, tumoră mulleriană mixtă, imunohistochimie

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INTRODUCTION

Malignant Mixed Müllerian Tumors (MMMT) also referred to as carcinosarcomas are very rare and extremely aggressive tumors of the uterine corpus accounting for less than 1% of all gynecologic malignancies, 2-5% of all uterine malignancies and more than 15% of all uterine cancer associated deaths[1]. They occur almost exclusively in post-menopausal women, but have been reported in premenopausal women as well, including young girls[2]. Carcinosarcomas have poor prognostic outcome, regardless of stage at diagnosis. The five-year survival rate ranges between 5% and 40% for patients with tumors of all stages[2-5] and does not improve significantly even with the introduction of increasingly aggressive adjuvant therapies. Patients with carcinosarcoma present worse outcome but the same associated risk factors as those reported in endometrial carcinoma[6]: obesity, nulliparity, long-term unopposed estrogen exposure and tamoxifen therapy. Scientific studies reveal that roughly 37% of the females diagnosed with MMMT present with history of radiotherapy and tend to be of younger age, the average time interval between radiation and tumor development being 10-20 years[7].

MARERIAL AND METHODS

We report the case of a 66 years old multiparous female with no known family history of gynecologic malignancy, presenting to the Department of Obstetrics-Gynecology of the University Emergency Hospital Bucharest Romania with abnormal vaginal bleeding. The patient was in good general condition. Cardiac, pulmonary and breast examinations were normal. Ultrasonography of the pelvis and full-body CT scan revealed an intramural tumoral mass limited to the uterine corpus. The patient underwent a curettage biopsy which revealed a moderately differentiated endometrial carcinoma with bizarre stromal component. Thus, a radical hysterectomy with bilateral salpingo-oophorectomy was carried out under general anesthesia and the surgically resected specimen was sent to the Department of Pathology of the same hospital unit for histopathological evaluation.

Following macroscopic examination, the tissue samples were fixed in 10% buffered formalin for 24 hours, then processed and embedded in paraffin. Afterwards, three-micron thick sections were stained with hematoxylin and eosin. Immunohistochemical studies were performed on unstained paraffin sections using an indirect tristadial Avidin-Biotin complex method. These sections were deparaffinized in toluene, dehydrated in alcohol series, rehydrated and washed in phosphate buffered saline. Afterwards, they were incubated with primary antibody overnight, washed with carbonate buffer and developed in 3,3'-diaminobenzidine (DAB) hydrochloride / hydroperoxide nuclear counterstaining. The following markers were used: Pan Cytokeratin (mouse monoclonal cocktail antibody, clone AE1/AE3, dilution 1:50, Biocare, catalog number: VP 011 G, G25), Vimentin (rabbit monoclonal antibody, clone SP20, dilution 1:50, Biocare, catalog number: CRM 312 A, B), ER – estrogen receptor (mouse monoclonal antibody cocktail, clone 1D5, dilution 1:100, Biocare, catalog number: ACI 054 A,C), PR – progesterone receptor (mouse monoclonal antibody, clone 16, dilution 1:50, Biocare, catalog number: ACA 424 A, C), CD10 (mouse monoclonal antibody, dilution 1:50, clone 56C6, Biocare, catalog number: CM 129 AK, BK, CK), CD56 (mouse monoclonal antibody, dilution 1:50, clone BC56C04, Biocare, catalog number: CM 164 A, B, C), Synaptophysin (mouse monoclonal antibody, dilution 1:100, clone 27G12, Biocare, catalog number: CM 371 AK, CK) and S100 (rabbit polyclonal antibody, dilution 1:100, Biocare, catalog number: CP 021 A, B, C).

RESULTS

Gross examination revealed a slightly enlarged uterine corpus due to a 7/6/6 cm poorly circumscribed intramural lobulated mass with plump, moist, white to gray cut surface, infiltrating more than half of the myometrium (Figure 1), with no uterine serosa involvement and macroscopically normal adnexa. Histopathological analysis performed on standard hematoxylin and eosin (HE) stained slides revealed an admixture of malignant epithelial and mesenchymal elements. The epithelial component was represented by an endometrial

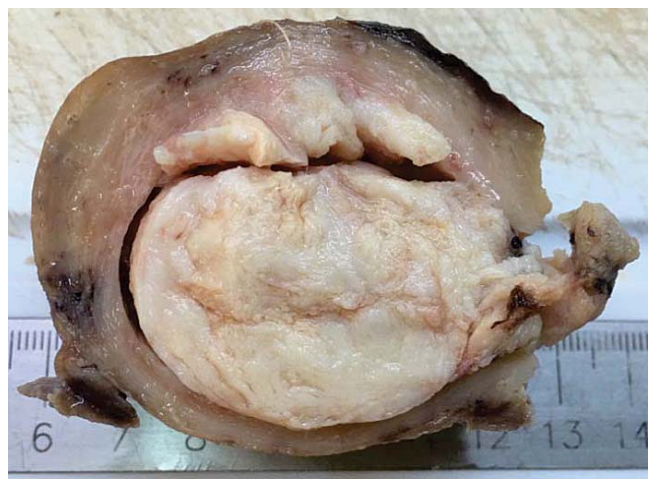

Figure 1. Gross aspect of the uterine corpus containing an intramural mass with moist, white to gray cut surface.

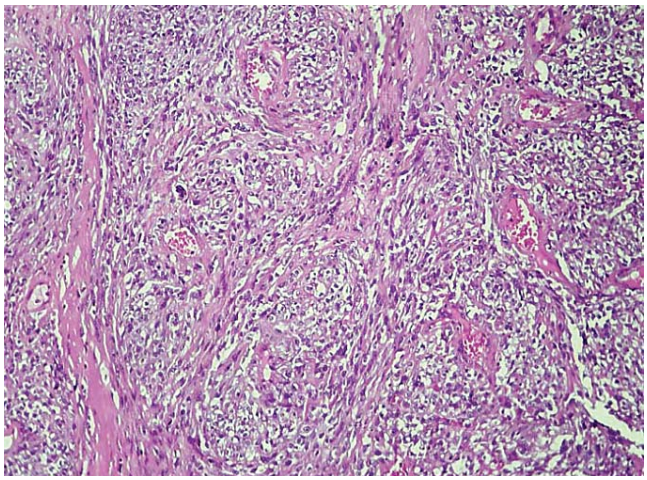

Figure 2. Microscopic aspect showing an admixture of malignant epithelial and mesenchymal elements (ob. 10x, H.E.).

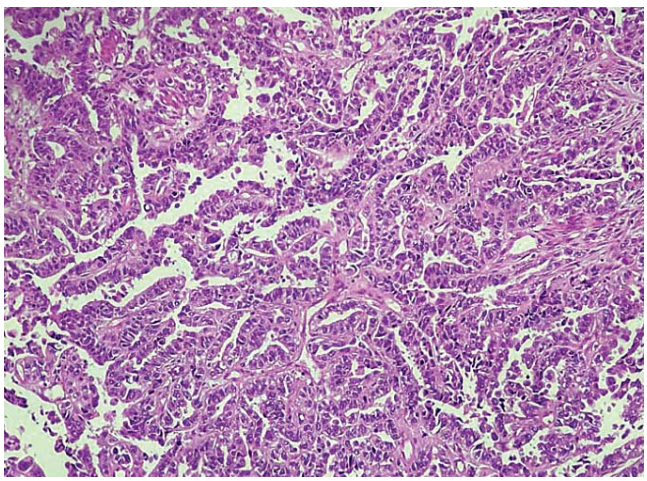

Figure 3. The epithelial component of the tumor mainly represented by a villoglandular endometrioid carcinoma (ob. 10x, H.E.).

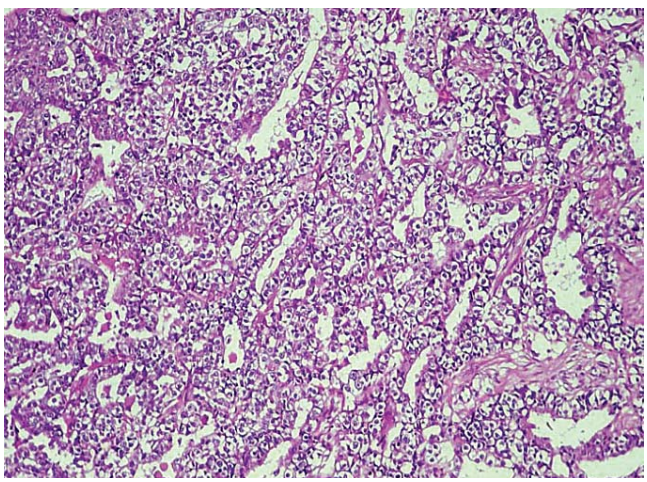

Figure 4. The epithelial component also contained small areas of clear cell carcinomatous differentiation (ob. 10x, H.E.).

endometrioid carcinoma with villoglandular pattern. The mesenchymal component was composed of poorly defined nodular-like structures with increased cellularity and nuclear pleomorphism, frequent bizarre mitotic figures (18-20 per HPF), necrotic areas and small foci of heterologous elements (represented by scattered strap-shaped rhabdomyoblasts and areas of glioma-like neuroectodermal differentiation). The epithelial component also revealed focal clusters of clear cell carcinoma, bearing a negative impact on the overall prognosis (Figure 4).

Immunohistochemical studies have been performed on multiple tumor slides. Cytokeratins AE1/AE3 and vimentin were highly positive in both the epithelial and mesenchymal components of the tumor (Figure 5, 6). In the epithelial component, estrogen receptor (ER) expressed moderate positivity while progesterone receptor (PR) expressed noticeable lower positivity. CD10 was highly positive in the mesenchymal component (Figure 7). We were surprised to find focal CD56 (Figure 8) and Synaptophysin positivity. S-100 presented diffuse positivity in the stromal component.

All these findings were consistent with the diagnosis of Malignant Mixed Müllerian Tumor or carcinosarcoma of the uterine corpus with pathological stage pT1cN0Mx.

DISCUSSION

Carcinosarcoma is defined as a biphasic malignant neoplasm composed of high-grade epithelial and mesenchymal elements, intimately admixed in variable proportions[8]. Most frequently, the two elements are individualized and sharply demarcated but sometimes merging may occur[6]. Traditionally, carcinosarcomas are considered a subtype of uterine sarcoma with epithelial and stromal differentiation. However, because most

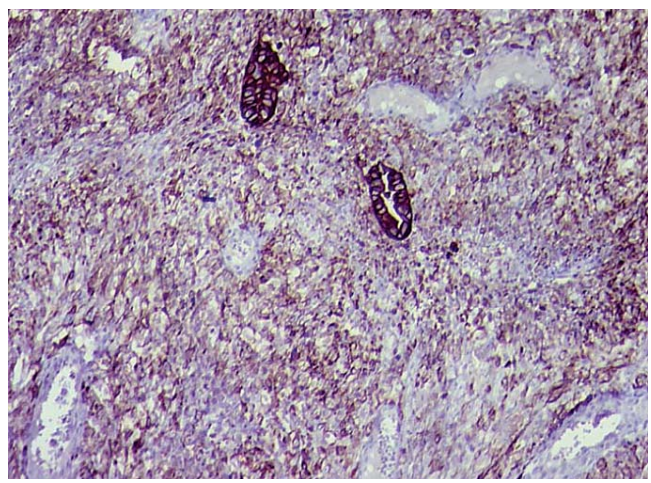

Figure 5. Immunopositivity for cytokeratins AE1/AE3 in the epithelial and mesenchymal components of the tumor (ob. 20x, DAB chromogen).

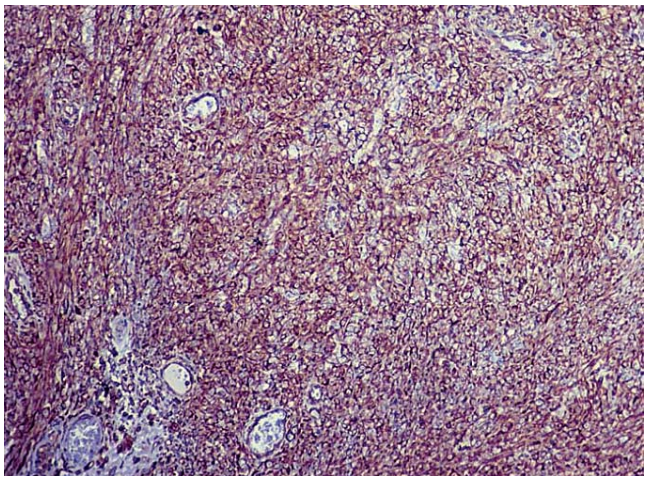

Figure 6. Immunopositivity for vimentin in both the epithelial and mesenchymal components of the tumor (ob. 10x, DAB chromogen).

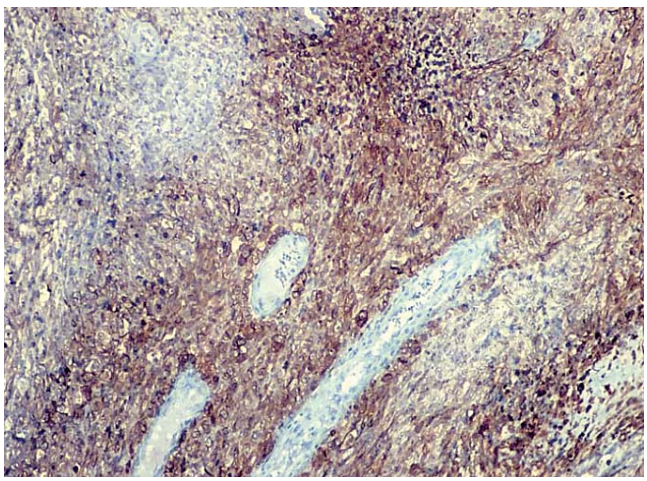

Figure 7. Immunopositivity for CD10 in the stromal component of the tumor (ob. 10x, DAB chromogen).

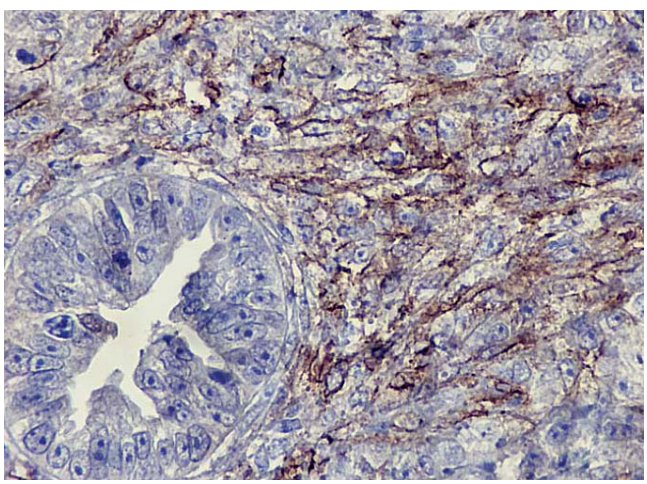

Figure 8. Slight focal immunopositivity for CD56 (ob. 40x, DAB chromogen).

patients were not responding to oncological treatment for high-grade uterine sarcoma, researchers developed four main theories in order to explain the histogenesis of this tumor: (1) the 'composition' theory suggests that the spindle element represents a pseudosarcomatous stromal reaction to a preexisting carcinoma; (2) the 'collision' theory suggests that carcinosarcoma results from the collision of two independent tumors of different origin; (3) the 'conversion' theory suggests that the sarcomatous element developed through metaplasia of the carcinomatous element; and (4) the 'combination' theory suggests that both the epithelial and mesodermal elements originate from the same precursor cell[6]. The composition theory can be easily discarded because the sarcomatous component in carcinosarcoma shows clear histological features of malignity. This theory may be applicable to carcinofibroma, in which a malignant glandular component is surrounded by a prominent but benign stroma. However, this entity is extremely rare and not all pathologists agree whether it truly exists[9]. Current literature data contains ample genetic, molecular, histopathologic and immunohistochemical evidence that most if not all carcinosarcomas are derived from a monoclonal cancer cell[10-11]. The immunohistochemical findings in our case support this theory as well. Some authors have even proposed terms such as 'sarcomatoid carcinoma of the uterus' or 'metaplastic carcinoma' to describe this neoplasm. Although the scientific evidence for adopting this nomenclature is very persuasive, many pathologists are hesitant to make this terminological adjustment and retain, as we do here, the term carcinosarcoma[5].

The molecular profile in carcinosarcoma is governed by TP53 which appears to be the most common genetic alteration in this malignancy[12]. Mutations of the PI3K/AKT and/or RAS/RAF pathways are present in almost half of all cases, the most frequent being those affecting PIK3CA, which appear in approximately 20% of cases[13-14]. A multitude of other molecular defects have been recently observed in carcinosarcomas, including: VEGFA[15], HMGA2[16], HPRT1[17] and dysregulation of microRNA in a single small imprinted region of chromosome 14q32[18]. Alterations in the Akt/ß-catenin pathway and transcriptional repression of E-cadherin appear to be fundamental for phenotype determination in carcinosarcomas[6,19-20].

Differential diagnosis of carcinosarcoma should be made with pure homologous or heterologous sarcoma as well as with spindle, high grade and undifferentiated (or dedifferentiated) endometrioid carcinoma. However, from our point of view, the most challenging differential diagnosis would involve 'collision' tumors in which an adenocarcinoma and a sarcoma occur independently, within the same uterus. Upon gross exami-

nation, a 'collision' tumor should present two separate and discrete neoplasms. In doubtful cases, diagnosis must rely on mitotic count: tumors with 20 or more mitoses per 10 HPF being regarded as high-grade malignancies[9].

Only about 65% of carcinosarcomas are confined to the uterus at the time of diagnosis[21]. Patients with carcinosarcoma must be treated by radical hysterectomy with bilateral salpingo-oophorectomy and systematic pelvic, common iliac and para-aortic lymphadenectomy. All patients should also undergo omentectomy and peritoneal washing cytology in order to assess the full extent of the tumor. Although the most appropriate therapeutic approach depends on the stage at diagnosis and varies from case to case, several scientific studies have proven the efficiency of cytoreductive surgery associated with other therapeutic strategies such as hyperthermic intraperitoneal chemotherapy (HIPEC)[22-24]. Research has demonstrated that the behavior of carcinosarcoma is determined by the epithelial component, and that its invasive pattern is very similar to high-grade endometrial carcinoma[25-27]. Studies conducted by The Gynecologic Oncology Group (GOG) revealed that when metastases are found, only the epithelial component of the tumor is present. Epithelial components metastasize through lymphatic and vascular spaces, while the sarcomatous component has very limited metastatic potential[1,27]. This view is supported by multiple studies conducted by different groups[27] and is of extremely important clinical significance when planning the adjuvant treatment. Metastatic spread typically includes the pelvic and para-aortic lymph nodes, with frequent intra-abdominal and retroperitoneal metastases[27], positive peritoneal cytology, adnexal or omental metastases as well as occasional hematogenous extent to the lung, liver, spleen, bone or brain[6,28,29]. Although the importance of omentectomy and peritoneal biopsy seems uncertain, both of them represent a recommended staging procedure in high risk endometrial carcinoma and should be performed in women with early stage carcinosarcomas. In regards to treatment, current literature data suggests that although radiation therapy does provide improved local control, it does not offer any major survival advantage. Lymph node sampling and staging are fundamental for patients with early-stage disease.

Carcinosarcomas are staged similarly to endometrial carcinomas using the TNM and FIGO classification of nontrophoblastic tumors of the uterine corpus[30-31] and they seem to have worse prognosis than endometrial serous and clear cell carcinomas. Clinical prognostic factors associated with survival include: age, race, presentation, lymphadenectomy and radiation[2]. Pathologic factors revolve around the histopathological type of the endometrial component and, of course, tumor stage. The presence of serous or, as in our case, clear cell carcinomatous elements is associated with worse prognosis[25,32]. While the depth of myometrial invasion and lymphovascular involvement in early stages are directly related to the outcome, the presence of heterologous elements within the sarcomatous component has a significant impact on the overall prognosis and survival rates in all stages of disease[6]. Despite the fact that roughly half of all carcinosarcomas are confined to the uterus at the time of diagnosis, the overall survival rates do not exceed 60% and most recurrences appear within the first 2 years. Most patients die from pelvic or abdominal recurrence rather than from metastatic disease. However, due to the progress established by the newly developed operative techniques and postoperative clinical management, the overall survival after pelvic exenteration is slightly higher.

CONCLUSIONS

Our histopathological and immunohistochemical findings further support the widely accepted histogenesis theory which suggests that carcinosarcoma arises through transdifferentiation of uterine carcinoma into sarcoma. We emphasize the fundamental importance of early detection and rigorous histopathological and immunohistochemical evaluation in order to establish a correct final diagnosis when dealing with patients with carcinosarcoma.

Conflict of interests: none declared.

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