Correlation of cyto-histological findings in a patient with carcinosarcoma

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ABSTRACT

The study shows a case of a 74 years-old woman, whose only clinical data was suspicion of carcinosarcoma. An exfoliative cytology and biopsy were performed and sent to laboratory for study. Cytology showed atypical cells with arrangement in “moruloid” groups, cytoplasmic vacuolization and marked nuclear pleomorphism. Similar observations were found with biopsy.

Immunohistochemical studies were positive for Cytokeratin 7, PAX 8, Vimentin, CD 10, Desmin and p53. Cytological, histological and immunohistochemical findings were compatible with diagnosis of Carcinosarcoma (Malignant Mixed Müllerian Tumor). This neoplasm is very rare, it usually occurs in postmenopausal women, causing bleeding and abdominal pain, and its treatment is chemotherapy and radical hysterectomy.

Key-words: carcinosarcoma, neoplasia, atypia, glandular cells

INTRODUCTION

Carcinosarcoma of the uterus, also known as malignant mixed Müllerian tumor is a rare neoplasm entity, accounting for less than 5% of all uterine malignancies[1-4]. Traditionally this tumor has been classified as a subtype of uterine sarcoma, and its origin remains controversial. The exact nature is still not clear and various theories have been given for its histogenesis; the 'conversion theory', broadly accepted, where the sarcomatous element derives from transdifferentiation of epithelial component; and the combination theory, where both components are derived from a single stem cell (common origin)[1,5]. This tumor is highly malignant in behavior and generally has a poor prognosis[1,2]. Generally, carcinosarcoma shows preponderance in postmenopausal women and radiotherapy is a possible etiological factor for its development. Vaginal bleeding, abdominal mass and pelvic pain are the usual clinical symptoms of the patients. Carcinosarcomas are considered a high-risk variant of endometrial adenocarcinoma because they share similarities in epidemiology, risk factors and clinical behavior with endometrial carcinoma as opposed to uterine sarcomas[3]. Uterine carcinosarcomas have high rates of lymphatic spread and metastasis. Patients reveal extrauterine spread in up to 45% at presentation, and over 10% of patients initially present distant metastasis[2,6].

CASE PRESENTATION

A 74 years-old woman with a bleeding episode of 7 days of evolution, greenish vaginal discharge and previous dark bleeding was present. A gynecological examination was performed in which the cervix was seen with an atrophic appearance, pointed external cervical orifice, with minimal secretion of lympho-hematic appearance, and on ultrasound an ill-defined endometrial mass of 74x44 mm with anechoic spaces inside was observed; a right adnexal cyst of 34x27 mm, and no left annex was visualized. A cervical-vaginal triple collection was performed in which a slightly hematic dirty background was observed, cells with irregular shape, orangophilia, pleomorphic nuclei with increased nucleus-cytoplasm ratio, hyperchromatic and with some prominent nucleolus (**Figure 1**).

In addition, in a dirty background, cells in disposition of "moruloid" groups, orangophilia with cytoplasmic vacuolization and marked nuclear pleomorphism were observed (**Figure 2**).

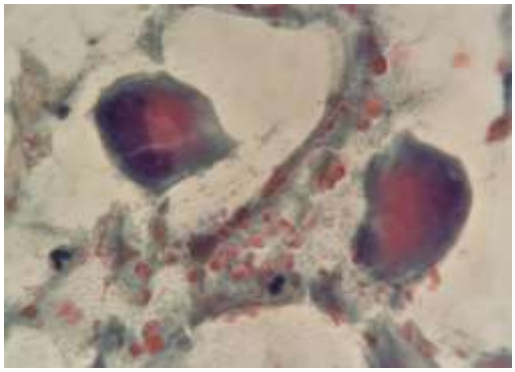

Figure 1 - Orangophilic cells seen though microscopic observation of cytology sample. Papanicolaou staining. Magnification: 400x

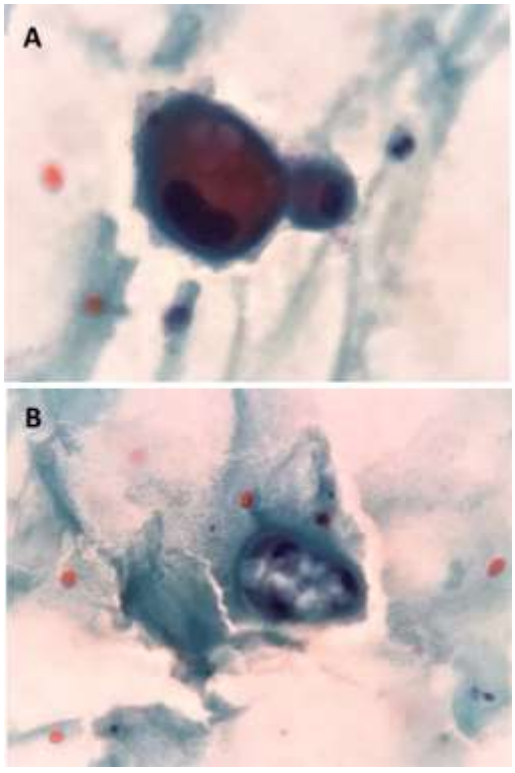

Figure 2 - Microscopic representation of the cells arranged in “moruloid” groups, with cytoplasmic vacuolation, orangophilia, and nuclear pleomorphism (**A** and **B**). Papanicolaou staining. Magnification: 400x.

INITIAL DIAGNOSTIC PROPOSAL

According to cytological findings observed there was suggestive criteria of atypia of glandular cells, a category 5: suspected of malignancy according to Bethesda system.

CASE ANALYSIS AND DISCUSSION

Atypical cells observed showed morphological features (disposition in "moruloid" groups, cytoplasmic vacuolization, marked nuclear pleomorphism) which could be compatible with an epithelial neoplastic proliferation of glandular differentiation. Due to the limitations of cytological studies, a histological study was recommended to determine both the origin of the lesion and its possible neoplastic nature.

Later studies

Imaging studies (CT scan of chest and abdomen) revealed endometrial thickening (6 cm thick), lymph nodes on the right external iliac chain with increased density, but no significant increase in size. There was no evidence of retroperitoneal lymphadenopathies or in thoracoabdominal lymph node chains. Hysteroscopy and endometrial loop biopsy were performed; multiple irregular and grayish fragments were obtained, with a combined size of 4x3.8 cm, in a total inclusion.

On biopsy, at low magnification, irregularly shaped glandular lumens were seen, large areas of necrosis, and a dense stroma (**Figure 3A**). With higher magnification we were able to observe glandular lights, stroma between them, and some cells with nuclear hyperchromasia (**Figure 3B**).

At higher magnification cells with irregular nuclei were observed (**Figure 4A**), and at maximum magnification we could see irregular cells with bizarre-looking, hyperchromatic, pleomorphic nuclei, with an increased nucleus-cytoplasm relationship (**Figure 4B**).

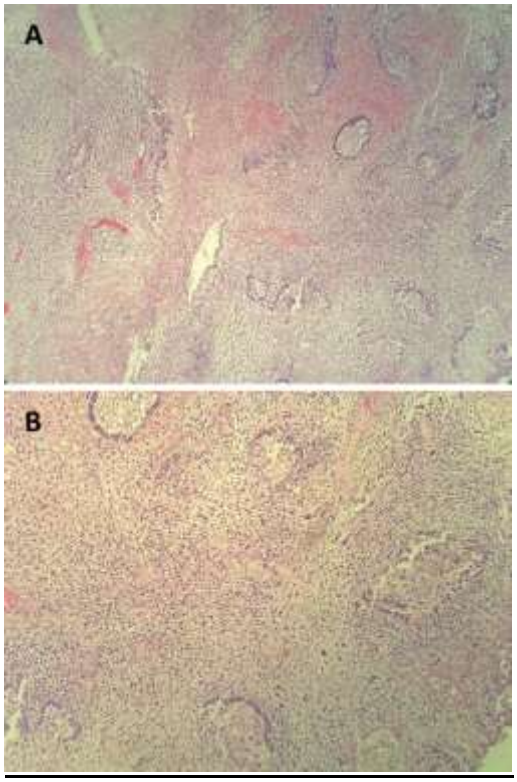

Figure 3. A: Microscopic observation of the biopsy shows irregular glandular lumens, dense stroma, and areas of necrosis. **B**: At higher magnification, it possible to observe in detail glandular lumens, stroma, and hyperchromatic cells. Hematoxylin and Eosin staining. Magnification: 100x.

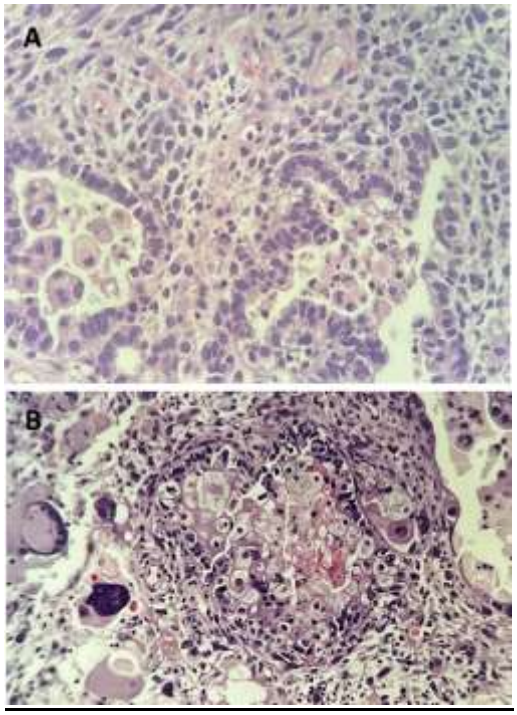

Figure 4. A: Glandular lumens with irregular cells identified through microscopic evaluation. **B**: Microscopic observation of bizarre-looking cells, pleomorphic and hyperchromatic nuclei. Hematoxylin and Eosin staining. Magnification: 400x.

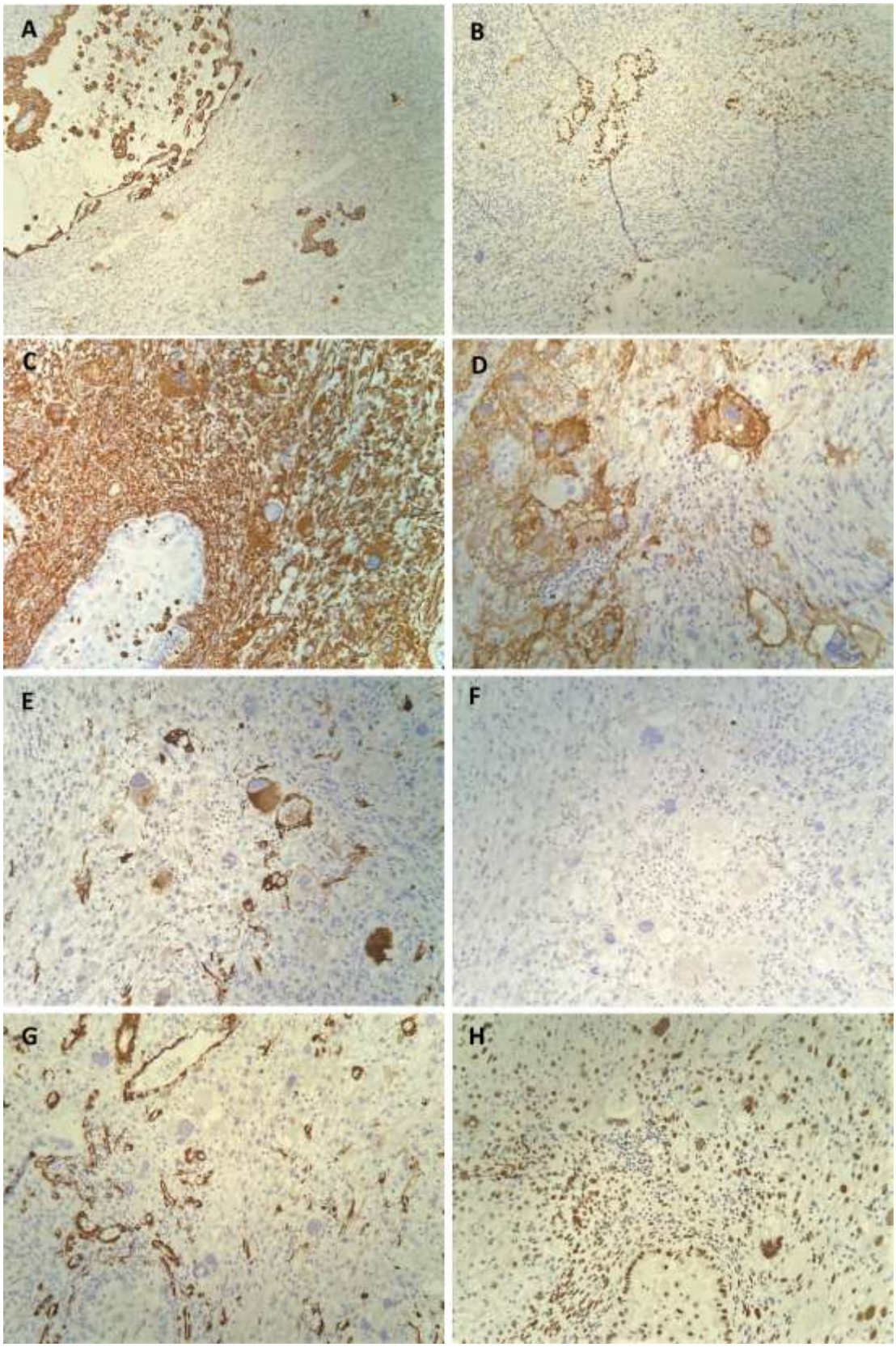

Figure 5. Biopsy tissue immunohistochemistry resulted positive for citokeratin 7 (CK7) (**A**); positive for PAX-8 (**B**); positive for Vimentin (**C**); positive for CD10 (**D**); positive for desmin (**E**); and negative for caldesmon (**F**) and Actin ML (**G**). Immunohistochemistry was positive for p53 (**H**). Magnification: 200x

Immunohistochemical study

Immunohistochemical results revealed positive for Cytokeratin 7 (CK7), PAX 8, Vimentin (mesenchymal component), CD 10, desmin and p53. Negative immunohistochemistry results were found for caldesmon and for smooth muscle actin antibodies. Moreover, the genome guardian p53 was negative. Thus, immunohistochemical study confirmed mesenchymal and sarcomatous origin, ruled out muscular origin, according to **Figure 5A-H**.

Pathological diagnosis

A malignant tumor was diagnosed with morphological and immunohistochemical findings compatible with Carcinosarcoma (Malignant Mixed Müllerian Tumor). Surgical intervention was scheduled for hysterectomy, bilateral adnexectomy, omentectomy and pelvic and para-aortic lymphadenectomy.

Anatomopathological study

A bilateral hysterectomy and adnexectomy specimen weighing 200g was received, measuring 8.5x5.5x3 cm. A mass that appeared through external cervical orifice of grayish color with yellowish areas, of friable consistency. The endometrial cavity was occupied by a mass of "pseudopolypoid" morphology, with approximately 7x6 cm, with histologic characteristics (**Figure 6**), which showed a gelatinous appearance with cystic-like areas when cut. Lesion infiltrated myometrium macroscopically, in a maximum thickness of 1.6 cm (> 50% thickness).

Under microscope, we observed necrotic areas, and at higher magnification, we saw again, irregular glandular lights, cells with pleomorphic and hyperchromatic nuclei (**Figure 7A-B**). At higher magnification, we saw cells with increased nucleo-cytoplasmic ratio, pleomorphic, hyperchromatic nuclei, cytoplasmic vacuolization (**Figure 7C-D**).

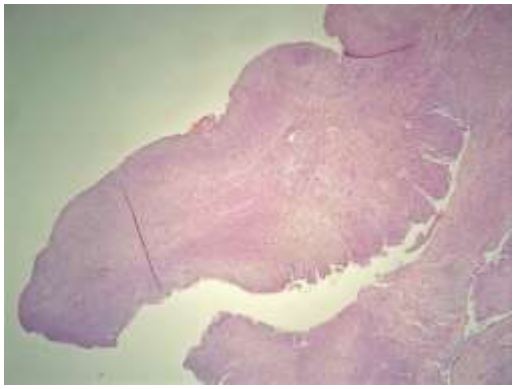

Figure 6. Low magnification of the histerectomy surgical product showing a mass of "pseudopolypoid" morphology. Hematoxylin and Eosin staining. Magnification: 100x

DISCUSSION AND CONCLUSION

In the present study, the diagnosis of carcinosarcoma (malignant mixed Müllerian tumor) was confirmed, classified as a pathologic stage of pT3b N2a (FIGO IIIC2). Carcinosarcoma is a rare tumor, accounting for less than 5% of gynecological carcinomas, and usually in postmenopausal women with mean age of 65 years[1-5]. The main risk factors for the disease include prior pelvic radiotherapy (within 5-20 years interval), Tamoxifen treatment (in 6% of cases) and other predisposing factors such us chronic estrogen exposure, nulliparity, diabetes, and obesity[3,6]. Macroscopically, it consists of a polypoid mass in the uterine body, which can appear through the external cervical orifice, with fleshy and gelatinous appearance, and frequent hemorrhage and necrosis. The microscopic findings include a biphasic tumor with juxtaposed carcinomatous and sarcomatous elements, both of high grade. The malignant epithelial elements are typically an adenocarcinoma of endometrioid type. However, serous, mucinous, clear cell, squamous cell and differentiated carcinomas are also frequent. The sarcomatous (mesenchymal) elements are usually high-grade sarcoma NOS; heterologous patterns include rhabdomyosarcoma, chondrosarcoma and osteosarcoma and liposarcoma[6].

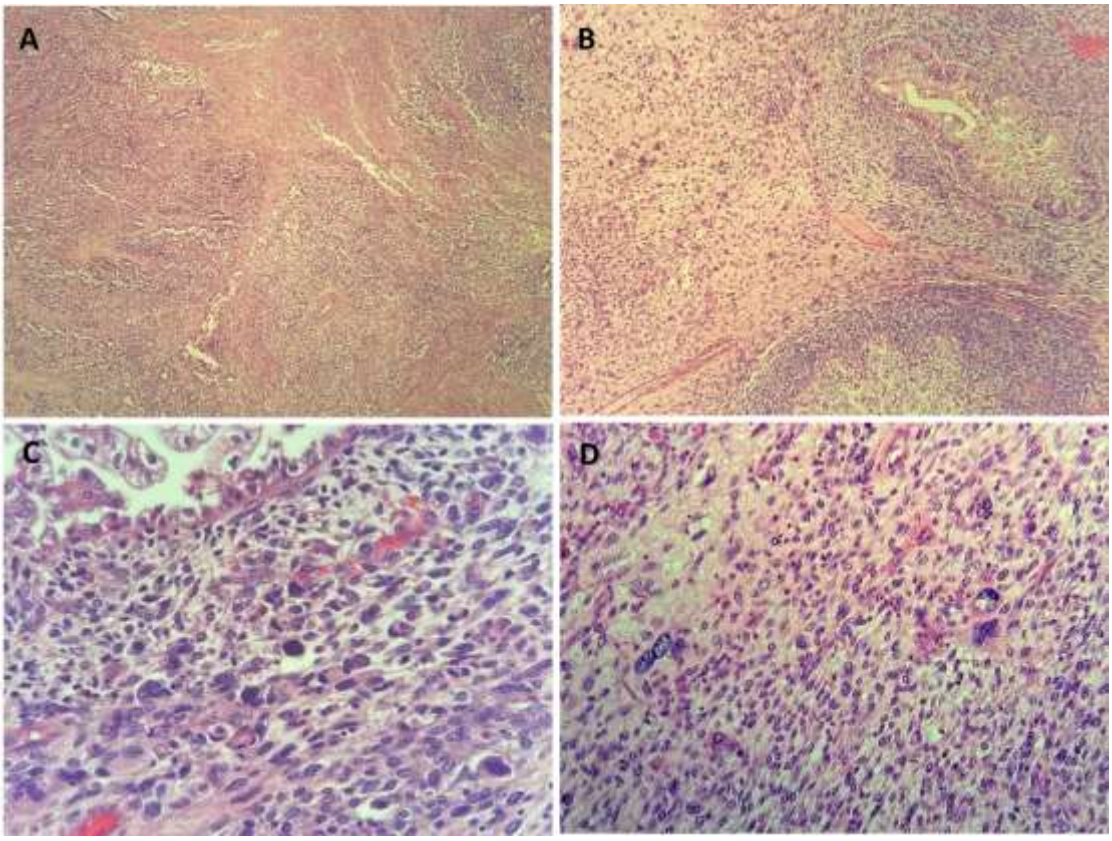

Figure 7. Through microscopic observation of the uterine mass it is possible to observe necrotic areas (**A**) Magnification: 100x; and at higher magnification, irregular glandular lights, cells with pleomorphic and hyperchromatic nuclei and necrotic areas (**B**), Magnification: 200x; in **C** and **D** pleomorphic, hyperchromatic and vacuolated cells are shown. Hematoxylin and Eosin staining. Magnification: 400x

The prognosis according to FIGO stage is poor, with 10% of survival at 5-years for stage IV patients. The worse prognosis is strictly related with disease factors including the tumor size higher than 5 cm, >50% of myometrial invasion, lymphovascular invasion and the heterologous rhabdoid component[3,6,7].

This pelvic malignancy was treated by multimodality therapy including surgery - total abdominal hysterectomy and bilateral salpingo-oophorectomy, chemotherapy and radiotherapy[1,4,6].

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