Autopsy Case Reports

Article / Clinical Case Report

Primary endometrial large cell neuroendocrine carcinoma with melanocytic differentiation

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ABSTRACT

High-grade endometrial carcinomas are aggressive neoplasms of difficult histological classification. Neuroendocrine differentiation in endometrial carcinomas is rare. This is the report of an endometrial large cell neuroendocrine carcinoma with foci of melanocytic differentiation in a 75-year-old woman with abnormal post-menopausal uterine bleeding for 2 years. Two initial biopsies were inconclusive. Histopathological examination of the uterus revealed large cell neuroendocrine carcinoma associated with endometrioid carcinoma and foci of melanocytic differentiation, pT3a (FIGO IIIA). There were metastases in the rectum serosa and lungs. After 8 months of diagnosis and surgical treatment, the patient is on chemotherapy and radiotherapy. We highlight the morphological characteristics and criteria that allow the definitive anatomopathological diagnosis, including immunohistochemical markers used to identify the cell types present in this unprecedented association.

Keywords
Endometrium; Carcinoma, Neuroendocrine; Carcinoma, Large Cell; Melanocytes; Immunohistochemistry.

INTRODUCTION

Endometrial carcinoma is the most common invasive neoplasm of the female genital tract.[1,2] Data from the Brazilian National Cancer Institute (INCA) estimate an incidence of 6.2 cases of uterine and ovarian malignancies per 100,000 women in the southeastern region of Brazil in 2018.[3] Such tumors may present a diagnostic challenge at microscopy, especially when they are poorly differentiated neoplasms of high histological grade. Neuroendocrine differentiation is uncommon. High-grade neuroendocrine carcinomas correspond to less than 1% of endometrial neoplasms.[4] Endometrial neuroendocrine carcinomas are underdiagnosed in 89% of cases[5]; most are of large cell type and associated with other histological types, especially endometrioid carcinoma.[5-7]

Melanocytic differentiation in endometrial neoplasms is even more uncommon. There are rare reports of melanocytic differentiation in carcinosarcoma and benign melanocytic lesions in the endometrium.[8-11] We present the rare case of a primary endometrial large cell neuroendocrine carcinoma with foci of melanocytic differentiation.

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CASE REPORT

A 75-year-old Brazilian non-white female attended the hospital reporting abdominal pain and post-menopausal bleeding for 2 years. Transvaginal ultrasonography (TVU) showed the uterus in anteversion, with regular contours, 5.7 × 3.5 × 4.8 cm, and 52.9 cm^3, plus myometrium with homogeneous echotexture. The endometrium was 0.32 cm of thickness and a bulky endometrial polyp measuring 3.5 × 2.5 cm with a stalk in the uterine posterior wall was observed. Both ovaries had an atrophic appearance, 1.8 × 1.2 × 1.2 cm, and 1.4 cm^3 (right); and 1.7 × 0.8 × 1.7 cm, and 1.4 cm^3 (left). Cervicovaginal cytopathological examination found *Gardnerella* sp. and inflammation; neoplasm was absent. Hysteroscopy was recommended for removal of the polyp; however, the patient only returned to the hospital for further treatment after 14 months. In a new TVU, the uterus was 8.0 × 5.5 × 5.2 cm, and 120.4 cm^3; the endometrium had heterogeneous echogenicity and was markedly thickened; and there was a solid projection within the uterine cavity, shown with Doppler flow. Both adnexae were uremarkable. Cervicovaginal cytology showed atypical cells, which was suggestive of invasive endometrial adenocarcinoma. The patient underwent hysteroscopy to remove the polyp. Histopathological examination demonstrated a necrotic pleomorphic neoplasm, which was undefined between pleomorphic rhabdomyosarcoma, undifferentiated carcinoma, and poorly differentiated adenocarcinoma. Due to extensive necrosis present in the sample, the immunohistochemical study was inconclusive. The patient was then hospitalized and underwent biopsy curettage. Immunohistochemistry was negative for all markers (AE1/AE3, desmin, PAX-8, S-100, myogenin). The tumor was labeled as epithelioid malignant neoplasm with extensive necrosis. Then, extended total hysterectomy (ETH) and adnexectomy were performed.

Gross findings (Figure 1) showed a pyriform uterus of 168g and 9 × 5 × 5 cm. In the uterine cavity, there was a pedunculated polypoid mass that occupied and expanded the entire cavity, with infiltration of more than 50% of the myometrial thickness in its base. The polypoid mass was 7.5 × 3.5 cm, predominantly white, soft, and shiny, with interspersed black areas. At the cervix, it was red and elastic.

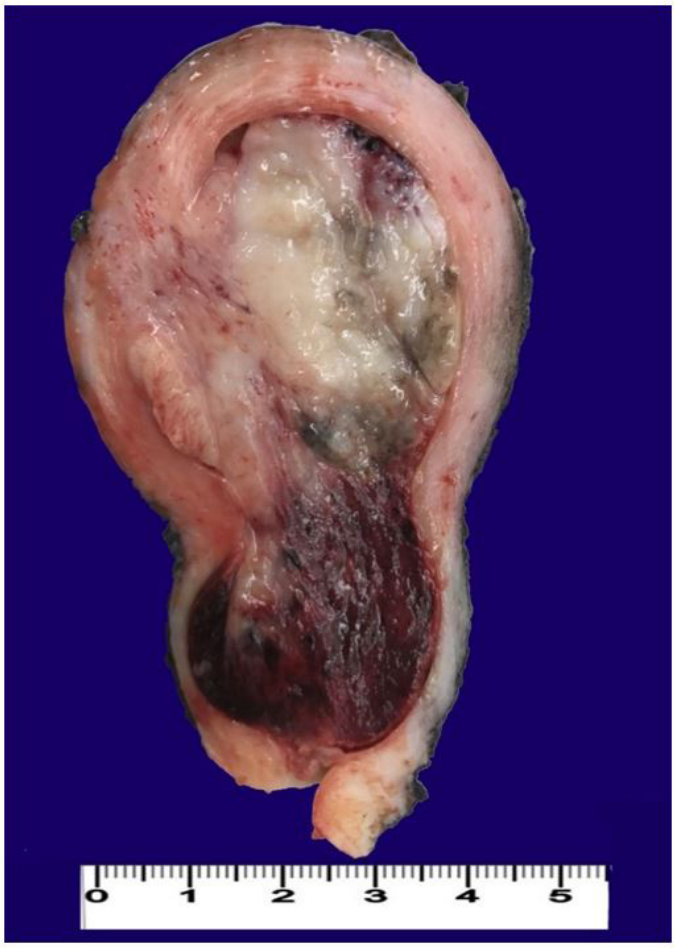

Figure 1. Gross features: a pedunculated polypoid endometrial mass with interspersed black and hemorrhagic areas.

Microscopic analysis showed a heterogeneous neoplasm, with glandular areas, solid areas that corresponded to more than 10% of the neoplasm, large bizarre atypical cells, and extensive regions of necrosis.

In the solid areas, the cells presented an occasional trabecular arrangement or nesting (Figure 2A), large nuclei, finely granular chromatin and occasional nucleoli, scarce cytoplasm interposed with cells that had bulky and bizarre nuclei (Figure 2B), and eosinophilic cytoplasm. Extensive vascular neoplastic infiltration was observed. The cells were positive for cytokeratin (AE1/AE3), synaptophysin (Figure 2C), chromogranin A and p16, and—weakly—for CD56. The mitotic index was higher than 10 mitoses/high power field, and the cell proliferation index, calculated by Ki-67 immunostaining, was 50%. In neoplastic glands, the cells were cohesive with vesicular and pleomorphic nuclei and eosinophilic cytoplasm, allowing the

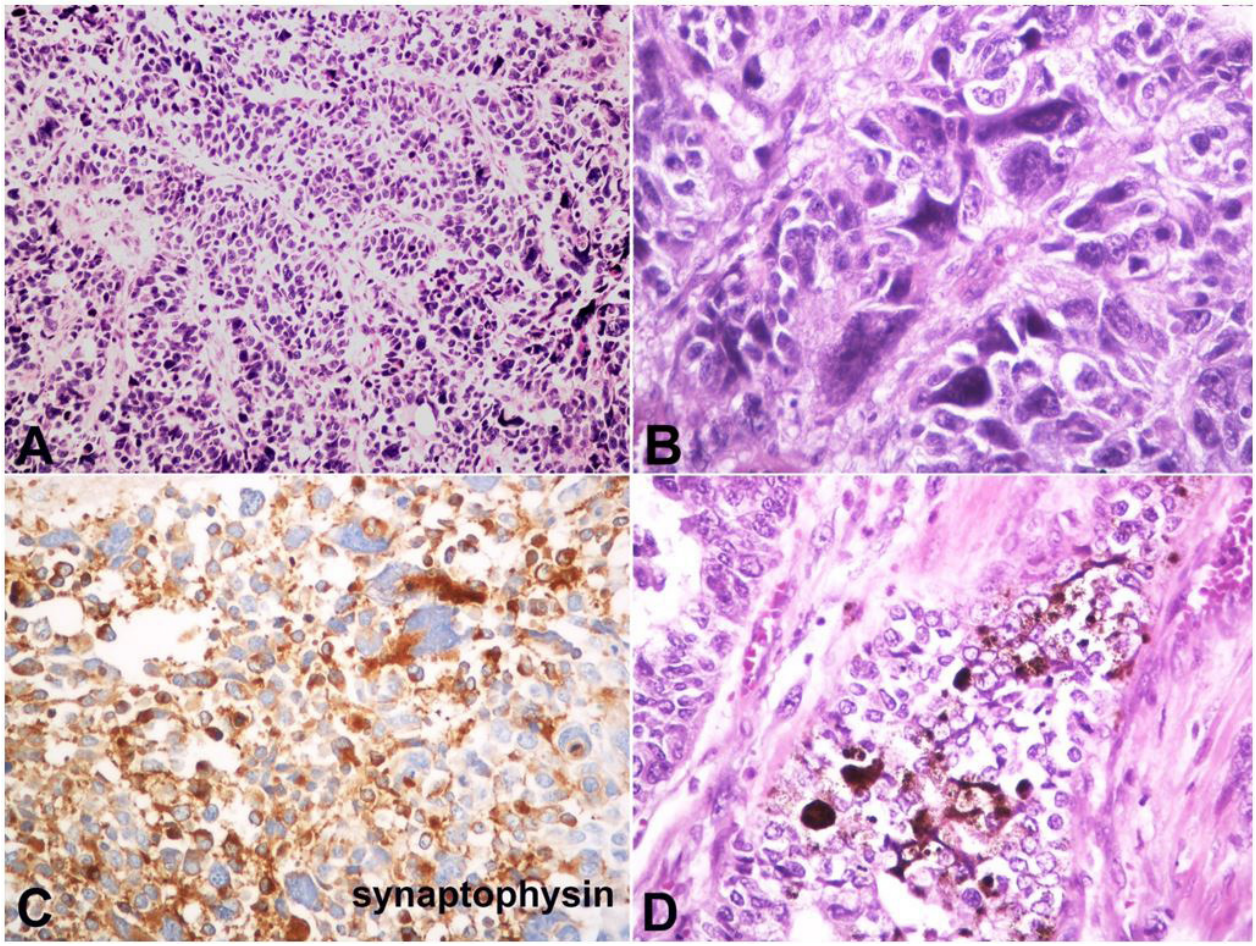

Figure 2. Photomicrograph of the tumor showing in **A –** nesting pattern (HE, 20x); **B –** Large cells with bulky and bizarre nuclei (HE, 40x); **C –** Neoplastic cells show strong cytoplasmic expression of synaptophysin (40x); **D –** Melanocytic differentiation: cells with granular brown pigment (HE, 40x).

diagnosis of endometrioid carcinoma of high nuclear grade. Occasionally, and in correspondence to the macroscopic black areas, there were cells with clear cytoplasm and granular brown pigment (Figure 2D).

Immunohistochemistry showed the expression of Melan-A in a greater extent than that occupied by cells with cytoplasmic pigment (Figure 3).

The carcinoma involved the anterior and posterior walls of the uterine body and isthmus to the subserosa. Extensive neoplastic infiltration was observed in the right mesosalpinx. The right ovary and left adnexa were free of neoplasia. There were metastases of undifferentiated large cell carcinoma in the rectum serosa, and pelvic lymph nodes were not resected. Staging was pT3aNxM1, FIGO IIIA.

Chest x-ray ordered after ETH showed pulmonary metastasis. The patient was referred to radiotherapy for endometrial neoplasia with a dose of 4,500 cGy, 25 doses, and chemotherapy (cisplatin 120mg + cyclophosphamide 830mg), six cycles of 28 days each. During treatment, she reported weight loss, 2.7 kg, hyporexia, and 10/10 intense burning vaginal pain. She was discharged from radiotherapy

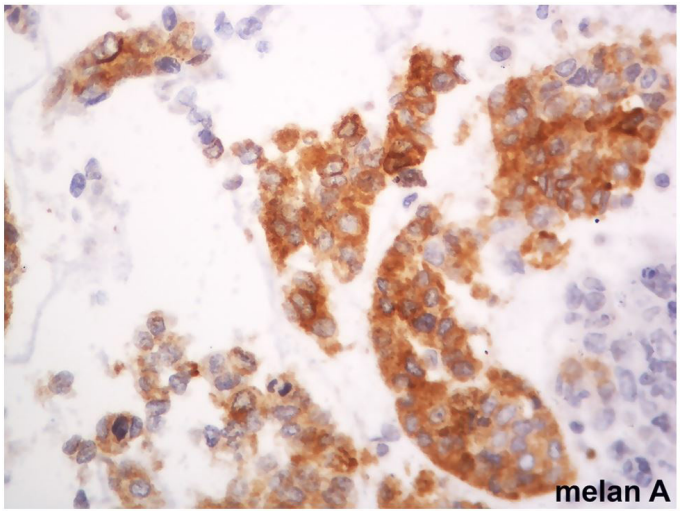

Figure 3. Photomicrograph of the tumor showing expression of melan-A in part of the neoplastic cells (40x).

and referred for complementary treatment with brachytherapy. Currently, 8 months after diagnosis, the patient is stable, is followed up by oncology, and is waiting for brachytherapy.

DISCUSSION

High-grade endometrial malignancies may be extremely heterogeneous neoplasms, which are histologically difficult to classify.[12] The microscopic features of large cell neuroendocrine carcinomas at hematoxylin & eosin (H&E) staining may mimic several other malignant neoplasms, such as poorly differentiated adenocarcinoma, undifferentiated sarcoma, malignant mixed Müllerian tumor, undifferentiated carcinoma, primitive neuroectodermal tumor, and atypical carcinoid tumors.[5,13,14] There are various associations of large cell neuroendocrine carcinomas with other endometrial malignancies: endometrioid carcinoma, serous carcinoma, and undifferentiated sarcomatoid carcinoma.[4,15,16] In the fourth edition of the WHO Classification of Tumors of Female Reproductive Organs, neuroendocrine carcinomas of large cells are defined as neoplasms that show a "neuroendocrine growth pattern in at least part of the tumor, with expression of one or more of the neuroendocrine markers chromogranin, CD56, synaptophysin in more than 10% of the neoplastic cells."[17]

In the present case, synaptophysin and chromogranin A were expressed in more than 10% of the neoplastic cells. Pocrnich et al.[5] have reported that the neuroendocrine marker most commonly expressed in neuroendocrine carcinoma of the endometrium is synaptophysin, and that expression of the three markers was seen in 5 of 25 cases (20%). In this case, there was diffuse expression of p16, which is also reported in other studies.[4,5,7,18] The polypoid aspect is another characteristic present in several studies; however, it is not the only form of macroscopic presentation.[7,17,18] Multinucleated bizarre cells are not commonly observed in endometrial large cell neuroendocrine carcinomas; however, 16% of cases described by Pocrnich et al.[5] exhibited such a characteristic. Some studies report that endometrial small cell neuroendocrine carcinomas are more common than those of large cells, which makes this report even more unusual.[6,18]

In our patient's case, there were unusual areas with melanocytic differentiation, which is rare in uterine neoplasms. There are few reports of this differentiation in carcinosarcoma.[8,9] Neuroendocrine carcinomas are complex neoplasms composed of cells able to produce substances that can generate paraneoplastic syndromes, and melanin, through melanosomes present in these cells, which can be observed by electron microscopy.[19]

Endometrial neuroendocrine carcinoma is a rare, extremely aggressive neoplasia that requires a specific type of chemotherapy.[5,14] In the literature, there was no report of the association between two rare conditions in endometrial neoplasms: large cell neuroendocrine carcinoma and melanocytic differentiation.

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Author contributions: Guimarães LC reviewed the case and wrote the manuscript. Garcia PL reviewed the medical record and wrote the clinical report. Castro Filho JB was in charge of the gross examination of the surgical specimen, microscopic analysis and the anatomopathological report. Meneses ACO was in charge of the gross examination of the surgical specimen, microscopic analysis and reviewed the pathological report. All the authors collectively proofread and approved the final version for publication.

The authors retain an informed consent signed by the patient authorizing the publication and the manuscript was approved by the Institutional Ethics committee.

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