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Case report

Serous carcinoma of endometrium in combination with neuroendocrine small-cell: A case report and literature review

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ABSTRACT

Endometrial serous carcinomas are very clinically aggressive, which constitutes 40% of all deaths and recurrences associated with endometrial cancer. Small-cell carcinoma of the endometrium is relatively rare but aggressive, and often presents a component of endometrioid carcinoma, and is not generally associated with serous carcinoma. Herein, we report a case of 74-year-old African-American female, who presented with intermittent post-menopausal bleeding for >1-month. She underwent robotic-assisted laparoscopic hysterectomy, bilateral salpingo-oophorectomy, sentinel lymph node mapping, and pelvic-and-aortic lymphadenectomy. Final pathology was consistent with serous carcinoma of the endometrium in combination with neuroendocrine small-cell carcinoma. This extremely rare combination of tumors presents a challenge for treatment. The mainstay of treatment seems to be surgery followed by chemotherapy ± radiation therapy. To our knowledge, it represents an under-reported area of gynecological medicine.

1. Introduction

Endometrial serous carcinomas, which compromise approximately 10% of endometrial carcinomas, are very clinically aggressive (Clement and Young, 2004). This tumor type constitutes 40% of all deaths and recurrences associated with endometrial cancer (Fader et al., 2010).

Small-cell carcinoma (SCC) of the endometrium is relatively rare but aggressive, and often presents a component of endometrioid carcinoma, and is not generally associated with serous carcinoma. The endometrium is the least common site of this disease in the female genital tract (Matsumoto et al., 2011). Histologically, small-cell neuroendocrine tumors present very similarly in the endometrium as it does, more commonly, in the lung (Kumar, 1984). An optimal treatment for patients with SCC has not yet been well defined due to its rare occurrence. Approximately 85 cases of SCC of the endometrium have been reported to date.

In this case study, we report a unique and challenging case that covers the unusual combination of serous carcinoma of endometrium with small-cell neuroendocrine. To our knowledge, it represents an under-reported area of gynecological medicine.

2. Case presentation

A 74-year-old African-American female (BMI 32.9 kg/m^2), presented with intermittent post-menopausal bleeding for more than one month. She denied any breast, gynecologic and/or colon cancers in her family. The patient had four spontaneous vaginal deliveries at term.

On transvaginal ultrasound exam, her uterus measured 11 × 6 × 7.1 cm. There were two fibroids noted measuring 3.8 cm and 2.3 cm, along with a 0.8 cm calcification at the fundus, probably a small fibroid. Endometrial stripe was 0.3 cm, and the ovaries were unremarkable. The right ovary measured 1.1 × 0.7 × 1.1 cm, while the left ovary measured 1.8 × 1.0 × 1.6 cm. The patient's Pap-Smear was negative. She underwent examination with her gynecologist. For further assessment, endocervical curettage (ECC), endometrial biopsy and cervical biopsy were obtained that showed a poorly-differentiated carcinoma. There was also a polyp from the endocervix which showed poorly-differentiated carcinoma.

The patient was then seen in consultation with our Gynecologic Oncology Service. Pathology slides were reviewed at our hospital, which showed a high-grade poorly differentiated carcinoma with cervical involvement (Figs. 1–3). Pre-operative immunohistochemistry (IHC) tests showed positivity for keratin, CK7, p63, p16, and focal estrogen receptor, which raised the possibility of a serous carcinoma. Pathology assessment revealed a malignant neoplasm in all specimens and minute fragments of high-grade poorly differentiated carcinoma (Figs. 1–3).

A computed tomography (CT) of the chest, abdomen and pelvis was recommended, given the possibility of a serous carcinoma, and to

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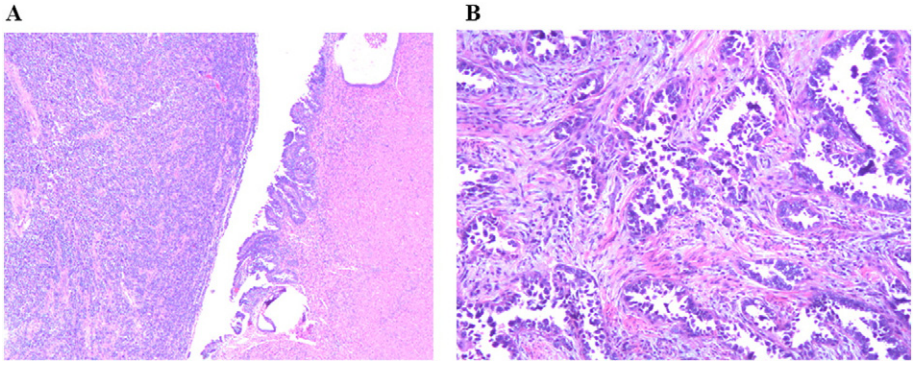

Fig. 1. (A) Polypoid endometrial small-cell carcinoma (left) and serous intraepithelial carcinoma (H&E, 4×). (B) Serous adenocarcinoma with infiltrative glands lined by cells that have a "hobnail" appearance (H&E, 20×).

determine the extent of her disease. The scan showed endometrial cancer which invaded to the level of the uterine serosa, with no evidence of parametrial invasion or metastatic disease in the abdomen or pelvis. The cervix appeared grossly normal and no lymphadenopathy was noted. On CT of the chest, there was a 5 mm non-specific nodule in the anterior right upper lobe. Recommendation was for robotic-assisted laparoscopic hysterectomy, bilateral salpingo-oophorectomy, sentinel lymph node (SLN) mapping, and pelvic-and-aortic lymphadenectomy.

Accordingly, the patient underwent these surgical procedures without issues. At the time of surgery, the patient's uterus was approximately 8-weeks size. There were some fibroids noted. Tubes and ovaries appeared normal. The upper abdomen surveyed normal with smooth-appearing liver surface and diaphragm. The omentum was without abnormalities. With SLN mapping, utilizing FireFly technology, there were green dye positive external iliac lymph nodes bilaterally. These nodes had no blue dye uptake.

Surgical pathology findings revealed a stage II, serous endometrial adenocarcinoma located in the anterior and posterior endometrium, measuring 9.5 × 7.8 × 2.5 cm with 87% myometrial invasion and lymphovascular space invasion. There was also cervical stromal involvement. Benign nabothian cysts, intramural leiomyomas and a benign para-tubal cyst on the left fallopian tube were also noted. All 33 lymph nodes retrieved were negative for malignancy.

Intra-disciplinary tumor board review of the post-surgical pathology showed areas of apparent neuroendocrine differentiation within the tumor. The IHC showed diffuse immunoreactivity for CD56 within the tumor, with focal immunoreactivity for synaptophysin. p53 was diffusely immunoreactive, while CD99 was negative (Figs. 1–3). These results were most consistent with a combined serous adenocarcinoma and small-cell neuroendocrine carcinoma of the endometrium, each component compromising approximately half of the tumor. DNA mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) were tested by immunohistochemistry.

Recommendations from our tumor board was sandwich therapy consisting of etoposide/cisplatin with whole pelvic radiation. The patient relocated after surgery closer to her family and was lost to follow-up for 3-months. She was instructed to begin therapy as soon as possible. Unfortunately, she did not follow through with the treatment recommendations in a timely manner. She subsequently returned to our institution with evidence of widespread, progressive disease. Chemotherapy was initiated. The patient received two-cycles and then refused further treatment. She died of disease (DOD) 2-months thereafter.

3. Comments/discussion

Endometrial cancer is the most common gynecological malignancy in the United States. Annually, 319,600 women are diagnosed with this disease worldwide (Torre et al., 2015). Serous carcinoma of the endometrium is a clinically aggressive disease and tends to spread early, via myometrial invasion, lymphovascular space invasion (LVSI), intra-abdominal invasion as well as distant spread. Prognosis is generally poor, with a 50% relapse rate and a 5-year survival rate of 18–27% (Acharya et al., 2005). The survival rate of women with stage I-II disease is 35–50%, while stage III-IV disease patients show a survival rate of 0–15% (Acharya et al., 2005).

Small-cell neuroendocrine carcinoma is an extremely rare and aggressive disease of the female genital tract, representing 2% of all gynecological malignancies (Crowder and Tuller, 2007), and 0.8% of all endometrial carcinomas (Ishida et al., 2014). Proposed diagnostic criteria by van Hoeven et al. (1995) for small-cell neuroendocrine tumors are as follows: i) uniform, small- to medium-sized tumor cells form flaky or nested cell mass, which may or may not be associated with other tumors, such as adenocarcinoma, ii) at least one neuroendocrine marker should be positive in IHC examination, and iii) clear evidence of primary SCC of the endometrium must be identified to exclude the possibility of invasion or transfer of SCC from other parts

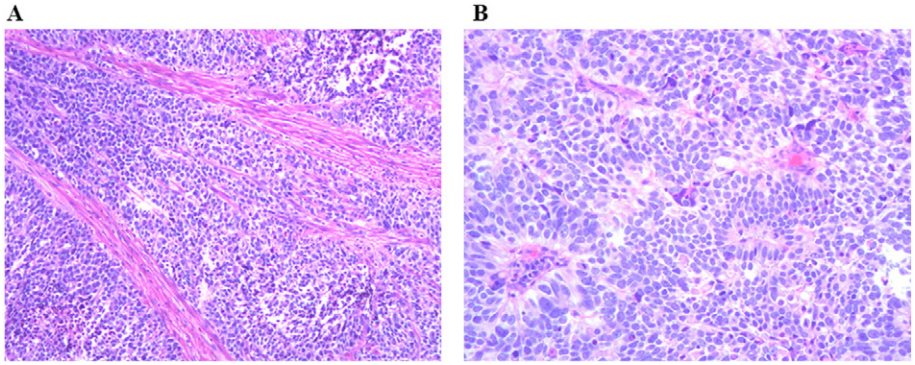

Fig. 2. (A) Small-cell carcinoma invading the myometrium (H&E, 10×). (B) Small-cell carcinoma with perivascular pseudorosettes (H&E, 20×).