

## 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 postmenopausal 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.

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## 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<sup>2</sup>), 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.

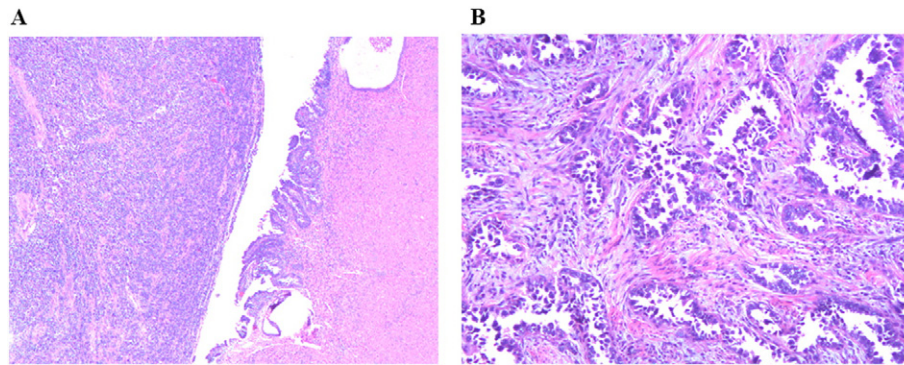
On transvaginal ultrasound exam, her uterus measured 11 × 6 × 7.1 cm. There were two fibroids noted measuring 3.8 cm and 2.3 cm, along with a 0.8 cm calcification at the fundus, probably a small fibroid. Endometrial stripe was 0.3 cm, and the ovaries were unremarkable. The right ovary measured 1.1 × 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 $\times$ ). (B) Serous adenocarcinoma with infiltrative glands lined by cells that have a “hobnail” appearance (H&E, 20 $\times$ ).

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  $\times$  7.8  $\times$  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.

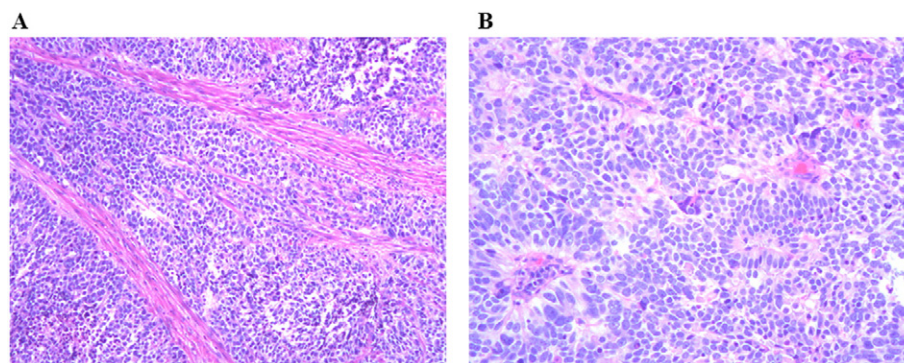
Intra-disciplinary tumor board review of the post-surgical pathology showed areas of apparent neuroendocrine differentiation within the tumor. The IHC showed diffuse immunoreactivity for CD56 within the tumor, with focal immunoreactivity for synaptophysin. p53 was diffusely immunoreactive, while CD99 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 comprising 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.

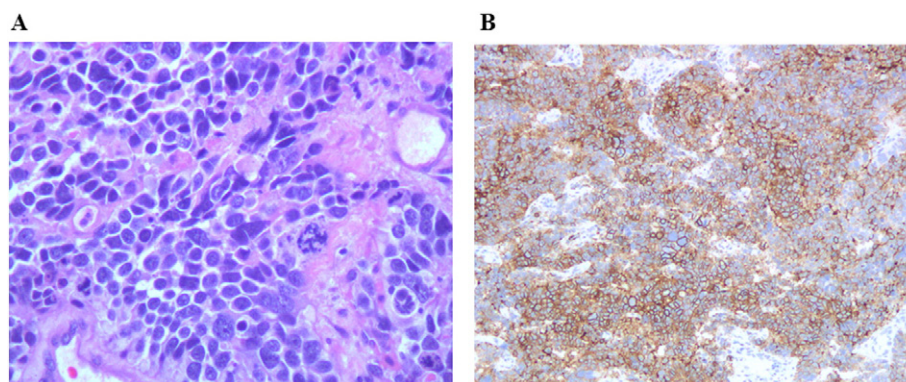
### 3. Comments/discussion

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 Hoesven 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 $\times$ ). (B) Small-cell carcinoma with perivascular pseudorosettes (H&E, 20 $\times$ ).



**Fig. 3.** (A) High power image of the tumor demonstrating cells with a high nuclear-cytoplasmic ratio, minimal cytoplasm, nuclear molding, fine chromatin and abnormal mitoses (H&E 40 $\times$ ). (B) The tumor shows diffuse expression of CD56 and was also positive for synaptophysin, keratins and p53 (not shown) (10 $\times$ ).

of the body (van Hoesen et al., 1995). The IHC markers, which are very consistently positive in cases of small-cell neuroendocrine, include CD56, chromogranin A, synaptophysin, p53, and p16.

Due to the rarity of this tumor type, there is no standard management. Surgery is the mainstay approach, with adjuvant therapy consisting of chemotherapy and radiotherapy. Because of the histological similarities between small-cell neuroendocrine tumor of the endometrium and lung, successful treatment of cases involving the lung can be extrapolated and applied to cases of the endometrium.

In Eichhorn's review of the literature for cases with endometrial SCC, two-thirds of patients with follow-up observation of at least 1-year died within the year, with recurrences developing in a majority of the remaining patients (Eichhorn and Young, 2001). With advanced-stage disease, and the reported median survival of this pathology is only 5-months (Matsumoto et al., 2011). In the descriptive review by Matsumoto et al. (2011) of 53 cases of small-cell disease of the endometrium, 20 patients (37.7%) were shown to have long-term (>1 year) survival, with 17 of those patients (85%) having stage I or II disease while the three remaining patients (15%) had stage III or IV disease (Matsumoto et al., 2011). The prognosis of small-cell neuroendocrine tumors is poor, but early detection along with surgery and adjuvant therapy may have better patient outcome (Katahira et al., 2004).

Following the publication of Matsumoto et al. (2011), we found seven new cases of small-cell neuroendocrine carcinoma of the endometrium in peer-reviewed literature, summarised in Table 1. The

mean age at time of consultation was 57.4 years, which correlates with Matsumoto's findings of mean age of 60 years (Matsumoto et al., 2011). Four patients (57.1%) had stage I disease, one patient (14.3%) had stage III disease, while the remaining two (28.6%) had stage IV disease (Table 1). Associated neoplasms were present in five patients (71.4%), while the remaining two (28.6%) presented small-cell neuroendocrine tumor exclusively. The IHC markers were noted with five patients, in which they all tested positive for synaptophysin and CD56, among other markers (Table 1). All patients underwent surgery and chemotherapy, with four patients (57.1%) having etoposide/cisplatin included in their regimen. Furthermore, three patients (42.9%) underwent radiotherapy, in addition to surgery and chemotherapy (Table 1). Patient outcome was reported in five cases, with four patients (80%) alive at the time of publication, while one patient (20%) died of the disease 7-months post-diagnosis (Table 1). The deceased patient had stage IV disease, and followed the pattern of early death with an advanced-stage tumor of this type, emphasizing the significance of early detection. Our patient did not seek care for adjuvant therapy after relocating and DOD at 6-months post-operatively.

This extremely rare combination of tumors presents a challenge for treatment. The mainstay of treatment seems to be surgery followed by chemotherapy  $\pm$  radiation therapy. Although small-cell neuroendocrine tumors are rarely seen in the endometrium, its prevalence in other sites such as the lung has allowed for extrapolation of adjuvant chemotherapy regimens that may be successful. Early detection

**Table 1**

Review of recent cases of small-cell neuroendocrine carcinoma of the endometrium.

Author	Age (Year)	Stage	Associated Neoplasm	IHC Markers	Treatments	Outcomes
Abaid et al. (2012)	73	IA	Leiomyoma	Synaptophysin, pancytokeratin, CD56	Surgery, Chemo (etoposide/cisplatin)	Unknown
Kurtay et al. (2012)	67	IB	None	Synaptophysin, NSE, CD56, chromogranin A	Surgery, Chemo (etoposide/cisplatin) and radiotherapy	NED at 6-months
Üreyen et al. (2013)	52	IC	Polypoid tumor filling endometrial cavity that may be uterine sarcoma or a MMMT	NSE, pancytokeratin, low-molecular weight keratin	Surgery, Chemo (etoposide/cisplatin) and radiotherapy	NED at 58-months
	35	IIIC	Undifferentiated endometrioid carcinoma	Unknown	Surgery, Chemo (cisplatin/adriamycin) and radiotherapy	NED at 13-years
Chen et al. (2014)	45	IVB	Endometrial carcinoma	Unknown	Surgery, Chemo (endoxan/doxorubicin/vincristine followed by etoposide/cisplatin)	DOD after 7-months
	50	IB	None	Synaptophysin, CD56, Ki67, antikeratin AE1	Surgery, Chemo (paclitaxel/carboplatin)	NED at 2-years
Ishida et al. (2014)	80	IVA	Small focus of endometrioid adenocarcinoma	Synaptophysin, CD56, chromogranin A	Surgery, Chemo (paclitaxel/carboplatin)	Unknown
Current Case,	74	II	Serous adenocarcinoma	CD56, synaptophysin, p53, keratin, CK7, p63, p16, focal estrogen receptor	Surgery, Chemo (etoposide/cisplatin) and radiotherapy	Died at 6-months

**Abbreviations:** IHC = immunohistochemistry, NSE = neuron-specific enolase, Chemo = chemotherapy, DOD = died of disease, NED = no evidence of disease, MMMT = malignant mix Mullerian tumor.

remains a major prognostic factor in small-cell neuroendocrine tumors, along with prompt surgical and adjuvant therapy.

#### Conflict of interest statement

The author declare that there are no conflicts of interest associated with this manuscript.

#### Patient consent

This study was deemed exempt by our Florida Hospital Institutional Review Board.

#### Financial disclaimer

None.

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