Case Series

Endometrioid adenocarcinoma associated with endometrial stromal sarcoma: A rare, often unrecognized collision tumor

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A B S T R A C T

We are reporting 3 cases of the uterine corpus with collision of endometrioid adenocarcinoma (EAC) with endometrial stromal sarcoma (ESS). The patients’ ages ranged from 36 to 59 years old. The major clinical presentation was abnormal uterine bleeding. Microscopically, all 3 cases presented with 2 separate components, EAC Grade 1 and ESS (one low grade and two high grades). The EAC component ranged from 10% to 70%, and the ESS component ranged from 30% to 70% of total tumor volume. The EAC component was stage IA in two cases and stage II in one case. The ESS component was stages IA, IIB, and IIIB. Adjuvant hormonal therapy was administered to one patient while a second patient was treated with chemo/radiation therapy. Two patients were still alive with no evidence of disease at 4 years post-therapy. One patient was lost for follow-up. Collision tumor should be distinguished from carcinosarcoma due to its different treatment modality, outcome and, prognosis.

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1. Introduction

Malignant uterine mixed epithelial–non-epithelial tumors are rare tumors. Based on the WHO system, they characterize a spectrum of neoplasms including adenosarcoma, carcinosarcoma and carcinosarcomas or malignant mixed Mullerian tumors (MMMT). These tumors are characterized by proliferation of both mesenchymal and epithelial components and each of these components may be benign or malignant. Carcinosarcoma is the most common tumor of this classification. It is characterized by a bulky uterine tumor that histologically shows an admixture of both malignant epithelial and mesenchymal elements. Molecular studies have previously shown that these two components are monoclonal in about 80–90% (Reichert, 2012), and it is the common belief that carcinosarcomas are in fact metaplastic carcinomas, with the carcinomatous component driving the biphasic tumor (Sreenan and Hart, 1995). The remaining 10–20% of carcinosarcoma cases is believed to be biconal, with topographically separate carcinoma and sarcoma elements, suggesting that these tumors may in fact better categorized as “collision tumors”. These collision tumors are believed to originate from the same organ site, or from adjacent organs, or metastasis from one organ site to another (Sreenan and Hart, 1995). Collision tumors are infrequent, probably under recognized, and currently described only in rare case reports.

Three interesting cases from our practice highlight the rare findings of a concurrent endometrial endometrioid adenocarcinoma and endometrial stromal sarcoma.

2. Material and methods

Three cases of uterine endometrioid adenocarcinoma and concurrent endometrial stromal sarcomas were seen in our practice. Clinical history including age, race, initial presentation, treatment and follow-up were collected from electronic medical records are illustrated in Table 1.

2.1. Patient #1

A 36-year-old Hispanic woman presented with 6 years of abnormal uterine bleeding. An endometrial pipelle biopsy showed simple endometrial hyperplasia without atypia. Definitive surgical management was recommended and 6 months after her initial abnormal biopsy, she underwent an uncomplicated laparoscopic assisted vaginal hysterectomy. On sectioning of the hysterectomy specimen, the endometrial cavity showed multiple polypoid lesions, the largest measuring 0.8 cm. The myometrium was bulky. The hematoxylin–eosin (HE) sections showed endometrioid adenocarcinoma (EAC) FIGO 1 without invasion of the myometrium. However, other sections showed
proliferation of endometrial stromal cells infiltrating 33% of the myometrium. These cells had similar morphology to those seen on the previous endometrial biopsies. The tumor cells formed irregular nodules infiltrating the myometrial wall. Cytologically, these cells resembled endometrial stromal cells, small in size, with scant cytoplasm and a very low mitotic rate. They were positive for ER (estrogen receptor)/PR (progesterone receptor) and CD10, and negative for pancytokeratin, desmin, and SMA (smooth muscle actin). Ki67 was positive in 5% (Fig. 1A–D). Of importance, the two components of the tumor (EAC and LG ESS) were geographically separate from one another. The EAC component was a stage IA, constituting 70% of the tumor volume, and the ESS component was a FIGO 1A, comprising 30% of the tumor volume. The pelvic washing was negative. Following hysterectomy the patient was started on megestrol acetate with ongoing surveillance. Today she is alive with no evidence of disease (ANED) at 41 months (3.4 years).

2.2 Patient #3

A 55-year-old Hispanic woman initially presented to our facility with 3 years of abnormal uterine bleeding managed with combined oral contraceptives. On initial pelvic exam at our hospital, there was heterogenous appearing tissue protruding through a dilated cervical os with biopsies showing only necrotic tissue. A subsequent endometrial polype biopsy was performed and diagnosed as endometrial adenocarcinoma FIGO Grade 1. One month later, an open modified radical hysterectomy and bilateral salpingo-oophorectomy was performed. The uterine cavity showed a sessile, fleshy mass obliterating the endometrial cavity, measuring 3 × 4 cm, with invasion through the uterine wall to the broad ligament. Histologically the mass showed two distinct components. The first was an EAC, FIGO1, invading through 63% of the myometrial thickness and involving the endocervical stroma. A second component, an ESS, showed tumor cells cytologically resembling endometrial stromal cells. They infiltrated the myometrium as jagged irregular islands and nodules with foci of necrosis. In some areas, the tumor cells still retained classic histology of a LG ESS. However, in other areas, the tumor cells exhibited moderate atypia and a high mitotic rate, more representative of a HG ESS. The ESS component involved 100% of the myometrial thickness with involvement of the right adnexa and broad ligament (Fig. 2A–D). These tumor cells were positive for CD10, SMA, ER and PR, while negative for pancytokeratin and desmin. The EAC component constituted 50% of the tumor (stage II) and the ESS component formed 50% of the tumor (FIGO stage IIB). Following surgical staging, the patient completed systemic treatment with carboplatin (AUC 5) and paclitaxel (175 mg/m²) dosed every 21 days, followed by whole pelvic radiotherapy (5040 cGy) and vaginal brachytherapy (2283 cGy). Currently, she is undergoing surveillance, and she ANED at 4 years after treatment completion.

2.3 Patient #4

A 59-year-old Hispanic woman presented with abdominal pain and 2 months of post-menopausal vaginal bleeding. Pelvic exam revealed an enlarged 18-week sized uterus. An endometrial polype biopsy diagnosed high grade sarcoma and radiographic evaluation showed ascites and multiple peritoneal and omental lesions. Ten days after the initial diagnosis, the patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy and optimal tumor reductive surgery. On gross examination of the specimen, the uterine cavity showed a large, polyoid, necrotic mass in the right anterior wall measuring 15 × 7.5 × 6 cm. HE sections of the mass showed 2 separate components: An EAC FIGO grade I with no myometrial invasion and a HG ESS infiltrating 76% of the myometrial thickness in irregular islands and nodules with extensive lymphovascular invasion. There was involvement of the left and right adnexa, pelvic wall, peri-rectal and peri-cecal tissue, and omentum. The tumor cells were focally positive for desmin and CD10, and negative for pancytokeratin, SMA, and ER/PR (Fig. 3A–B).
The EAC component constituted 10% of the tumor volume (stage IA) and
the ESS component 90% of the tumor volume (FIGO IIIB). The patient
was planned for systemic treatment with adriamycin and ifosfamide
following surgery, however, the patient was lost to follow-up. Her cur-
crent medical status is unknown.

3. Discussion

Presence of endometrial glands in endometrial stromal sarcomas
(ESS) has been well documented in the literature where they can be
found in anywhere between 11 and 40% of cases (McCluggage et al.,
2010). Furthermore, and analogous to the variable presence of sex-
cord stromal-like elements, focal smooth muscle differentiation, and
myxoid or fibrous change, the presence of endometrial glands have
been regarded simply, as a variance in ESS. Clement and Scully de-
scribed 3 cases of LG ESS with extensive endometrioid glandular differ-
entiation (Clement and Scully, 1992). In their series, the ESS component
was admixed with a glandular component. Only one of which showed
this glandular component to be atypical and even malignant. As conven-
tion goes, a tumor with malignant mesenchyme and high grade malig-
nant epithelium habitually warrants a diagnosis of a carcinosarcoma,
which in our cases would be a misdiagnosis. The coexistence of two
adjacent and histologically distinct tumor components, endometrioid
adenocarcinoma and ESS, is best de
fined as a collision tumor. Collision
tumors have been reported in various organs, such as the esophagus,
stomach, colon, lung, skin, thyroid gland, breast, and ovary. Few report-
ed cases have been described in the uterus and some were reported
before the immunohistochemistry era in the 1960s. In 1969 a case of a
55 year old woman with a collision tumor of EAC with leiomyosarcoma
was reported. However, from review of the microscopic description of
this sarcomatous component, ESS is likely the more appropriate diagno-
sis. Immunohistochemistry, however, was neither performed nor widely
used at that time. Additionally, no follow-up was available (Patwardhan
and Gadgil, 1969). In 1987 Liftschitz-Mercer et al. described 4 cases of
ESS, one of which was a low grade ESS stage I associated with an EAC
FIGO1, stage IA (Liftschitz-Mercer et al., 1987). However, no follow-up
was reported. The newest series in the literature were of two case re-
ports in 1999 by Lam et al., regarding an 85 and 45 year old woman
(Lam et al., 1999). Both patients had an EAC, FIGO grade 1 with collision
of a stage III and stage I HG ESS, respectively. Both patients were ANED
in 1.5 years and 6.5 years postoperatively (Table 1). Treatment regimens
were not noted in their report.

Collision tumors should be mainly distinguished from carcino-
sarcoma. In carcinosarcoma, the majority of the tumor with careful ex-
amination should classically show a sarcomatous background with an
intimate comingling of regularly distributed and easily identifiable car-
cinomatous elements which usually are high grade tumors. On the con-
trary, collision tumors, which likely have been misclassi
fied as a subset
(10–20%) of biclonal carcinosarcomas, histologically show two individ-
ual, separate tumor components. Additionally, these two components
deviate from the usual high-grade features of both carcinoma and sarco-
ma as is typically seen in carcinosarcomas. All 3 cases in our series and
those in the literature were composed of a FIGO 1 endometrioid adeno-
carcinoma, abutting and distinctly separate from an ESS (LG ESS or HG
ESS). Neither of the endometrial stromal sarcomas exhibited features
classifiable as an undifferentiated endometrial sarcoma (UES). Due to
the vicinity of these components, collision tumors could be the result of
the epithelial–mesenchymal transition (EMT) theory, a process by
which epithelial cells lose their cell polarity and cell–cell adhesion,
and gain migratory and invasive properties to become mesenchymal

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**Fig. 1.** A: A low power scanned image of two hematoxylin-eosin (HE) slides of the tumor shows a polypoid mass (asterisk), which at this magnification appears to be composed of solid sheets of hyperchromatic cells (endometrial stromal sarcoma (ESS)). Adjacent to this mass is glandular crowding (endometrioid adenocarcinoma (EAC)). B: At low magnification, these tumor cells are arranged in nodular patterns. C: Pancytokeratin (AE1/3) immunostaining highlights the EAC component (asterisk) that was limited to the endometrium (non-invasive), while the ESS component (dotted lines) exhibits negative staining. D: Smooth muscle actin (SMA) immunostaining emphasizes both the EAC component (asterisk) and the ESS component (dotted lines) by contrasting positive and negative staining respectively.
Fig. 2. A: A scanned picture of the hematoxylin–eosin (HE) slide of the endometrial mass shows two separate components: An ESS component (asterisk), which in this particular section is polypoid with no notable myometrial invasion, and an EAC component which appears to invade into the superficial part of the myometrium. B: Another scanned picture (HE) of a different part of the tumor shows the ESS component invading into the myometrium in a very characteristic fashion: irregular, jagged islands of neoplastic stromal cells between smooth muscle bundles of surrounding normal myometrium. C: The EAC component shows irregular, cribriform, back-to-back glands invading the myometrium. D: The EAC component stains positive for pancytokeratin while the ESS (asterisk) fails to stain.

Fig. 3. A: Whole slide imaging of a full section of tumor shows deep myometrial infiltration by characteristic islands and tongues of clustered tumor cells. Lymphovascular invasion is easily identified. B: Another part of the mass shows two distinct components: ESS (asterisk) and an EAC component highlighted by pancytokeratin (inset). In contrast, the ESS component is negative for pancytokeratin.
stem cells; these are multipotent stromal cells that can differentiate into a variety of cell types.

It is of great importance to differentiate collision tumor from carcinosarcoma due to the impact of the diagnosis on clinical management and prognosis. Although both entities are surgically managed, adjuvant therapy may be quite different. Because of the propensity for distant and nodal metastases, even with early stage disease, carcinosarcomas typically would receive systemic chemotherapy. Active agents for carcinosarcomas include paclitaxel, ifosfamide, carboplatin and cisplatin. On the other hand, management of collision tumors is determined by taking into consideration the grade and depth of invasion of the carcinomatosous component, or characteristics of the endometrial stromal sarcoma. If both components are low grade and early stages, progestin therapy with surveillance would be considered. There are some published data showing that aromatase inhibitors may be promising in the treatment of ESS. Radiotherapy may prevent locoregional recurrences, but its clinical efficacy is uncertain. ESS tends to recur in distant locations many years from the time of the primary diagnosis. Adjuvant therapy for ESS staged II–IV is debatable, and may include endocrine therapy and chemoradiation. Due to the scarce number of ESSs, there is a lack of sufficient data to guide treatment decisions. Small published series identify clinical responses to doxorubicin, docetaxel, and gemcitabine albeit with short response intervals.

The prognosis of uterine carcinosarcoma as compared to a collision tumor of endometrial adenocarcinoma and ESS are determined by stage and are drastically different. Stage by stage, the 5-year survival rate for a carcinosarcoma ranges from 5 to 40%, which is dismal compared to 65–76% of endometrial stromal sarcomas over a 10 year span. Even more, ESSs generally have an indolent course, with an overall survival rate of 65–76% at 10 years. Patients with undifferentiated endometrial sarcomas, in comparison, succumb to the disease within 3 years of diagnosis regardless of stage. The outcome of a collision tumor is simply better than a similarly staged carcinosarcoma. Based on our series and those of Lam et al., all patients were ANED at postoperative follow-ups ranging from 1.5 years to 6.5 years (Lam et al., 1999). However, more cases of collision tumors need to be studied to accurately predict survival and outcomes. Additionally, adjunct surgical therapies, such as lymphadenectomy and adjuvant chemoradiation significantly increase morbidity amongst carcinosarcoma patients. These treatment modalities can be avoided in those with collision tumors, which all the more emphasize the importance of an accurate pathologic diagnosis.

Herein, we reported 3 cases of unrecognized and underdiagnosed collision tumors (endometrial endometrioid adenocarcinoma associated with endometrial stromal sarcoma), that should be differentiated form carcinosarcoma due to their different treatment and outcome.

Conflict of interest statement
All authors declare no conflict of interest.

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