

## Case report

## Clinically aggressive “low-grade” uterine carcinosarcoma: A case report

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## 1. Introduction

Carcinosarcoma (CS), also known as malignant mixed Mullerian tumor (MMMT), of the uterus is a rare malignancy accounting for less than 4% of all uterine cancers (Arend et al., 2011). The tumor is characterized as mixture of carcinomatous and sarcomatous elements. There is considerable diversity in the histological types of the tumor elements. The carcinomatous component is most commonly serous or high-grade endometrioid, while the sarcomatous component may display a wide range of morphology, such as leiomyosarcoma and rhabdomyosarcoma, but is generally poorly differentiated (de Jong et al., 2011). Uterine CS is considered a Type II epithelial endometrial malignancy with high rates of *p53* mutations, like other high-grade endometrial cancers. The cancer is often advanced at presentation and follows an aggressive clinical course associated with poor survival rates.

We present an unusual case of uterine CS exhibiting low-grade histology in both the carcinomatous and sarcomatous components in a patient who presented with advanced disease with rapid progression.

## 2. Case report

## 2.1. Clinical presentation

A 52-year-old gravida 2, para 1, perimenopausal female presented to the emergency department (ED) with vaginal bleeding and

symptomatic anemia after having an office endometrial biopsy. The patient had regular menses until one month before presentation, when she began to have continuous light bleeding and crampy lower abdominal pain. In the ED, pelvic exam demonstrated a friable, yellow mass occupied the upper vagina. A thin rim of the cervix was palpated around the mass, and the uterus was enlarged. An abdominopelvic CT scan revealed a 9.2 × 8.4 × 9.2 cm intra-uterine mass with cystic and solid components and foci of gas and an adnexal soft tissue mass. Multiple biopsies of the mass showed only fibrin clots and necrotic matter. Following stabilization as an inpatient, the patient underwent an exploratory laparotomy, radical abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic lymphadenectomy. A metastatic tumor implant measuring 7.5 × 6.5 × 2.5 cm was superficially attached to the small bowel and was excised. Intraoperative frozen section revealed a sarcomatoid malignancy.

## 2.2. Pathology

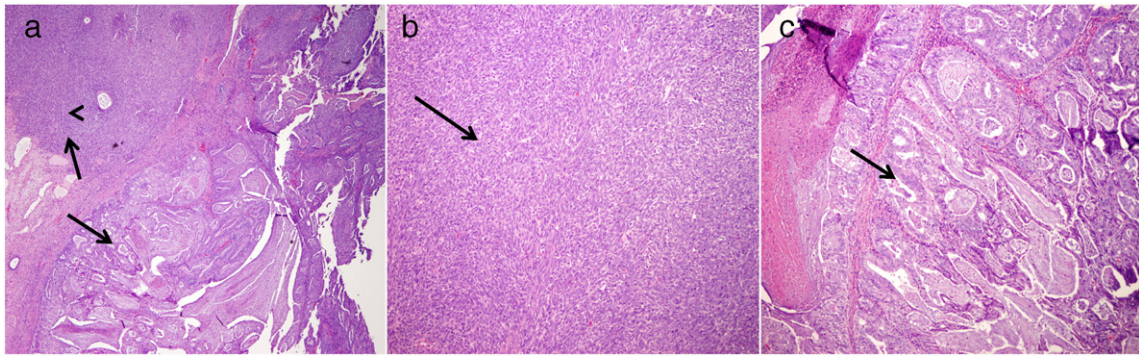
Macroscopic examination revealed a 420 g uterus with distended endometrial cavity filled with yellow-tan necrotic material. Microscopic examination showed very unusual and intriguing histology. Essentially, the tumor was composed of two components: low-grade sarcomatous component resembling stromal sarcoma and carcinomatous component composed of well to moderately differentiated endometrioid adenocarcinoma. The two components were sharply demarcated (Fig. 1) without comingling interface. The tumor was extensively necrotic. The sarcomatous component was immunoreactive for CD10 which supported the diagnosis. Although this tumor met the criteria for CS, the histologic findings were very unusual since these are typically composed of high-grade sarcomatous and carcinomatous elements. In addition, the two components in CS are often merging, which was not present in this case. It also appeared that the two components had separate metastatic potential since the small bowel metastases were morphologically similar to sarcomatous component (Fig. 1b) and metastatic foci in the omentum and ovary were composed of carcinoma only (Fig. 1c). The carcinomatous component expressed estrogen- and progesterone-receptor, but the sarcomatous component was negative for both.

## 2.3. Post-operative Course

After an uneventful post-surgical recovery, the patient initially received 3 cycles of intravenous carboplatin-paclitaxel chemotherapy. After the last cycle, the patient had worsening abdominal pain and a

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**Fig. 1.** a. Sharply demarcated component of well to moderately differentiated carcinoma (solid arrow) and endometrial sarcoma (dotted arrow). The boundary between the solid and dotted arrows denotes the biphasic tumor. b. Sarcomatous component with low-grade features (Olympus BX41, 10 $\times$ ). c. Well to moderately differentiated carcinoma (Olympus BX41, 10 $\times$ ).

follow-up CT scan revealed multiple new deep pelvic, serosal, and omental implants, consistent with peritoneal carcinomatosis. An image-guided core biopsy was performed to confirm the pathology given rapid progression; this confirmed that the intraperitoneal lesions were the sarcomatous component consistent with the primary uterine tumor. The patient subsequently received intravenous ifosfamide/mesna/paclitaxel and experienced symptomatic progression of disease after 5 cycles. Her disease was also refractory to carboplatin-pegylated liposomal doxorubicin (PLD). At the time of last contact, the patient enrolled in a phase I clinical trial of an immune-therapeutic agent, TRX518, the humanized, Fc disabled, anti-human GITR (glucocorticoid-induced tumor necrosis factor receptor) monoclonal antibody. One year after the initial diagnosis, the patient passed away from disease progression.

#### 2.4. Genetic testing

The patient had a strong family history of cancer, including her mother who survived uterine cancer (29 years old), 2 maternal aunts diagnosed with breast cancer (48 years old, 50 years old), maternal cousin diagnosed with breast cancer at age 30 and ovarian cancer at age 45, and father diagnosed with prostate cancer (age 70+). The maternal cousin with breast and ovarian cancer was diagnosed with a 5677insA *BRCA-1* mutation. It is not known if other family members have undergone genetic testing. The patient's 25-gene myRisk™ panel (Myriad Genetics) was negative for any germline mutations.

Both the sarcomatous and carcinomatous tumor samples were evaluated for somatic genetic mutations through the institutional precision medicine laboratory. Mutations in *KRAS*, *PTEN*, and *ARID1A* were detected in the sarcomatous component. In addition, a large scale amplification was found in *FCGR2B*, which is the Fc fragment of IgG and a low-affinity IIb receptor for CD32. In the carcinomatous component, *PTEN* and *NFE2L2* (nuclear-factor (erythroid-derived 2)-like 2) missense mutations were detected.

### 3. Discussion

We present an unusual case of uterine CS where both the sarcomatous and carcinomatous components showed low-grade pathology. This patient's clinical course was very aggressive with chemotherapy-resistant disease. In the subsequent discussion, we will present a brief clinical review of uterine CS, discuss the known molecular alterations in this tumor, and the emerging role of germline and somatic genetic testing.

The primary treatment of all endometrial cancers, including CS, is surgery (Arend et al., 2011). Adjuvant therapies, such as radiotherapy, chemotherapy, or hormonal therapies, may be offered, but there is no consensus on their use. Surgical treatment includes laparotomy or laparoscopy with total abdominal hysterectomy, bilateral salpingo-oophorectomy and surgical staging including pelvic and periaortic

lymph node dissection and omentectomy. Surgical cytoreduction in cases of advanced intraperitoneal disease has shown to benefit progression free survival in other high-grade endometrial cancers (Moller et al., 2004). Given the rarity of uterine CS, efforts supporting surgical cytoreduction are extrapolated from other uterine carcinoma and soft tissue sarcoma literature. Randomized cooperative group trials have shown efficacy of doublet-based initial chemotherapy in uterine CS. These agents include cisplatin–ifosfamide (CI), ifosfamide–paclitaxel (IP), and carboplatin–paclitaxel (CP) (Einstein et al., 2012; Powell et al., 2010; Homesley et al., 2007; Sutton et al., 2005). CI and IP have an overall response rates of 32% and 54%, respectively (Homesley et al., 2007; Sutton et al., 2005). Regardless, the mean progression-free benefit of CI was 4 months vs 6 months with IP (Homesley et al., 2007; Sutton et al., 2005). Given the high rates of grade 3–4 toxicity and no benefit of overall survival, retrospective and phase II clinical trial data support the use of CP as the primary therapy in chemotherapy-naïve patients; response rate in a phase II trial was 54% (13% complete, 41% partial) (Powell et al., 2010). Results of a phase 3 randomized trial comparing IP vs CP are currently pending (ClinicalTrials.gov Identifier: NCT00954174).

Given that CSs are heterogeneous tumors, there are several theories of their pathogenesis, including the collision and monoclonal origin theories. The collision theory states that the epithelial and sarcomatous components arise independently of each other in the uterus (Arend et al., 2011). The current belief is that of the monoclonal hypothesis where a single clone differentiates into the epithelial (carcinomatous) and the sarcomatous component (Arend et al., 2011). Further analyses show that when CS metastasizes outside the uterus or recurs, it is the epithelial component that is likely present in those implants (de Jong et al., 2011). Our patient's pathology was distinct in that at the time of initial surgery, both the carcinomatous and the sarcomatous components were present outside the uterus. When she experienced disease progression, the peritoneal disease was also sarcomatous. The reported case may be a rare presentation of a biphasic epithelial and sarcomatous tumor which behaved independently of each other.

The somatic mutation profile of this patient's tumor is also unique for uterine CS. Uterine CS is considered a type II endometrial cancer, with high rates of *p53*, *FBXW7*, and *PIK3CA* mutations such as those found in serous endometrial cancers (Kandoth et al., 2013; Bashir et al., 2014). In contrast, low proliferative endometrioid endometrial carcinomas commonly have somatic mutations in *PTEN*, *PIK3CA*, *ARID1A*, *KRAS*, and *ARID5B* (Kandoth et al., 2013). The molecular profile of this patient's tumor makes it a grade 1 tumor, further indicating that this could be a biphasic tumor. There is a dearth of published literature in the molecular profiles of the sarcomatous and carcinomatous components of uterine CS. One study indicated that DNA mismatch-repair genes were absent in both the sarcomatous and carcinomatous components in 21% of tumor samples (Taylor et al., 2006). This was not detected in the profile of our patient's tumor. In addition, the molecular profile of the tumor showed any actionable agents and did not support the use

of targeted therapies for off-label or in-clinical trial. High dose progesterone and anti-estrogen therapies were not considered since the sarcomatous component, which was the burden of recurrent disease, did not express these receptors.

In summary, we report a unique pathological type of uterine carcinosarcoma composed of low-grade epithelial and sarcomatous components. These tumors are different from hereditary cancer syndromes. The patient is a true negative even though her family has homologous-recombination deficient breast and ovarian cancer syndromes. Molecular profiling of the tumor further characterizes the unique qualities of this tumor. Further understanding of molecular profiles and somatic mutations will help develop a classification system for uterine carcinomas and may lead to targeted therapy trials.

#### Conflict disclosure

None of the authors have any conflict to report related to this manuscript.

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