



Case report

Müllerian carcinosarcoma arising from atypical pelvic endometriosis

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1. Introduction

Müllerian carcinosarcoma (MC), otherwise known as Malignant Mixed Müllerian Tumor, or MMMT is an uncommon tumor of female genital tract, comprising < 5% of all gynecological malignancies. The tumor is composed of both malignant epithelial and malignant mesenchymal elements that commonly exhibit sharp demarcation on histology. Sarcomatous elements may be homologous consisting of mesenchymal tissue native the site of origin or heterologous consisting of non-native elements such as striated muscle, cartilage or bone (Soslow, 2009). MC is an aggressive tumor with an overall prognosis worse than that of high-grade uterine endometrial carcinoma (Zhu et al., 2016). Most studies suggest that it is the carcinomatous component that plays a dominant role in tumor biology and survival (Sreenan & Hart, 1995). Although the uterus is the most common site of origin, MC infrequently arises from the ovaries, fallopian tubes, cervix and vagina (Soslow, 2009). Rare cases have been described in extragenital sites and even rarer is MC arising in endometriosis. Endometriosis-associated MC has been reported in ovaries (Marchevsky & Kaneko, 1978), urinary bladder (Schildhaus et al., 2008), ureter (Noel et al., 2006), retroperitoneum (Booth et al., 2004) intestines (Slavin et al., 2000) and cesarean-section scar (Leng et al., 2006). To our knowledge the only case of MC arising in pelvic endometriosis described in the literature was published more than thirty years ago (Chumas et al., 1986). In this report we describe second such case.

2. Case report

A 69 year old gravida two para two woman initially presented to the emergency department with obstructive urinary symptoms. A computed tomography (CT) scan revealed a cystic pelvic mass. Her Ca-125 level was 40. She had no pertinent medical history and her family history was negative for any malignancies. Her surgical history was notable for appendectomy and bilateral salpingo-oophorectomy with a diagnosis of left ovarian “dermoid cyst”. Additionally, she had a supracervical hysterectomy and pelvic biopsies for uterine leiomyomas interpreted as “recurrent dermoid cysts”. These procedures were performed five and one years prior to the patient's current visit, respectively. Given her obstructive pelvic mass, the patient underwent

resection of the mass with trachelectomy. At that time, she was diagnosed with a mucinous cystadenoma, adherent to the sigmoid colon. The specimen was reviewed by our pathology department, with agreement on the outside diagnosis. The mass was situated in a background of atypical endometriosis with squamous metaplasia.

She returned to the emergency department six months later with a one week history of vaginal bleeding accompanied by menstrual-like cramping and diarrhea. She otherwise felt well with stable vital signs and denied any other symptoms. Her external genitalia were normal-appearing, with thin red-brown fluid in the vagina. A soft mass affixed to the anterior abdominal wall was discovered during pelvic exam. A CT scan revealed a complex cystic and solid mass measuring 7.7 × 6.5 × 5.9 cm within the lower right hemipelvis at the superior vaginal cuff, in the same area as the previous pelvic mass. The mass abutted the colon without a definite intervening tissue plane. Her CA-125 was 18. After gynecologic oncology consultation at our institution the patient underwent laparotomy with resection of the mass, radical upper vaginectomy, ureteral resection with ureteroneocystostomy, sigmoid resection with reanastomosis, and diverting loop ileostomy. The mass was strongly adherent to the sigmoid colon, upper vagina, and ureter. Numerous adhesions were encountered intra-operatively.

3. Pathologic findings

The resected pelvic mass measured 5.2 × 4.5 × 2.2 cm and was grossly tan-white, nodular, and gelatinous. Histologic sections revealed sheets of confluent malignant cells without obvious differentiation. Over 90% of the tumor consisted of high-grade sarcoma with heterologous rhabdomyoblastic elements. The high-grade carcinoma elements comprised < 10% (Fig. 1 A and B). Concurrently resected upper vagina and pelvic peritoneum demonstrated a similar morphology to the pelvic mass. Glands with squamous and mucinous metaplasia, suggestive of atypical endometriosis, were identified in both specimens (Fig. 1 C and D). On immunohistochemistry, the foci of endometriosis glands were well-organized with strong epithelial membrane antigen (EMA), progesterone receptor (PR), and estrogen receptor (ER) positivity. Carcinomatous elements within the tumor were diffusely EMA positive (Fig. 1 E). Spindle-cell areas of the sarcomatous tumor component were focally positive for CD117 and smooth muscle actin (SMA).

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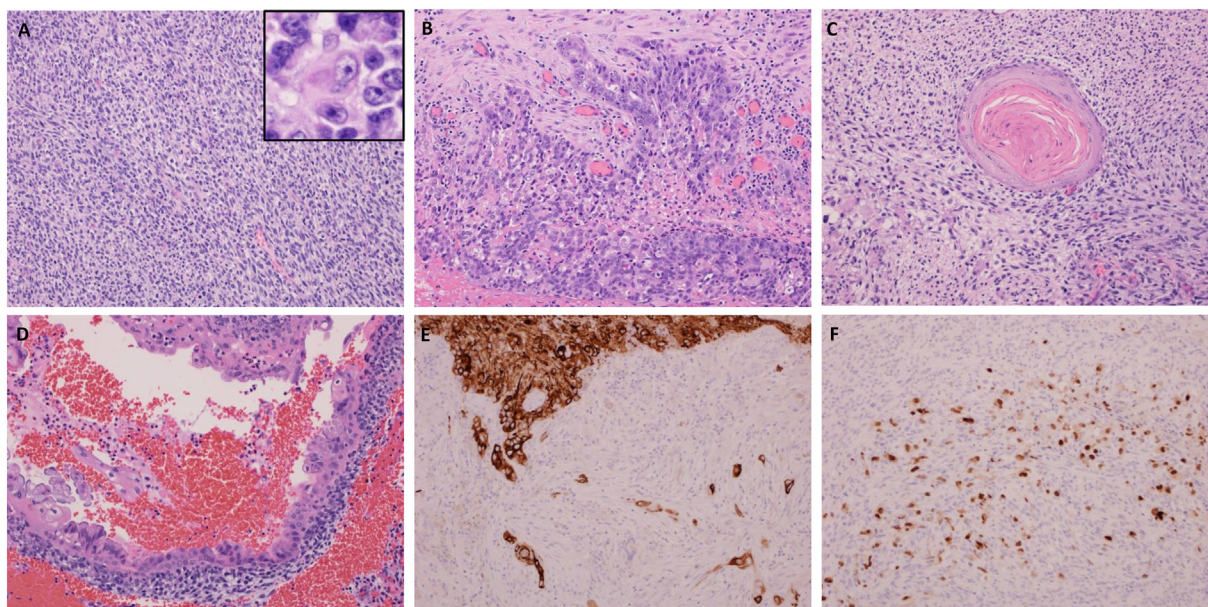


Fig. 1. (A–F) Histologic and immunohistochemical features of pelvic Mullerian Carcinosarcoma: A, Sarcomatous component with rhabdomyoblasts (inset) (H&E, 200x; inset 400x); B, High-grade epithelial component (H&E, 200x); C, Focus of atypical endometriosis with squamous metaplasia (H&E, 200x); D, Atypical endometriosis with mucinous metaplasia (H&E, 200x); E, EMA immunostain highlighting the high-grade epithelial component (200x); F, Myogenin immunostain with nuclear staining of rhabdomyoblasts (200x).

Sarcomatous elements morphologically suggestive of endometrial stroma sarcoma were strongly positive for CD10. The tumor was also diffusely positive for markers of smooth muscle and myofibroblastic differentiation, calponin and CD44. The rhabdomyoblasts were positive for myogenin (Fig. 1 F). Although the mass did not penetrate the resected sigmoid colon, it was significant for numerous serosal fibrous adhesions with atypical endometriosis and mucinous metaplasia, similar to what was found within the current mass as well as the previously-resected “mucinous cystadenoma”.

Pathologic review of the previous specimens that included uterus, bilateral tubes and ovaries, pelvic mass and appendix confirmed the absence of malignancy in all sections examined. However, the prior right pelvic mass interpreted as “mucinous cystadenoma” exhibited features suggestive of their origin on a background of endometriosis and possibly representing squamous and mucinous metaplasia in atypical endometriosis rather than mucinous cystadenoma (Fig. 2 A and B). The left ovarian cyst that were interpreted as “dermoid cysts” did not feature other germ-layer derivatives, did not have skin adnexal structures and were set amid endometriotic foci (Fig. 2C). Accordingly, these were reinterpreted as squamous metaplasia of pre-existing endometriosis. Given this history, and the fact that the patient was status post hysterectomy and bilateral salpingo-oophorectomy at the time of presentation, she was diagnosed with Müllerian carcinosarcoma, likely arising from pre-existing pelvic endometriosis.

Following post-operative recovery, the patient received six cycles of adjuvant carboplatin and paclitaxel and eventually underwent take-down of her ileostomy. Nine months later, tumor recurred in posterolateral hemipelvis and patient also developed numerous pulmonary nodules and mediastinal lymphadenopathy concerning for metastatic disease. Molecular studies of recurrent tumor revealed a PIK3CA mutation. Patient received pelvic radiation therapy for this recurrence and is currently undergoing everolimus/letrazole chemotherapy.

4. Discussion

Although MC itself is a relatively rare entity, the uterus is the most common site for tumors of mixed epithelial and mesenchymal origin, perhaps because of the shared mesodermal origin of the urogenital ridge mesenchyme and coelomic lining epithelium, from which the Müllerian organs develop (Soslow, 2009). MC can vary in their proportions of sarcomatous and carcinomatous components. The “sarcoma-predominant” tumors convey a slightly better prognosis than the “carcinoma-predominant” variant. MC is currently believed to originate from epithelial endometrial cells which have undergone malignant transformation and metaplasia to sarcomatous elements via epidermal-mesenchymal transformation. As with many carcinomas of the female reproductive tract, increased lifetime exposure to estrogen (via nulliparity, obesity, and/or exogenous estrogen or tamoxifen use) is a risk

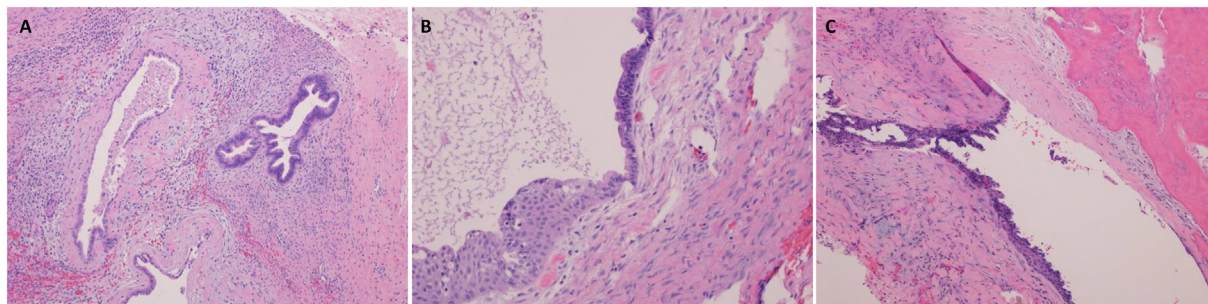


Fig. 2. A–B, Histologic features of previous right pelvic mass misinterpreted as mucinous cystadenoma showing background endometriosis (A, H&E, 100x) and focal squamous metaplasia of cyst lining (B, H&E, 200x); C, Left ovarian cystic lesion with squamous and osseous metaplasia misinterpreted as dermoid cyst (H&E, 200x).

factor for the development of Müllerian carcinoma (D'Angelo & Prat, 2011).

Endometriosis, a very common disease effecting 5–10% of all reproductive-age women is often treated with hormonal therapy and concordantly estrogen exposure is a known risk factor for malignant transformation of endometriosis (Slavin et al., 2000). Long-standing endometriosis can undergo various types of metaplastic, hyperplastic and/or nuclear changes resulting in transformation into a heterogeneous entity called atypical endometriosis. Atypia in endometriosis is defined by papillary and adenomatous change comparable to what is otherwise diagnosed as atypical endometrial hyperplasia. Many experts believe that atypical endometriosis serves as an intermediate lesion between endometriosis and development of endometriosis associated malignancies (EAM), a hypothesis supported by several studies (Krawczyk et al., 2016). Malignant transformation of endometriosis was first described by Sampson in 1925. His rather strict criteria for diagnosing EAM, which our case fulfills, include 1) the presence of endometriosis in close proximity to the malignancy, 2) the absence of a likely primary tumor and, 3) histologic features supporting origin from endometriosis (Sampson, 1925). About 80% of EAM have been found in the ovary, whereas 20% are localized in extragonadal sites like intestine, rectovaginal septum, abdominal wall, pleura and others. Endometrioid and clear cell carcinoma are the two most common types of EAM (Modesitt et al., 2002).

Carcinosarcoma arising from endometriosis is exceedingly rare. The first case of MC arising in association with endometriosis in ovaries was described by Marchevsky & Kaneko, (1978). Chumas et al. in 1986 published the first case of extragenital MC arising in a background of atypical endometriosis presenting as a pelvic mass (Chumas et al., 1986). Interestingly it shared several features with our case, including presentation as a pelvic mass, history of seromucinous cystadenoma, involvement of the vagina and most importantly presence of atypical endometriosis. The epithelial abnormalities associated with endometriosis include squamous, mucinous, ciliated, eosinophilic and clear cell metaplasia, simple and complex hyperplasia and cytologic atypia. The risk of malignant transformation of endometriosis is increased especially if there is associated complex hyperplasia and atypia. Presence of these abnormalities, particularly in older patients, should initiate a thorough and careful examination of the entire lining of the cyst and a strict follow-up of the patient (Prefumo et al., 2002). It is also important to be aware of these abnormalities to avoid any misinterpretation, as seen in our case where the extensive squamous metaplasia and cystic change of ovarian endometriosis was misinterpreted as dermoid cyst. The cystic lesion of the right ovary in our case, originally diagnosed as mucinous cystadenoma, mostly like represented atypical endometriosis with extensive mucinous and focal squamous metaplasia and it is conceivable this might be true for the case described by Chumas et al., (1986).

In summary, extragenital MC represents one of the rarest endometriosis associated malignancies. The presence of atypical endometriosis with various types of epithelial abnormalities including metaplastic changes and cytologic atypia as seen in our case not only

pose diagnostic challenges but also supports the hypothesis that atypical endometriosis serves as an intermediate lesion in the development of endometriosis associated malignancies.

Authors contribution

1. Khalid Amin participated in manuscript writing, data acquisition, literature search and submission.
2. Beatrice Brumley participated in manuscript writing and literature search.
3. Brit Erickson participated in manuscript writing and data acquisition.
4. Mahmoud Khalifa participated in developing study concept, manuscript writing, data acquisition and literature search.

Disclosure

No disclosure to report.

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