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# The valid evidence to reveal the effect of sex hormone on primary retroperitoneal malignant mixed müllerian tumor: a case report

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**Summary**

Extragenital malignant mixed Müllerian tumor (MMMT) is rare, and the retroperitoneum is one of the rarest sites. The etiology and risk factors are yet ill-understood. The authors report a case of primary retroperitoneal Müllerian carcinosarcoma in a pregnant woman. Initially, a pure cystic mass was found when she was four months' pregnant. After drainage of the cyst, the follow-up ultrasound detected rapid recovery of the cyst, the appearance of septation within the cyst, blood flow signal in the septation, more and thickened septation, and nodules on the septation and cystic wall with progressing pregnancy. After delivery, the follow-up imaging examination revealed a relatively dormant mass. The contrary clinical manifestations were consistent with sex hormone levels, which surged during pregnancy and dropped rapidly postpartum. Moreover, immunohistochemistry staining showed that both ER and PR were positive for the epithelial and stromal component. Given the clinical manifestations and pathology, for the first time, the authors can explicitly conclude that sex hormone played a direct and evident role in the development of extragenital malignant mixed Müllerian tumor.

*Key words:* Malignant mixed Müllerian tumor; Sex hormone; Retroperitoneum; Hormonal receptor status.

## Introduction

Müllerian carcinosarcoma, also known as malignant mixed Müllerian tumor (MMMT), commonly arises in the female genital tract, predominantly in uterine corpus. Cases originating from extragenital sites, such as the peritoneum, omentum, and pelvic wall, have also been reported, among which the retroperitoneum is one of the rarest sites [1]. MMMT is considered an aggressive neoplasm and responds poorly to treatment with poor prognosis. A majority of the MMMTs occur in postmenopausal women. Although the predisposing factor of MMMT remains unknown, the sex hormone is suspected to play a role in the occurrence and development of this disease. Some reports suggested that estrogen administration may potentially be associated with the occurrence of the malignant Müllerian neoplasms [2, 3]. Several case reports and case series showed an increased risk of uterine MMMT after tamoxifen therapy for breast cancer [4-7]. However none of them can provide direct evidence to confirm the association between them. Here, the authors report a case of primary retroperitoneal Müllerian carcinosarcoma in a 30-year-old pregnant female in which the development of the tumor was consistent with sex hormone levels, which surged during pregnancy and dropped rapidly postpartum. Moreover, immunohistochemistry staining showed that both ER and PR were positive for the epithelial and stromal component. Given the clinical manifestations and pathology, for the first time, the authors can explicitly conclude that sex hormone played a direct and evident role in the development of extragenital malignant mixed Müllerian tumor, which may be crucial for exploring the pathogenicity and improving the treatment strategy.

## Case Report

A 30-year-old woman who was four months' pregnant presented with a one-month history of abdominal distension and fullness. She had undergone three abortions after first delivery at the age of 23 years. A history of irregular vitamin E administration for four years was recorded; however, no remarkable gynecological history or another systemic disease was reported.

Physical examination revealed a large, slightly tender mass in the left abdomen. Ultrasound demonstrated a pure cystic mass without septation or solid component in the left abdomen, inferior to the stomach cranially and superior to the uterus fundus caudally, measuring 19 cm at a maximum diameter. The cystic wall was thin and color flow was not detected. The uterus carrying a four-month fetus was slightly compressed by the cystic mass. The woman underwent ultrasound-guided percutaneous puncture catheter drainage. Almost all the cyst fluid was extracted, which yielded a 1,500-mL bright yellow thin fluid. The cytology was negative for malignancy. After 1.5 months, an ultrasound revealed the recovery of the cystic mass, which measured 7×5×5cm with some thin septation [Figure 1(a)]. Re-examinations were performed at seven and eight months of pregnancy. The cystic mass was compressed by the uterus against the left abdominal wall, but

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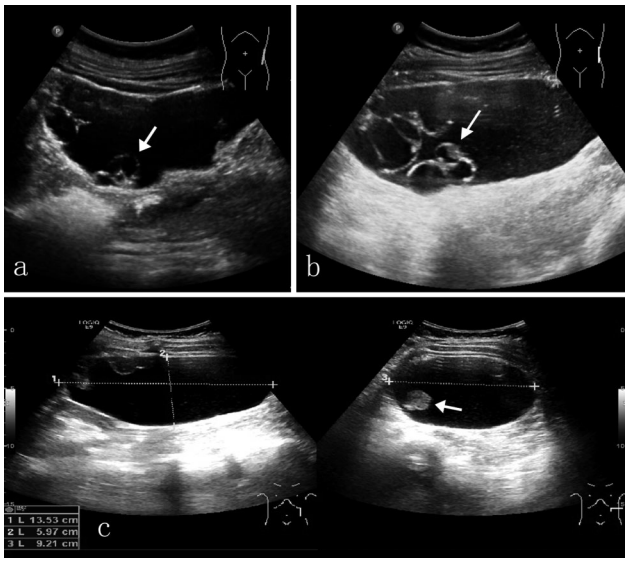


Figure 1. — (a) Ultrasound imaging 1.5 months after drainage showing the cystic mass with clear cystic fluid and some thin septation (white arrow) in it. (b) Ultrasound imaging when the woman was eight months' pregnant showing unevenly thickened septation (white arrow) and turbid cystic fluid. (c) Ultrasound imaging seven months after the delivery showing the cystic mass with fused septation presenting a nodular appearance and enlarged papillary nodules (white arrow) on the septation and cystic wall. The cystic fluid is clearer with less debris floating in it.

grew rapidly, and measured 10×7×6cm and 15×8×6 cm, respectively. An increasing amount of septation was found. The septation and cystic wall became unevenly thickened, and color flow signal was detected within both. Moreover, little papillary nodules appeared on the septation and cystic wall. The cyst fluid initially anechoic altered gradually into intensively dotted [Figure 1(b)]. During this period, no treatment was administered. When the woman was 37-weeks pregnant, she delivered a healthy baby through a cesarean section. The exploration of the uterus and bilateral adnexa revealed no abnormal findings. Contrast-enhanced CT scan performed one month after the delivery showed a cystic mass in the left retroperitoneum, measuring 13×8×7 cm with enhanced septation [Figure 2]. The woman was admitted to the hospital after seven months for the mass resection. Ultrasound before the surgery demonstrated that the cystic mass was a similar size to that in CT. Most septation fused presenting a nodular appearance. The papillary nodules on the septation and cystic wall enlarged slightly. It also showed a clearer cystic fluid with less debris floating in it. Color flow mapping showed no detectable blood supply [Figure 1(c)].

Laparotomy showed a large, encapsulated cystic mass in the left retroperitoneum, extending from the lower pole of the spleen to the level of the anterior superior spine. The mass was dissected from the surrounding structures by complete excision.

The gross pathological findings showed a 13×9×6-cm cystic mass with a smooth surface. The tumor was predominantly cystic with pale nodules dispersed over the inner surface, measuring 2.5×1×1 cm–4.5×3.4×1 cm. Histological findings demonstrated carcinosarcoma (homologous type) with the ratio of epithelial to stromal component 4:6 [Figure 3(a)]. The epithelial component, predominantly adenocarcinoma, consisted of the following subtype: endometrioid carcinoma, serous papillary carcinoma, and clear cell carcinoma with local cords and nest-like arrangement. The predominant cell type of stromal component was fibrosarcoma with nucleus mitotic count 8/10 HPF. Any hemorrhage or necrosis was not found. Immunohistochemistry (IHC) staining of the epithelial component was positive for CK7, CA125, villin, β-catenin, and CEA while staining of the stromal component was positive for vimentin. Both epithelial and stromal component were positive for ER, PR [Figure 3(b,c)], and Ki67 while both were negative for CK20, p53, and Inhibin-α. The histological findings, as well as IHC staining, were supportive of Müllerian origin.

Postoperatively, the woman ceased vitamin E administration and did not receive any treatment. Serum tumor markers, abdominal CT or ultrasound and gynecological ultrasound were re-examined at an interval of six months. Currently, it has been two years since the surgery, and no evidence of recurrence is found.

This study has been approved by institutional review board and the patient has signed informed consent.

## Discussion

Extragenital neoplasms of Müllerian origin occur rarely. Thus, the etiology and risk factors are not yet clearly elucidated. Here, the authors report a case of primary retroperitoneal Müllerian carcinosarcoma in a pregnant woman to show that sex hormone played a crucial role in the occurrence and development of this disease, which provides a basis for prevention and treatment.

Two major hypotheses have been proposed about the histogenesis of extragenital malignant Müllerian neoplasms: the endometriosis-origin theory and the secondary-Müllerian-system theory. The former has been supported by some case reports that demonstrated a coexistence of endometriosis with the neoplasm [2, 3, 8]. In the present case study, additional sections were sliced for critical review of the specimen and no endometrioid tissue was found. The second hypothesis, "secondary Müllerian system," was proposed by Fujii *et al.* [9], which suggested that coelomic epithelium-related tissues and Müllerian-derived epithelia of the adult share an embryologic ancestry based on the expression of CA 125 in both the coelomic cavity and the Müllerian duct. However, epithelial tissue is known to be absent in the retroperitoneum; thus, in the present case, either of the hypotheses cannot explain the origin perfectly. Ferrie *et al.* described a retroperitoneal MMMT and suggested the remnants of the Müllerian duct in the retroperitoneum as a possible origin of the tumor [10]. In the present case, the authors preferred the last assumption owing to its occurrence along the course of the embryologic Müllerian duct.

The etiological factor of MMMT is yet unclear. The female patient in this case study presented a history of irregular vitamin E administration for four years. As is known, tocopherol, the hydrolysis product of vitamin E, can stimulate the sex hormone secretion to maintain it at a high level. In addition, the woman underwent three abortions, and sex hormone fluctuated greatly around this period. The present authors suspected an association between the oc-

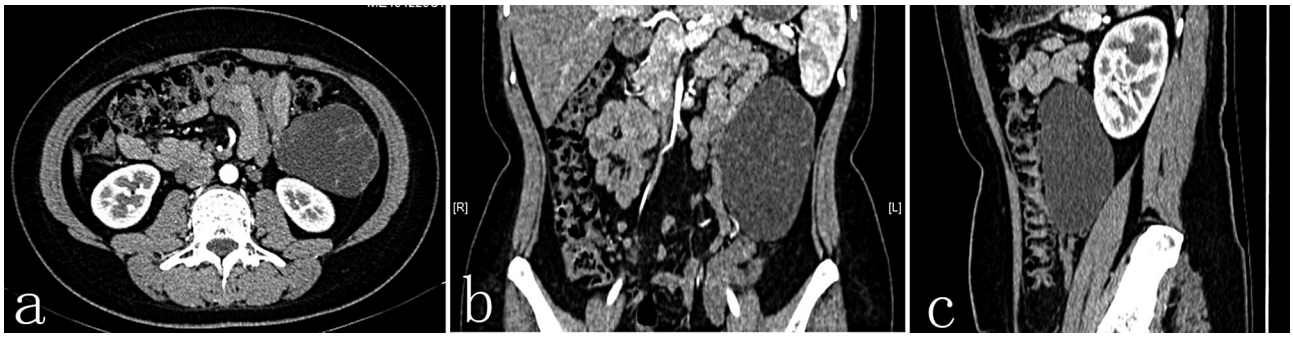


Figure 2. — Contrast-enhanced CT scan one month after the delivery showing a cystic mass in the left retroperitoneum with enhanced septation.

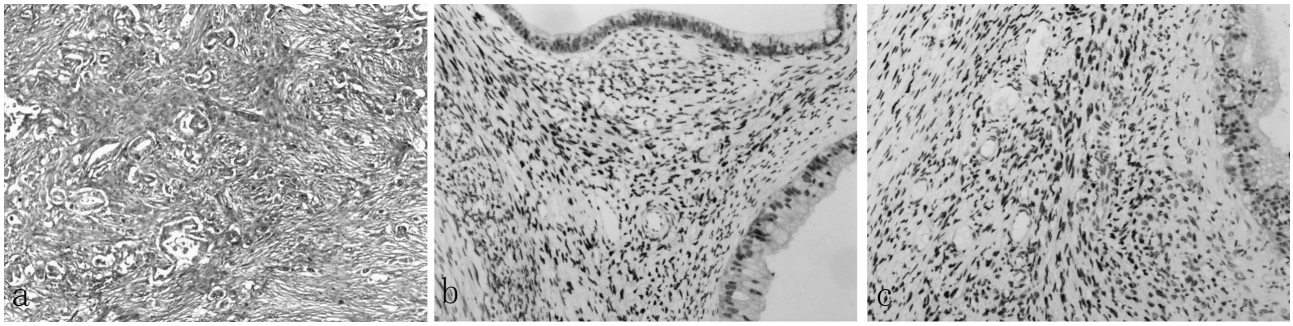


Figure 3. — (a) Histological findings demonstrating the tumor cells comprised both epithelial and stromal component (homologous type) (×100). (b, c) IHC staining demonstrating both the epithelial and stromal component positive for ER and PR (×100).

currence of the retroperitoneal Müllerian carcinosarcoma and persistent high sex hormone level with fluctuation. Teng *et al.* discovered that estradiol administration could stimulate the growth of the chick Müllerian duct in vivo by accelerating the translocation of estrogen receptor from the cytoplasm of the embryonic chick Müllerian duct cell into the nucleus and then exert the hormonal effect [11]. The estrogen abnormality is also suspected to be a risk factor of MMMT. Booth *et al.* reported a retroperitoneal MMMT associated with endometriosis and the patient reported a history of postmenopausal estrogen use [2]. Tanaka *et al.* reported a primary retroperitoneal Müllerian adenocarcinoma, wherein the patient received estrogen-replacement therapy for 14 years after total hysterectomy and bilateral salpingo-oophorectomy [3]. Estrogen administration has been suggested to associate with the development of malignant Müllerian tumor in both reports. Several case reports and retrospective studies showed an increased risk of uterine MMMT after tamoxifen therapy for breast cancer [4-7]. Tamoxifen was speculated to paradoxically act as a partial estrogen agonist on the endometrium and increasing the incidence of proliferative endometrial lesions [12]. This assumption was supported by estrogen receptor-α, which has been observed in tamoxifen-exposed endometrial cells [13]. In the present case, the mass was discovered as a pure cyst when the woman was four months' pregnant. After drainage of the cyst, the follow-up ultrasound detected a rapid recovery of the cyst, the appearance of septation within the cyst, blood flow signal in the septation, thickened septation, nodules on the septation and cystic wall, and much debris floating in the cystic fluid during pregnancy. These changes were characteristics of rapid proliferation and active metabolism. However, within seven months after delivery, no significant change was observed in the mass size. Also, the cystic fluid was clearer with less debris, and no blood supply was detected within the nodules and septation. The above assessments revealed a relatively dormant mass. The contrary clinical manifestations were consistent with the estrogen level that surged during pregnancy and dropped rapidly postpartum. Notably, both ER and PR were positive for the epithelial and stromal component; thus, progestin might also exert a direct effect on the development of the disease. Given the clinical manifestations and pathology, for the first time, the present authors can explicitly propose that sex hormone played a direct and evident role in the development of MMMT.

MMMT is an aggressive neoplasm with poor prognosis. Due to its strong aggressiveness, it is recommended not to break the neoplasm during surgery to avoid any peritoneal implantation. The clinical stage at diagnosis seemed to be the most reliable predictor of prognosis in MMMT. On pathology, MMMTs with sarcomatous overgrowth or with

heterologous elements are suggested to be associated with worse prognosis [14,15]. In addition, there may be an association between positive hormone receptor and superior clinical outcome [16]. MMMT responds poorly to treatment. Neither radiotherapy or chemotherapy after surgery can prevent the recurrence effectively. According to the present case, sex hormone played a crucial role in the development of MMMT. Further studies should aspire to focus on the therapeutic role of hormonal manipulation in MMMT.

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