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*Case Report*

# Mixed endometrial stromal and smooth muscle tumor with heart metastasis: report of a case and review of literature

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**Abstract:** We presented a case of mixed endometrial stromal sarcoma and smooth muscle cell tumor of the uterus with intravenous metastasis into the right heart. 50 hot mutated key genes of solid tumors were detected by next generation sequencing. The literature about the diagnostic and therapeutic strategies of the disease were reviewed.

**Keywords:** Mixed endometrial stromal and smooth muscle tumor, uterus, intracardiac metastasis, next-generation sequencing, gene

## Introduction

Mixed endometrial stromal and smooth muscle tumor (MESSMT) of the uterus with intravascular and intracardiac extension are not very common [1-10]. Literature review shows that there are only 3 cases with intracardiac extension reported [5, 9, 10]. Owing to its rarity, MESSMT has been reported only in sporadic case and pathology. Furthermore there wasn't any exploration on gene mutation of reported cases. Here we present the fourth case of this composite tumor, in which the original tumor developed into a huge mass in the uterus and progressed through the iliac vein, inferior vena cava (IVC), right atrium, and right ventricle. Moreover the next-generation sequencing was adopted in present study to explore potential gene mutation in the patient.

## Case report

A 45-year-old lady had a hysterectomy for a benign leiomyoma when she was 42 years old. 2 years later, uterine fibroid was discovered by regular B-ultrasonic inspection and developed slowly. Then chest tightness after activity appeared gradually. Physical examination showed she had a diastolic cardiac murmur and mild lower extremity edema. Serum E2 was 1084 pmol/ml and CA125 was 41.1 U/ml. Serum CEA, AFP, CA153, CA199, HCG was normal. Echocardiogram revealed an echogenic mass in the right atrium (**Figure 1**). Left and right ventricular systolic function was normal. Pulmonary CT angiography revealed irregular filling defect in right atrium and right ventricle but normal in pulmonary artery (**Figure 2A**, **2B**). Multiplanar reformatted CT images showed an intravascular filling defect extending from the pelvic veins to the right atrium through an enlarged inferior vena cava (IVC) (**Figure 3A-C**). Magnetic resonance imaging (MRI) displayed a giant mass in pelvis (**Figure 4A**, **4B**). Two-stage operation was planned. Total hysterectomy with bilateral salpingo-oophorectomy, including the removal of the huge mass from pelvic retroperitoneal and bladder wall was first performed. The extremely difficult operation bleed about 5000 ml due to lots of nodules which covered and infiltrated the bladder. One month after the surgery, she underwent the second-stage resection, in which the intracardiac and intracaval tumor was removed through a right atriotomy and iliac vein lump was removed by general

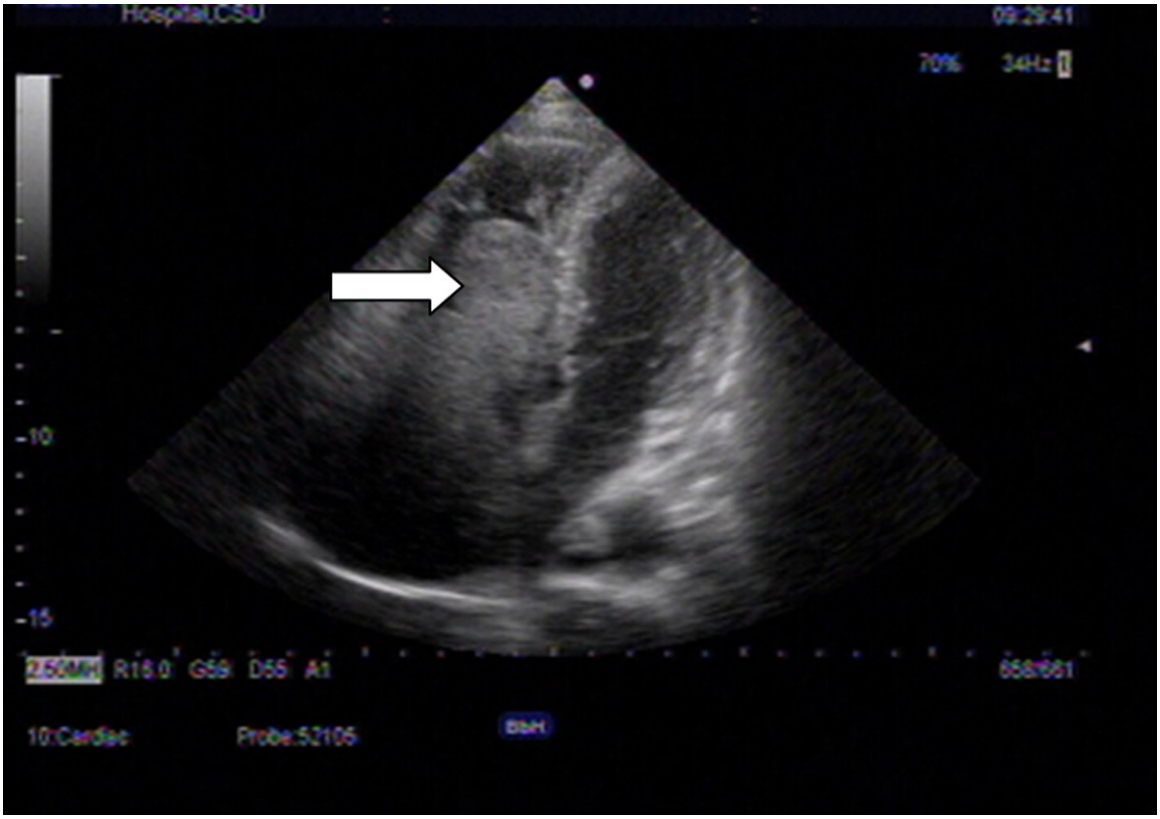


Figure 1. Heart echocardiography showing mass in the right atrium.

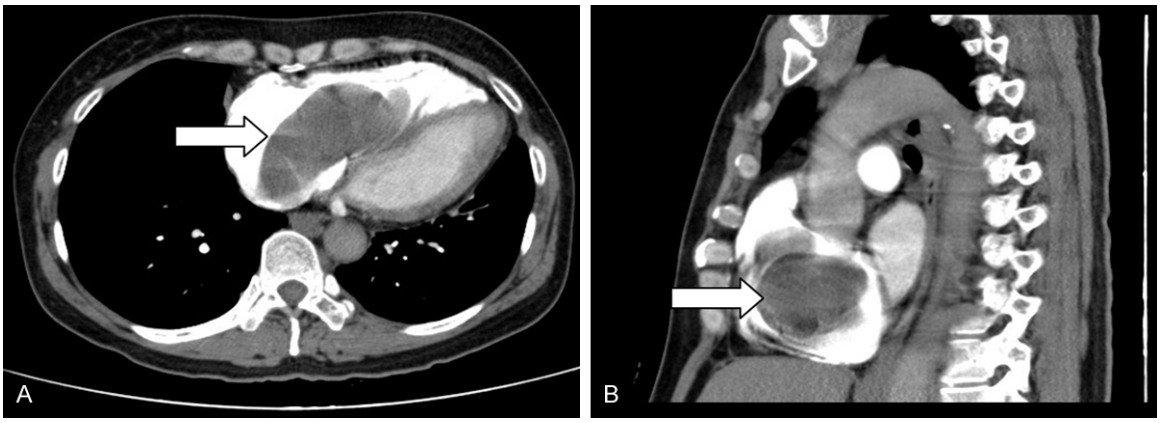
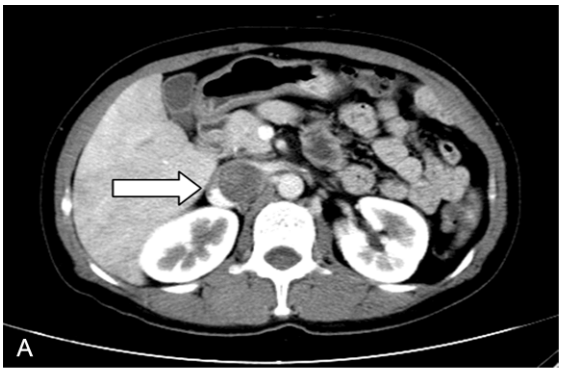
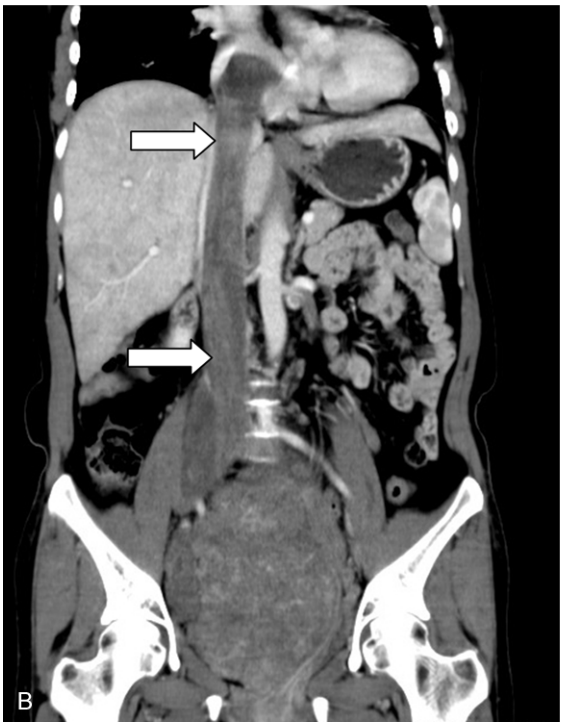



Figure 2. A. Axial CT pulmonary angiography revealed irregular filling defect in right heart cavities. B. Capital CT pulmonary angiography revealed irregular filling defect in right heart cavities.

surgery through excision of the abdomen midline incision. Grossly the mass seemed like a long continuous, white hollow cylinder that extended from the right iliac vein to the right ventricle (**Figure 5A**). Pathology revealed round and short spindle cell tumor with features of both intravenous leiomyomatosis and low grade endometrial stromal sarcoma (**Figure 5B**, **5C**). The tumor was positively immune-labeled with CD10, vimentin, desmin, ER, PR and positive with focal SMA. The intravenous mass showed identical morphology as to the abdominal mass. Review of the previous hysterectomy specimen showed that it was the origin of the tumor. Tissue sample and peripheral blood of the patient were collected and sent to conduct



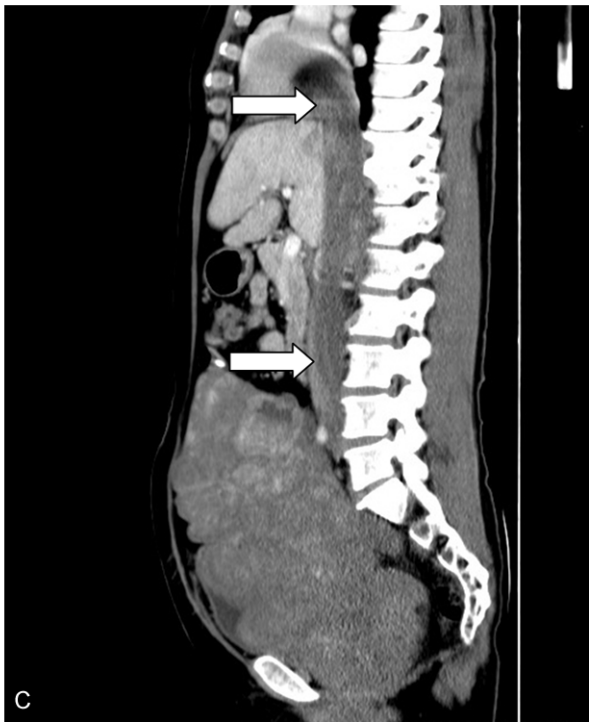




**Figure 3.** A. Intraluminal filling defect in IVC. B. Multiplanar reformatted coronal CT images showed an intravascular filling defect extending inferiorly from the pelvic veins to the right atrium through an enlarged IVC. C. Multiplanar reformatted sagittal CT images showed an intravascular filling defect extending inferiorly from the pelvic veins to the right atrium through an enlarged IVC.

next-generation sequencing analysis. 50 hot mutated key genes of solid tumors were detected. Unexpectedly, we detected no mutation in EGFR, CDKN2A MET, KIT, KRAS, BRAF, PIK3CA, PDGFR, which mutated relative frequently in common malignant solid tumors. Five months after the surgery, the patient showed no signs of recurrence while her serum E2 declined dramatically to normal value.

## Discussion

Mixed endometrial stromal and smooth muscle tumor (MESSMT), first reported by Tang and formerly known as uterine endometrial stromal tumors (EST), is a rare tumor. The etiology is unknown [11]. Patients' age ranged from 29 to 68 years. The clinical manifestation of this tumor is very similar to that of low grade endometrial stromal sarcoma or intravenous leiomyomatosis, ranging from sudden death, cardiac tamponade, dyspnoea, tachycardia and arrhythmias to abdominal pelvic pressure, abnormal bleeding, oedema of the inferior limbs and even Budd-Chiari syndrome [1]. Enlarged uterus or abdominal mass are the most common complaints in reported cases. However, the most prominent clinical presentation of our case was chest discomfort which is not a typical symptom for MESSMT diagnosis.

Endocrinologic studies and image examination is helpful to the preoperative diagnosis and detection of recurrence of MESSMT. The tumor is estrogen dependent. E2 was very high but dropped dramatically postsurgery in our patient. Although analysis of 194 intracardiac

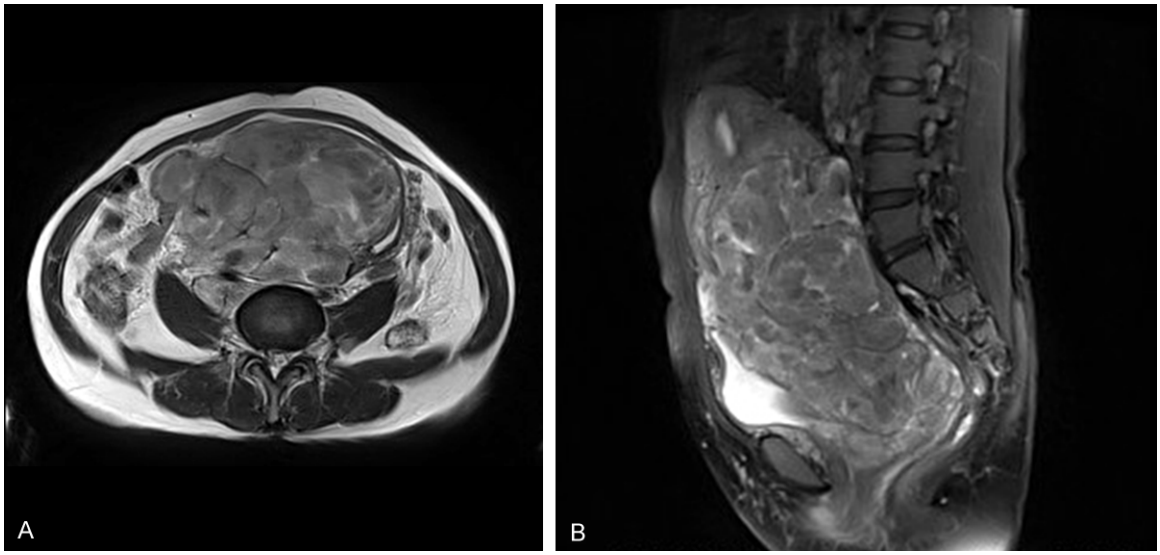



**Figure 4.** A. On axial magnetic resonance imaging (MRI), a giant mass was identified in pelvic. B. On sagittal magnetic resonance imaging (MRI), a giant mass was identified in pelvic.

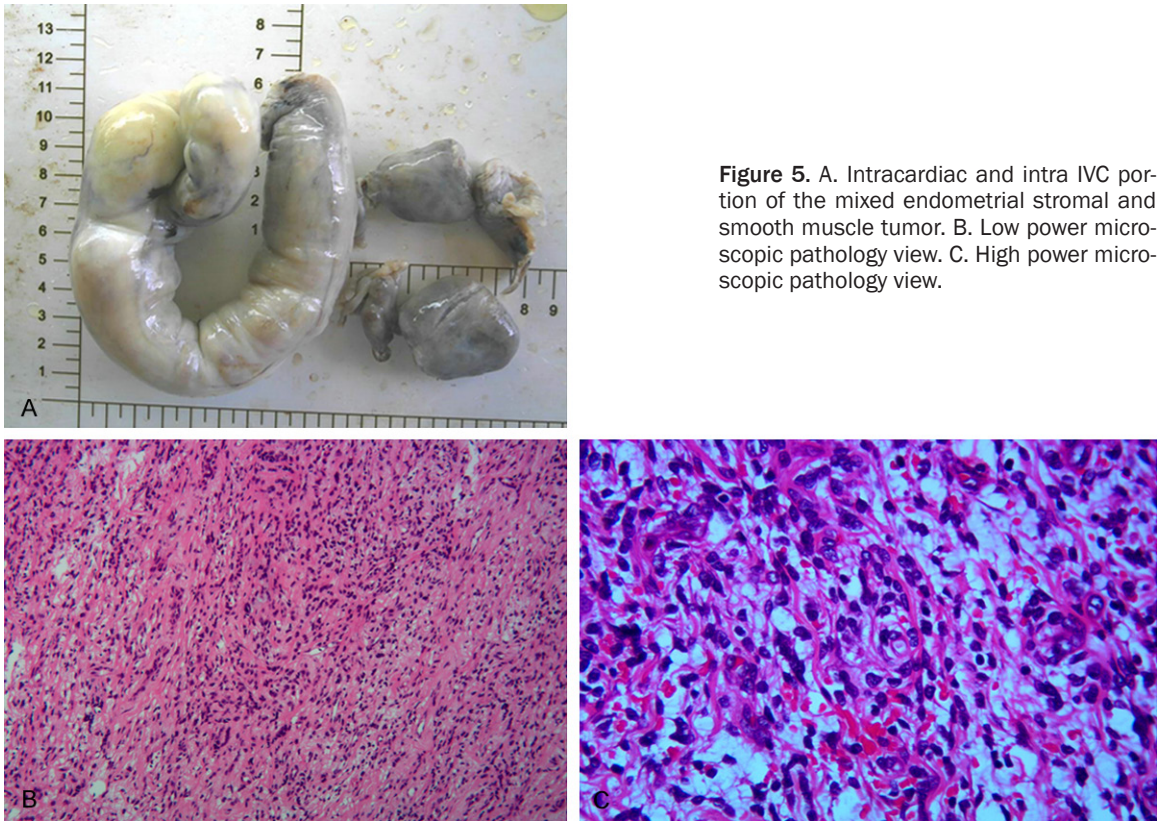



**Figure 5.** A. Intracardiac and intra IVC portion of the mixed endometrial stromal and smooth muscle tumor. B. Low power microscopic pathology view. C. High power microscopic pathology view.

leiomyomatosis cases showed that postoperative anti-estrogen therapy does not help to prevent recurrence, there weren't any similar study and result in MESSMT [12]. Because the tumor is estrogen dependent, anti-estrogen therapy should be prescribed [13]. In the present case, with positively immunolabelled estrogen receptor and progesterone receptors, the patient received toremifene daily to decrease the likelihood of recurrence. Long-term follow-up should be arranged. According to the limited literature, the prognosis and stage of this rare tumor is

consistent with the tumor of endometrial stroma.

Several pathological alterations were identified in MESSMT, but the molecular aberrations remained unclear and explorations have yet to be conducted. Somatic mutations have been described at low frequency in the majority of the tyrosine kinase growth factor family gene and their downstream targets [14]. We had hoped to discover some remarkable molecular mutations and then clarify the mechanisms, however we detected no mutations even in EGFR-TKIs therapeutic pathway. But it is still too early to make a conclusion only accord to a simple case and more investigation should be done to further explore the possibilities of therapeutic targets. In addition, mutation of TP53 was not detected in this sample. This patient should have good prognosis according to findings in previous studies [15-17].

It is very difficult to distinguish endometrial stromal cells with smooth muscle cells under optical microscope. Then the immunohistochemical detection such as CD10, SMA, desmin can have very good auxiliary to use. In general, in the endometrial stroma, CD10 positive and caldesmon, SMA, desmin negative but in smooth muscle, caldesmon, SMA, desmin positive, CD10 negative. Mixed tumors are those tumors in which each of the 2 components comprises at least 30% of the area of the whole tumor. If not, it is endometrial stromal neoplasms with smooth muscle differentiation [18]. Immunohistochemical research in our case shows MESSMT endometrial stromal elements' CD10 positive, smooth muscle composition's SMA and desmin positive, and both are more than 30%. MESSMT are benign in histological and biological behavior, but a surrounding infiltration is similar to low differentiation of endometrial stromal sarcoma or intracardiac leiomyomatosis. Olive's study showed only one case which had surrounding infiltration, and pelvic recurrence lesions were observed in 48 months after the operation [1]. Because our patient displayed diffuse bladder infiltration, more attention should be paid as there is a high risk of recurrence.

Echocardiography is a convenient method and can provide real-time information of intracardiac tumors. To make a correct diagnosis of MESSMT before surgery is challenging. Enhanced CT and MRI are usually used to evaluate the size, location, origin and extent of MESSMT for their excellent anatomical information. Accurate diagnosis relies on the postoperative pathology. Surgical resection (single or staged procedures) is the treatment choice of MESSMT, and complete removal of the tumor is mandatory since that is the key to the prevention of recurrences [19]. However, it places a much heavier burden on the patient and some patients are ineligible for surgery because of a poor clinical condition due to cardiac and pulmonary comorbidities or the large range of lesion invasion which can not be completely removed by surgery from the patient. In our case, we chose a double-staged strategy because of the complexity of the combined cardiovascular and gynecological surgery and the risk of bleeding. This instructive case which has the surrounding infiltration indicates that this type of tumor should be treated cautiously as a malignant tumor with the potential of distant metastasis. Non-surgical treatment of MESSMT is still under investigation. There is no accurate evidence as to whether the tumor is sensitive to radiation and chemotherapy as it is benign or low-graded.

In conclusion, although this patient had a very slow disease progression and was almost diagnosed as benign or low-graded tumor, its malignant biological behavior will make the tumor easy to recur and disseminate within blood vessels, even endanger the patient. However it is encouraging that it can be cured. Because of the limitations on the surgery, more research is needed in the treatment of MESSMT in the long run.

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**Disclosure of conflict of interest**

None.

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