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## Association of endometrioma with ovarian teratoma and mucinous cystadenoma in a patient diagnosed with endometriosis: A case report

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### Abstract

#### BACKGROUND

Co-occurrence of different tumor types in a same patient's ovaries diagnosed with endometriosis is a rare phenomenon.

#### CASE SUMMARY

In this article we present an uncommon association of three distinct ovarian pathologies in a same woman presenting with adnexal mass. A 31-year-old nulliparous woman with a large persistent adnexal mass underwent laparoscopic surgery. Imaging demonstrated a multi-cystic mass with internal echoes. Tumor markers were within normal range. Based on histopathologic assessment, benign mucinous cystadenoma and mature cystic teratoma of the right ovary together with endometrioma of left ovary were revealed.

#### CONCLUSION

In cases of large adnexal mass, the of existence of more than one tumor type and the involvement of the contralateral ovary is possible. Also, the possibility of concurrent underlying malignancy or diminished ovarian reserve should be kept in mind.

**Key words:** Endometriosis; Ovary; Teratoma; Mucinous cystadenoma; Laparoscopy; Case report

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**Core tip:** Existence of three distinct tumor types in the ovary is a rare phenomenon. This manuscript presents scarce association of endometrioma with teratoma and mucinous cystadenoma which was confirmed by histologic assessment.

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## INTRODUCTION

Though its true incidence is not defined yet, endometriosis affects approximately 10% of women in their reproductive life<sup>[1,2]</sup>. Endometrioma is considered as a common manifestation with the incidence of more than 40% in women diagnosed with endometriosis<sup>[1-3]</sup>. According to a large study by Grammatikakis *et al*<sup>[3]</sup>, endometriosis was the most common diagnosis amongst 1522 women with adnexal mass in whom laparoscopy was performed. Coincidence of endometrioma which is of epithelial origin with other ovarian tumors and particularly those with a different cellular origin, however, is not frequent. Dermoid cysts or mature cystic teratomas are regarded as the most frequent germ cell tumors of the ovary and mucinous cysts are the second most common masses of epithelial origin<sup>[4,5]</sup>. Only few cases of the endometrioma concurrence with other epithelial masses like mucinous cystadenoma or germ cell tumors have been reported in the literature<sup>[4-7]</sup>. It is well established that the pathogenesis of ovarian endometriosis could harbor malignant transformation<sup>[8]</sup>. Although endometriosis is not considered a premalignant condition, based on epidemiologic, histopathologic, and molecular data, it may lead to some specific subtypes of ovarian cancer particularly for atypical endometrioma or lesions larger than 10 cm<sup>[6,8]</sup>. Generally, there is a 2 to 3 fold increase in the risk of ovarian malignancy in patients suffering from endometriosis with the endometrioid and clear cell carcinoma as the most common subtypes<sup>[8,9]</sup>. According to a study by Pearce *et al*<sup>[9]</sup>, there is also a significant association between the pre-existing endometriosis and low-grade serous ovarian malignancy. This study presents the coincidence of three different ovarian cellular growths in a same woman who underwent laparoscopic surgery for management of a large adnexal mass.

## CASE PRESENTATION

### Chief complaints

A 31-year-old woman presented with progressive dysmenorrhea and abdominal fullness.

### Laboratory examinations

Laboratory examination indicated serum tumor markers including CA-125, HE4, CA19-9, AFP, CEA and HCG within normal range. Due to the reason that she had no children and had a low ovarian reserve, she was referred to the infertility clinic for oocyte preservation first.

### Imaging examinations

Trans rectal ultrasound reported a tubular multicystic lesion with a size of 9 cm suggestive of hydrosalpinx in the right adnexa accompanied by a small endometrioma in the left ovary (Figure 1).

## FINAL DIAGNOSIS

According to pelvic MRI which was requested three months later, a 95 mm × 90 mm cystic area was revealed in the midline with internal septae. The second trans rectal ultrasound revealed a multi cystic mass with internal echoes and the size of 11 cm suggestive of mucinous cystadenoma. Finally, she was scheduled for laparoscopic surgery due to the increase in the size of the mass. During operation, a huge cystic mass was uncovered occupying the whole pelvic cavity.

## TREATMENT

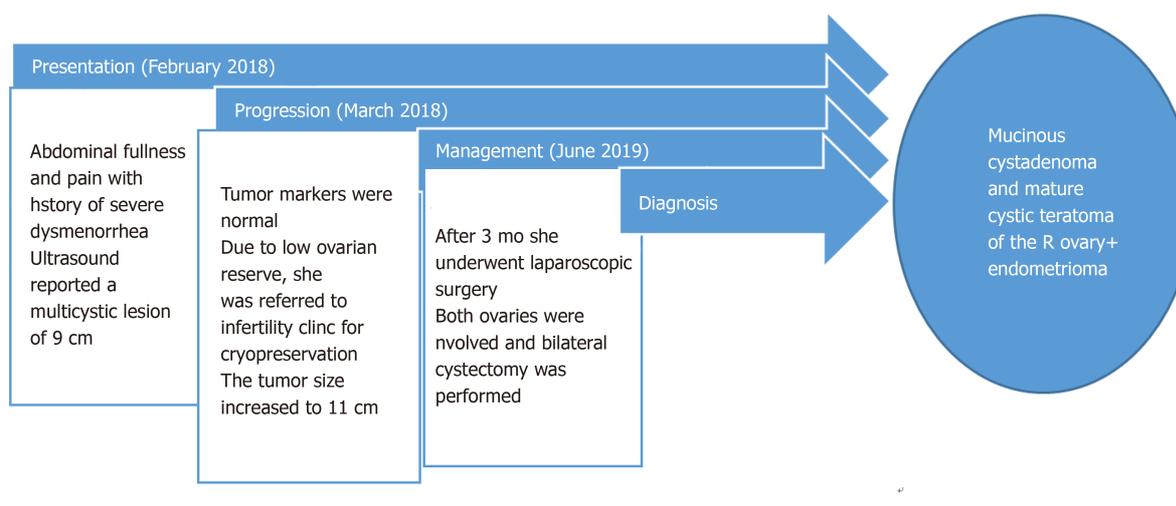


Figure 1 Timeline of the patient's progression of her disease.

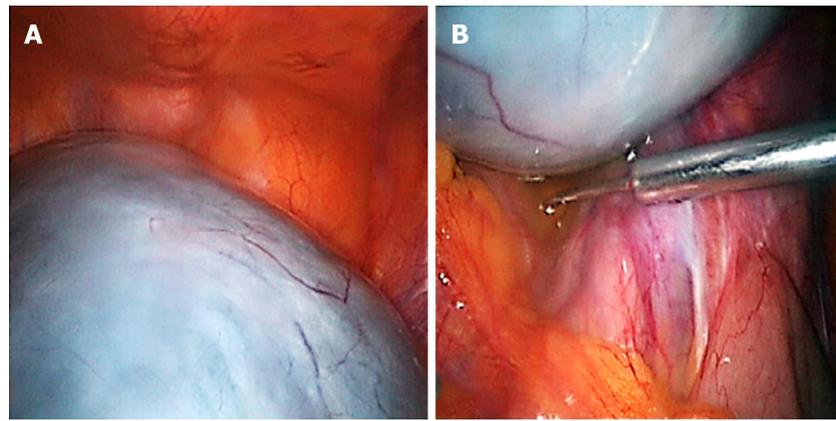
After obtaining the fluid sample for cytological assessment, the cyst was aspirated through the suprapubic port without any spillage of its content (Figure 2). Then, the ovaries were appeared. Another lesion was found which was adhered to the first cyst and originated from the right ovary (Figure 3A). A small endometrioma was also detected in the left ovary (Figure 3B).

## OUTCOME AND FOLLOW-UP

Cystectomy was performed and all these lesions were sent for pathologic evaluation. Moreover, the uterosacral endometriotic nodule (histologically confirmed) was excised. Microscopically, 3 tumor types were revealed: Mucinous cystadenoma together with mature cystic teratoma of the right ovary and endometrioma of the left ovary.

## DISCUSSION

This study presented a case of the simultaneous mucinous tumor associated with mature cystic teratoma and endometriosis in the same patient ovaries in her reproductive age. Although each of these cystic pathologies are commonly managed by laparoscopic approach, their co-existence together is rare especially when there are more than two tumor types<sup>[4-7]</sup>. There are a few studies in the literature on the simultaneous occurrence of two ovarian histopathologic findings in a same ovary of a patient or the ovaries of a same patient<sup>[4-7]</sup>. This study was a collision tumor case (consisting of mucinous cystadenoma and dermoid) of the right ovary accompanied by an endometrioma of the left ovary. Collision tumors are uncommon tumors composed of two or more histologically distinct neoplasms coinciding at the same organ<sup>[7]</sup>. However, the specific feature of this case is the coexistence of three different ovarian pathologic findings in a patient suffering from endometriosis. There was also a similar study by Joo *et al*<sup>[4]</sup> in which three different tumor types including borderline mucinous tumor, mature cystic teratoma, and endometriosis in the same ovary were revealed. Their case was a 42-year-old woman with severe dysmenorrhea and a huge unilateral ovarian mass<sup>[4]</sup>. For our case, endometrioma was derived from the left ovary and mature cystic teratoma adhered to a large mucinous cystadenoma was related to the right ovary. Chae *et al*<sup>[5]</sup> in another study described a 28-year-old Gravida 1 woman with bilateral ovarian cysts who underwent laparoscopic surgery due to her persistent vaginal bleeding and positive serum  $\beta$ -hCG (more than 5000 IU) suspicious of ectopic pregnancy. Imaging evaluation was in favor of bilateral mature cystic teratomas which was confirmed by final histologic assessment but involvement of the left ovary by endometriosis was also reported<sup>[5]</sup>. For all these cases, simultaneous presence of different tumor types was affirmed only after histopathologic examination. For the Chae *et al*<sup>[5]</sup> case, the surgeons did not expect to be encountered with more than one ovarian pathology based on imaging. The type of ovarian tumor or cyst is of paramount importance concerning the ovarian reserve. While large or



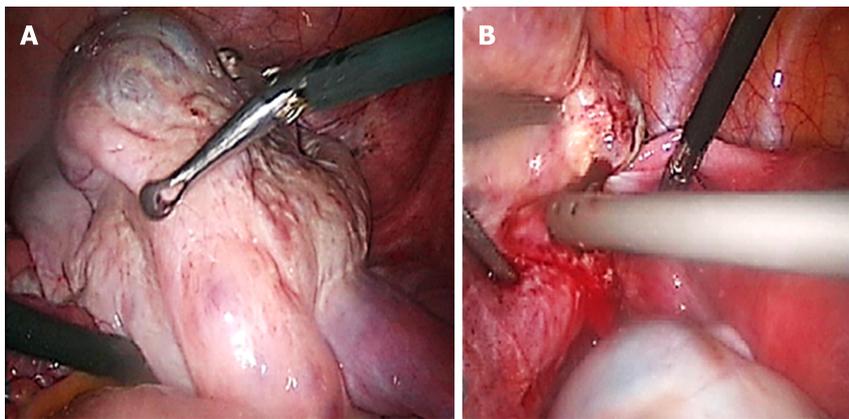
**Figure 2** Large mucinous cystadenoma of the right ovary. A: Laparoscopic view following entry; B: Cytological sample was obtained from pelvic fluid.

bilateral dermoid cyst do not significantly alter the ovarian reservoir, even a small endometriotic implant could jeopardize the future fertility of a woman<sup>[10,11]</sup>. Our patient declared a history of aggravating dysmenorrhea. In addition, her anti mullerian hormone level was only 1.05 ng/mL, both of which were compatible with the diagnosis of endometriosis. Hence, some measures were taken before she was scheduled for the surgery. First, she was referred to the infertility clinic for oocyte cryopreservation. Furthermore, with respect to the mass size (> 10 cm) which was suspicious of malignancy, written informed consent was obtained from the patient including the possibility of salpingo-oophorectomy. Endometriosis concurrence with other gynecological diseases like adenomyosis has been noted in the literature<sup>[4,5,11]</sup>. Matalliotaki *et al*<sup>[11]</sup> evaluated 1000 women with endometriosis during a 10-year period. More than 90% of their patients were also diagnosed with other benign conditions with adenomyosis, leiomyoma and benign ovarian cysts at the top of the list. Under the influence of genetic, environmental and inflammatory factors, benign tumors can occur in a same woman<sup>[7,11,12]</sup>. However, the perplexing nature of endometriosis with various underlying mechanisms further could complicate the process of disease in women<sup>[8-10]</sup>. Hence, as Matalliotaki *et al*<sup>[11]</sup> reported, women suffering from endometriosis should be informed of the possibility of being diagnosed with other benign conditions. Another finding in their study was the left ovary predominance for developing endometrioma which was also consistent with our case<sup>[12]</sup>.

Each constituent in a collision tumor has its own biologic behavior which could harbor malignancy<sup>[7]</sup>. Since the appropriate management could differ depending on the most aggressive component, the exact diagnosis is quite important and should be reaffirmed<sup>[4-7]</sup>. Patients diagnosed with these tumors should be followed strictly due to the added potential of malignant transformation of different cell types<sup>[6,7]</sup>. Also, more emphasis should be given to those who are suffering from endometriosis as they are at risk for recurrence and further progression of disease like this case<sup>[2,6,10]</sup>.

## CONCLUSION

In conclusion, considering the scarcity of coincidence of more than two histopathologic findings related to the ovary, special attention should be given to appropriate diagnosis, management and long-term follow-up of patients suffering from these types of tumors in order to increase their quality of life.



**Figure 3** Laparoscopic views of ovaries after aspiration of the cyst. A: Dermoid cyst adhered to the mucinous cystadenoma of the right ovary; B: Endometrioma of the left ovary.

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## Primary extragenital mixed malignant Mullerian tumour presenting as a painful splenic mass: A case report and review of the literature

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### Abstract

#### BACKGROUND

Mixed malignant Mullerian tumours (MMMTs) are highly aggressive cancers that present at a late stage and are associated with a poor long-term prognosis. They are characterised by the presence of both epithelial and sarcomatous tissue types on histological examination and hence are known as biphasic tumours or carcinosarcomas. MMMTs almost always arise in the female genital tract (most commonly the uterus) but extragenital sites are also possible. Treatment options are limited and usually consists of surgery and adjuvant chemotherapy.

#### CASE SUMMARY

A 74-year-old woman presented with a 1-wk history of worsening left upper quadrant abdominal pain and a perisplenic mass on computed tomography (CT) scan. Features on imaging raised the possibility of a malignant process but were not diagnostic. Splenectomy was performed and histology confirmed the presence of a mixed malignant Mullerian tumour. A subsequent pelvic ultrasound identified another heterogenous cystic mass in the Pouch of Douglas without evidence of primary pathology in the uterus or adnexa. A second operation was performed for this with curative intent but previously-unknown widespread metastases were encountered at laparotomy. A biopsy of the pelvic mass confirmed it was also a MMMT with identical histological features to the perisplenic mass. There was no clinical or histological evidence of the MMMT having arisen primarily from the female genital tract. The patient subsequently suffered multi-organ failure and was palliated, succumbing to death on the 19<sup>th</sup> post-operative day.

#### CONCLUSION

Primary extragenital MMMT arising from the spleen or peritoneum represents an atypical form of an already rare gynaecological tumour.

**Key words:** Mixed malignant Mullerian tumour; Carcinosarcoma; Extragenital; Spleen; Metastatic; Case report

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**Core tip:** Mixed malignant Mullerian tumours (MMMTs) are rare tumours that normally arise from the female genital tract, with the uterus and cervix being the most common sites. Very rarely they may arise from extragenital sites such as the spleen or the peritoneum. We describe the case of a 74-year-old woman who presented with left-sided upper abdominal pain due to a MMMT involving her spleen. Further investigations revealed additional extensive disease in the pelvis and there was evidence that it specifically did not arise from the genital tract. This case represents a highly atypical presentation of an already rare gynaecological tumour.

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## INTRODUCTION

Mixed malignant Mullerian tumours (MMMTs) are rare and highly aggressive gynaecological malignancies which feature a biphasic appearance on histological examination, consisting of both epithelial and mesenchymal tissue. First reported by Gerhardt in 1989, they most commonly arise from the uterine body but can also originate from the cervix, ovaries, Fallopian tubes and vagina (in decreasing order of frequency)<sup>[1,2]</sup>. Tumours arising from extragenital sites such as the spleen and peritoneum are exceedingly rare. Other potential sites of extragenital origin include the retroperitoneum, greater omentum, colonic serosa, mediastinum and even the prostate, testes and seminal vesicles in men<sup>[3,4]</sup>. MMMTs affect fewer than 2 per 100000 women per year (accounting for 2%-5% of all uterine tumours) and carry a poor long-term prognosis<sup>[1,5,6]</sup>.

The usual presenting symptoms of MMMT include lower abdominal or pelvic pain and the passage of blood or necrotic tissue per vaginum<sup>[1]</sup>. They are mainly encountered in post-menopausal women, with an average age of onset between 56-67 years<sup>[7,8]</sup>. Risk factors include nulliparity, diabetes, obesity, prior pelvic irradiation and tamoxifen use, the last of which is associated with up to an 8-fold increased risk of developing a MMMT<sup>[1,6]</sup>. Common findings include a large polypoid tumour protruding through the cervical os on speculum examination and a cystic, heterogenous, hypodense/hypoechoic mass that dilates the endometrial cavity on ultrasound and CT<sup>[9,10]</sup>. At time of diagnosis, between 33%-50% of patients have evidence of lymph node or distant metastases and overall 5-year survival for all patients with MMMTs is poor at 21%<sup>[1,8,9]</sup>. This reduces to only 0%-10% for those with Stage III or IV disease, with up to 90% of tumour-related deaths occurring within 18 mo<sup>[8,11]</sup>. When resectable, management of these aggressive tumours includes total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy. The role of bilateral pelvic and para-aortic lymphadenectomy remains uncertain<sup>[7,8,12]</sup>. Adjuvant platinum-based chemotherapy with ifosfamide and paclitaxel is now considered the standard of care and the addition of radiotherapy has been shown to improve local control but without translating into an overall survival benefit<sup>[7,8]</sup>. Negative prognostic factors include age > 70 years, positive surgical margins and Stage III-IV disease<sup>[5,12]</sup>. Metastases most often occur in regional lymph nodes although transcoelomic and haematogenous spread is also possible<sup>[10]</sup>.

By comparison, patients with extragenital MMMT tend to present at an earlier age and suffer a more aggressive course of disease<sup>[13]</sup>. Fu *et al*<sup>[9]</sup> reported that there is a higher probability of relapse within 12 mo for these patients and that survival can be as short as 7 d following diagnosis. Median survival is better for those with the primary tumour arising in the pelvic peritoneum (21.5 mo) compared with those whose tumour originated elsewhere (7.6 mo for those with colonic/rectal peritoneal origin and 4.3 mo for all other sites)<sup>[14]</sup>. Unfortunately, due to the scarcity of cases in the literature and the inability to conduct adequately-powered trials, the optimum management strategy for extragenital MMMT remains elusive.

We aim to raise awareness of this rare gynaecological tumour to improve its recognition in the medical community and to encourage earlier onward referral to the

appropriate specialists. The importance of prompt identification and comprehensive pre-operative staging cannot be underestimated.

We describe herein the highly unusual presentation of an extragenital MMT causing left upper quadrant pain from splenic involvement in an elderly female who presented to a general tertiary referral hospital.

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## CASE PRESENTATION

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### **Chief complaints**

An active and independent 74-year-old woman presented to our Emergency Department with localised left upper quadrant abdominal pain.

### **History of present illness**

The pain had been present for 1 wk and had been gradually worsening, unable to be controlled by simple analgesia. She had experienced no diarrhoea or vomiting, no recent weight loss and no other constitutional symptoms. There had been no recent injury or trauma to the region.

### **History of past illness**

Her past medical history included a myocardial infarction eleven years earlier and long-standing hypertension, hypercholesterolaemia and type II diabetes mellitus. Previous surgery included a left total hip replacement and tubal ligation. A colonoscopy 2 years earlier had revealed two benign low-grade colonic tubular adenomas for which she was being surveilled. Regular medications included metformin 500 mg daily, hydrochlorothiazide 12.5 mg daily, aspirin 100 mg daily, rosuvastatin 40 mg daily and valsartan 160 mg daily. There was no known personal or family history of malignancy and she had no history of abdominal or pelvic irradiation. The patient was a lifelong non-smoker and denied any regular alcohol intake.

### **Family history**

There was no known family history of malignancy.

### **Physical examination**

Physical examination revealed a well-looking but overweight woman in no obvious distress (BMI 28.5 kg/m<sup>2</sup>). Vital signs were all within normal limits (blood pressure 145/76 mmHg, heart rate 71 beats/min, respiratory rate 18 breaths/min, temperature 36.4°C, oxygen saturations 97% on room air). Her abdomen was soft with left-sided tenderness on light palpation but no clinically-obvious palpable masses.

### **Laboratory examinations**

Initial biochemical investigations revealed a mild normochromic, normocytic anaemia (haemoglobin 111 g/L; reference range 115-165 g/L) and acute kidney injury [estimated glomerular filtration rate 39 mL/min per 1.73 m<sup>2</sup>]. White cell count was normal at 8.86 × 10<sup>9</sup>/L, platelet count was normal at 315 × 10<sup>9</sup>/L and liver function tests were unremarkable. Serum lipase was normal at 47 U/L. Internationalised normalised ratio and activated partial thromboplastin time were both normal at 1.1 and 27.8 s respectively.

### **Imaging examinations**

An outpatient CT scan of her abdomen and pelvis (with intravenous contrast in the portal venous phase) had been performed the day prior to hospital presentation, having already been arranged by her general practitioner. It revealed a cystic, hypodense, peripherally-enhancing heterogenous mass measuring 117 mm x 61 mm x 83 mm involving the lower pole of the spleen near the splenic flexure of the colon and causing medial displacement of her left kidney (Figure 1-2). The exact nature of the lesion was not able to be determined but was thought to be either infective or neoplastic. No other abnormalities were noted in the abdomen or pelvis. A subsequent left upper quadrant ultrasound revealed the mass to be heterogenous with internal vascularity, consistent with the earlier CT scan findings.

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## TREATMENT

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The patient was admitted for analgesia and to expedite further investigations. Aspirin was continued throughout her admission and thromboprophylaxis was commenced



**Figure 1** Coronal slice of computed tomography abdomen (with IV contrast in portal venous phase) showing a cystic, hypodense and heterogenous mass closely related to the inferior aspect of the spleen.

with a low molecular weight heparin (enoxaparin).

Consideration was given to performing a percutaneous biopsy of the splenic mass but this was ultimately decided against due to the presence of hypervascularity. A colonoscopy was performed to exclude primary colonic pathology in the region of the splenic flexure and it revealed only uncomplicated diverticulosis.

Due to ongoing poorly-controlled pain, uncertainty of diagnosis after numerous investigations and the possibility of malignancy, an open splenectomy was performed. At operation, a left subcostal incision was made and a large exophytic cystic mass was noted to be adherent to the inferior pole of the spleen (Figure 3). There was a small volume of old blood in the left upper quadrant but no ascites or suspicious peritoneal nodules were observed. The mass was in close proximity to the tail of the pancreas but was safely dissected free of both it and the colon. Due to the position of the incision, the pelvis was not well-visualised. Post-operatively she was administered post-splenectomy vaccinations in accordance with guidelines from Spleen Australia<sup>[15]</sup>. This consisted of vaccines against *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type B and influenza virus. She was also commenced on amoxicillin 250 mg daily as lifelong prophylaxis by the consulting infectious diseases physician.

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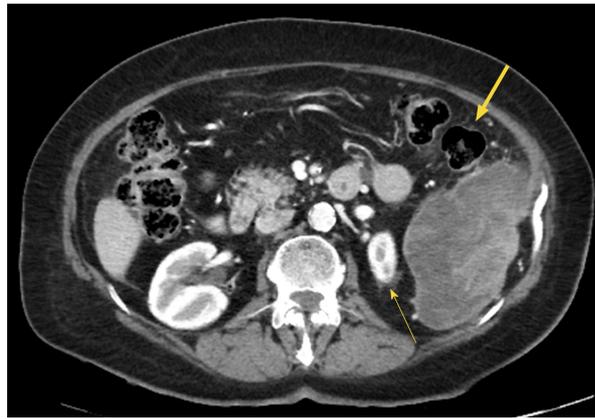
## OUTCOME AND FOLLOW-UP

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The patient's recovery was complicated by post-operative delirium for which a contrast-enhanced CT and gadolinium-enhanced magnetic resonance imaging (MRI) of the brain were performed. She did not develop any focal sensorimotor neurological signs or symptoms. These imaging investigations revealed acute left temporal, occipital and thalamic cerebral infarcts for which she was commenced on apixaban 5 mg twice daily by the consulting Neurologist. Aspirin was ceased following the commencement of apixaban. Carotid artery ultrasound revealed 50%-69% stenosis in the left internal carotid artery, representing the likely embolic source of her stroke. Transthoracic echocardiogram revealed only mild aortic stenosis and no evidence of mural thrombus. Within several days the patient made a full neurological recovery and her cognitive function had returned to baseline.

Histopathology of the splenic tumour revealed a fatty cystic mass at its lower pole with large areas of necrosis and calcification. The tumour was biphasic, containing both epithelial and sarcomatoid tissue (Figure 4). Multiple immunohistochemical stains were performed: The epithelial components stained positively for cytokeratin 7 (CK7) and epithelial membrane antigen (EMA) whilst the sarcomatoid components stained positively for desmin, vimentin and CD10 (Figures 5-6). The tumour was negative for p53, chromogranin, synaptophysin and CK20. The overall morphology and specific staining characteristics favoured the diagnosis of a malignant mixed Mullerian tumour with homologous differentiation. One lymph node (out of four) was found to have metastatic disease and there was evidence of microvascular invasion into the splenic parenchyma.

Given the histological characteristics of the tumour, a gynaecological origin was strongly favoured. Trans-abdominal and trans-vaginal pelvic ultrasounds were performed which showed a highly-vascular, well-circumscribed mass with mixed



**Figure 2** Axial slice of computed tomography abdomen (with IV contrast in portal venous phase) demonstrating medial displacement of the left kidney (thin arrow) due to the cystic splenic mass and its close relationship to the splenic flexure of the colon (thick arrow).

cystic and solid components in the Pouch of Douglas, measuring 39 mm x 36 mm x 45 mm (Figures 7-8). Neither ovary was optimally visualised. CT scan of the chest did not reveal any evidence of metastatic disease. Serum tumour markers were requested which found CA-125 to be mildly elevated at 53 kU/L (reference range 0-40 kU/L), although CA-19.9 and carcinoembryonic antigen (CEA) levels were both normal. After consulting with a gynaecologist, a fluorodeoxyglucose positron emission tomography (<sup>18</sup>F-FDG PET) scan was performed which revealed a 48 mm x 54 mm mass in the posterior pelvis with high FDG avidity (standardised uptake value: 6.8), consistent with a malignant lesion (Figures 9-10). Speculum examination was unremarkable – the vagina and cervix appeared normal and no abnormal masses or discharge were seen.

The patient was discharged home on the 15<sup>th</sup> post-operative day with plans to undergo an elective total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy at a sub-specialty quaternary referral centre by an oncological gynaecologist. Unfortunately, this subsequent operation was delayed by six wk due to a combination of reasons such as deconditioning after her first surgery and the need for further cardiac and neurological investigations following her recent peri-operative stroke. No repeat abdominal or pelvic imaging was performed in the interim. At the second operation multiple malignant nodules were noted on the small bowel mesentery, sigmoid colon and greater omentum. The tumour in the Pouch of Douglas was confirmed and noted to be affixed to the pelvic floor but was not arising from the uterus. Both ovaries and Fallopian tubes were macroscopically normal. Due to a combination of reasons (widespread peritoneal dissemination with inability to achieve complete tumour clearance, recent stroke and need for post-operative anti-coagulation), it was decided that embarking on extensive pelvic surgery was not clinically indicated nor in the best interests of the patient. A bilateral salpingo-oophorectomy and pelvic mass biopsy were performed, but the uterus and pelvic mass were left *in-situ*. Intra-operative hysteroscopy revealed a normal endometrial cavity and no abnormal lesions were seen.

In the days following her second operation, the patient developed severe multi-organ failure and was referred for palliative care in keeping with her wishes and those of her family. She died on the 19<sup>th</sup> day after surgery.

Histopathological examination of the Fallopian tubes revealed multiple foci of serous intraepithelial carcinoma and one fimbrial focus of invasive, high-grade serous carcinoma (Figure 11). No sarcomatoid areas were seen and neither ovary showed any evidence of dysplasia or malignancy. The pelvic tumour biopsy contained a high-grade sarcomatous lesion with some components of poorly-differentiated adenocarcinoma consistent with the diagnosis of a MMMT and it was similar in appearance to the splenic tumour (Figure 12).

## DISCUSSION

MMMTs are also known as carcinosarcomas due to their biphasic nature and can be classified according to the subtypes of epithelial and mesenchymal tissues that are present. The most common epithelial tissue subtype is endometrioid but other variants include serous, clear cell, mucinous, papillary-serous, squamous and

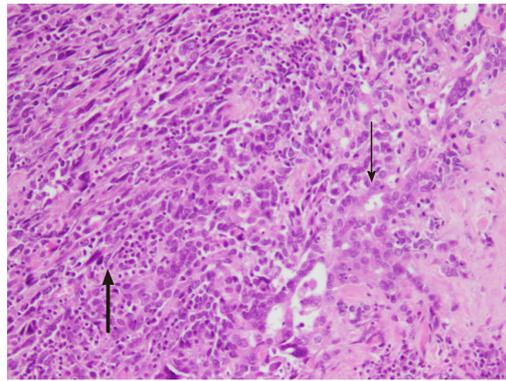


**Figure 3** Macroscopic photograph of the spleen following splenectomy (measuring 105 mm x 65 mm x 45 mm). The arrow indicates the position of the splenic hilum. Attached to the lower pole of the spleen is a necrotic, cystic mixed malignant Mullerian tumour measuring 100 mm x 60 mm x 30 mm.

basaloid<sup>[8,16]</sup>. The sarcomatous component can be described as being homologous (containing tissue which is native to the female genital tract, such as smooth muscle or endometrial stroma) or heterologous (containing tissue which does not normally occur naturally in the female genital tract)<sup>[1]</sup>. Examples of heterologous tissue include skeletal muscle (rhabdomyosarcoma), cartilage (chondrosarcoma), bone (osteosarcoma) or fat (liposarcoma), in decreasing order of frequency<sup>[6]</sup>. Overall, there does not seem to be a difference in prognosis based on the type of sarcomatous tissue present within a MMT although some studies suggest patients with homologous tumours fare better than those with heterologous tumours<sup>[7,8]</sup>. Immunohistochemical stains are not usually required for diagnosis of an MMT although they can be useful for identifying specific types of heterologous tissue if they are suspected of being present. Epithelial components typically stain positive for EMA and cytokeratin whilst sarcomatous tissue usually stains positive for vimentin<sup>[2,5,6,17,18]</sup>, consistent with the pattern of staining in our case.

There are three main theories that have attempted to explain the development of MMTs: Collision, combination and conversion<sup>[12]</sup>. The *collision theory* postulates that two independent tumours (a carcinoma and a sarcoma) develop independently in close proximity to one another but remain macroscopically and histologically distinct. This theory was popularised early on but is no longer thought to be the most likely explanation for the genesis of MMTs. The *combination theory* was also popular for many years and suggests that a common pluripotent stem cell gives rise to a tumour consisting of two tissue types. The current prevailing *conversion theory* proposes that malignant epithelial tissue undergoes a process of metaplastic de-differentiation to give rise to sarcomatous elements, a process known as epithelial-mesenchymal transition (EMT). This is supported by immunohistochemical evidence in embryos involving basement membrane disruption and loss of E-cadherin expression<sup>[12,18]</sup>. As such, MMTs can be considered a rare metaplastic form of endometrial carcinoma<sup>[6]</sup>. While the presence of sarcomatous tissue represents regression of the tumour to a more primitive phenotype, it is actually the characteristics of the epithelial component which determine tumour behaviour, metastatic propensity and overall prognosis<sup>[19]</sup>. This is reflected in the histology of metastatic MMT lesions which almost always consist exclusively of the epithelial component<sup>[6,12,19,20]</sup>.

MMTs arising primarily in extragenital sites are extremely rare and have been explained by three possible mechanisms. In the presence of endometriosis, malignancy can theoretically arise from this ectopic tissue and may lead to development of an extragenital MMT<sup>[20]</sup>. Splenogonadal fusion is a rare congenital abnormality in which there is an abnormal connection of the spleen to the female mesonephric derivatives and as such, may be a possible mechanism for the displacement of Mullerian-derived tissue to this extragenital site<sup>[21]</sup>. There have only been five previous case reports of carcinosarcomas arising primarily from the spleen: In four of these<sup>[2,21-23]</sup> the patient presented with a painful left upper quadrant mass while the fifth<sup>[24]</sup> presented with weight loss, anaemia and a painless left upper quadrant mass on physical examination and imaging. The third possibility involves the secondary Mullerian system as described by Lauchlan<sup>[25]</sup>: Unlike the primary Mullerian system (which arises from the urogenital ridge and ultimately gives rise to the uterine body, Fallopian tubes, cervix and upper vagina), the secondary Mullerian system consists of the parietal peritoneum, visceral peritoneum and underlying



**Figure 4** Haematoxylin and eosin (HE) stain of splenic mixed malignant Mullerian tumour demonstrating both sarcomatous (thick arrow) and epithelial (thin arrow) tissue types (magnification 200 x).

mesenchymal tissue that retains its potential to differentiate into gynaecological tissue. This has been proposed as an explanation for the occurrence of primary MMMTs arising from the pelvic peritoneum in the absence of uterine, adnexal, cervical or vaginal malignancy<sup>[20]</sup>.

The mainstay of treatment is early and aggressive surgery but high rates of local and distant recurrence have necessitated the use of adjuvant therapies<sup>[26]</sup>. Numerous chemotherapy regimens incorporating ifosfamide, paclitaxel, cisplatin and carboplatin have been trialled, without any strong evidence to indicate superiority of one combination over another. However, use of single-agent chemotherapy has been shown to lead to poorer progression-free and overall survival<sup>[26]</sup>. The addition of adjuvant radiotherapy does not seem to improve overall survival but may reduce local recurrence<sup>[8]</sup>. Targeted therapy using monoclonal antibodies (sorafenib and imatinib) has also been trialled but their utility remains controversial and unproven.

Directions for further research into this field include direct comparisons of different chemotherapy regimens as well as exploring the utility of radiotherapy and even targeted biological therapies. However, large trials on MMMT are difficult to conduct due to their rarity and would certainly require a multi-centre or multi-national study design in order to recruit an adequate number of patients and to achieve sufficient statistical power.

Our case is interesting for a number of reasons: Firstly, although the origin of the metastatic MMMT remains unknown findings at laparotomy and hysteroscopy excluded the uterus, cervix, vagina and ovaries, from which the vast majority of MMMTs develop. Secondly, although histological examination of the Fallopian tubes revealed numerous foci of serous intraepithelial carcinoma and one area of high-grade invasive serous carcinoma, sarcomatous tissue was absent making the diagnosis of a primary tubal MMMT less likely. Therefore, the most likely explanation is that our patient had a primary extragenital MMMT arising from either the pelvic peritoneum or the spleen which then metastasised by transcoelomic spread. Additionally, it is highly unusual for MMMT metastases to contain sarcomatous tissue components as was present in this instance.

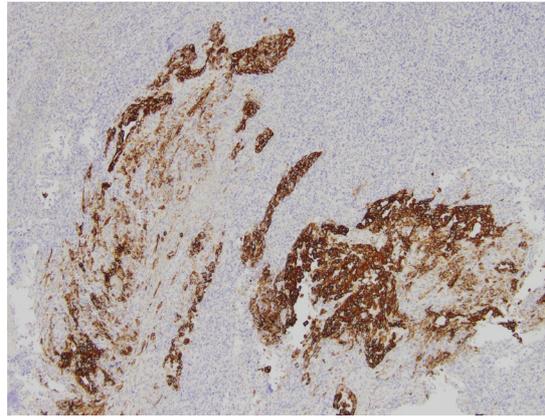
We acknowledge that some aspects of clinical care could have been improved upon in this case. Firstly, a diagnostic laparoscopy at the first operation may have identified the presence of peritoneal nodules and pelvic pathology, despite not being detected on the initial CT scan. Even if they were identified, however, splenectomy would have still been indicated for symptomatic relief due to the persistence of poorly-controlled pain. Secondly, tumour markers were only performed after histology of the splenic mass suggested a MMMT. Performing them earlier in the clinical course may have raised suspicion of pelvic pathology sooner and expedited diagnosis of the MMMT in the Pouch of Douglas. Thirdly, there was a prolonged but unavoidable delay to the second operation due to the patient's co-morbidities. When this occurs consideration should be given to repeating the imaging studies to detect any evidence of disease progression that may preclude surgery. Such an approach may have allowed earlier identification of inoperable disseminated peritoneal disease and helped our patient avoid a futile second operation.

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## CONCLUSION

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MMMTs are unusual metaplastic malignancies and those arising primarily from



**Figure 5** Positive cyokeratin 7 staining (dark brown) of epithelial component of mixed malignant Mullerian tumour and negative staining of sarcomatous component (magnification 100 x).

extragenital sites are exceptionally rare. Unlike most tumours, they undergo a process known as epithelial-mesenchymal transition which results in both epithelial and sarcomatous tissue types being present on histological examination. For this reason, they are also known as carcinosarcomas. MMMTs present at a late stage, are aggressive and are associated with a poor long-term prognosis. Management usually consists of surgery, adjuvant combination chemotherapy and possibly radiotherapy. The role of targeted biological agents has not been well established. Early recognition and referral for expedient surgery are of the utmost importance. Further research is essential in order to delineate optimal treatment strategies but such studies will be difficult to perform due to the rarity of the condition.

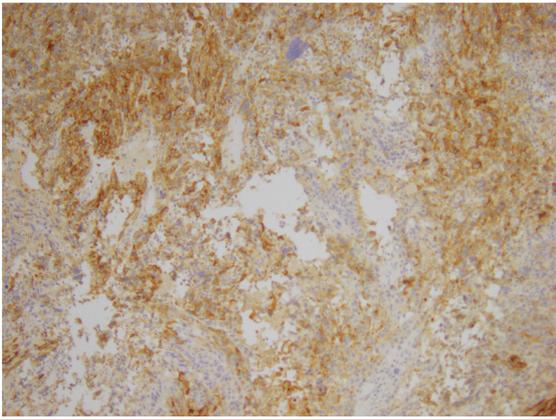


Figure 6 Positive desmin staining of sarcomatous component of splenic mixed malignant Mullerian tumour (dark brown) and negative staining of epithelial component (magnification 100 x).



Figure 7 Transvaginal ultrasound images of a well-circumscribed pelvic mass within the rectovaginal pouch with both cystic and solid components.

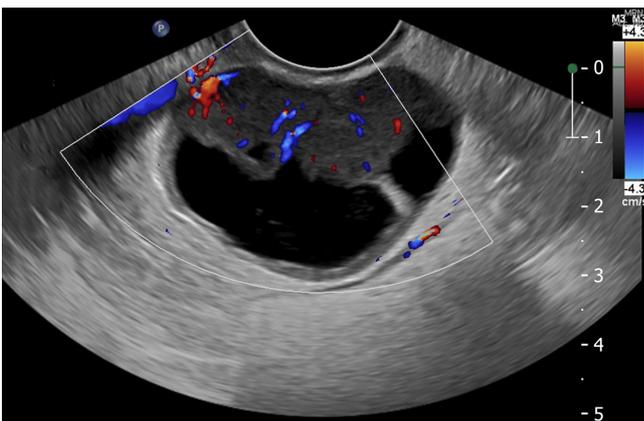


Figure 8 Colour doppler ultrasound demonstrating internal vascularity in the pelvic mass seen in Figure 7.

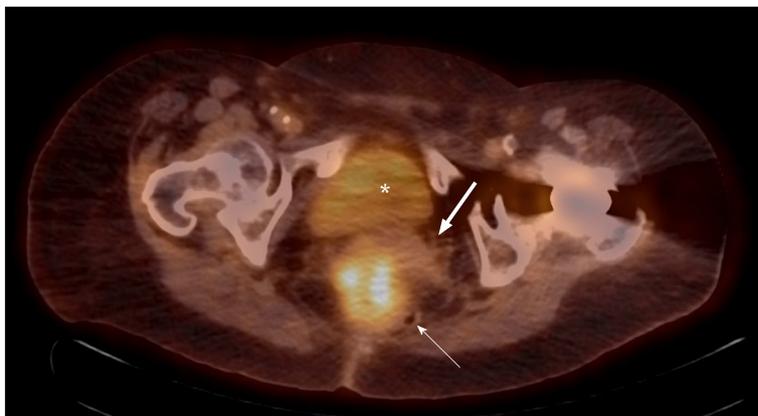


Figure 9 Axial slice of positron emission tomography-computed tomography showing high <sup>18</sup>F-fluorodeoxyglucose uptake by a 48 mm x 54 mm mass in the rectouterine pouch. The bladder (asterisk) and uterus (thick arrow) are seen anteriorly, while the rectum has been displaced to the left (thin arrow).



Figure 10 Coronal slice of positron emission tomography-computed tomography demonstrating the pelvic tumour causing mass effect on the rectosigmoid colon (arrow).

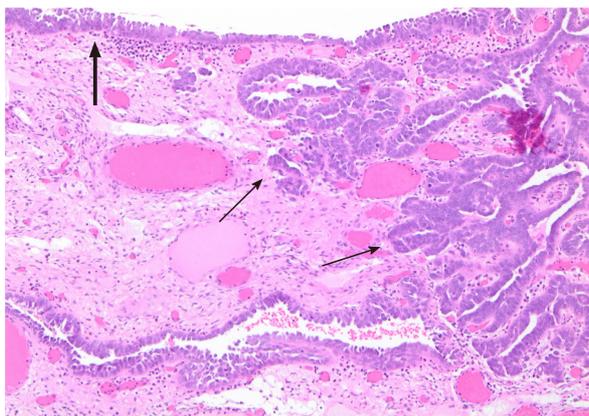
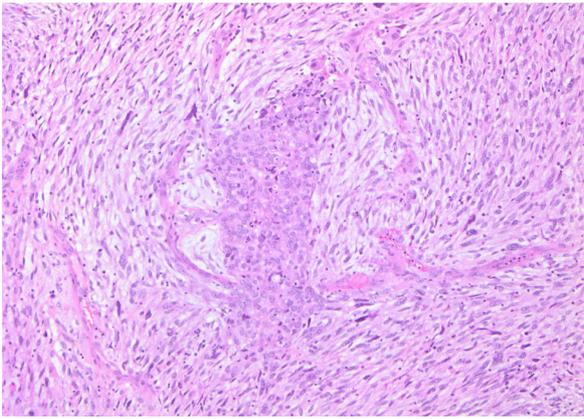


Figure 11 Section of fallopian tube demonstrating concurrent serous tubal intraepithelial carcinoma (thick arrow) and high-grade invasive serous carcinoma (thin arrows) (magnification 100 x). The invasive component shows crowded slit-like glands with focal nuclear hobnailing and marked cytologic atypia.



**Figure 12** Biopsy of pelvic tumour revealing features consistent with mixed malignant Mullerian tumour (magnification 100 x). There are cohesive clusters of epithelioid cells consistent with poorly differentiated adenocarcinoma (central area) surrounded by a sarcomatous tissue made up of malignant spindle cells. The appearances are similar to that of the patient's splenic tumour.

## ACKNOWLEDGEMENTS

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