Spontaneous uterine perforation secondary to uterine Malignant mixed mullerian tumor (MMMT) in a young unmarried female of north Indian origin: Case report and Review of literature

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ABSTRACT

Carcinosarcomas are highly aggressive tumors occurring after menopause, at a median age of 62 years. Most frequent presenting symptom is postmenopausal bleeding, occuring in 80% to 90% cases. Less common symptoms are vaginal discharge, abdominal or pelvic pain, weight loss, and passage of tissue from vagina. On physical examination, uterine enlargement is present in 50% to 95% of patients. Diagnosis determined by biopsy of endocervical mass or endometrial curettage or most often made post-operatively by histopathological examination and immuno-histochemical study.

Appropriate treatment includes surgical staging followed by total hysterectomy with bilateral salpingo-oophorectomy, removal of pelvic and aortic lymph nodes, omentectomy and peritoneal cytology. High rate of relapse and metastasis necessitate adjuvant therapy. Due to the aggressiveness of the tumor adjuvant chemotherapy is recommended even in stage 1 and 2 lesions. The most effective protocol for chemotherapy is still under study.

Taxanes and cisplatin based chemotherapy as well as ifosphamide, along with whole pelvic irradiation, might lead to increased survival in patients with metastatic carcinosarcoma especially in stage 3 and 4. On literature search, we found only two cases of carcinosarcoma who presented with tumor rupture and acute abdominal emergency with histopathological diagnosis of carcinosarcoma uterine cervix and uterine corpus. This is a rare case with unusual presentation in a young unmarried female with no prior risk factors presenting directly as an acute abdominal emergency with uterine rupture in shock.

Our present case expanded the clinical spectrum of uterine adenocarcinomas and highlights the atypical presentation of MMMT, which may be complicated by tumour rupture and pose a surgical emergency. The preventive measures, screening, and treatment measures that apply to the usual cervical adenocarcinoma may not be suitable for mesonephric tumours. More effort is needed to clarify the etiology and nature of mesonephric adenocarcinomas and MMMTs.

Key words: Carcinosarcoma, hysterectomy, Malignant mixed mullerian tumour (MMMT); uterine rupture

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Conflict of interest: None

INTRODUCTION

Malignant mixed mullerian tumors (MMMT) is a rare and aggressive soft tissue neoplasm usually presenting as a symptom triad of abnormal uterine bleeding with abdominal pain and passage of necrotic tissue per vagina. It represents 5 to 6% of all uterine tumors and accounts for 16.4% of all deaths caused by uterine malignancy[1]. Mesonephric adenocarcinoma and MMMT both arise from mesonephric remnants. Mesonephric remnants are not uncommon findings in the lateral wall of the vagina and cervix, and in the broad ligament, mesosalpinx, or ovarian hilus[2].

To best of our knowledge, most of the cases of MMMTs have been reported in women in 6th and 7th decade of life[3]. MMMT rarely presents as spontaneous haemoperitoneum. We, here in present a case of MMMT with atypical clinical manifestations in a young woman presenting as hemoperitoneum caused by spontaneous rupture of rapid growing MMMT in uterus along with a review of two other cases of MMMT presenting as uterine rupture. (Table 1).

Table 1: Review of all the cases in the literature of MMMT which presented as a case of uterine rupture.

Case Number	Author	Age	Presentation	Site	Size	Sarcomatous component	FIGO stage	Treatment	Follow-up
1	Aung C et al. [10]	61 years	Spontaneously ruptured Pyometra	Uterus	1.8cm	Spindle cell	IIIb	TAH+BSO	NA
2.	T. Chih-En [11]	59 years	Ruptured uterus	Cervix	6.3cm	Spindle cell	IIIb	Hys+BSO+LD+ChT+RT	4 months, NED
3.	Present	27	Hemoperitonium with ruptured	Uterus	5cm	Spindle cell	IIIb	TAH+BSO+ChT	Expired after 3

	Case	years	uterus						months

*TAH: Total Abdominal hystercotomy; BSO: Bilateral Salpingo-oophorectomy; LD: Lymph node dissection; ChT: Chemotherapy; RT: Radiotherapy; NED: No evidence of disease.

CASE REPORT

A 27 year old unmarried girl presented to our gynecological emergency with a 3-days complaint of severe abdominal pain, distention, breathlessness and intractable vomiting. She also had bleeding per vagina with passage of clots for past 2 months which did not respond to medical management.

She had undergone an abdominal myomectomy 3 months back .The histopathological examination of the well circumscribed, spherical 4.2×3.2 cm fibrous mass specimen was reported as leiomyoma uterus with cystic degenerative changes with scarce mitotic figures and no evidence of sarcomatous changes.

She was asymptomatic for 4 weeks following myomectomy when she started having pain abdomen and bleeding per vaginum. Ultrasound examination done 4 weeks post-operative reported a bulky uterus measuring 11.9 X 6.5 X 5.8 cm with a heterogeneous sub-mucosal fibroid in the body of the uterus measuring 5.5 x 3.9 x 3.5 cm & causing gross distortion of the endometrium.

Physical examination revealed a very pale patient with blood pressure of 90/60 mm Hg, pulse of 160/min and respiratory rate of 30/ min. She was febrile with a temp of 102^0F. There was abdominal distension with diffuse tenderness. On per vaginal examination, size of the uterus could not be ascertained because of distension. There was passage of fleshy, foul smelling material from the cervical os. Urine for pregnancy test was negative. Ultrasonography confirmed a bulky uterus with heterogeneous mass and presence of moderate free fluid in the peritoneal cavity.

The patient's condition deteriorated rapidly and in view of hypovolemic shock, decision for emergency laprotomy was taken. Exploratory laparotomy revealed 1000ml hemoperitoneum and chunks of fleshy, necrotic material were present in the abdominal cavity. Ileum was densely adherent to the fundus of uterus. After separating the bowel adhesions, the fundus of the uterus was found to be ruptured. A fleshy, grey colored necrotic

foul smelling mass, 6 x 6 cm arising from the fundus of the uterus and extending into the whole of endometrial cavity was seen. Bilateral hematosalpinx was also present. Ovaries were cystic and adherent to the uterus and fallopian tubes. Due to hemodynamic instability intra-operatively, the patient underwent suboptimal debulking surgery including sub-total hysterectomy with bilateral salpingo-oophorectomy. Figure 1, 2.

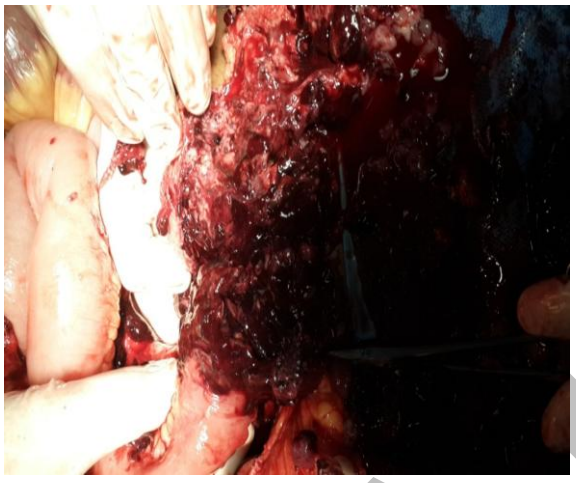

Figure 1: Intra-operative photograph showing the ruptured fundus of the uterus with fundus completely occupied by the tumour with adherent bowel loops to the fundus.

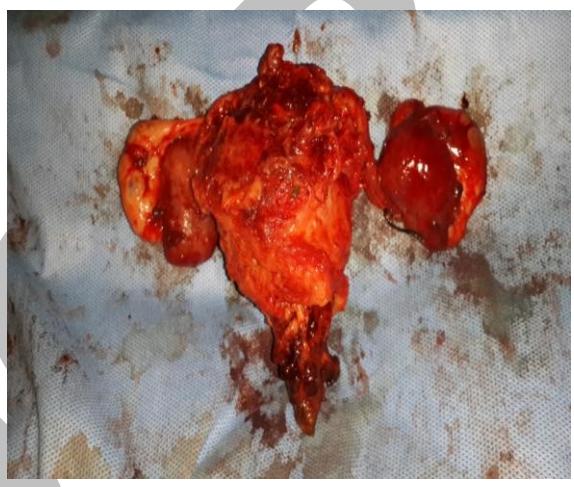

Figure 2: Post-operative photograph of the total hysterectomy with bilateral salpingo-oophorectomy specimen showing the breach of the fundus of the uterus by the tumour.

Histo-pathological analysis showed carcinosarcoma (malignant mixed mullerian tumor) stage 3A of the uterus corpus with rupture through the uterine body. There was hemorrhagic and fleshy necrotic tumor of size 5 X 4 X 3 cm filling the entire endometrial cavity. The tumor was found to be involving the full thickness of myometrium and was extending into the serosa and lower part of the uterus. The tumor was involving the left parametrium. Bilateral ovaries and fallopian tubes were normal. Tumor cells were positive for vimentin and focally positive for CK and SMA and negative for CD 10, LCA, INHIBIN and Desmin. (Figure 3(a) and (b)).

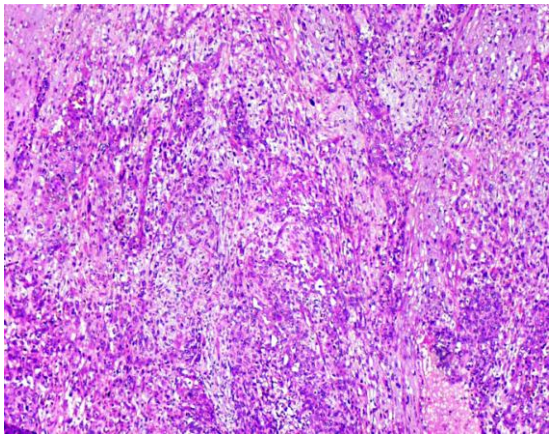

Figure 3(a): Low power photomicrograph of the tumour showing the carcinomatous cells and the spindle shaped sarcomatous element of the tumour. (H&E, ×150).

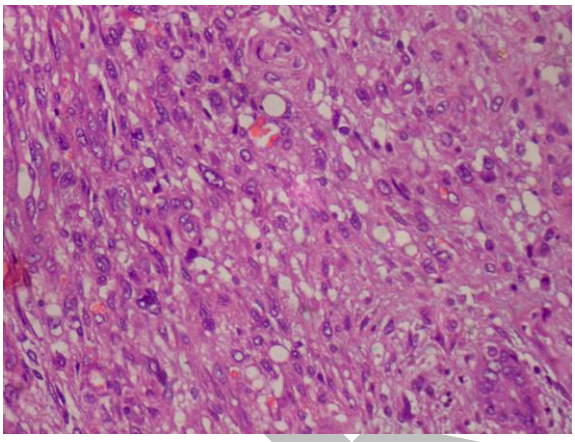

Figure 3(b): High power photomicrograph of the tumour showing the carcinomatous cells and the sarcomatous element. (H&E, ×450).

Post-operative period was unremarkable. Pelvic ultrasound and computed tomography (CT) done two weeks after surgery revealed a heterogeneous pelvic mass containing solid parts measuring 9.3 x 7.1 x 7.3 cm with involvement of bilateral parametrium and reaching the pelvic wall. Obturator and internal iliac lymph nodes were enlarged. Liver, spleen and gall bladder were normal. Bilateral lungs showed multiple variable –sized discrete round to oval shaped nodules in random distribution predominantly sub pleural suggestive of lung metastasis.

DISCUSSION

We report a case of a 27 years female with MMMT, presenting as uterine rupture and hemoperitonium. Our case was rare because of the very young age of presentation in an unmarried 27 year old female with no risk factors. She presented as a case of spontaneous uterine rupture as an acute abdominal emergency.

The aggressive nature of her tumor was revealed by her manner of presentation in advanced stage and post-operative spread. At presentation extra-uterine spread (stage III and IV) is found in upto 1/3rd of the cases. Carcinosarcomas are highly aggressive tumors, far more aggressive than usual endometrial carcinomas. Risk factors for the development of carcinosarcoma are similar to that of endometrial carcinoma such as nulliparity, advanced age, exposure to

exogenous estrogen and tamoxifen and pelvic radiation[4,5].

The most common presentation of either mesonephric adenocarcinoma or MMMT is vaginal bleeding. Other presentations include pelvic pain, coitalgia, incidental findings, uterine prolapse, and abnormal Pap smear[6-9].

On searching literature, we found only two cases of post-menopausal woman who presented with tumor rupture and acute abdominal emergency with histopathological diagnosis of carcinosarcoma uterine cervix[10] and uterine corpus[11]. All these cases including the present case confirm an unusual presentation as a surgical emergency (Table 1).

We must keep a high level of suspicion in a patient presenting with a clinical triad of pain abdomen, vaginal bleeding and necrotic foul smelling discharge irrespective of her age.

Malignant mixed mullerian tumor (MMMT) is a biphasic tumor of the female genital tract composed of epithelial and mesenchymal tissues. It has a monoclonal origin from a common multi-directional progenitor stem cell. Based on their sarcomatous components two categories, homologous and heterologous types of carcinosarcoma have been identified. Homologous type has a sarcoma composed of tissue native to the uterus such as endometrium and smooth muscles. Whereas in heterologous type, cartilage, skeletal muscle or bone is present, this is not native to the uterus. The carcinomatous component is the primary determinant of tumor aggressiveness and has a bearing on the treatment.

However, the origin, presentation and preoperative diagnosis and treatment of this tumor are all controversial. The overall 5 year survival for patients with carcinosarcomas with stages I/II are between 30%- 46%, and 0%-10% in advanced cancers, FIGO stages III/IV[5]. The prognosis of the disease depends on the surgical stage and particularly, depth of invasion at the time of diagnosis and the mitotic index[12]. Tumors containing serous and clear cell carcinoma are thought to have a higher frequency of metastases[13]. Women with tumor size >7 cm have a poor prognosis[14].

Diagnosis of carcinosarcoma is most often made post-operatively by histopathological examination and immunohistochemical study.

Histologically, distinguishing between mesonephric hyperplasia, mesonephric adenocarcinoma, and MMMT is a challenge. The histological findings of mesonephric adenocarcinoma vary from case to case. Clement et al. classified the morphologies into five patterns: ductal, tubular, solid, retiform, and sex cord-like[6].

The differential diagnosis includes endometrioid adenocarcinoma, clear cell carcinoma, serous adenocarcinoma, adenoma malignum, and mesonephric hyperplasia. The immuno-profile of mesonephric neoplasm is mostly but not consistently positive for vimentin, calretinin, CD10, and CK7 while negative for ER and PR[9]. Histology (including the presence of adjacent mesonephric remnants) combined with tumour immuno-profile is the best way to diagnose MMMT. Research is currently aimed at determining this malignancy preoperatively to differentiate it from other uterine malignancies particularly uterine carcinoma. USG abdomen and Trans-vaginal sonography (TVS) with Doppler, Contrast-enhanced Computed tomography (CECT) and Magnetic Resonance Imaging (MRI) are not yet sensitive in differentiating it from endometrial carcinoma.

Appropriate treatment includes surgical staging followed by total hysterectomy with bilateral salpingo-oophorectomy, removal of pelvic and aortic lymph nodes, omentectomy and peritoneal cytology. In our case oophorectomy was done as the ovaries were densely adherent to surrounding structures and could not be salvaged. Pelvic lymphadenectomy was not done as the patient condition was unstable and prior histological confirmation of malignancy was lacking.

High rate of relapse and metastasis necessitate adjuvant therapy. Due to the aggressiveness of the tumor adjuvant chemotherapy is recommended even in stage 1 and 2 lesions. The most effective protocol for chemotherapy is still under study. Taxanes and cisplatin based chemotherapy as well as ifosphamide, along with whole pelvic irradiation, might lead to increased survival in patients with metastatic carcinosarcoma specially in stage 3 and 4[3,15].

Our present case expanded the clinical spectrum of uterine adenocarcinomas and highlighted the

atypical presentation of MMMT, which may be complicated by tumour rupture and pose a surgical emergency. The preventive measures, screening, and treatment measures that apply to the usual type cervical adenocarcinoma may not be suitable for mesonephric tumours. More effort is needed to clarify the aetiology and nature of mesonephric adenocarcinomas and MMMTs.

CONCLUSION

In conclusion, we report the first case of MMMT of the uterine cervix with an unusual clinical presentation of tumour rupture in a young pre-menopausal female of 27 years. It reminds clinicians that MMMT may progress rapidly without any prodrome to tumour rupture and pose a surgical emergency. Owing to differences in etiology between MMMTs and other uterine tumours, their prevention, screening, and treatment should be further investigated.

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