Malignant mixed mullerian tumor: A case series

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ABSTRACT

Uterine carcinosarcoma, also known as malignant mixed mullerian tumor (MMMT) is a rare and aggressive malignancy. It is the only type of uterine carcinoma with both an epithielial-derived carcinoma and a mesodermal-derived sarcoma. Classically, they have been considered as a soft tissue sarcoma, however, recent studies ascertain the pathogenesis of carcinosarcomas as to that of a metaplastic transformation of a carcinoma to give rise to a sarcomatous component. With the paradigm shift on the pathogenesis of disease, treatments have been aligned to follow protocols used in aggressive uterine carcinomas and are in further evaluation for its applicability to the aforementioned carcinosarcoma.

This paper presents three cases of MMMT diagnosed in a Private Tertiary Hospital from October 2015 to February 2017. Among the three cases, two cases underwent endometrial sampling with results suggestive of MMMT and one case with an intraoperative frozen section done revealing carcinosarcoma. All cases underwent extrafascial hysterectomy with bilateral salpingo-oophorectomy (EHBSO) and bilateral lymph node dissection (BLND). Post-operatively, two of the cases underwent adjuvant chemotherapy and are currently alive. The one case that did not receive adjuvant chemotherapy succumbed to the disease eight months after diagnosis.

With the high propensity of MMMT to metastasis, relapse and recurrence, it is then imperative that all cases are properly managed.

Keywords: uterine carcinosarcoma, malignant mixed mullerian tumor

INTRODUCTION

Uterine carcinosarcoma, or malignant mixed mullerian tumor (MMMT), although rare, is a highly aggressive type of uterine cancer. It comprises only 1-2% of uterine cancers, but makes up 16.4% of deaths from all uterine cancers[1-3]. MMMT usually present as postmenopausal bleeding in a woman of low parity with a risk factor profile similar to that of uterine carcinomas[2]. Although the 5-year survival of MMMTs are less favorable than endometrial carcinomas, ranging between 33-39%[3], the behavior of MMMT is said to be more akin to the epithelial carcinomatous component[4,5]. Among the different identified hypotheses regarding its pathogenesis, recent studies are supporting the principle of metaplastic transformation of one cell type rather than that of a biphasic tumor[3,4]. As such, staging is similar to that of 2009 International Federation of Gynecology and Obstetrics (FIGO) staging for endometrial carcinomas (Table 1). Consequently, primary treatment of MMMTs follows treatment protocols for high-grade endometrial carcinomas.

This case series aims to discuss the idiosyncrasies of this disease entity, the difficulties in the diagnosis and management, and the prognosis of most cases despite adequate therapy.

CASE REPORT

Three (3) cases of histopathologically documented MMMTs, seen from October 2015 to February 2017 at a Private Tertiary Hospital are presented in this series.

The first case is that of a 49-year-old G1P1 (1-0-0-1) with a three-month history of postmenopausal bleeding. The patient is diabetic and hypertensive, with a normal body mass index (BMI). Ultrasound was done in another institution, which revealed submucous myoma uteri. In the interim, bleeding persisted and an endometrial biopsy was done two months after the initial presentation revealed MMMT. The patient subsequently underwent EHBSO with BLND. On gross examination of the uterine specimen, a light tan, thickened, fleshy mass measuring 5.2 x 2.0 cm was occupying the posterior endometrium 1.3 cm from the fundus and 1.2 cm from the isthmus. Cut section of the mass revealed a tan doughy surface with areas of necrosis invading less then one half of the myometrium (Figure 1a). Final histopathologic report revealed a MMMT, heterologous type. The epithelial component was endometrioid with squamous areas while the sarcomatous component was that of a chondrosarcoma. The tumor was positive for lymphovascular space invasion (LVSI) (Figures 1b to 1d). Final surgicopathologic stage is II. The patient was subsequently given five cycles of Paclitaxel at 175 mg/m^2 and Carboplatin at AUC 5-6 mg/ml given 3-4 weeks apart; followed by pelvic external beam radiotherapy (EBRT) at 5040 cGy in 28 fractions and vaginal stump brachytherapy at 2100 cGy in 3 fractions. The patient was apparently

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Table 1. AJCC TNM and FIGO Surgical Staging Systems for Endometrial Cancer

Primary Tumor (T)		
TNM Categories	FIGO Stages	Surgico-Pathologic Findings
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to the corpus uteri
T1a	IA	Tumor limited to the endometrium or invades less than one-half of the myometrium
T1b	IB	Tumor invades one-half or more of the myometrium
T2	II	Tumor invades stromal connective tissue of the cervix but does not extend beyond the uterus
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
	IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
T4	IVA	Tumor invades bladder mucosa and/or bowel (bullous edema is not sufficient to classify tumor as T4)
Regional Lymph Nodes (N)		
TNM Categories	FIGO Stages	Surgico-Pathologic Findings
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes (positive pelvic nodes)
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
Distant Metastasis (M)		
TNM Categories	FIGO Stages	Surgico-Pathologic Findings
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, intra-peritoneal disease, or lung, liver, or bone. It excludes metastasis to para-aortic lymph nodes, vagina, pelvis serosa, or adnexa)

well until 12 months after where she developed bouts of dyspnea. Work up done in another institution showed lung metastasis. However, patient opted not to be given further treatment. Currently, the patient remains functional and ambulatory.

The second case is that of a 63-year-old G3P2 (2-0-1-2) presenting with a one- month history of postmenopausal bleeding. The patient is hypertensive with a normal BMI. Initial transvaginal ultrasound done showed thickened endometrium (0.71 cm). The patient then underwent endometrial curettage, which on histopathologic evaluation revealed endometrioid adenocarcinoma, FIGO grade II, MMMT could not be entirely ruled out. The patient underwent EHBSO with BLND. The uterine specimen revealed an endometrial mass, yellow-tan measuring 3.5 x 3.0 x 0.5 cm occupying the fundus, 7.0 cm away from the ectocervix. Cut section of the mass showed a nodular yellow-tan lobulated soft to friable surface invading less than one half of the myometrium (Figure 2a). Final histopathologic report revealed a homologous MMMT FIGO grade 3, negative for LVSI (Figure 2b). Final surgicopathologic stage is IA. The patient was advised adjuvant therapy, however, the patient did not comply and succumbed to the disease eight months after the operation due to lung metastasis.

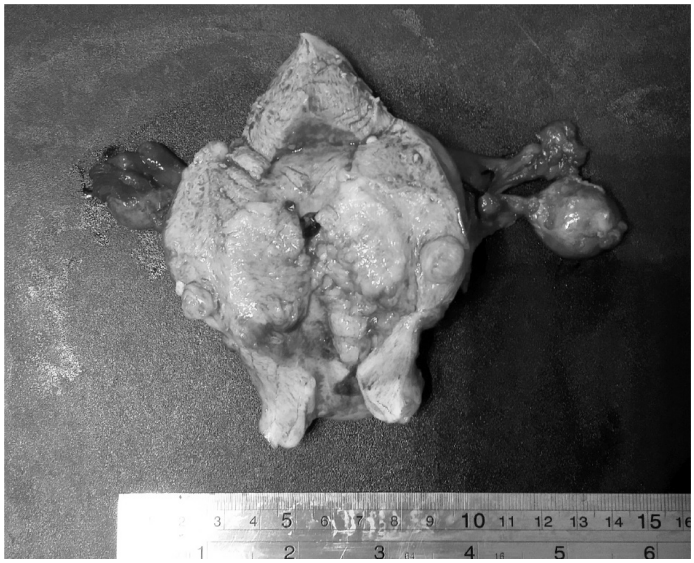


Figure 1a. First case, gross specimen on cut section. A light tan, thickened, fleshymass is seen on the endometrium measuring 5.2 x 2.0 cm in greatest dimensions occupying the endometrium 1.3 cm from the fundal area, 1.2 cm from the internalcervical os and 2.5 cm from the external cervical os. Cut section of the mass show a tan white doughy surface invading 1.4 cm of the 2.9 cm thick myometrial wall.

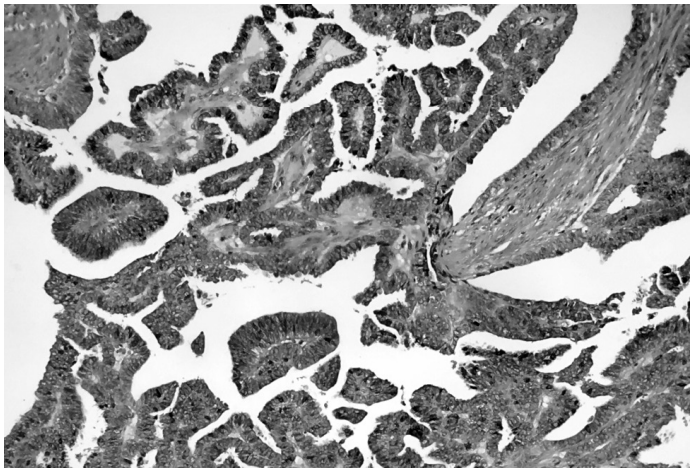


Figure 1b

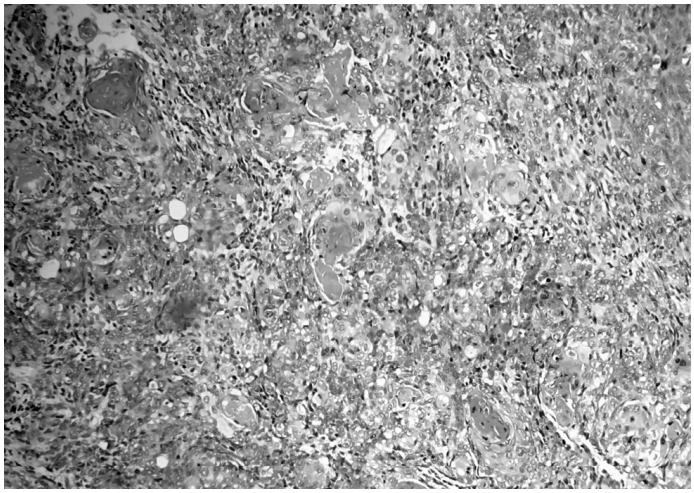


Figure 1c

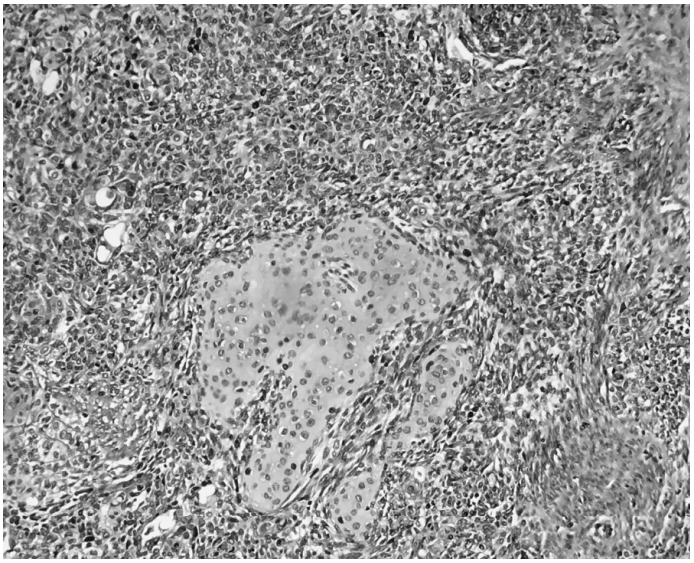


Figure 1d

Figures 1b to 1d. First case, histologic specimen. Microsection of the endometrial mass show a malignancy with epithelial and stromal elements. Positive for LVSI. (1b) The epithelial component is endometrioid, made up of dilated and fused glands lined with cuboidal to columnar cells with ovoid atypical nuclei, granular to dark staining chromatin, prominent nucleoli and scant cytoplasm, with squamous areas (1c). (1d) Heterologous elements (ex. Cartilage) were noted.

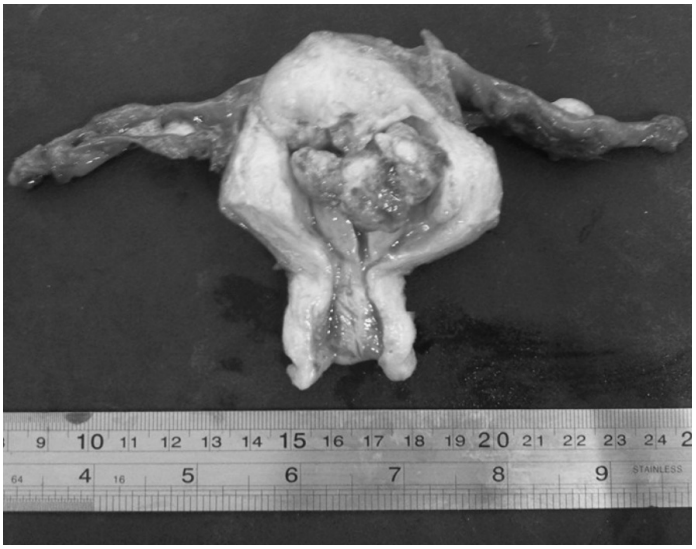


Figure 2a. Second case, gross specimen on cut section. A tan-yellow mass is found along the fundal area measuring 3.5 x 3.0 x 0.5 cm occupying the endometrium 7.0 cm away from the ectocervix. Cut section of the mass show a nodular yellow-tan lobulated soft to friable cut surface invading 0.9 cm of the 2.0 cm thick myometrium.

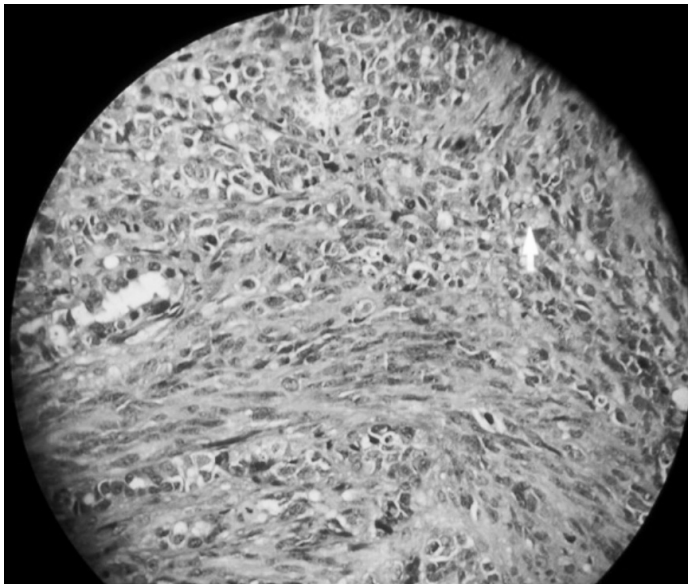


Figure 2b. Second case, histologic specimen. Microsection of the uterine mass show two distinct malignant populations. The malignant glandular cells exhibit mild to moderate pleomorphism, hyperchromatic nuclei with prominent nucleoli and scant eosinophilic cytoplasm. The malignant stromal cells are moderately pleomorphic with pale chromatin, prominent nucleoli and variable amorphilic cytoplasm. Negative for LVSI.

The third case is of a 65-year-old G3P3 (3003), presenting with a two-week history of postmenopausal bleeding. She is hypertensive, diabetic, obese (BMI of 29.9 kg/m^2) and dyslipidemic. Transvaginal ultrasound done showed an irregularly-shaped fungating mass originating from the posterofundal wall about 9.46 x 6.05 x 5.85 cm in size, with minimal to moderate color flow suggestive of non-benign sonologic features. The patient underwent an EHBSO with enterolysis and BLND. The uterine specimen revealed a large pink-tan lobulated friable mass attached to the posterior endometrium extending into the isthmus measuring 7.0 x 6.0 x 4.0 cm. Cut section of the mass showed invasion of less then one half the myometrium (Figure 3a). Frozen section of the endometrial mass revealed endometrioid adenocarcinoma with myometrial invasion. The final histopathologic report, however, revealed a heterologous MMMT, endometrioid adenocarcinoma with focal areas of clear cell carcinoma and chondrosarcoma, positive for LVSI (Figures 3b to 3d). Final surgiopathologic stage is IA. The patient was subsequently advised adjuvant therapy with chemotherapy, pelvic EBRT and vaginal brachytherapy. At present, the patient is on her 3rd cycle of Paclitaxel at 175 mg/m^2 and Carboplatin at AUC 5.

DISCUSSION

MMMT is a rare and aggressive uterine malignancy now recently classified together with high-grade uterine

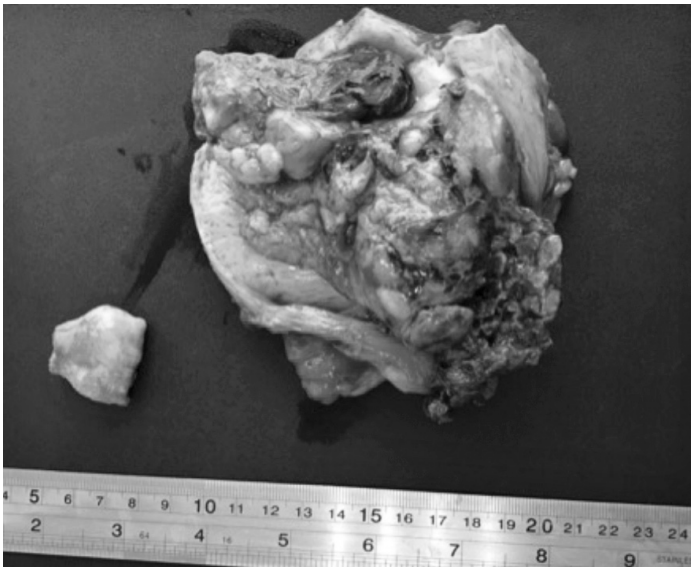


Figure 3a. Third case, gross specimen on cut section. A large pink-tan lobulated friable mass attached to the posterior wall of the endometrial cavity extending into the lower uterine segment and measures 7.0 x 6.0 x 4.0 cm. Cut section of the mass show invasion of less then one half the full thickness of the myometrial wall.

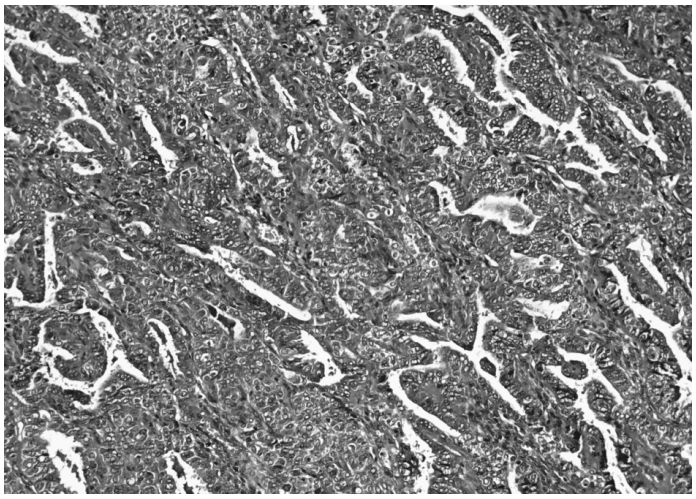
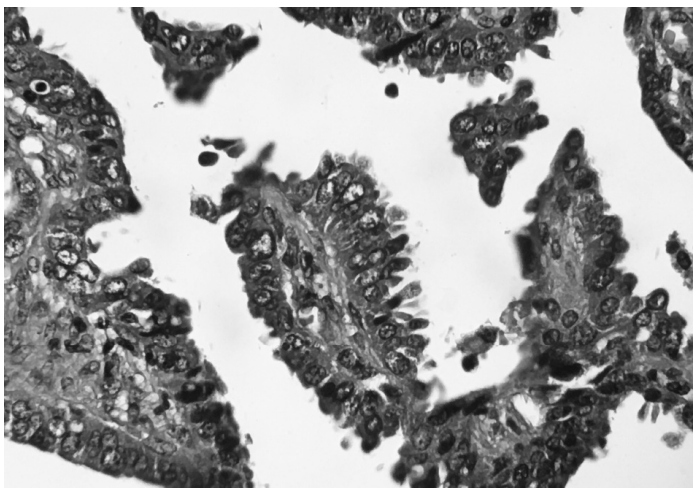


Figure 3b



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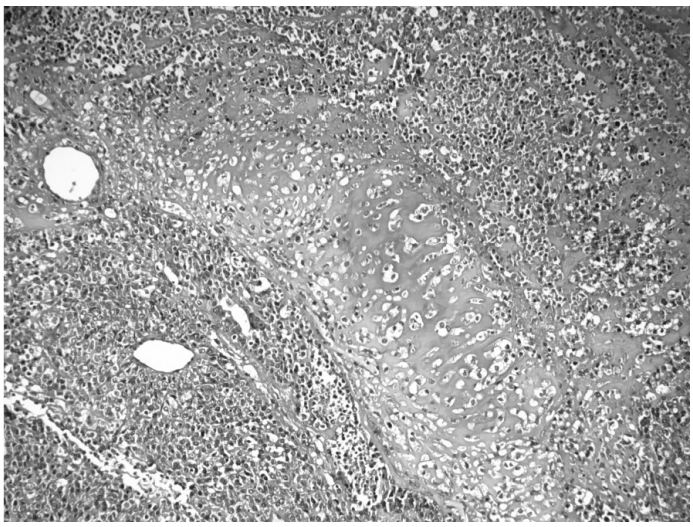

Figure 3d

Figures 3b to 3d. Third case, histologic specimen. Microsection of the endometrial mass show a malignancy with epithelial and stromal elements. Positive for LVSI. (3b) The epithelial component is endometrioid, with focal areas of clear cell carcinoma (3c). (1d) Heterologous elements (ex. Cartilage) were noted.

carcinomas. It usually presents as postmenopausal bleeding at a mean age of 62 years.[1,2,6]

The most common presentation of MMMT is abnormal uterine bleeding. In all 3 cases discussed, the index patients manifested with postmenopausal bleeding. Other clinical presentations include watery vaginal discharge, abdominal or pelvic pain and/or an abdominal mass. On occasion, a polypoid tumor may also protrude through the external os.[1,2]

Patients with MMMT usually have the same risk factors as those with endometrial adenocarcinoma.[2] As in the index cases, women are usually of low parity and are postmenopausal. Other known risk factors for uterine carcinoma include excessive weight and exogenous estrogen use.[2] One case had a BMI of 29.9 kg/m^2, while the other two had normal weights. No other risk factors were noted in the index patients. Oral contraceptive use protects against development of MMMTs.[2]

MMMTs have classically been considered a soft tissue sarcoma, and the hypothesis as to the pathophysiology of the disease has long been in debate. Initial speculations include (1) Collision hypothesis - origin from two distinct malignant cell population and, (2) Combination hypothesis - a common stem cell origin.[3] More recent studies, however, support that of a metaplastic hypothesis. Clinically, pattern of metastasis of MMMTs are more analogous to that of aggressive endometrial cancers than that of uterine sarcoma - MMMTs spread primarily via the lymphatic route, much like endometrial carcinomas, compared to hematogenous spread of sarcomas.[3]

Another compelling factor supporting the metaplastic transformation theory is the note of carcinomatous elements within lymphovascular channels and metaplastic tumor deposits. Coexistent sarcomatous elements are found in some cases but are rarely found alone. This contributes to the evidence that the epithelial component has the more aggressive behavior. Mitotic indices and proliferation indices as demonstrated by immunohistochemistry markers are higher in the carcinomatous elements than the sarcomatous elements demonstrating its dominance.[3] In addition, studies examining immunochemical expression of p53 demonstrated concordance of p53 staining with both elements being either positive or negative, an indirect support to MMMT being monoclonal in origin.[3]

MMMT can be classified as homologous or heterologous. MMMT with the sarcomatous component resembling the same cell type found in the uterus is classified as homologous while heterologous types carry a sarcomatous component resembling mesodermal components found elsewhere in the body including osteosarcoma and chondrosarcoma.[5] Although, with the paradigm shift on the pathogenesis of MMMT histological features of the sarcomatous component now bear no clinical significance: relationship to the likelihood of metastasis, response to chemotherapy and overall survival. Concurrently, the dedifferentiation of the carcinomatous component to a sarcoma manifests aggressiveness of the disease.[3]

Preoperative diagnosis of MMMTs may also post a dilemma. In most instances, initial imaging by ultrasound may not necessarily be suggestive of a malignancy. In the first case, the uterine mass was signed out to be a myoma uteri. MMMTs are diagnosed histopathologically. Accuracy of Endometrial biopsy is still uncertain as most are diagnosed as endometrioid adenocarcinoma. In a study by Helpman et al, 24% of high-grade endometrial cancers were diagnosed with a lower grade cancer preoperatively based on endometrial biopsy.[12] The second case, for example, was diagnosed as a case of endometrioid adenocarcinoma with MMMT not totally ruled out based on endometrial curettage. The third case, was signed out as a case of endometrioid adenocarcinoma, on frozen section but turned out to be MMMT on final histopathology.

The primary management of MMMT is surgery. As in endometrial cancers, EHBSO with complete staging and debulking is recommended. All cases underwent EHBSO with BLND.

As mentioned, the surgicopathologic staging of MMMT follows that of the 2009 FIGO Surgical Staging Systems for Endometrial Cancer. Majority of cases are

diagnosed on later stages (III and IV). In the presented cases, two were diagnosed as stage IA and one case was diagnosed as stage II.

While the primary treatment of MMMT is complete surgical debulking, the high rates of both local and distant relapse in MMMTs presuppose the need for effective adjuvant therapies. There is, however, still no clear consensus regarding therapeutic strategies for different stages of the disease.[3,6]

Historically, single agent adjuvant chemotherapy has been used. Different studies listed the most active single agents by response rate as follows: Ifosfamide (29-36%), Cisplatin (28-42%), Doxorubicin (10-25%) and Paclitaxel (18%).[6,10] More recently, combination therapy has been shown to be superior to single agent chemotherapies. In the study by Homesley, et al, Ifosfamide and Cisplatin has been shown to have a response rate of 54%, which is superior to Ifosfamide alone at 36%.[3,8,10] Hoskins, et al. reported their experience with the use of Carboplatin and Paclitaxel. Newly diagnosed cases had a response rate of 60%, while relapse cases had a response rate of 55%. Median progression free survival was 16 and 12 months, respectively.[6] Similar studies showed response rates ranging from 64% to 80%.[6] Toyoshima, et al. also evaluated the use of Carboplatin and Paclitaxel in advanced or recurrent MMMT and reported a median progression free interval (PFI) of 18 months (range, 0-32), and a median overall survival of 25 months (range, 3-32).[8]

NCCN gives the combination of Ifosfamide and Paclitaxel a Category 1 recommendation.[7] The Society of Gynecologic Oncologists of the Philippines (SGOP) Clinical Practice Guidelines recommends the combination of Cisplatin and Ifosfamide or Carboplatin and Paclitaxel for early stage disease, and the combination of Ifosfamide and Paclitaxel for advanced stage disease. In a study by Hoskins et al, the advantage of the combination of Carboplatin and Paclitaxel over Ifosfamide and Paclitaxel is in its relative convenience, tolerability and economy. Carboplatin-Paclitaxel takes about four hours once every three to four weeks to deliver in contrast to 3 days with Ifosfamide-Paclitaxel. Consequently, length of hospital stay is longer and cost is greater for the latter regimen. Ifosfamide-Paclitaxel had about 43% of the patients in the study discontinue treatment due to refusal or toxicity. Leukopenia rate was noted to be 87%, a number that may be considered too high considering most patients presenting with MMMT are 65 years of age with a higher propensity for sepsis. Hence, Filgastrim, a granulocyte colony-stimulating factor, is concurrently routinely administered to these patients. Addition of Filgastrim to the regimen poses an additional cost to these patients receiving the Ifosfamide-Paclitaxel regimen.[6]

In the cases presented, the chemotherapy given to the 2 cases was the combination of Carboplatin and Paclitaxel. The first patient completed 5 cycles, while the third patient is on her 3rd cycle, to complete 5 cycles.

Classically, RT was used to control local recurrence. In a study by Bosquet, et al, In stage I patients managed with adjuvant radiation therapy (RT) DFS was improved 66% vs 41%. Of note, 24% of Stage IA patients developed distant metastasis on follow up despite adjuvant RT. In the said study, while RT appeared to adequately control vaginal failures in all stages, Pelvic RT did not significantly impact DSS even in patients with early disease (Stage I and II).[3]

MMMT has a poorer prognostic outcome than that of endometrial carcinoma. Five-year relative survival of MMMT as compared to endometrial cancer are as follows: Stage I 70% vs 75-88%, Stage II 45% vs 69%, Stage III 30% vs 47-58% and Stage IV 15% vs 17%. Survival is very poor when the tumor is beyond the uterus and extrapelvic relapse is twice as common as pelvic failures.[10] The most important prognostic factor is the extent of the tumor at the time of treatment.[3] Yet, despite this, metastasis of MMMT is still relatively high even for early stages.[3] Other prognostic parameters remain controversial. Despite recommended therapies, most recurrences develop within twelve months and at distant sites. Among the index cases, the first case developed lung metastasis twelve months after initial diagnosis despite adjuvant therapy and the second case developed lung metastasis eight months after diagnosis and subsequently expired.

CONCLUSION

Uterine carcinosarcoma is a rare malignancy of the uterus with poor prognostic outcome. Primary treatment remains to be surgical debulking but given its propensity to metastasis, recurrence and relapse, effective adjuvant therapy can be offered to improve progression free survival and disease free survival. To date, no consensus has been established as to appropriate adjuvant chemotherapy for such cases. However, over-all survival remains to be unaffected by such efforts. ■

Table 2. Case summary

Case	Age (years)	Age (years)	Carcinomatous component (Type, LVSI)	Surgery	Adjuvant Chemotherapy (Courses)	Overall survival (months)
1	49	II	Endometrioid with squamous areas (Heterologous, +)	EHBSO + BLND	Carboplatin + Paclitaxel (5)	AWD (12)
2	63	IA	Endometrioid (Homologous, -)	EHBSO + BLND	None	DOD (8)
3	65	IA	Endometrioid with focal clear cell carcinoma (Heterologous, +)	EHBSO + BLND	Carboplatin + Paclitaxel (3)	AWN (4)

AWN: alive with no evidence of disease; AWD: alive with disease; DOD: died of disease

Table 3. Recommended chemotherapy agents (NCCN, 2016)

Multi-agent (Preferred, if tolerated)	Single agents
Carboplatin / Paclitaxel	Cisplatin
Cisplatin / Doxorubicin	Carboplatin
Cisplatin / Doxorubicin / Paclitaxel	Doxorubicin
Carboplatin / Docetaxel	Liposomal Doxorubicin
Ifosfamide / Paclitaxel*	Paclitaxel
Cisplatin / Ifosfamide	Topotecan
	Bevacizumab
	Temsirolimus
	Docetaxel
	Ifosfamide*

**Preferred for Carcinosarcoma*

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