
“A Rare Case Report –malignant Mixed Mullerian Tumour (MMMT)”

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Abstract

Malignant Mixed Mullerian Tumour is a rare uterine neoplasm that is seen always in postmenopausal woman although exceptions occur. They present with uterine bleeding and enlargement and the usual location is uterine body. Grossly they present as large, soft, polypoid growth involving the end myometrium and some times protruding through the cervix

MMMTs are a rare and aggressive tumour of the uterine corpus. A negative endometrial biopsy does not rule out diagnosis. The outcome correlates with the stage of the disease and the depth of myometrial invasion. A majority of the patients with advanced-stage disease had recurrence or progression within one year. With better understanding of the disease origin, combination chemotherapy with paclitaxel and carboplatin may be beneficial

Ours is a case report of post-menopausal lady with this aggressive tumour and her follow up till date.

Keywords – mullerian tumour, MMT, endometrial carcinoma

Introduction

A malignant mixed Mullerian tumour (MMMT), also termed uterine carcinosarcoma, is an extremely rare tumour, comprising only 1–2% of uterine neoplasms. These tumours are a dedifferentiated or metaplastic form of endometrial carcinoma. Based on recent data, this tumour is now considered to be uterine epithelial carcinoma rather than sarcoma. The management of MMTs has seen several advances in recent decades. Despite the use of aggressive adjuvant therapy, only modest improvement in survival is noted over the last couple of decades

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enlargement and the usual location is uterine body. Grossly they present as large, soft, polypoid growth involving the endomyometrium and some times protruding through the cervix.

MMMT, also referred to as the malignant mixed mesodermal tumor and carcinosarcoma, is a highly aggressive biphasic neoplasm comprised coexisting elements of cancer and sarcoma. Mostly deriving from the genital tract in postmenopausal elderly women, such as the uterus or the ovary, it also can be found in neck and head, peritoneum, biliary tract and gastrointestinal tract pre. Primary peritoneal MMT is extremely rare, and commonly occurs in the pelvic peritoneum. Furthermore, it has also been arisen in the serosal surface of the colon, rectal peritoneum, retroperitoneum, cul-de-sac, diaphragm peritoneum, anterolateral abdominal peritoneum, and omentum

Case report

A 55 year old female presented with white discharge for the past three months . Patient presented with mass descending per vagina since one month no history of loss of weight/ appetite, no bony metastasis patient was evaluated outside ultrasound suggestive of mass descending from cervix. Cervix appears bulky with well defined hypoechoic lesion the anterior wall and posterior wall measuring 7*4*3*2 MRI done report suggestive of - IMPRESSION: There is 8.0x4.8x4.1cm (CCxAPxTR) size, well marginated, polypoidal solid mass with internal necrotic areas, predominantly involving anterior, right lateral walls of cervix with intraluminal extension causing occlusion of cervical canal, resulting in mild secretions in uterine cavity. No obvious infiltration of mass into adjacent pelvic viscera. No obvious paracervical extension of mass. Mass is caudally protruding beyond the external OS into vaginal fornices. No infiltration of vaginal walls Patient underwent total abdominal hysterectomy with pelvic node clearance.

Intra op findings – large polypoidal growth from the uterine cavity protruding out towards the cervical OS, tumour broke down towards the vagina

Intra operative and Post operative period was uneventful. With no complication

HPE report turned out to be mixed mullerian tumour.

Patient subjected to adjuvant chemo and radiotherapy. Details -

Histopathology

Total abdominal hysterectomy with bilateral salpingo oophorectomy”: The uterus with distorted cervix measures 12.5(SI) x7.0 (ML) x4.0 (AP) cm. The distorted cervical canal measures 3.7 cm in length. The posterior lip of cervix appears to be elongated and enlarged. The cervix is distorted and shows an ulceroproliferative tumour involving in the anterior, posterior, right lateral, left lateral walls of cervix and infiltrating the lower uterine segment. The tumour has firm grey white fleshy cut surface. The ectocervical/vaginal cuff margin is focally present on the posterior wall of cervix and appears to be uninvolved by the tumour. The tumour is <0. 1 cm away from the inked paracervical soft tissue margin. A fibroid is identified within the elongated posterior lip of cervix.

Microscopy

Sections show of wall of cervix with presence of a cellular infiltrative tumour composed of fused, cribriform and well formed glands lined by mitotically active cells having moderately pleomorphic vesicular nuclei, prominent nucleoli and moderate ill defined cytoplasm (consistent with adenocarcinoma) alternating with nests and sheets of large polygonal cells having moderate to markedly pleomorphic vesicular nuclei, conspicuous nucleoli and moderate amounts of clear to eosinophilic cytoplasm with presence of intercellular bridges and foci of Individual cell keratinization and keratin pearl formation (consistent with Squamous cell carcinomatous). Some tumour cell nests have medium sized nuclei and show peripheral palisading. Also seen are fascicles of spindle shaped tumour cells having moderate to markedly pleomorphic nuclei and ill defined cytoplasm (consistent with sarcomatoid differentiation). Bizarre tumour cells and tumour giant cells along with areas of necrosis are seen. Tumour cells in a chondromyxoid background suggestive of chondroid differentiation also shows presence of tumour cell surrounded by eosinophilic homogenous lace like material suggestive of osteoid (heterologous differentiation). Extensive lymphovascular invasion is present. Perineural invasion is indeterminate. Tumour show features suggestive of high grade squamous Intraepithelial lesion (H-SIL).

Immunohistochemistry performed -

Vimentin highlights the sarcomatoid areas of tumour differentiation. Estrogen receptor shows nuclear immunoreactivity in tumour cells in glandular component. P16 shows non immunoreactivity in tumour cells.

SMA is immunoreactive in focal areas with sarcomatoid differentiation. CD10 highlights the epithelial component of tumour.

Tumour cells are immunoreactive for Vimentin and non immunoreactive for Pan cytokeratin.

A12, AFB1-AFB3 shows junction of body of uterus and isthmus with presence of tumour infiltrating the endometrium and less than one half of myometrium. Lymphovascular invasions are identified (AFB1 and AFB3),

Sections show wall of cervix with mucosal ulceration along with parts of a circumscribed tumour in the wall composed of interlacing fascicles of benign spindle shaped cells. Fock of hyalinization are seen. There is no evidence of atypia, necrosis or increase in mitotic activity.

Sections show wall of uterus lined by a hyperplastic endometrium composed of many crowded tubular, cystically and irregularly dilated endometrial glands exhibiting budding, out pouching and branching with an increased gland to stroma ration.

Final HPE report - Total abdominal hysterectomy with bilateral salpingo oophorectomy: Malignant Mixed Mullerian tumour/ Carcinosarcoma with heterologous differentiation- Cervix Components: Adenocarcinoma, Squamous cell carcinoma, High grade sarcoma including heterologous differentiation (chondroid and osteoid differentiation). Exact sized of the tumour could not be ascertained from the specimen as the specimen was distorted and tumour pieces

were recovered lying separately in the same container. The tumour infiltrates the lower uterine segment with less than half myometrial invasion. Right and left parametrium, free of tumour. Extensive lymph vascular invasions are present. Perineural invasion is indeterminate. Intramural leiomyoma, cervix Hyperplasia without atypia, uterus. Intramural leiomyoma, uterus. Right fallopian tube with features of hydrosalpinx. Left fallopian tube with no specific pathology. Bilateral ovaries, free of tumour Bilateral paratubal cysts present.

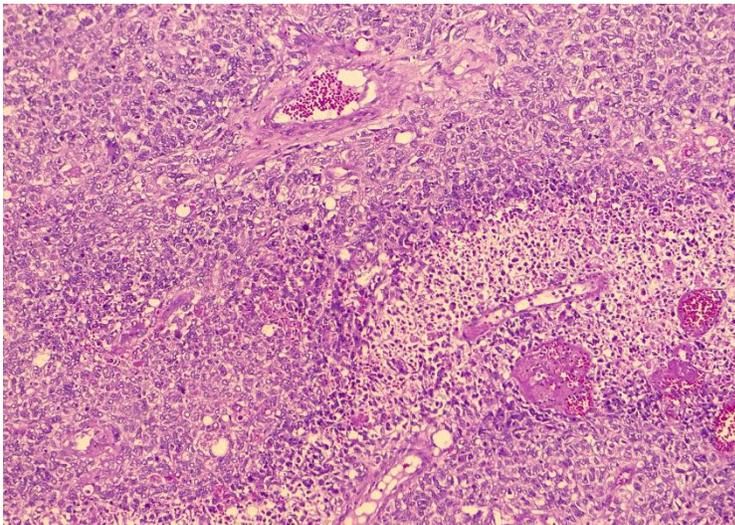


Fig 1) Sarcomatous areas with necrosis

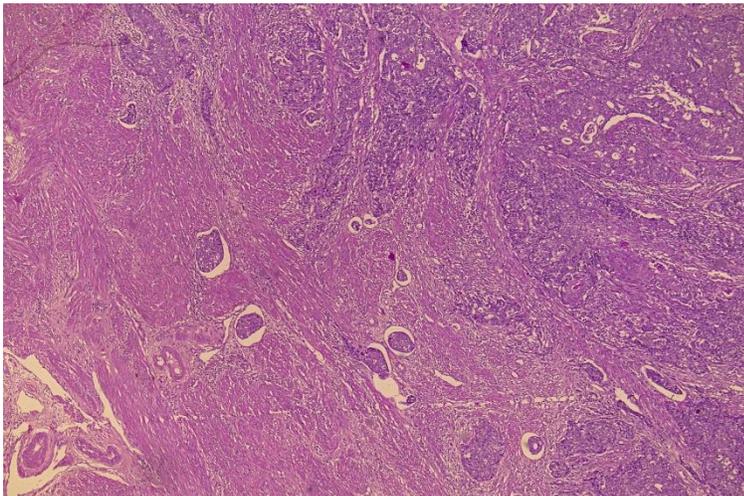


Fig2) Extensive lymphovascular invasion

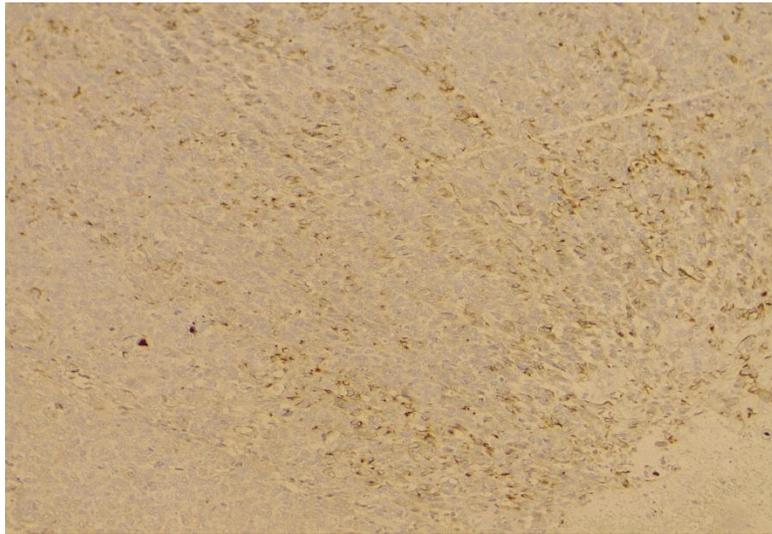


Fig 3) PanCK

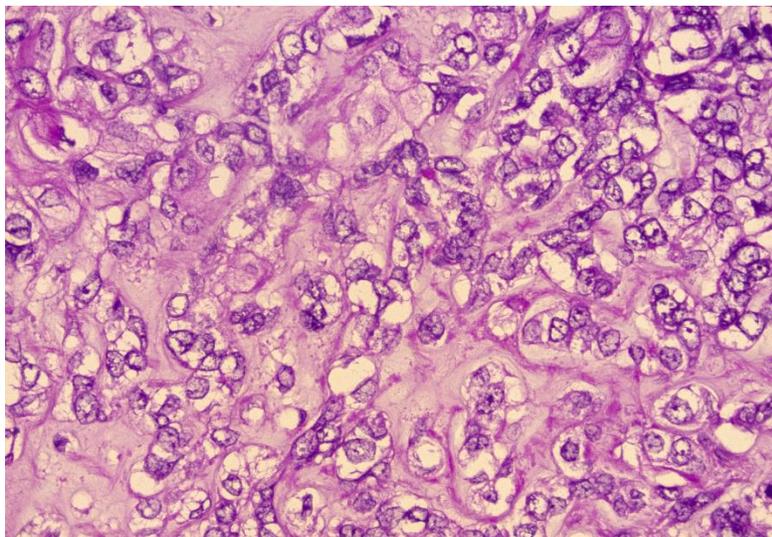


Fig 4) Chondro part of the tumour

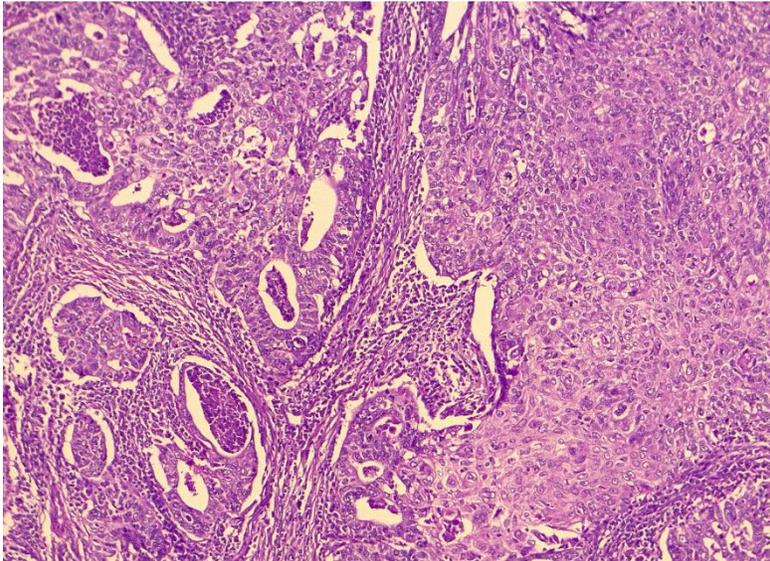


Fig 5) Adenosquamous part of the tumour

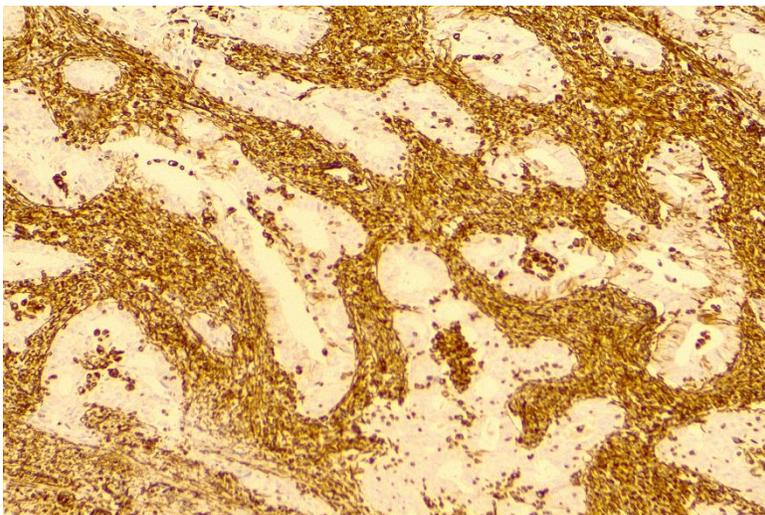


Fig 6) Vimentin sarcomatous area of the

Discussion

Our patient presented with postmenopausal bleeding with passage of clot for last three months and also gradual abdominal swelling for the same periods. She also complained of foul smelling discharge from vagina. These all coincides with the usual presentation of Malignant Mixed Mullerian Tumour. Sarcomas collectively made up about 5% or less of uterine tumours, the commonest variant being mixed mesodermal tumors, leiomyosarcomas, endometrial stromal sarcomas. Malignant mixed Mullerian tumor is called carcinosarcomas because they consists of both glandular and stromal elements. The present case also showed carcinosarcoma in histopathology. The stromal components may differentiate into a variety of malignant

mesodermal components like muscle, cartilage and bone; malignant mixed Mullerian tumors are highly aggressive. In recent years convincing evidence suggested that most not all are monoclonal in origin rather than true collision tumors. Various data confirms that the sarcomatous component is derived from the carcinoma or from a stem cell that undergoes divergent differentiation. Thus uterine carcinosarcomas are best regarded as metaplastic carcinomas.

Although Malignant Mixed Mullerian tumours are rare neoplasm's occurring mostly in uterus, rare cases of malignant mixed mullerian tumours have also been noted in the cervix (4,5,6), and the omentum (7). The lesion in the cervix was a poorly differentiated lesion composed of poorly differentiated epithelial component (cytokeratin positive), and a spindle cell component (vimentin positive) with heterologous (myeoblastic) differentiation. Also there was a report of primary peritoneal Mullerian adenosarcoma with sarcomatous overgrowth associated with endometriosis in a 50-year-old female (8). Histologically the tumor was composed of benign mullerian glands and a sarcomatous stroma. Multiple foci of endometriosis were associated with pelvic mass. Both estrogen and progesterone receptors differ in function and expression with different neoplastic states. Recent studies has shown that Malignant Mixed Mullerian Tumours and Endometrial adenocarcinomas exhibit decreased ER alpha expression and significant loss of PR protein (9).

A recent study which studied clinical and pathological analysis of 106 cases (10) of uterine sarcoma showed that the malignant mixed mullerian tumour presented in 15.1% of the total cases, while the predominant sarcoma was leiomyosarcoma (63.2%), malignant endometrial interstitial sarcomas (21.7%). They noticed that the patients with leiomyosarcoma and malignant endometrial stromal sarcoma were younger and less than 50 years of age (70.1% and 60.9% respectively), while most of the malignant mixed mullerian tumour patient were above 50 years of age. The presenting complaints of these patients were abnormal vaginal bleeding (67.0%), palpable lower abdominal mass (32.1%), vaginal discharge (27. symptoms of uterine sarcoma are non specific (mostly abnormal vaginal bleeding) and the prognosis was poor. The prognosis of uterine sarcoma is related to histopathological sub types, clinical stages and age of the patient. The mainstay of treatment is surgery with adjuvant chemotherapy and radiotherapy.

MMMT is the most common subtype of uterine sarcoma [5]. There is a scarcity of data in Indian context about this disease. Little is known about the clinical profile and outcome in our setting. All of these patients underwent endometrial biopsy for diagnosis. However, only a small amount of tissue is obtained by this procedure, and a high proportion of biphasic nature of MMMTs may be missed by this method [8]. This leads to misdiagnosis and mismanagement.

Due to the aggressive nature and poor prognosis of MMMTs, various therapeutic modalities have been employed. Surgical management should include total abdominal hysterectomy and bilateral salphingo-oophorectomy, infracolicomentectomy, bilateral pelvic and para-aortic lymphadenectomy. The role of combined adjuvant radiotherapy and chemotherapy still remains

to be defined. Historically, ifosfamide alone was considered the most effective drug; now, based on the GOG 161 study, ifosfamide/paclitaxel is considered the standard of care [9]. Recent data suggests that paclitaxel/carboplatin is equally effective [10] as adjuvant chemotherapy.

Prognostic factors included the presence of myometrial invasion ($p = 0.001$) and advanced stage of disease ($p = 0.006$), which were associated with poor outcome. Other studies have reported similar data [11, 12].

Even though we noted a better outcome in patients treated with chemoradiotherapy versus chemotherapy alone, this result was not statistically significant ($p = 0.9$), probably due to the small number of patients in the chemoradiotherapy arm. The addition of radiotherapy also reduces the local recurrence rates.

Conclusion

At present, the treatment of primary peritoneal MMMT is guided by experience of prior patients and treatment recommendations for uterine sarcoma, owing to limited data on its management and treatment. In terms of MMMT treatment, surgical tumor resection is the most effective method, and we should try to reach the status of no evidence of tumor by the surgeon's unaided eye. Systemic adjuvant chemotherapy is essential for all patients after operation. Ifosfamide and cisplatin are usually the preferred chemotherapy regimen, and the reaction rate of ifosfamide is 25% and that of cisplatin as a single drug for uterine carcinosarcoma is 17%. The effect of radiotherapy is controversial for MMMT. There is no clear conclusion as to whether to undergo radiotherapy.

In conclusion, MMMTs are a rare and aggressive tumour of the uterine corpus. A negative endometrial biopsy does not rule out diagnosis. The outcome correlates with the stage of the disease and the depth of myometrial invasion. A majority of the patients with advanced-stage disease had recurrence or progression within one year. With better understanding of the disease origin, combination chemotherapy with paclitaxel and carboplatin may be beneficial. Concurrent chemoradiation improves local control and may delay recurrence but has shown little survival advantage. The optimal adjuvant treatment for this uncommon disease is yet to be established, highlighting the need for larger multicentric studies on this tumour.

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