Malignant mixed mullerian tumor of uterus - An unusual presentation

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ABSTRACT

Malignant Mixed Mullerian Tumor (MMMT), also called as carcinosarcoma, is an aggressive rare variant of uterine malignancy. MMMT is commonly associated with post-menopausal, nulliparous females with hyperestrogenic states and with median age at presentation being 65 years. It is unusual for the tumor to be seen in pre-menopausal, multiparous female with no history of exogenous hormonal therapy. Less than 5% of the patients are younger than 50 years. MMMT's are one such tumors which have not seen better treatment outcome owing to aggressive nature of the tumor and advanced stage of it and hence provide greater challenge to understand the tumor biology. This case report elucidates that factors other than hyperestrogenism should be considered to understand the mechanisms involved in genesis of such tumors possibly a denovo activation of stem cells and their differentiation into two different components.

Keywords : Malignant Mixed Mullerian tumor, uterus, multiparity, premenopausal age group

INTRODUCTION

Malignant uterine neoplasm's containing both carcinomatous and sarcomatous elements are designated in the World Health Organization (WHO) classification of uterine neoplasm's as carcinosarcomas[1]. MMMT is an aggressive tumor with poor prognosis and accounts for between three and five percent of all tumors derived from the body of the uterus. Of all the theories proposed to explain the origin of these biphasic lesions, the "combination theory" is most widely held[2]. MMMT's of uterus is a rare entity and they are found predominantly in postmenopausal women[1, 2, 3] usually in most advanced stage with bleeding PV, abdominal pain and/ or as abdominal mass. MMMT's may be uterine or extrauterine. Risk factors are similar to those of adenocarcinomas and include obesity, exogenous estrogen therapies, and nulliparity. MMMT's have a biphasic morphology with an admixture of carcinoma (cancer showing epithelial differentiation) and sarcoma. Prognosis of MMMT's is generally worse and as such demands attention and time of researchers to better understand the etiopathogenesis of these lesions to improve treatment modalities and widen the understanding of MMMT[4].

CASE REPORT

A fourty year old para 4 female presented with symptoms of continuous bleeding PV associated with foul smelling. Personal history revealed no usage of exogenous hormonal therapies and no pelvic irradiation. Details of menarche were not available. There was no previous history of previous bleeding per vaginum. No previous endometrial biopsy or curettage was done. No previous radiological data are available.

Colposcopic examination revealed a friable mass protruding from cervical os. USG abdomen resulted with a preliminary diagnosis of degenerated fibroid. CT / MRI scan were not performed. Preoperatively limited investigations were done and the patient was posted for surgery. Per operatively, the mass was markedly friable and primarily considered to be arising from endocervical region which was also markedly friable. There was no involvement of bladder anteriorly and rectum posteriorly. However, adhesions were seen with omentum and parts of colon. The mass couldn't be resected in toto and as such was resected piece meal. Grossly we received a morcellated specimen of uterus, cervix and multiple friable to spongy and solid grey white soft tissue bits (Figure 1). Uterus on sectioning showed a brownish fleshy polypoid mass measuring 4x2x2cms arising from upper posterior wall of uterine cavity and projecting down. Cut section of the polyp showed hemorrhagic, necrotic and greyish brown areas. Cervix showed solid stroma. Cut surface of other soft tissue masses showed a similar solid to soft, grey brown, hemorrhagic and necrotic appearances. Ovaries and tubes were grossly unremarkable. Omentum, peritoneal washings, lymph node sampling and biopsies of segments of intestine with adhesions were not submitted for histopathology.

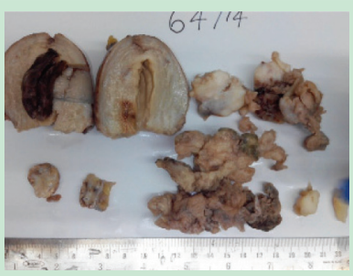

Fig 1. Gross Specimen of uterus in multiple bits.

Microscopy showed a biphasic tumor with epithelial (carcinomatous) component present as sheets and tubuloglandular structures with columnar epithelial lining showing evidence of stratification, pleomorphism, anisokaryosis and hyperchromasia (Figure2). Foci of endometrioid and clear cell differentiation were seen (Figure3, 4, 5). Stromal component shows discrete endometrial stromal cell like morphology with cells seen permeating around the glandular structures with pushing margins (Figures 1, 6, 7). Heterologous mesenchymal elements were not seen and tumor was seen infiltrating cervical stroma (Figure 6). Body of uterus showed myometrium with less than 50% infiltration by tumor, focally. Sections from multiple discrete masses received separately also showed tumor with areas of necrosis and hemorrhage. Occasional giant cells with multiple nuclei were also seen (Immunohistochemistry to ascertain their nature couldn't be done). Per operative details showed that the multiple discrete masses submitted for histopathology were from around the region of the lower uterine segment. Parametrial extension, vaginal cuff involvement couldn't be assessed in view of morcellated nature of the specimen submitted. Sections from ovaries showed mild stromal hyperplasia. Tubes and ovaries showed no metastatic deposits.

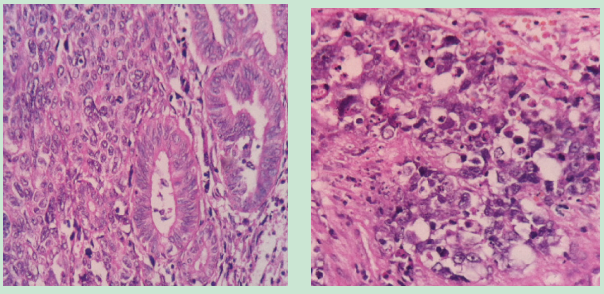

Figure2. Section showing Carcinomatous and Stromal Component [H&E,x40]

Figure3. Section showing Clear cell differentiation [H&E,x40]

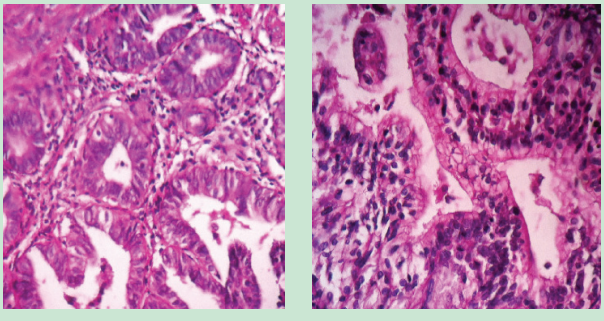

Figure4. Section showing Endometrioid Differentiation [H&E,x40]

Figure5. Section showing Endometrioid Differentiation [H&E,x100]

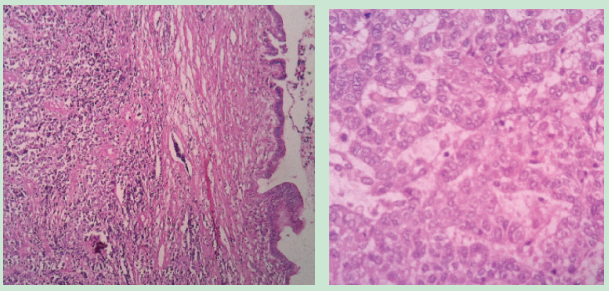

Figure6. Section showing Stromal component infiltrating cervix [H&E,x10]

Figure7. Section showing stromal component of tumor [H&E,x40]

DISCUSSION

Malignant mixed mullerian tumor is an aggressive rare variant of uterine malignancy accounting for a disproportionate percentage of mortality. As the name implies, it has a biphasic morphology with an admixture of carcinoma (cancer showing epithelial differentiation) and sarcoma (cancer showing mesenchymal differentiation) components.

A few theories have been proposed to explain the origin of these biphasic lesions. The "collision theory", in which the different types of tissues are believed to either develop separately or join into a single mass; the "composition theory or conversion theory", that an adenocarcinoma stimulates the stroma to create a tumor; the "combination theory", that the tumor is the result of a stem cell that differentiates into different cell types. "Collision" tumors are normally easily recognized and not considered true MMMTs; the "combination" theory is most widely held, and is due to evidence that the tumors develop from a single line of cells, developing in a fashion similar to the fundus of the uterus from the Müllerian duct - first from a stem cell into a population of cells, that then differentiates into epithelial and stromal components.

Majority of the MMMT cases present with bleeding per vaginum while a few cases present with pain and as mass per abdomen[5]. MMMT of uterus are practically always seen in postmenopausal women, although exceptions occur rarely[6,7]. The usual location of MMMT's is uterine body, particularly the posterior wall in the region of fundus[8,9,10]. Associated risk factors include obesity, exogenous estrogen therapies, and nulliparity. Other less well-understood but potential risk factors include high levels of estrogen, endometrial hyperplasia, lynch syndrome, hypertension, polycystic ovary syndrome, infertility, early menarche, late menopause, endometrial polyps, tamoxifen therapy and pelvic irradiation[11].

In the present case study, the tumor was seen associated with a premenopausal, multiparous individual with no associated hyperestrogenic state. The presentation with foul smelling

continuous bleeding PV and gross characteristics including typical polypoid lesion were all confirming with the features given in literature. Histopathology revealed an aggressive biphasic tumor infiltrating the myometrium and involving cervical stroma and probably extending beyond the uterine limits. There were features of omental and colonic adhesions, per-operatively, which were not sampled for histopathology. Peritoneal washings and lymph node sampling were also not available. As such, the exact staging was not feasible. The case was not further available and is lost for follow up and prognostic details.

Although, hyperestrogenic state, nulliparity and post-menopausal status have been long implicated in association with MMMT of uterus, the present case highlights its association with a pre-menopausal, multiparous individual with no hyperestrogenic state and no pelvic irradiation and further upholds the combination theory in the genesis of such tumours.

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Please cite this article as: Prashanth M, Sukumar P. Malignant mixed mullerian tumor of uterus - An unusual presentation. Perspectives in medical research 2016;4:1:64-66.

Sources of Support: Nil,Conflict of interest:None declared