Malignant Mixed Mullerian Tumor of Cervix

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ABSTRACT

Malignant mixed Mullerian tumors of the cervix are very rare tumors, constituting only 0.005% of all cervical malignancies. It usually presents with abnormal vaginal bleeding in post-menopausal women. The tumor has high rates of metastasis, so careful management including surgery, chemotherapy and/or radiotherapy is done for these patients. Here, we present a case of a 47 year old woman who present with an ectocervical polyp. The patient underwent hysterectomy and the polyp was diagnosed on histopathological examination as malignant mixed Mullerian tumor of the cervix.
Introduction
Malignant Mixed Mullerian Tumors (MMMTs) are rare biphasic neoplasms, first described by Ferriera in 1951. The commonest site of occurrence in the female genital tract is the uterine corpus. MMMT of the cervix are extremely rare and constitute 0.005% of all malignancies of the cervix. Only around 50 cases of cervical MMMT have been reported in the literature so far.

The age range of patients with cervical MMMT varies from 12 to 93 years, but it usually seen to occur in post-menopausal women with a mean age at diagnosis of 61 to 69 years. The most common presenting symptom is abnormal vaginal bleeding. Abnormal vaginal cytology, polypoidal cervical mass, abdominal or pelvic pain may also be seen in these patients.

Case Report
A 47 years old female presented with excessive vaginal bleeding and discharge to a gynecologist. On Examination, there was a polyp found on the ectocervical lip and she was finally subjected to total hysterectomy. The hysterectomy specimen without adnexa was sent to us for examination.

Gross Findings: The specimen comprised of uterus measuring 5x3x3 cm and polypoidal tissue measuring 2x1 cm (Figure 1) with variegated appearance. Cervix appeared unremarkable and endocervical canal measured 1.5 cm in length. The endometrial cavity was unremarkable and average myometrial thickness was 1 cm. Polyp was attached at the 3 o’clock position on the cervix and showed dark brown to pale white friable tissue on cut surface.

Light Microscopic Examination: Section from the cervical polyp showed presence of atypical cells forming syncytial pattern, pseudoglandular pattern in the subepithelial layer with cells showing moderate cytoplasm with presence of central round to oval nuclei with prominent nucleoli and increased mitotic activity (Figure 2A). The stroma showed hypercellular and hypocellular areas comprising of chondro-myxoid areas (Figure 2B) with atypical stromal cells. These cells were large with clear cytoplasm, oval nuclei and prominent nucleoli. Tumor giant cells and binucleate cells were also seen (Figure 2C). There were foci of chronic inflammatory cells comprising of lymphocytes and histiocytes.

Immunohistochemical Marker Studies: Microscopically the tumor was composed of two different parts. The epithelial part was composed of basaloïd squamouscell carcinoma (HMW CK+, EMA+) whereas the mesenchymal part was represented by homologous high-grade stromal sarcoma (CD 10+, vimentin+, desmin+/−, MSA−, SMA−, S100−). The endocervix was intact, without the infiltration, and samples from the endocervical curettage were negative as far as the malignancy was concerned. Uterus showed unremarkable histology.

Discussion
MMMTs of cervix are very rare neoplasms, usually seen in postmenopausal females. Grossly, cervical tumors range in size from 1.1 to 10 cm in maximal dimension. The tumors are usually large, soft, broad-based and polypoid with a fleshy cut surface, often with areas of hemorrhage and necrosis.

Microscopically, MMMTs are biphasic tumors, composed of distinctive and separate, but admixed, malignant appearing epithelial and mesenchymal elements. The epithelial component is usually poorly differentiated
and represents a variety of different subtypes, alone or in combination, including squamous cell carcinoma, basaloid squamous carcinoma, adenocarcinoma, adenosquamous carcinoma, adenoid basal carcinoma, adenoid cystic carcinoma and undifferentiated carcinoma. The sarcomatous component may be homologous or heterologous. The homologous sarcoma has the appearance of a spindle cell sarcoma, often poorly differentiated, and contains fibroblasts or smooth muscle cells. Heterologous tumors contain one or more of the following elements in descending order of frequency: rhabdomyoblasts, mature appearing cartilage or chondrosarcoma, osteoid, bone or osteosarcoma and lipocarcoma. Rarely, it may contain neural or neuroendocrine elements.

On immunohistochemical examination, both epithelial and sarcomatous components may show positivity for broad spectrum cytokeratins, low molecular weight cytokeratins, high molecular weight cytokeratins and epithelial membrane antigen. Immunoreactivity for a variety of muscle specific markers such as actin, desmin, myosin and myoglobin are almost invariably confined to the sarcomatous cells.

In the histopathological differential diagnoses, sarcomatoid carcinoma, endometrial stromal sarcoma and Mullerian adenosarcoma must be considered. In sarcomatoid carcinomas, there is always a sharp merging between the obvious epithelial component and the sarcomatoid component, whereas this merging is not seen to the same degree in MMMTs. The distinction between MMMT and Mullerian adenosarcoma is easier because in adenosarcoma, the epithelial component is clearly benign. Endometrial stromal sarcomas arising in the cervix is extremely rare. Only three cases have been reported so far and the tumor can be differentiated from MMMT by absence of a malignant epithelial component.

MMMTs may be misdiagnosed as pure carcinomas or sarcomas, especially in small or inadequate biopsies. Also, because of its rarity, the cervical extension from the uterine corpus must be excluded since this condition is more common and most cervical MMMTs are microscopically indistinguishable from its endometrial counterpart. In such cases, the correct diagnosis depends mainly on the dominant localization of the neoplasm based on the findings of pelvic examination, imaging studies, curettage and in some patients, a hysterectomy specimen.

The etiologic factors involved in the development of MMMTs are not clear. Factors of concern, which may have an effect on the development of carcinosarcoma, are radiation exposure to the pelvic area, previous chemotherapy, obesity, hypertension, nulliparity, human papilloma virus (HPV) infection and exogenous estrogen use. Another matter of persistent controversies is the histogenesis of MMMTs of the female genital tract. Theories which have been proposed include the “collision”, “combination” and “composition” theories. The fourth and currently favored theory is the metaplastic theory of histogenesis. This theory is supported by the detection of HPV 16 and 18 in cases of MMMTs of the female genital tract. In a study done by Grayson et al., HPV 16-DNA was detected in the nuclei of both the epithelial and sarcomatous components of three cases. Yet another theory, the “neometaplasia of Mullerian origins”, states that mesodermal stem cells differentiate along many divergent cells lines leading to the development of the different elements in MMMTs.

The prognosis is cervical MMMTs depends on the clinical stage of the disease and presence of metastasis.
carcinosarcomas is primarily via the lymphatic system. The most frequent areas of spread are the pelvis, lymph nodes, lungs and liver.\(^{16,17}\) Clement et al. reported the largest single series of nine cases of cervical MMMTs, and suggested that their prognosis is better than that of their uterine counterparts, as they are more often confined to the uterus at presentation and frequently have a non-glandular epithelial component.\(^{11}\) The clinical behavior of these tumors is dominated by the carcinomatous component. However, because of the limited number of cases studied and their short follow-up periods, it is too early to be conclusive about the exact behavior and prognosis of these tumors.\(^{12}\)

MMMTs are managed with surgery, chemotherapy and radiotherapy. Surgery should include hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Carcinosarcomas also require comprehensive peritoneal surgical staging including peritoneal cytology and biopsies.\(^{16,18}\) The role of adjuvant chemotherapy and radiotherapy are not well defined. Radical radiotherapy with or without chemotherapy is recommended for locally advanced disease. Patients with metastatic disease are treated with palliative chemotherapy and have a poor prognosis. Evidence-based guidelines for treatment of cervical MMMTs are not available due to its rarity.\(^{14}\)

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**References**