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Case Report

Heterologous Malignant Mixed Mullerian Tumor in a Diabetic Patient

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Abstract

Uterine malignant mixed müllerian tumor (MMMT) is an uncommon carcinosarcomatous neoplasm with a highly malignant, biphasic pattern consisting of both epithelial and mesenchymal components. This paper reports the clinical, pathological and immunohistochemical features of heterologous MMMT of a diabetic and hypertensive patient.

A 73-year-old white woman presented with post- menopausal bleeding for six months. The patient underwent TAH&BSO with pelvic lymph nodes dissection. In pathologic evaluations, a polypoid solid and white mass measuring 4.5cm×3cm×1.5cm was identified. Light microscopy showed biphasic pattern of epithelial component with clear cell change and sarcomatous elements of spindle cells with cartilage and bone differentiation. Immunohistochemistry was performed on formalin fixed and paraffin embedded tissue with a panel of immunohistochemical markers comprising cytokeratin (CK), vimentin and S_{100}. The epithelial component was reactive for CK and vimentin. S_{100} positivity was seen in stromal and chondroid elements; so the diagnosis of MMMTS was confirmed. CONCLUSION: There may be an association between diabetes mellitus and the development of malignant mixed mesodermal tumor. Special attention should be paid when attempting to sample the endometrium of these patients. But further studies are needed to verify this hypothesis.

KEYWORDS: Post- menopausal bleeding, Heterologous Malignant Mixed Mullerian Tumor, Diabetes mellitus, Hypertension.

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Uterine malignant mixed müllerian tumor (MMMT) is an uncommon carcinosarcomatous neoplasm with a highly malignant, biphasic pattern consisting of both epithelial and mesenchymal components.[1-3] The epithelial component may be any type of müllerian carcinoma: mucinous, squamous, endometrioid, high-grade papillary, clear cell, undifferentiated, or mixtures of these types. It is traditional to divide the stromal components into homologous (leiomyosarcoma, stromal sarcoma, fibrosarcoma) and heterologous (chondrosarcoma, rhabdomyosarcoma, osteosarcoma, liposarcoma) types. Carcinosarcoma, with rare exceptions, is a disease of elderly menopausal women.[4,5] The clinical course of tumor is highly aggressive and it is usually diagnosed in advanced stage.[6] This neoplasm has sometimes been associated with a history of radiation therapy.[7] Some patients have developed carcinosarcoma while taking tamoxifen[8] and raloxifene.[9] Diabetes mellitus and hypertension have been introduced as predisposing factors for uterine adenocarci-

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noma, but the relationship between these factors and MMMT is not clear.[10,11] This article reports the clinical, pathological and immunohistochemical features of heterologous MMMT in a diabetic and hypertensive patient.

Case report

A 73 year-old white woman with chronic diabetes mellitus (type II) and hypertension presented with post- menopausal bleeding for six months. The patient's diabetes mellitus (type II) and hypertension were well controlled, using insulin injections, atenolol and captopril. The height, body weight and body mass index (BMI) of the patient in the initial physical examination were 155 cm, 75 kg and 31.21 kg/m2, respectively. Pelvic examination showed slight uterine enlargement. A mixed cystic and solid mass measuring 43mm ×41mm×36mm was found using trans- abdominal ultrasonography. In addition Pap smear and dilation curettage were performed and the diagnosis of adenocarcinoma was suggested for the patient. Afterwards, the patient underwent surgery. The type of operation was total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH&BSO) with pelvic lymph node dissection. Adjuvant therapy was also included in treatment program following surgery.

In pathologic evaluations, grossly, the mass was polypoid, solid, white and without necrosis with foci of hemorrhage, measuring 4.5cm×3cm×1.5cm. Light microscopy showed a heterogenous malignant neoplasm with a biphasic pattern. The epithelial part of the tumor consisted of glandular component with clear cell appearance (figure 1). Furthermore, sarcomatous areas consisting of spindle cells with oval nuclei, focally arranged in bundles accompanied by foci of mature cartilage and bone were found (figure 2, 3). Mitotic figures were moderate. Immunohistochemistry was performed on formalin fixed and paraffin embedded tissue with a panel of immunohistochemical markers comprising cytokeratin (CK), vimentin and S_{100}. The epithelial component was reactive for CK and vimentin. S_{100} positivity was seen in stromal and chondroid elements. The pathologic stage of the tumor seemed to be IB. In post-operation follow up, the patient didn't have any serious compliant up to one month after surgery.

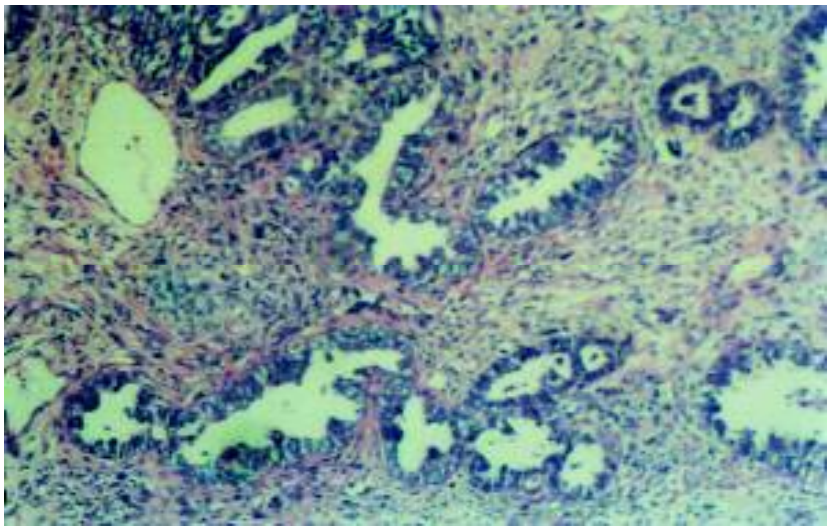

Figure 1. Glandular components of mixed mullerian tumor (H&E *400)

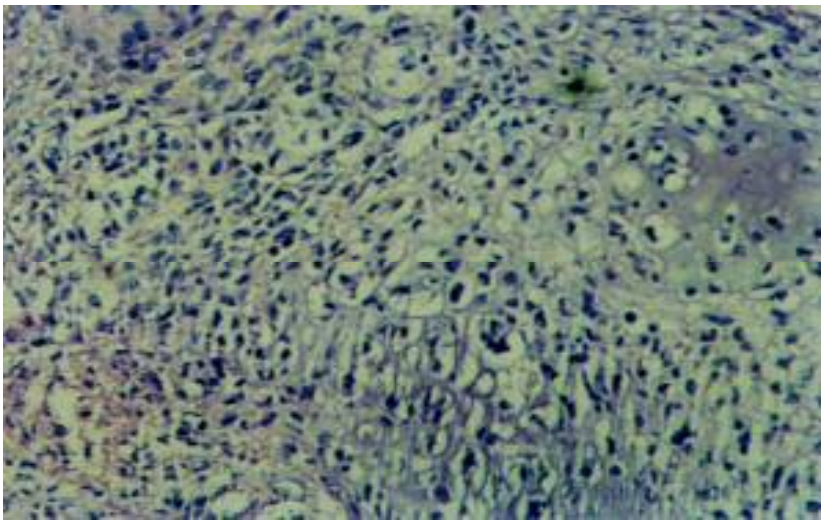

Figure 2. Mesenchymal componenents of mixed mullerian tumor (H&E *400).

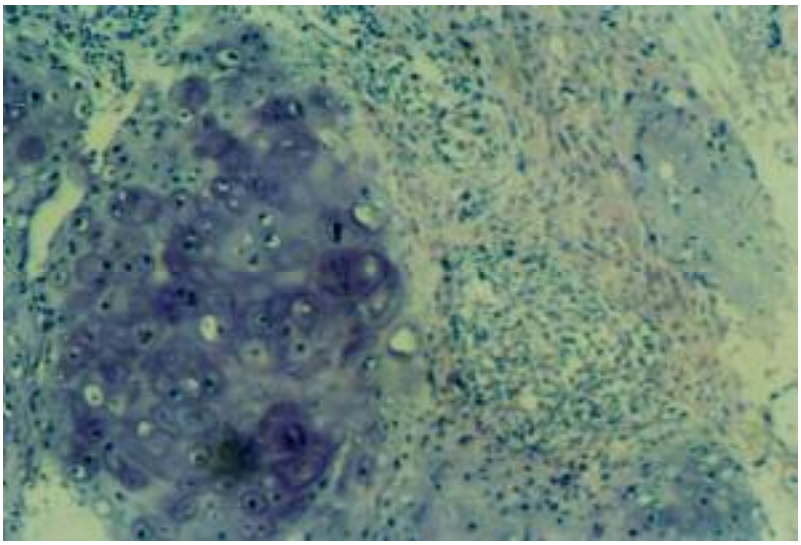

Figure 3. Heterologous elements of mixed mullerian tumor in the form of cartilage (H&E *400).

Discussion

Malignant mixed mullerian tumors of the uterus are rare neoplasms that are practically always seen in postmenopausal patients. They present with uterine bleeding and enlargement.[4,5] The usual location is the uterine body, particularly the posterior wall of the fundus but a few cases with MMMT of uterine cervix have been reported as well.[12-13] Infertility and obesity have been reported in some patients.[12] The relationship between diabetes mellitus, hypertension and BMI with endometrial cancers was evaluated in a research in Sweden by Weiderpass et al and 6 cases of MMMT were excluded from the study.[14]

Grossly, these tumors present as large, soft, broad based and polypoid masses involving the endometrium and myometrium with fleshy surfaces. Necrosis and hemorrhage are commonly found as well.[1,2] The characteristic microscopic features of MMMTs are the admixture of carcinomatous and sarcoma-like elements resulting in a biphasic pattern.[4] The carcinomatous component is usually a poorly-differentiated adenocarcinoma. The appearance of the sarcomatous component is

the basis for division of these neoplasms into homologous and heterologous varieties.[5] 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 liposarcoma. The rarest type of differentiation in MMMTs is neural.[12] The homologous sarcoma has the appearance of a spindle cell sarcoma.

MMMTs with only homologous elements are also called carcinosarcoma. Immunohistochemical studies revealed that cytokeratin was always detectable in the epithelial areas, but was also present in the sarcomatous component in over half of the cases. Vimentin is more diffuse and intense in the sarcomatous component.[5] Various muscle markers, CD_{10}, and HER_2/ neu also have been encountered in MMMTs.[12]

The etiologic factors, involved in the development of MMMTs are not clear. Fotiou et al reported two cases of MMMT secondary to tamoxifen treatment in patients with a previous diagnosis of carcinoma.[15] Huang YT et al reported a patient with stage IIIB cervical squamous cell carcinoma in whom MMMT developed 5 years after radiotherapy.[7] MMMTs have also been seen with chronic estrogenic stimulation (ovarian thecoma, polycystic ovarian disease, and prolonged estrogen therapy.[5,16,17] In differential diagnosis, mullerian adenosarcoma should be considered. In adenosarcoma, the epithelial component is clearly benign. MMMTs may be misdiagnosed as pure carcinomas or sarcomas mainly in small biopsies and the lesion may be misinterpreted by inadequate sampling as occurred in our case.

MMMTs are highly aggressive neoplasms. Staging is the most important predictive factor in prognosis.[4,5] There are some evidences that the prognosis of MMMTs of the cervix is better than their corpus counterparts. In our patient, light microscopy showed biphasic pattern of epithelial component with clear cell change and sarcomatous elements of spindle cells with cartilage and bone differentiation. Malignant features in epithelial component ruled out adenosarcoma, so the diagnosis of MMMT was confirmed.

Conclusion

There may be an association between diabetes mellitus and the development of malignant mixed mesodermal tumor. Special attention should be paid when attempting to sample the endometrium of these patients. But further studies are needed to verify this hypothesis.

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